Oxford Textbook of Critical Care

SECOND EDITION

Edited by
Andrew Webb
Derek Angus
Simon Finfer
Luciano Gattinoni
Mervyn Singer

OXFORD

Oxford Textbook of

Critical Care

Free personal online access for 12 months

Individual purchasers of this book are also entitled to free personal access to the online edition for 12 months on *Oxford Medicine Online* (www.oxfordmedicine.com). Please refer to the access token card for instructions on token redemption and access.

Online ancillary materials, where available, are noted at the end of the respective chapters in this book. Additionally, *Oxford Medicine Online* allows you to print, save, cite, email, and share content; download high-resolution figures as Microsoft PowerPoint slides; save often-used books, chapters, or searches; annotate; and quickly jump to other chapters or related material on a mobile-optimized platform.

We encourage you to take advantage of these features. If you are interested in ongoing access after the 12-month gift period, please consider an individual subscription or consult with your librarian.

Oxford Textbook of

Critical Care

SECOND EDITION

Edited by

Professor Andrew Webb, MD, FRCP, MFMLM

Clinical Professor, Division of Critical Care, Faculty of Medicine,
The University of British Columbia, Canada

Professor Derek C. Angus, MD, MPH, FRCP

Distinguished Professor and Mitchell P. Fink Endowed Chair

Department of Critical Care Medicine

University of Pittsburgh and UPMC Health System

Professor Simon Finfer, MBBS, FAHMS, FRCP, FRCA, FCICM, DrMed

Professor of Critical Care, The George Institute for Global Health, University of Sydney

Senior Staff Specialist in Intensive Care, Royal North Shore Hospital, Sydney

Professor Luciano Gattinoni, MD FRCP

Chief of the Department of Anaesthesia, Resuscitation and Emergency Medicine,
Fondazione IRCCS Ca' Granda—Ospedale Maggiore Policlinico

Full Professor in Anesthesiology and Intensive Care Medicine, Department
of Pathophysiology and Transplantation, University of Milan

Professor Mervyn Singer, MD FRCP, FRCP, FFICM

Professor of Intensive Care Medicine, University College London

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide. Oxford is a registered trade mark of
Oxford University Press in the UK and in certain other countries

First Edition Published in 1999
Second Edition Published in 2016
Impression: 1

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America

British Library Cataloguing in Publication Data
Data available

Library of Congress Control Number: 2015939284

ISBN 978–0–19–960083–0

Printed in China through
Asia Pacific Offset Ltd

Foreword

One may ask in today's internet-based world whether there is still a need for textbooks when there is so much opinion and advice already available online. Although possibly not able to capture and include the very latest research results, textbooks provide a solid basis and background of the subject in question giving an essential framework of understanding on which to build. This *Oxford Textbook of Critical Care* is a true example of quality. All the authors are well-known experts in their field, the chapters have all been carefully reviewed and the contents are, therefore, relevant and reliable. What is more, as with many recent publications, this textbook is also available as an online version for easy reference.

This completely revised and comprehensive version of the 1999 edition covers all possible aspects of intensive care medicine making it an impressive tome. The chapters are short, concise and to the point, and thus easy to read and understand. The book is well-illustrated and the layout is fresh and attractive. The key points, highlighted at the start of each chapter, provide a useful summary of each topic and the book in general is clinically-orientated, making it of value for the practicing clinician, as well as physicians in training. The book benefits from an impressive list of true experts from around the globe, giving it international appeal and insight—it is a real credit to the editors that so many leading authorities have contributed!

I believe textbooks still have an important role in providing a trustworthy source of knowledge. As different textbooks will have a slightly different focus, include different authors, and use various presentation formats they can complement each other. This book will occupy an important place in this field and is a highly recommended reference for all involved in the care of critically-ill patients.

Jean-Louis Vincent, MD PhD
Professor of Intensive Care Medicine, Université Libre de Bruxelles

Preface

Since the first edition of the *Oxford Textbook of Critical Care* was published there have been many advances in our understanding and management of critical illness. We prefaced the first edition with a note on the exacting nature of critical care; the holistic complexity of the patient with multisystem dysfunction, the out-of-hours commitment, the often stressful and highly charged situations requiring considerable agility of brain and hand, and the continuing evolution (and occasional revolution) in perceived 'best practice'. However, these challenging demands are precisely what attract the critical care practitioner to the specialty. The importance of strong support mechanisms—from colleagues, from national and international societies, and from robust educational and research outputs—is paramount to not only sustain but also enhance the quality of care given.

Recognizing the increasing use of electronic media for reference, we have continued the format used in the first edition. The traditional chapter layout of a textbook gave way to system-orientated sections. Each section has been subdivided into short topics grouped within the section according to clinical problems. We believe the reader will often come to this book, in paper or electronic format, wishing to update on a specific clinical problem that matches an issue experienced at the bedside. Furthermore, this layout facilitates manageable and relevant searches in electronic media.

The *Oxford Textbook of Critical Care* is a single-volume major reference book aiming to cover the breadth of clinical and organizational aspects of adult critical care medicine in readable chunks. We clearly acknowledge that every single topic cannot possibly be covered in detail, but hope its comprehensive nature will be found useful by all health care providers who look after critically-ill patients.

We recognize there are often local, national, and international differences in philosophy and management strategy. Some of these differences are seemingly contradictory and it is often difficult for physicians in one country to assimilate information produced for another. We intended from the outset to offer the *Oxford Textbook of Critical Care* as an international text. We have attempted to give a balanced view where international differences exist and, in many cases, have sat squarely on the fence. We make no apology for this since we believe the book should inform rather than dictate.

Producing this edition has been a mammoth task, co-ordinating the efforts of over 600 authors from all corners of the world. We thank all those who have contributed to this project and to members of the staff of Oxford University Press for persuading us to take on this second edition, and whose skill and support have been essential to the editorial and production process. Finally, the editors are saddened to hear of the passing of Dr Mitchell Fink, Prof Albert Jaeger and Dr Jan Kornder since the submission of their contributions to the book.

Andrew Webb
Derek C. Angus
Simon Finfer
Luciano Gattinoni
Mervyn Singer

Contents

SECTION 4
The respiratory system

PART 4.1
Physiology

PART 4.2
Respiratory monitoring

PART 4.3
Upper airway obstruction

PART 4.4
Airway access

PART 4.5
Acute respiratory failure

PART 4.6
Ventilatory support

SECTION 12
The skin and connective tissue

PART 12.1
Skin and connective tissue disorders

PART 12.2
Wound and pressure sore management

SECTION 13
Infection

PART 13.1
Diagnosis and surveillance

PART 13.2
Nosocomial infection

PART 13.3
Infection in the immunocompromised

PART 13.4
Tropical diseases

Abbreviations

18F-FDG	fluorine-18 fluorodeoxyglucose
5-HIAA	5-hydroxyindoleacetic acid
5HT	5-hydroxytryptamine
A–a PO2	alveolar–arterial oxygen gradient
AA	amino acids
AAA	abdominal aortic aneurysm
AACN	American Association of Critical Care Nurses
AAD	anti-arrhythmic drugs
AAG	alpha 1-acid glycoprotein
AAN	American Academy of Neurology
AAOS	American Academy of Orthopedic Surgeons
AASLD	American Association for the Study of Liver Disease
AST	aspartate aminotransferase
ABA	American Burn Association
ABC	Airway, Breathing Circulation
ABCD	airway, breathing, circulation, and disability
ABCDE	airway breathing circulation disability exposure
ABG	arterial blood gas
ABLE	age of blood evaluation
ABM	acute bacterial meningitis
ABO	red cell antigen
AC	assist control
ACA	American College of Cardiology
ACCM	American College of Critical Care Medicine
ACD	active compression-decompression
ACE	angiotensin-converting enzyme
ACH	air changes per hour
AChR	acetylcholine receptors
AChS	acute chest syndrome
ACLF	acute on chronic liver failure
ACLS	advanced cardiac life support
ACOS	Adult Respiratory Distress Cognitive Outcomes
AcPC	activated protein C
ACR	acute cellular rejection
ACS	acute coronary syndrome
ACT	activated clotting time
ACTH	adrenocorticotropic hormone
AD	autonomic dysreflexia
ADC	apparent diffusion coefficient
ADE	antibody dependent enhancement
ADH	antidiuretic hormone
ADHD	attention-deficit hyperactivity
ADL	activity of daily living
ADMA	asymmetric dimethylarginine
ADP	adenosine diphosphate
ADQI	Acute Dialysis Quality Initiative
AED	automatic external defibrillator
AEP	auditory-evoked potentials
AF	atrial fibrillation
AFE	amniotic fluid embolism
AFLP	acute fatty liver of pregnancy
AG	anion gap
AG_c	anion gap corrected
AGE	advanced glycosylation end-products
AGEP	acute generalized exanthematouspustulosis
AHA	American Heart Association
AHF	acute heart failure
AHL	acyl-homoserine-lactones
AHR	adjusted hazard ratio
AIDP	acute inflammatory demyelinating polyradiculoneuropathy
AIDS	acquired immune deficiency syndrome
AIH	autoimmune hepatitis
AIHA	auto-immune haemolytic anaemia
AIIR	airborne infection isolation room
AIVR	accelerated idioventricular rhythm
AJ	adherens junction
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
ALDH	alcohol dehydrogenase
ALF	acute liver failure
ALI	acute lung injury
ALL	acute lymphoblastic leukaemia
ALS	advanced life support
ALT	alanine transaminase
AMAN	acute motor axonal neuropathy
AML	acute myeloid leukaemia
AmLS	amyotrophic lateral sclerosis
AMOFS	acute multi-organ failure syndrome
AMPA	α-amino-3-hydroxy-5-methyl-4-is axazole-proprionic acid
AMS	acute mountain sickness
AMSAN	acute motor and sensory axonal neuropathy
ANA	antinuclear antibody
ANCA	anti-neutrophil cytoplasmic antibodies

ANP	atrial natriuretic peptide
ANT	adenine nucleotide translocase
AP	action potential
APACHE	Acute Physiology and Chronic Health Evaluation
APC	argon plasma coagulation
APE	acute pulmonary embolism
APF	alveolopleural fistula
APL	acute promyelocytic leukaemia
APP	abdominal perfusion pressure
aPPT	activated partial thromboplastin time
APR	acute phase reaction
APRV	airway pressure release ventilation
APS	Acute Physiology Score
APSAC	acylated plasminogen-streptokinase activator complex
APTT	activated partial thromboplastin time
AR	aortic regurgitation
ARB	angiotensin II receptor blockers
ARDS	acute respiratory distress syndrome
ARF	acute respiratory failure
ARS	acute radiation syndrome
ART	assisted reproductive technology
AS	mitral stenosis
aSAH	aneurysmal subarachnoid haemorrhage
ASA-PS	American Society of Anesthesiologists Physical Status
ASC	active surveillance cultures
ASIA	American Spinal Injury Association
ASPEN	American Society for Parenteral and Enteral Nutrition
AST	aspartate transaminase
AT	antithrombin
ATC	acute traumatic coagulopathy
ATCH	adrenocorticotrophic hormone
ATh	anaerobic threshold
ATICE	Adaptation to the Intensive Care Environment
ATLS	advanced trauma life support
ATN	acute tubular necrosis
ATP	adenosine triphosphate
ATS	American Thoracic Society
ATSe	antitetanus serum
AUC	area under the curve
AUIC	area under the inhibitory curve
AUROC	area under the receiver operating characteristic curve
AV	atrioventricular
AVM	arteriovenous malformations
AVNRT	atrioventricular nodal re-entry tachycardia
AVP	arginine-vasopressin
AVR	aortic valve replacement
AWS	acute withdrawal syndrome
BABT	behind armour blunt trauma
BabyBIG-IV	baby botulinum immune globulin
BAL	broncho-alveolar lavage
BARTS	battlefield advanced resuscitation techniques and skills
BATLS	battlefield advanced trauma life support
BB	β blocker
BBB	blood–brain barrier
BBP	blood-borne pathogens
BCG	Bacillus Calmette–Guérin
BCNE	blood culture-negative endocarditis
BD	base deficit
bd	twice daily
BDE	base deficit/excess
BDG	base deficit gap
BDI-II	Beck Depression Inventory-II
BDNF	brain-derived neurotrophic factor
BDZ	Benzodiazepine
BE	base excess
BEE	basal energy expenditure
BiLE	bilirubin, lactate, and aetiology score
BIPAP	bi-phasic positive pressure
BIS	bispectral index
BiV	biventricular
BiVAD	biventricular assist device
BKCa	large conductance calcium-activated potassium
BLS	basic life support
BMI	body mass index
BMPR	bone morphogenetic protein receptor
BMR	basic metabolic rate
BMT	bone marrow transplants
BNP	B-type natriuretic peptide
BOS	bronchiolitis obliterans syndrome
BP	blood pressure
BPS	behavioural pain scale
BPW	biphasic waveform
BRAIN-ICU	Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU
BSA	body surface area
BSI-30	Brief Symptom Inventory-30
BSS	balanced salt solutions
BTE	biphasic truncated exponential
BTF	Brain Trauma Foundation
BUN	blood urea nitrogen
BVM	bag valve mask
BW	body weight
C	compliance
CA	carbonic anhydrase
CA-AKI	contrast-associated acute kidney injury
CAB	circulation, airway and breathing
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CaMK	calcium/calmodulin-dependent protein kinases
cAMP	cyclic adenosine monophosphate
CA-MRSA	community-acquired methicillin-resistant Staphylococcus aureus
CAP	community-acquired pneumonia
CARS	compensatory anti-inflammatory syndrome
cART	combination antiretroviral therapy
CAUTI	catheter-associated urinary tract infections
CBF	cerebral blood flow
CBG	corticosteroid-binding globulin
CBV	cerebral blood volume
CC	closing capacity
CCB	calcium channel blocker (163)
CCHR	Canadian CT Head Rule
CCI	chronic critical illness

CCK	cholecystokinin
CCM	critical care medicine
CCTV	closed circuit televisions
CD	collecting duct
CDC	Centers for Disease Control
CDI	cranial diabetes insipidus
CDS	clinical decision support
CDSS	computerized decision support systems
cEEG	continuous EEG monitoring
CEPD	chronic equilibrated peritoneal dialysis
CES-D	Center for Epidemiological Studies Depression Scale
CEUS	contrast-enhanced ultrasonography
CFPD	continuous flow peritoneal dialysis
CFTR	cystic fibrosis transmembrane conductance regulator
CG	Cockcroft-Gault
cGM	continuous glucose monitors
CgMD	congenital muscular dystrophies
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
CHEST	Crystalloid versus Hydroxyethyl Starch Trial
CHF	congenital heart failure
CHR	reticulocyte haemoglobin concentration
CHS	cerebral hyperperfusion syndrome
CI	confidence interval
CICal	circulatory indirect calorimetry
CIDP	chronic inflammatory demyelinating polyneuropathy
CIM	critical illness myopathy
CINM	critical illness neuromyopathy
CINV	chemotherapy-induced nausea and vomiting
CIP	critical illness polyneuropathy
CIPN	chemotherapy-induced peripheral neuropathy
CIRCI	critical illness-related corticosteroid insufficiency
CK	creatine kinase
CKD	chronic kidney disease
CKD-EPI	CKD Epidemiology Collaboration
CKMB	creatinine kinase MB isozyme
CLABSI	central line-associated bloodstream infections
CLD	chronic lung disease
CLP	caecal ligature and puncture
CLR	C-type lectin receptors
CLS	combat lifesaver
Cmax	maximum concentration
CMD	cerebral microdialysis
CML	chronic myelogenous leukaemia
CMRO2	cerebral metabolic rate for oxygen
CMV	cytomegalovirus
CN	cyanide
CNS	central nervous system
CO	cardiac output
CoA	coenzyme A
COHb	carboxyhaemoglobin
COMPACCS	Committee on Manpower of Pulmonary and Critical Care Societies.,
CoNS	Coagulase-negative staphylococci
COPD	chronic obstructive pulmonary disease
COPE	Critical Care Outcome Prediction Equation
COX	cyclo-oxygenase
CP	cancer procoagulant
CPA	cardiopulmonary arrest
CPAP	continuous positive airway pressure
CPAx	Chelsea Critical Care Physical Assessment Tool
CPB	cardiopulmonary bypass
CPE	cardiogenic pulmonary oedema
CPET	cardiopulmonary exercise testing
CPIS	Clinical Pulmonary Infection Score
CPK	creatinine phosphokinase
CPOE	computerized physician order entry
CPP	cerebral perfusion pressure
CPR	cardiopulmonary resuscitation
CR	complement receptors
CR-BSI	catheter-related blood stream infections
CrCl	creatinine clearance
CRE	carbapenem-resistant enterobacteriaceae
CRF	corticotropin-releasing factor
CRH	corticotropin-releasing hormone
CRM	crew resource management
$CRMP_2$	collapsin response mediator protein 2
CRP	C-reactive protein
CRRT	continuous renal replacement therapy
CS	cardiogenic shock
CSA	compressed spectral array
CSCI	cervical spinal cord injury
CSF	cerebral spinal fluid/cerebrospinal fluid
CSS	Churg–Strauss syndrome
CSV	continuous spontaneous ventilation
CSW	cerebral salt wasting
CSWS	cerebral salt wasting syndrome
CT	computed tomography
CTA	computed tomography angiography
CTEPH	chronic thromboembolic pulmonary hypertension
CTP	Child–Turcotte–Pugh
CT-PA	computed tomographic pulmonary angiography
CTSI	CT severity index
CUS	compression ultrasonography
CUSP	Comprehensive Unit-based Safety Programme
CV	closing volume
CVA	cerebrovascular accident
CVC	central venous catheter
CVD	cerebrovascular disease
CVP	central venous pressure
CVS	cardiovascular system
CVVH	continuous veno-venous haemofiltration
CXR	chest X-ray
CyC	cystatin C
CYP	cytochrome-P450 superfamily
DA&O	Disclosure, Apology and Offer
DAF	decay-accelerating factors
DAI	diffuse axonal injury
DALY	disability-adjusted life years
DAPT	dual antiplatelet therapy
DAT	direct antiglobulin test
DBD	donation after brain death
dBP	diastolic blood pressure
DC	dendritic cells
DCCV	direct current cardioversion

DCR	damage control resuscitation
DCS	decompression sickness
DCT	distal convoluted tubule
DDAVP	desamino-D-arginine vasopressin
DECT	dual-energy CT
deoxyHb	deoxyhaemoglobin
DGA	diglycolic acid
DSA	digital subtraction angiography
DH	dorsal horn
DHA	docosahexaenoic acid
DHP	dihydropyridine
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DILI	drug-induced liver injury
DIS	daily interruption of continuously infused sedative
DKA	diabetic ketoacidosis
DL	decompressive laparotomy
DLBCL	diffuse large B cell lymphoma
DMARD	disease-modifying anti-rheumatic drug
DMD	Duchenne muscular dystrophy
DMV	difficult mask ventilation
DNAR	Do Not Attempt Resuscitation
DND	delayed neurological deficits
DNR	Do Not Resuscitate
DO_2	oxygen delivery
DPA	diagnostic peritoneal aspirate
DPG	diphosphoglycerate
DPL	diagnostic peritoneal lavage
DSS	dengue shock syndrome
DSV	Dengue Strain Virulence
DTI	diffusion tensor imaging
DTPA	diethylenetriaminepentaacetate
DVT	deep vein thrombosis
DWI	diffusion-weighted imaging
EA	endotracheal aspirates
EACA	Epsilon amino-caproic acid
EBL	Endoscopic band ligation
EBM	evidence-based medicine
EBP	evidence-based practice
EBV	Epstein–Barr virus
EC	extracellular
$ECCO_2R$	extracorporeal carbon dioxide removal
ECDC	European Centre for Disease Control
ECF	extracellular fluid
ECG	electrocardiogram
ECLA	extracorporeal lung assist
ECLS	extra-corporeal life support
ECMO	extracorporeal membrane oxygenation
ECPR	extracorporeal cardiopulmonary resuscitation
ECT	electroconvulsive therapy
ED	emergency department
EDD	extended daily dialysis
EDP	end-diastolic pressure
EDTA	ethylenediaminetetraacetic acid
EDV	end-diastolic volume
EE	energy expenditure
EEG	electroencephalogram
ETT	endotracheal tube
eFAST	extended focused assessment with sonography for trauma
EFIC	exception from informed consent
EGA	extraglottic airway devices
EGDT	early goal-directed therapy
EGF	epidermal growth factor
EGL	endothelial glycocalyx layer
EGNB	enteric gram-negative bacteria
EGPA	eosinophilic granulomatosis with polyangiitis
EHEC	enterohaemorrhagic E. coli
EHF	Ebola Haemorrhagic Fever
EI	emotional intelligence
EIA	enzyme immunoassays
eICU	electronic intensive care unit
ELAD	extracorporeal liver assist device
ELNEC	The End-of-Life Nursing Education Consortium
EMG	electromyography
EMR	electronic medical record
EMS	emergency medical services
EN	enteral nutrition
EOL	end-of-life
EPA	eicosapentaenoic acid
EPAP	expiratory positive airway pressure
EPCR	endothelial protein C receptors
EPIC	European Prevalence of Infection in Intensive Care
EPIC II	Extended Prevalence of Infection in Intensive Care
EPP	exposure prone procedures
EQ	emotional quotient
EQ-I	Emotional Quotient Inventory
ER	endoplasmic reticulum
ERC	European Resuscitation Council
ERCP	endoscopic retrograde cholangiopancreatography
ERP	enhanced recovery programmes
ERV	expiratory reserve volume
ESA	erythropoiesis stimulating agent
ESBL	extended spectrum beta lactamase
ESKD	end stage kidney disease
ESL	endothelial surface layer
ESLD	end-stage liver disease
ESPEN	European Society for Clinical Nutrition and Metabolism
ESPVR	end-systolic pressure volume relationship
ESRD	end-stage renal disease
ET	endotracheal
ET-1	endothelin-1
ETA	endothelin-1 receptor antagonists
ETC	oesophageal tracheal combitube
$ETCO_2$	end-tidal CO_2
ETT	endotracheal tube
EUS	endoscopic ultrasound
EVD	external ventricular drain
EVL	endoscopic variceal ligation
EVLW	extravascular lung water
EVLWI	extravascular lung water index
FABP	fatty acid binding protein
FACTT	Fluid and Catheter Treatment Trial
$FADH_2$	flavin adenine dinucleotide
FAST	focused assessment with sonography for trauma
FCCS	Fundamental Critical Care Support

FCD	functional capillary density
FDP	fibrin degradation products
FEAST	fluid expansion as supportive therapy
FES	fat embolism syndrome
FET	forced expiratory technique
FFA	free fatty acid
FFM	fat-free mass
FFP	fresh frozen plasma
FFS	five factor score
FGR	fetal growth restriction
FHVP	free hepatic venous pressure
FIM	Functional Independence Measure
F_IO_2	fraction of inspired oxygen concentration
FLAIR	fluid attenuated inversion recovery
fMRI	functional magnetic resonance imaging
FMV	facemask ventilation
FNHTR	febrile non-haemolytic transfusion reactions
FO	fluid overload
FO_2Hb	fractional saturation of haemoglobin
FPR	false positive rate
FRC	functional residual capacity
FSH	follicle-stimulating hormone
FST	forward surgical teams
FT3	free triiodothyronine
FT4	free thyroxine
FTc	corrected flow time
FV	flow velocity
FVC	forced vital capacity
GABA	γ-aminobutyric acid
GAD	generalized anxiety disorder
GAG	glycosaminoglycan
GALT	gut-associated lymphoid tissue
GAVE	gastric antral vascular ectasia
GBS	Glasgow Blatchford score
GBStr	group B Streptococci
GC	glucocorticoids
GCS	Glasgow Coma Scale
G-CSF	granulocyte colony-stimulating factor
GDFT	goal-directed fluid therapy
GDS	Geriatric Depression Scale
GDT	goal-directed therapy
GEDV	global end-diastolic volume
GEDVI	global end-diastolic volume index
GFAP	glial fibrillary acidic protein
GFR	glomerular filtration rate
γGT	gamma-glutamyltransferase
GH	growth hormone
GHB	gammahydroxybutyrate
GHRH	growth hormone releasing hormone
GI	gastrointestinal
GIP	glucose-dependent insulinotropic peptide
GLA	γ-linolenic acid
GLC	gas liquid chromatography
GLP-1	glucagon-like peptide-1
GLP-2	glucagon-like peptide-2
GLUT	glucose transporter
GM-CSF	granulocyte-macrophage colony-stimulating factor
GNB	Gram-negative bacilli
GnRH	gonadotropin-releasing hormone
GOS	Glasgow outcome scores
GPA	granulomatosis with polyangiitis
GR	glucocorticoid receptors
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
GRE	glucocorticoid response element
GRV	gastric residual volumes
GSH	glutathione
GST	pi-glutathione-S-transferase
GS-VL	GlideScope® videolaryngoscope
GTN	glyceryltrinitrate
GuBS	Guillain–Barré syndrome
GVHD	graft-versus-host disease
GVO	gastric varicealobturation
GWA	genome-wide association
GWAS	genome-wide association studies
H2RA	histamine-2-receptor antagonist
HA	hepatic artery
HAAF	hypoglycaemia-associated autonomic failure
HABR	hepatic arterial buffer response
HACO	high altitude cerebral oedema
HADS	Hospital Anxiety and Depression Scale
HAI	health care-associated infection
HAP	hospital-acquired pneumonia
HAPO	high altitude pulmonary oedema
HAT	haemorrhage after thrombolysis
HAV	hepatitis A
Hb	haemoglobin concentration
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B envelope antigen
HBO	hyperbaric oxygen therapy
HbO_2	haemoglobin-bound O2
HBsAg	hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HCN	hydrogen cyanide
Hct	haematocrit
HCV	hepatitis C virus
HCW	health care worker
HDL	high-density lipoprotein
HDU	high-dependency unit
HDV	hepatitis D
HE	hepatic encephalopathy
HEAA	hydroxyethoxyacetic acid
HELICS	Hospital Infection Link for Infection Control through Surveillance
HELLP	haemolysis, elevated liver enzymes, low platelets
HEPA	high efficiency particulate air
HES	hydroxyethyl starch
HEV	hepatitis E
HF	haemofiltration
HFE	human factors engineering
HFMD	hand, foot, and mouth disease
HFOV	high-frequency oscillatory ventilation
HFPV	high-frequency percussive ventilation
HFRS	Haemorrhagic Fever with Renal Syndrome
HFV	high-frequency ventilation
HGF	hepatocyte growth factor
HH	heated humidifier
HHS	hyperglycaemic hyperosmolar state

HHV	human herpes virus
HICP	intracranial hypertension
HIE	health information exchange
HIET	high-dose insulin euglycaemia therapy
HIF	hypoxia-inducible factor
HIG	human antitetanus immunoglobulin
HIR	Host Innate Responses
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HL	Hodgkins lymphoma
HLA	human lymphocyte antigen
HME	heat and moisture exchanger
HMGB	high mobility group box
hMPV	human metapneumovirus
HPA	hypothalamic-pituitary-adrenal
HPLC	high-performance liquid chromatography
HPS	hyperperfusion syndrome
HPV	hypoxic pulmonary vasoconstriction
HR	heart rate
HRCT	high resolution computed tomography
HRE	hypoxia-responsive element
HRIG	human rabies immunoglobulin
HRQL	health-related quality of life
HRS	hepatorenal syndrome
HRSD	Hamilton Rating Scale for Depression
HSC	haematological stem cells
HSCT	haematopoietic stem cell transplantation
Hs-cTn	high sensitivity cardiac troponins
HSD	hydroxysteroid dehydrogenase
HSV	herpes simplex virus
HTLV-1	Human T-lymphotropic virus 1
HTR	haemolytic transfusion reactions
HU	Hounsfield units
HUS	haemolytic uraemic syndrome
HUSEC	haemolytic uraemic syndrome–associated enterohaemorrhagic *E. coli*
HVPD	High volume PD
HVPG	hepatic venous pressure gradient
I/E	inspiratory/expiratory
I/R	ischaemia/reperfusion
IABP	intra-aortic balloon pump
IAH	intra-abdominal hypertension
IAP	intra-abdominal pressure
IASP	International Association for the Study of Pain
IAV	intra-abdominal volume
IBD	inflammatory bowel disease
IBW	ideal body weight
IC	intracellular
ICal	indirect calorimetry
ICAM-1	intercellular adhesion molecule-1
ICBT	intercostobronchial
ICD	implantable cardioverter defibrillator
ICG	indocyanine green
ICH	intracranial hypertension
ICmax	maximal insufflation capacity
ICNARC	Intensive Care National Audit and Research Centre
ICP	intracranial pressure
ICRP	International Commission of Radiological Protection
ICU	intensive care unit
ICUAW	ICU-acquired weakness
ID	internal diameter
IDF	incident darkfield
IDMS	isotope dilution mass spectrometry
IE	infective endocarditis
IED	improvised explosive device
Ig	immunoglobulin
IGF	insulin-like growth factor
IGFBP	insulin-like growth factor-binding protein
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	Interferon Gamma release Assay
IGV	isolated gastric varices
IHCA	in-hospital cardiac arrest
IHD	intermittent haemodialysis
IHI	Institute for Healthcare Improvement
IJV	internal jugular vein
IL	interleukin
iLA	interventional lung assist
ILE	intralipid emulsion
ILMA	intubating laryngeal mask airway
im	intramuscular
IMV	intermittent mandatory ventilation
iNO	inhaled nitric oxide gas
iNOS	inducible nitric oxide synthase
INR	international normalized ratio
INvR	interventional neuroradiology
IPAP	inspiratory positive airway pressures
IPC	infection prevention and control
iPC	inhaled PCs
IPPB	intermittent positive pressure breathing
IPPV	intermittant positive pressure ventilation
IPPW	intermittent pyloric pressure waves
IPSS	transjugular intrahepatic portosystemic shunt
iPV	inhaled pulmonary vasodilator
IQ	intelligence quotient
IR	infrared light
IRB	institutional review board
IRIS	immune reconstitution inflammatory syndrome
IRV	inverse ratio ventilation
IS	incentive spirometry
ISF	interstitial fluid
IT	information technology
ITBVI	intrathoracic blood volume index
ITP	intrathoracic pressures
ITT	insulin tolerance test
ITU	intensive treatment unit
iv	intravenous
IVC	inferior vena cava
IVIg	intravenous immunoglobulin
IVPC	intravenous prostacyclin
JAM	junctional adhesion molecules
KDIGO	Kidney Disease Improving Global Outcomes
KE	kinetic energy
KIM-1	kidney-injury molecule-1
KIU	Kallikrein inhibitory units
LACI	lacunar infarcts
LAH	lactic acid
LAP	left atrial pressure

LBBB	left bundle branch block
LBW	lean body weight
LDF	laser Doppler flowmetry
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LED	light emitting diode
LEMS	Lambert–Eaton myasthenic syndrome
L-FABP	liver fatty acid-binding protein
LGIB	lower gastrointestinal bleeding
LGM	limb girdle myopathies
LH	luteinizing hormone
LIP	lower inflection point
LIS	locked-in syndrome
LMA	laryngeal mask airway
LMWH	low molecular weight heparins
LOC	lower-oesophageal contractility
LODS	Logistic Organ Dysfunction System
LOH	the loop of Henle
LOS	length of stay
LP	lumbar puncture
LPS	lipopolysaccharide
LSD	Lysergic acid diethylamide
LSF	least square fitting
LT	liver transplantation
LTA	light transmission aggregometry
LTACH	long-term acute care hospital
LTACH	long-term acute care hospital
LTP	long-term potentiation'
LUS	lung ultrasound
LV	left ventricle
LVAD	left ventricular assist device
LVEDD	left ventricle end-diastolic diameter
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
LVESD	left ventricle end-systolic diameter
LVF	left ventricular overload or failure
LVH	left ventricular hypertrophy
MA	metabolic acidosis
mAb	monoclonal antibody
MAC	minimum alveolar concentration
MALDI-TOF	matrix-assisted laser desorption ionization–time of flight
MAMC	mid-arm muscle circumference
MAMP	microbial-associated molecular patterns
MAOI	monoamine oxidase inhibitor
mBP	mean blood pressure
MAPK	mitogen-activated protein kinases
MARS	molecular adsorbent recirculating system
MAT	multifocal atrial tachycardia
MBA	Masters of Business Administration
MBI	Maslach Burnout Inventory
MBP	myelin basic protein
MBTI	Myers Briggs Type Inventory
MCA	middle cerebral artery
MCE	mass casualty event
MCI	multiple-casualty incident
MCP	membrane cofactor proteins
MCP-1	monocyte chemotactic protein-1
McR	mineralocorticoid receptor
MCS	minimally cognitive state
MDCT	multidetector computed tomography
MDI	metered dose inhaler
MDMA	3,4-methylenedioxy-N-methylamphetamine (ecstasy)
MDR	multidrug resistance
MDRD	modification of diet in renal disease
MDR-GNR	multidrug resistant gram negative rods
MDS	monophasic damped sinusoidal
MEE	measured energy expenditure
MEGX	monoethylglycinexylidide
MELD	model for end-stage liver disease
MEP	maximal expiratory pressures
MERS-CoV	Middle East respiratory syndrome coronavirus
MET	medical emergency teams
MetHb	methaemoglobin
MEWS	modified early warning system
MG	myasthenia gravis
MgIF	migrating inhibitory factor
MH	malignant hyperthermia
mHLA-DR	monocytic expression of antigen leukocyte-DR
MHRA	Medicine and Healthcare Products Regulatory Agency
MI	myocardial infarction
MIBG	metaiodobenzylguanidine
MIC	minimum inhibitory concentration
MICA	MHC Class I chain A
mid-AC	mid-arm circumference
MIF	micro-immunofluorescence
MILS	manual in-line stabilization
MIP	maximal inspiratory pressures
MMC	migrating motor complex
MMF	Mycophenolate mofetil
MMP	matrix metalloproteinases
MMT	manual muscle testing
MNC	mononuclear cells
MNTX	methylnaltrexone
MODS	multiple organ dysfunction syndrome
MOF	multi-organ failure
MPA	microscopic polyangiitis
mPAP	mean pulmonary arterial pressure
MPM	Mortality Probability Model
MPN	myelo-proliferative neoplasias
MPTP	mitochondrial permeability transition pore
MPV	mean platelet volume
MRCC	manual rib-cage compression
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MRP	multidrug resistance associated proteins
MRS	maximum recruitment strategy
MRSA	methicillin-resistant Staphylococcus aureus
MS	mitral stenosis
MSC	mesenchymal stem cells
MSc	multiple sclerosis
MSFP	mean systemic filling pressure
mTOR	mammalian target of rapamycin
MUSK	muscle specific protein kinase
MUST	Malnutrition Universal Screening Tool
MV	mechanical ventilation
MVA	motor vehicle accident
MVT	multi-visceral transplant

MyD	myeloid differentiation factor
NAAT	nucleic acid amplification tests
NAC	N-acetylcysteine
NADH	nicotine adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NAFLD	non-alcoholic fatty liver disease
NAPQI	N-acetyl-p-benzoquinonimine
NAT	nucleic acid detection test
NAVA	neurally-adjusted ventilatory assist
NCCT	non-contrast computed tomography
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NCS	nerve conduction studies
NCSE	non-convulsive seizures or status epilepticus
NDMR	non-depolarizing muscle relaxants
NF-κβ	nuclear factor-κβ
NG	nasogastric
NGAL	neutrophil gelatinase-associated lipocalin
NGT	nasogastric tube
NHL	non-Hodgkin lymphomas
NHP	nonhuman primates
NHSN	National Healthcare Safety Network
NICE	National Institute for Health and Clinical Excellence
NIHSS	National Institutes of Health Stroke Scale
NIPPV	non-invasive positive pressure ventilation
NIRS	near-infrared spectroscopy
NIV	non-invasive ventilation
NJ	nasojejunal
NK	natural killer (cells)
NLOI	neurological level of injury
NLR	Nod-like receptors
NMBA	neuromuscular blocking agents
NMDA	N-methyl-D-aspartate
NMES	neuromuscular electrical stimulation
NMJ	neuromuscular junction
NMR	nuclear magnetic resonance
NMS	neuroleptic malignant syndrome
NNRTI	non-nucleoside reverse transcriptase inhibitor
NNT	number need to treat
NO	nitric oxide
NOAC	new oral anticoagulants
NOC	New Orleans Criteria
NP	nurse practitioner
NPE	neurogenic pulmonary oedema
NPPV	non-invasive positive pressure ventilation
NPT	negative pressure therapy
NRI	Nutritional Risk Index
NRS-2002	Nutritional Risk Screening tool 2002
NRTIs	nucleoside reverse transcriptase inhibitors
NS	nociceptor-specific
NSAID	non-steroidal anti-inflammatory drug
NSBB	non-selective beta-blockers
NSE	neuron-specific enolase
NSTE-ACS	non-ST segment elevation-acute coronary syndromes
NSTEMI	non- ST segment elevation myocardial infarction
NT-BNP	N-terminal pro-B type natriuretic peptide
NTS	nucleus tractus solitaries
ntSAH	non-traumatic subarachnoid haemorrhage
NTSCI	non-traumatic spinal cord injury
NVE	native valve endocarditis
O_2ER	O_2 extraction ratio
OA	open abdomen
OAS	original antigenic sin
OCD	obsessive-compulsive disorder
OCSP	Oxfordshire Community Stroke Project
OD	outer diameter
od	once daily
ODM	oesophageal Doppler monitor
OFS	organ failure scores
OG	osmolal gap
OGD	oesophagogastroduodenoscopy
OH	orthostatic hypotension
OHCA	out-of-hospital cardiac arrest
OHS	obesity-hypoventilation syndrome
OHSS	ovarian hyperstimulation syndrome
OLT	orthotopic liver
OP	organophosphorus
OPS	orthogonal polarized spectral
OR	odds ratio
ORT	oral rehydration therapy
OSA	obstructive sleep apnoea
oxyHb	oxyhaemoglobin
PA	pulmonary artery
PAC	pulmonary artery catheter
PACE	probing, alerting, challenging, emergency language
PACI	partial anterior circulation infarcts
$PACO_2$	alveolar partial pressure of carbon dioxide
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PAcR	protease-activated receptor
PACS	picture archiving, and communication systems
PACU	post-anaesthesia care unit
PAD	peripheral arterial disease
PAF	platelet-activating factor
PAH	pulmonary arterial hypertension
PAI	plasminogen activator inhibitor
PAMOR	peripheral μ-opioid receptor
PAMP	pathogen-associated molecular pattern
PAO_2	alveolar partial pressure of oxygen
PaO_2	partial pressure of oxygen in arterial blood
PAOP	pulmonary artery occlusion pressure
PAP	pulmonary artery pressure
PAR	pressure-adjusted heart rate
PARP	poly(ADP-ribose)polymerase
PAV	percent alpha trend
P_{AW}	airway pressure
PAWP	pulmonary artery wedge pressure
P_B	Barometric pressure
PBN	phenyl-t-butylnitrone
PbO_2	brain tissue oxygen tension
$PbtO_2$	brain tissue oxygenation
PBW	predicted body weight
PC	prostacyclins
PCA	patient-controlled analgesia
P-ACV	pressure-assist control ventilation
PC-APRV	pressure-controlled airway pressure release ventilation

PCC	prothrombin-complex concentrate
PC-CMV	pressure controlled continuous mandatory ventilation
PC-CSV	pressure controlled continuous spontaneous ventilation
PCD	percutaneous catheter drainage
PCI	percutaneous coronary intervention
PC-IMV	pressure controlled intermittent mandatory ventilation
PC-IRV	pressure-controlled inverse-ratio ventilation
PCP	phencyclidine
PCR	polymerase chain reaction
PCS	physical component score
PCT	pro-calcitonin
PCV	pressure-controlled ventilation
PD	programmed cell death
PDE	phosphodiesterase
PDEI	phosphodiesterase inhibitor
PDGF	platelet-derived growth factor
Pdh	pyruvate dehydrogenase
Pdk1	pyruvate dehydrogenase kinase, isoenzyme 1
PE	pulmonary embolism
PEA	pulseless electrical activity
$PECO_2$	partial pressure of expired carbon dioxide
PEEP	positive end-expiratory pressure
PEF	pericardial effusion
PEG	polyethylene glycol
PEM	protein energy malnutrition
Pes	oesophageal pressure
PET	positron emission tomography
$P_{ET}CO_2$	end tidal partial pressure of carbon dioxide
PET-CT	positron emission tomography-computed tomography
PFIT	Physical Function ICU Test
PFO	patent foramen ovale
PGD	primary graft dysfunction
PGEI	prostaglandin E-1
PGI2	prostaglandin I-2
PH	pulmonary hypertension
PH_2O	partial pressure of fully saturated water vapour
PHG	portal hypertensive gastropathy
PI	protease inhibitor
PICC	peripherally/percutaneously-inserted central venous catheter
PICU	paediatric intensive care unit
PINI	Prognostic Inflammatory Nutritional Index
PIP	positive inspiratory pressure
PJP	Pneumocystis jirovecii pneumonia
PKA	protein kinase A
PLED	periodic lateralized epileptiform discharge
PLGF	placental growth factor
P_{liq}	pleural liquid pressure
PLR	passive leg raise
PLT	platelets
PM	predictive modelling
pMDI	pressurized metered-dose inhalers
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclear neutrophils
PMP	polymethlypentane
PN	parenteral nutrition
PNF	primary non-function
PNI	Prognostic Nutritional Index
PNMT	phenylethanolamine-N-methyltransferase
po	oral, by mouth
POC	point-of-care
POCI	posterior circulation infarcts
POCT	point-of-care testing
PONV	post-operative nausea and vomiting
PORC	post-operative residual curarization
POSSUM	Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity
PP	pancreatic polypeptide
Ppulse	pulse pressure
PPH	primary pulmonary hypertension
PPHTN	porto-pulmonary hypertension
PPI	proton pump inhibitor
PPID	positive patient identification
Ppl	pleural pressure
PPT	partial prothrombin time
PPV	pulse pressure variation
PQOL	perceived quality of life
pr	per rectum
PRA	panel-reactive antibodies
pRBC	packed red blood cells
PRES	posterior reversible encephalopathy syndrome
PRIS	propofol-related infusion syndrome
PRM	prolonged recruitment manoeuvre
prn	as needed
PROWESS	Protein C Worldwide Evaluation in Severe Sepsis
PRR	pattern recognition receptor
PRx	pressure reactivity index
PS	pituitary surgery
PSB	protected sheath brush
PSI	pneumonia severity index
PSV	pressure support ventilation
PT	prothrombin time
PTH	parathyroid hormone
$PtiO_2$	brain-tissue oxygenation probes
P_{TP}	post-transfusion purpura
PTP	transpulmonary pressure
PTS	post-traumatic seizures
PTSD	post-traumatic stress disorder
PTV	pulmonary thermal volume
PUD	peptic ulcer disease
PUFA	polyunsaturated fatty acid
PVD	pulmonary vasodilators
PVA	polyvinyl alcohol
PVC	premature ventricular contractions
PVE	prosthetic valve endocarditis
PVL-SA	Panton–Valentine leukocidin-producing Staphylococcus aureus
PVN	paraventricular
PVR	pulmonary vascular resistance
PVT	pulseless ventricular tachycardia
PxCT	proximal convoluted tubule
PYY	peptide YY
QALY	quality-adjusted life years
Qb	blood flow

Qd	dialysis flow
qEEG	quantitative EEG
Qf	of flow
QI	quality improvement
QTc	QT corrected for heart rate
QWB	quality of health and well-being
RA	right atrium
RAAS	renin-angiotensin-aldosterone system
RAG	recombinase gene
RAGE	receptor for advanced glycation end-products
RAI	relative adrenal insufficiency
RAP	right atrial pressure
RAR	rapidly-adapting stretch receptor
RASS	Richmond Agitation-Sedation Scale
RAST	radioallergosorbent test
RBB	right bundle branch block
RBBB	right-bundle branch block
RBC	red blood cells
RBF	renal blood flow
RCT	randomized controlled trial
REE	resting energy expenditure
REM	rapid eye movement
RES	reticuloendothelial system
RFID	radio frequency identification
rFVIIa	recombinant activated factor VIIa
RhA	rheumatoid arthritis
RI	reduced intensity
RIC	reduced intensity conditioning
RIJ	right internal jugular
RLB	rectilinear biphasic
RLG	riboleukograms
RLN	recurrent laryngeal nerve
RM	recruitment manoeuvres
RMI	Rivermead Mobility Index
RMI	Rivermead Mobility Index
RMR	resting metabolic rate
RN	registered nurse
RNA	ribonucleic acid
ROC	receiver operator characteristic
ROS	reactive oxygen species
ROSC	return of spontaneous circulation
RoTEG	rotational TEG
ROTEM	rotational thrombelastography
RPC	reactive protein C
RPTCs	renal proximal tubular epithelial cells
RPTCs	renal proximal tubular epithelial cells
RQ	respiratory quotient
RR	relative risk
RRRs	relative risk reduction
RRS	rapid response system
RRT	renal replacement therapy
rSO_2	NIRS oxygen saturation
RSS	Ramsay Sedation Scale
RSV	respiratory syncytial virus
RT	reptilase time
RTLS	real time locating systems
rtPA	recombinant tissue plasminogen activator
rt-PCR	real-time polymerase chain reaction
RT-PCR	reverse transcriptase polymerase chain reaction
RV	right ventricle
RVAD	right ventricular assist device
RVEDP	right ventricular end-diastolic
RVEF	right ventricle ejection fraction
RVF	Rift Valley Fever
RVF	right ventricular overload or failure
RVSP	right ventricular systolic pressure
RWMA	regional wall motion abnormalities
Rx	treatment
SA	sinoatrial
SAD	supraglottic airway devices
SAH	subarachnoid haemorrhage
SaO_2	arterial blood oxygen saturation
sBP	systolic blood pressure
SAPS	Simplified Acute Physiology Score
SAR	slow-adapting stretch receptor
SARS	severe acute respiratory syndrome
SAS	Sedation Agitation Scale
SB	spontaneous breathing
SBAR	situation, background, assessment, recommendation
SBE	standard base excess
SBP	spontaneous bacterial peritonitis
SBT	spontaneous breathing trial
sc	subcutaneous
SCAP	severe community-acquired pneumonia
SCCM	Society of Critical Care Medicine
SCD	sickle cell disease
SCDC	subacute combined degeneration of the cord
SCID	Structured Clinical Interview for DSM-IV
SCN	suprachiasmatic nucleus
SCr	serum creatinine
$ScvO_2$	central venous oxygen saturation
SD	sudden death
SDD	selective decontamination of the digestive tract
SDF	sidestream dark field
SE	standard error
SEMs	self-expandable metal stents
sEng	soluble form of endoglin
SENIC	Study on the Efficacy of Nosocomial Infection Control
SET	signal extraction technology
SGA	subjective global assessment
SGLT1	sodium-dependent glucose co-transporter
SGRQ	St. Georges Respiratory Questionnaire
SI	sustained inflation
SIADH	syndrome of inappropriate antidiuretic hormone
sICH	symptomatic intracerebral haemorrhage
SID	strong ion difference
SIDa	apparent SID
SIDe	effective SID
SIG	strong ion gap
SIGN	Scottish Intercollegiate Guidelines Network
SIGRR	single-immunoglobulin-interleukin-1 receptor-related
SIMV	synchronized intermittent mandatory ventilation
SIP	Sickness Impact Profile
SIRS	systemic inflammatory response syndrome
SJS	Stevens–Johnson syndrome

$SjvO_2$	jugular venous oxygen saturation
SLAF	subcutaneous linea alba fasciotomy
SLE	systemic lupus erythematosis
SLED	slow low-efficiency dialysis
SMA	spinal muscular atrophy
SMC	smooth muscle cell
SMR	Standardized Mortality Ratio
SNP	single nucleotide polymorphism
SNRI	serotonin norepinephrine reuptake inhibitor
SNS	sympathetic nervous system
SOAP	Sepsis Occurrence in Acutely Ill Patients
SOCS	suppressor-of-cytokine signalling
SOD	superoxide dismutatase
SOFA	Sequential Organ Failure Assessment
SON	supra-optic nuclei
SOpD	selective oropharyngeal decontamination
SPAD	single pass albumin dialysis
sPAP	pulmonary artery systolic pressure
SPECT	single photon emission computed tomography
SPV	systolic pressure variation
SRUS	Solitary rectal ulcer syndrome
SS	serotonin syndrome
SSC	Surviving Sepsis Campaign
SSEP	somatosensory-evoked potentials
SSG	surviving sepsis guidelines
SSRI	selective serotonin reuptake inhibitor
SST	short tetracosactride test
StE	status epilepticus
STEMI	ST segment elevation myocardial infarction
sTFR	soluble transferrin receptor
STICH	Surgical Treatment of Intracerebral Haemorrhage
StO_2	tissue oxygen saturation
SUP	stress ulcer prophylaxis
SV	stroke volume
Vsys	systolic volume
SvAP	severe acute pancreatitis
SVC	superior vena cava
SvO_2	venous oxygen saturation
SVR	systemic vascular resistance
SVT	supraventricular tachyarrhythmias
SVV	stroke volume variation
sBP	systolic blood pressure
T3	triiodothyronine
T4	thyroxine
TA	tranexamic acid
TAAA	thoracoabdominal aortic aneurysm
TAAR	trace amino-associated receptors
TAC	temporary abdominal closure
TACI	total anterior circulation infarcts
TACO	transfusion-associated circulatory overload
TAFI	thrombin activatable fibrinolysis inhibitor
TAPSE	tricuspid annular plane systolic excursion
TAR	titrable acid/alkali reserve
TAVR	transcatheter aortic valve replacement
TBI	traumatic brain injury
TBSA	total body surface area
TBV	total blood volume
TBW	total body water
TCA	tricyclic antidepressants
TCCC	tactical combat casualty care
TCD	transcranial Doppler
TCR	T-cell receptor
TDP	torsade de pointes
tds	three times a day
TEB	thoracic electrical bioimpedance
TED	thromboembolic disease
TOE	transoesophageal echocardiography
TEG	thromboelastography
TEMS	Tactical Emergency Medicine Services
TEN	toxic epidermal necrolysis
TEnE	total energy expenditure
TEVAR	thoracic endovascular aneurysm repair
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TGF	transforming growth factor
TH	therapeutic hypothermia
T-H	trauma-haemorrhage
THAM	tris-hydroxymethylaminomethane
THC	T helper cells
TIA	transient ischaemic attack
TIC	trauma-induced coagulopathy
TIMP	tissue inhibitor of metaloprotinases
TIPSS	transjugular intrahepatic portosystemic shunt
TISS	Therapeutic Intervention Scoring System
TJ	tight junction
TKI	Thomas–Kilmann Conflict Mode Instrument
TLC	total lung capacity
TLR	toll-like receptors
TLS	tumour lysis syndrome
TM	thombomodulin
TNA	total nitrogen appearance
TNF	tumour necrosis factor
TNM	Tumor Nodes Metastases
TOF	train of four
TOLLIP	toll-interacting protein
t-PA	tissue plasminogen activator
TPE	Therapeutic plasma exchange
TPN	total parenteral nutrition
TR	tricuspid regurgitant
TRALI	transfusion-associated acute lung injury
TREM	triggering receptor expressed on myeloid cells
TRH	thyrotropin-releasing hormone
TRIP	translating research into practice
TRP	transient receptor potential
TSCI	traumatic spinal cord injury
TSH	thyroid-stimulating hormone
TST	Tuberculin skin testing
TT	thrombin time
TTE	transthoracic echocardiography
TTI	transthoracic impedance
TTM	targeted temperature management
TTP	thrombotic thrombocytopenic purpura
TTr	transthyretin
TXA	tranexamic acid
TxA_2	thromboxane A2
UAI	upper airways infection
UAO	upper airway obstruction
UCH-L1	ubiquitin C-terminal hydrolase-1

UDS	urine drug screening
UDS	urine drug screening
UF	ultrafiltration
UFH	unfractionated heparin
UGIH	upper gastrointestinal haemorrhage
UIP	upper inflection point
UMA	unmeasured anion
uN2	urinary nitrogen component
UO	urine output
u-PA	urokinase-type plasminogen activator
US	ultrasound
V/Q	ventilation–perfusion
VA	veno-arterial
VAD	ventricular assist device
VA-ECMO	veno-arterial extracorporeal membrane oxygenation
VAED	Victorian Department of Health Administrative Episode Dataset
VALI	ventilation-associated lung injury
VAP	ventilator-associated pneumonia
VASST	Vasopressin in Septic Shock Trial
VAT	ventilator-associated tracheobronchitis
VATS	video-assisted thoracoscopic surgery
VC	vital capacity
VCAM-1	vascular cell adhesion molecule 1
VC-CMV	volume controlled continuous mandatory ventilation
VC-CSV	volume controlled continuous spontaneous ventilation
VCD	vocal cord dysfunction
VCE	video capsule endoscopy
VC-IMV	volume controlled intermittent mandatory ventilation
VC-IRV	flow-controlled, inverse ratio ventilation
VCO_2	amount of CO_2 produced
VCV	volume-controlled ventilation
VD	dead space ventilation
VDAC	voltage-dependent anion channel
VEGF	vascular endothelial growth factor
VF	ventricular fibrillation
VFB	ventilator-free breathing
VGCC	voltage-gated calcium channels
VGSC	voltage-gated sodium channels
VHF	viral haemorrhagic fever
VIDD	ventilator-induced diaphragmatic dysfunction
VILI	ventilator-induced lung injury
VIP	vasoactive intestinal peptide
VL	videolaryngoscopy
VLPO	ventrolateral pre-optic area
VMA	vanillylmandelic acid
VO2	amount of O_2 consumed
VOC	vaso-occlusive crises
VOD	veno-occlusive disease
VR	ventilator rate
VRE	vancomycin-resistant enterococci
VS	vegetative state
VSD	ventricular septal defect
VSMC	vascular smooth muscle cell
Vt	tidal volume
VT	ventricular tachycardia
VTE	venous thromboembolism
VTI	velocity-time integral
VV	veno-venous
VVO	vesiculo-vacuolar organelle
vWF	von Willebrand Factor
VZV	varicella zoster virus
WBC	white blood cell
WDR	wide dynamic range
WFNS	World Federation of Neurosurgeons Scale
WHO	World Health Organization
WHVP	wedged hepatic venous pressure
WLST	withdrawal of life-sustaining treatment
WOB	work of breathing
WPGS	whole pathogen genome sequencing
WPW	Wolff–Parkinson–White
XD	xanthine dehydrogenase
YAG	yttrium-aluminum-garnet
YF	yellow fever
βB	β-blockers

Contributors

Sara J. Aberle University of Minnesota, Minneapolis, USA

Wissam Abouzgheib Assistant Professor of Medicine, Infectious Diseases and Critical Care, Cooper Medical School of Rowan University, Camden, USA

Gareth L. Ackland William Harvey Research Institute, Barts and The London, Queen Mary's School of Medicine and Dentistry, Charterhouse Square, London, UK

Banwari Agarwal Consultant in Critical Care Medicine, Royal Free Hospital, London, UK

Hérnan Aguirre-Bermeo Intensive Care Medicine, Intensive Care Medicine Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Carles Agusti Institutd'Investigacion sBiomèdiques August Pi , iSunyer, Barcelona, Spain

Mohammed Ahmed Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada

Imoigele Aisiku Assistant Professor, Department of Emergency Medicine, Harvard University, Brigham and Women's Hospital, Boston, MA, USA

Levent Akyüz Charité Universitätsmedizin Berlin, Berlin, Germany

Tyler J. Albert Clinical Instructor, Hospital and Specialty Medicine, Department of Medicine, University of Washington, Puget Sound Veterans Affairs Hospital, Seattle, WA, USA

Waleed Alhazzani Assistant Professor, Department of Medicine, Department of Clinical Epidemiology and Biostatistics, McMaster University, and St Joseph's Healthcare Hamilton, Hamilton, Canada

Ali Al-Khafaji Associate Professor, Consultant, and Director, Transplant Intensive Care Unit, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, USA

Marcelo Amato Professor, Hospital das Clínicas da Faculdade de Medicina, Universidade de São Paulo, Heart Institute (Incor), São Paulo, Brazil

Craig Anderson Senior Director, Professor of Stroke Medicine and Clinical Neuroscience, and Head, Neurological and Mental Health Division, University of Sydney, and Department of Neurology, Royal Prince Alfred Hospital, Sydney, Australia

Peter J. D. Andrews Consultant Intensivist and Anaesthetist, Department of Anaesthesia and Critical Care, University of Edinburgh & NHS Lothian Western General Hospital, Edinburgh, UK

Derek C. Angus Distinguished Professor and Mitchell P. Fink Endowed Chair Director, Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center, and Professor of Critical Care Medicine, Medicine, Health Policy and Management, and Clinical and Translational Science, University of Pittsburgh School of Medicine, Pittsburgh, USA

Djillali Annane General ICU Department at Raymond Poincaré Hospital (Assistance Publique hôpitaux de Paris) & Laboratory of Infection and Inflammation U1173, University of Versailles SQY – INSERM, 104 boulevard Raymond Poincaré, 92380 Garches, France

Massimo Antonelli Professor of Anaesthesiology and Intensive Care Medicine, Catholic University of the Sacred Heart, Policlinico Universitario, Milan, Italy

Robert M. Arnold Professor of Medicine, Leo H Criep Chair in Patient Care Chief, Section of Palliative Care and Medical Ethics, University of Pittsburgh, Pittsburgh, USA

Antonio Artigas Director of Critical Care Center, Sabadell Hospital, CIBER Enfermedades Respiratorias, Corporacion, Sanitaria Universitaria Parc Tauli, Universidad Autonoma de Barcelona, Barcelona, Spain

Nishkantha Arulkumaran General Intensive Care Unit, St George's Hospital, St George's Medical School, University of London, London, UK

Rónan Astin Clinical Research Fellow and Clinical Lecturer in Intensive Care, UCL Institute for Human Health and Performance and UCLH BRC, and Whittington Hospital, London, UK

Georg Auzinger Lead Consultant Liver ICU and ECMO Service, Kings College Hospital, London, UK

Alfred Ayala Professor of Surgery (Research), Division of Surgical Research, Department of Surgery, Rhode Island Hospital/Alpert Medical School of Brown University, Providence, RI, USA

Sean M. Bagshaw Associate Professor, Critical Care Medicine, Faculty of Medicine and Dentistry, School of Public Health, University of Alberta, Edmonton, Canada

Jan Bakker Professor of Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Michele C. Balas Associate Professor, Center of Excellence in Critical and Complex Care, Ohio State University College of Nursing, Columbus, OH, USA

Steve Ball Senior Lecturer and Consultant Endocrinology, Newcastle University and Newcastle Hospitals NHS Trust, Newcastle, UK

Philip S. Barie Professor, Departments of Surgery and Public Health, Weill Cornell Medical College, New York, NY, USA

Matthew Barnard Consultant Anaesthetist, The Heart Hospital, London, UK

Gabriele Bassi Servizio di Anestesia e Rianimazione 1, Ospedale Niguarda, Milano, Italy

João Batista Borges Senior Scientist, Department of Surgical Sciences, Section of Anesthesia and Intensive Care, Uppsala University Hospital, Uppsala, Sweden

Jane Batt Clinician Scientist and Associate Professor of Medicine, University of Toronto, Toronto, Canada

Simon Baudouin Consultant in Critical Care Medicine, Royal Victoria Infirmary, Newcastle upon Tyne NHS Foundation Trust, Newcastle, UK

Michael Bauer Professor and Chief Executive Director, Center for Sepsis Control and Care, Department of Anaesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany

Kristy A. Bauman Assistant Professor of Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA

Graciela Bauzá Assistant Professor of Surgery and Critical Care, University of Pittsburgh Medical Centre, Pittsburgh, USA

Scott R. Beach Associate Program Director, Assistant Psychiatrist, and Assistant Professor of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, USA

Derek Bell Professor of Acute Medicine, Imperial College, London, UK

Robert M. Bell Clinical Lecturer and Honorary Cardiology Consultant, Hatter Cardiovascular Institute, University College Hospitals NHS Foundation Trust, London, UK

Mark C. Bellamy Professor in Critical Care Medicine, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Giacomo Bellani Università degli Studi Milano Bicocca, Dipartimento di Scienze della Salute, A.O. San Gerardo, Dipartimento di Emergenza e Urgenza, Via Pergolesi 33, Monza (MB), Italy

Geoffrey Bellingan Reader in Intensive Care Medicine, University College London, London, UK

Rinaldo Bellomo Co-Director, Australian and New Zealand Intensive Care Research Centre, Melbourne, Australia

Carolyn Benson Neurosurgery Resident, Department of Clinical Neurological Sciences, London Health Sciences Centre, London, Canada

Rachel P. Berger Safar Center for Resuscitation Research, University of Pittsburgh School of Medicine, Pittsburgh, USA

Greet Van den Berghe Professor of Medicine and Head & Director, Department of Intensive Care Medicine, University Hospital Gasthuisberg, Leuven, Belgium

Giorgio Berlot Department of Anaesthesia and Intensive Care, Ospedale di Cattinara, Trieste, Italy

William Bernal Reader in Liver Intensive Medicine, Institute of Liver Studies, Kings College Hospital, London, UK

Gordon R. Bernard Melinda Owen Bass Professor of Medicine, Associate Vice Chancellor for Research, Vanderbilt University, Nashville, TN, USA

Andrew D. Bersten ICCU, Flinders Medial Centre, Adelaide, Australia

Laurent Beydon Anaesthesiology and Intensive Care, Pôle d'Anesthésie Réanimation, CHU d'Angers, Angers, France

Julian Bion Professor of Intensive Care Medicine, University of Birmingham, Birmingham, UK

Martin Bircher Consultant Orthopaedic Surgeon, St George's Hospital, London, UK

Patrick Biston Head, Department of Intensive Care, CHU Marie Curie, Charleroi, Belgium

Santanu Biswas Staff Cardiologist, Trihealth Heart Institute, Cincinnati, USA

Edward A. Bittner Department of Anesthesiology, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Francesco Blasi Professor Respiratory Medicine, Department of Pathophysiology and Transplantation University of Milan, IRCCS Fondazione Cà Granda, Milan, Italy

Thomas P. Bleck Professor of Neurological Sciences, Neurosurgery, Anesthesiology, and Internal Medicine, Rush University Medical Centre, Chicago, USA

Deanna Blisard Attending Critical Care Physician, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, USA

Frank Bloos Director, Department of Anesthesiology and Intensive Care Medicine, Jena University, Jena, Germany

Olivier Bodart Coma Science Group, Cyclotron Research Centre and Neurology Department, University and University Hospital of Liege, Liege, Belgium

Andrew R. Bodenham Consultant in Anaesthesia and Intensive Care Medicine, Leeds General Infirmary, Leeds, UK

Jean-Michel Boles Service de Réanimation Médicale, Hôpital de la Cavale Blanche, Brest, France

Marc Bonten Clinical Microbiologist and Professor of Molecular Epidemiology of Infectious Diseases, Department of Medical Microbiology and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Robert J. Boots Department of Intensive Care Medicine, Royal Brisbane and Womens' Hospital, Brisbane, Australia

Bárbara Borgatta Critical Care Department, Vall d'Hebron University Hospital, Barcelona, Spain

Stephen W. Borron Professor of Emergency Medicine and Medical Toxicology, Texas Tech University Health Sciences Center at El Paso, West Texas Regional Poison Center, El Paso, Texas, USA

Abderrezak Bouchama King Abdullah International Medical Research Center/ King Saud bin Abdulaziz University for Health Sciences, Experimental Medicine Department, King Abdulaziz Medical City, Ministry of National Guard, Health Affairs, Riyadh, Saudi Arabia

Ghada Bourjeily Associate Professor of Medicine, Warren Alpert Medical School of Brown University, The Miriam Hospital, Providence, USA

Fernando A. Bozza Intensive Care Unit, Instituto de Pesquisa Clínica Evandro Chagas, FIOCRUZ, Rio de Janiero, Brazil

Brigitta Brandner University College Hospital, London, UK

Antonio Braschi Professor, Anesthesia and Intensive Care Division, Emergency Department, Fondazione IRCCS Policlinico San Matteo, and Anesthesia, Intensive Care and Pain Therapy, University of Pavia, Pavia, Italy

David Brealey Consultant in Intensive Care Medicine and Anaesthesia, University College London Hospitals, London, UK

Nicolas Bréchot Service de Réanimation, Institut de Cardiologie, Hopital Pitié-Salpêtrière, iCAN, Institute of Cardiometabolism and Nutrition, Université Pierre et Marie Curie, Paris, France

Serge Brimioulle Department of Intensive Care, Erasme University Hospital, Brussels, Belgium

Peter G. Brindley Professor of Critical Care Medicine, University of Alberta Hospital, Edmonton, Canada

Laurent Brochard Keenan Chair in Critical Care and Respiratory Medicine, Head of Interdepartmental Division of Critical Care Medicine, Professor of Critical Care Medicine, Keenan Research Centre, St Michael's Hospital, and University of Toronto, Toronto, Canada

Elizabeth Brodkin Fraser Health Authority, Surrey BC, Canada

Tim Buchman Department of Surgery, Emory University Hospital, Atlanta, USA

Johnny Canlas Paediatric Specialist Registrar, Department of Paediatrics, Whittington Hospital, London, UK

Edoardo Carretto Clinical Microbiology Laboratory, IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia, Italy

Pietro Caironi Associate Professor in Anaesthesia and Intensive Care Medicine, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, And Dipartimento di Anestesia, Rianimazione ed Emergenza Urgenza, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy

Gordon Carlson Consultant Surgeon and Honorary Professor of Surgery, National Intestinal Failure Centre, Salford Royal NHS Foundation Trust, Salford, UK

Annalisa Carlucci Penumologia Riabilitativa, Fondazione S. Maugeri Pavia, Pavia, Italy

Rodrigo Cartin-Ceba Mayo Clinic, Rochester, USA

Steve Casha Foothills Medical Centre, Calgary, Canada

Hugo ten Cate Head, Laboratory for Clinical Thrombosis and Haemostasis, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands

Jean-Marc Cavaillon Cytokines & Inflammation Unit, Institut Pasteur, Paris, France

Maurizio Cecconi Anaesthesia and Intensive Care Medicine, St George's Hospital and Medical School, London, UK

Jody Cervenak Principle, The Chartis Group, Chicago, USA

Benoit Champigneulle Medical Intensive Care Unit, Cochin Hospital, Assistance Publique-Hôpitaux de Paris and Paris Descartes University, Sorbonne Paris Cité, Paris, France

Chee M. Chan Director, Medical Intermediate Care Unit, Medstar Washington Hospital Centre, Washington DC, USA

Jean Chastre Professor of Medicine and Head of Medical ICU, Groupe Hospitalier Pitié-Salpêtrière, University Paris 6 Pierre-et-Marie Curie, Paris, France

Robert L. Chatburn Professor of Medicine, Lerner College of Medicine of Case Western Reserve University, Research Manager, Respiratory Institute, Cleveland Clinic, Cleveland, OH, USA

Irshad H. Chaudry Professor, Departments of Surgery, Microbiology, Cell, Developmental and Integrative Biology, University of Alabama at Birmingham, Birmingham, AL, USA

Jack Chen Associate Professor and Senior Research Fellow, The Simpson Centre for Health Services Research, University of New South Wales, Sydney, Australia

Paolo Chiarandini Department of Anaesthesia and Intensive Care Medicine, University Hospital S. Maria della Misericordia, Udine, Italy

Francis Chin Kuok Choon Senior Consultant, Department of Radiation Oncology, National Cancer Centre, Singapore

Davide Chiumello Dipartimento di Anestesia, Rianimazione e Terapia del Dolore, Fondazione IRCCS Ca' Granda -Ospedale Maggiore Policlinico, Milan, Italy

Gordon Y. S. Choi Consultant in Intensive Care, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China

Benjamin Chousterman Anesthesiology and Intensive Care, Hôpital Foch, Inserm, Syndicat des Internes des Hôpitaux de Paris, Paris, France

Rolando Claure-Del Granado Professor of Medicine, School of Medicine, Universidad Mayor de San Simon, Cochabambra, Bolivia

Edmond Cohen Professor of Anesthesiology, Director of Thoracic Anesthesia, The Icahn School of Medicine at Mount Sinai, New York, NY, USA

Jeremy Cohen Senior Staff Specialist in Intensive Care, The Royal Brisbane and Women's Hospital, Brisbane, Australia

Jonathan Cohen Professor and Associate Director, Department of Intensive Care, Rabin Medical Centre, Petah Tikvah, Israel

Raul Coimbra The Monroe E. Trout Professor of Surgery, Surgeon-in-Chief UCSD Health System, and Executive Vice-Chairman, Department of Surgery Chief Division of Trauma, Surgical Critical Care, Burns, and Acute Care Surgery, UCSD Health Sciences, San Diego, USA

Alain Combes Professor of Critical Care Medicine, Medical-Surgical Critical Care Department, Institut de Cardiologie, Hopital Pitié-Salpêtrière, iCAN, Institute of Cardiometabolism and Nutrition, Paris, France

Deborah J. Cook Academic Chair of Critical Care Medicine, Professor of Medicine, Clinical Epidemiology & Biostatistics, St Joseph's Healthcare Hamilton, Hamilton, Canada

Colin R. Cooke Assistant Professor of Internal Medicine, Pulmonary & Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA

Bruce Andrew Cooper Clinical Senior Lecturer Medicine, Northern Clinical School, University of Sydney, Sydney, Australia

Mark S. Cooper Professor of Medicine, ANZAC Research Institute, University of Sydney, Concord Repatriation General Hospital, Concord, Sydney, Australia

Silvia Coppola Dipartimento di Anestesia, Rianimazione e Terapia del Dolore, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy

Ricardo Luiz Cordioli Hospital Israelita Albert Einstein and Oswaldo Cruz Hospital, São Paulo, Brazil

Howard L. Corwin Director Critical Care Services, University of Arkansas for Medical Science, Little Rock, USA

Clay Cothren Burlew Director Surgical Intensive Care Unit, Program Director Trauma & Acute Care Surgery Fellowship, and Professor of Surgery, University of Colorado, Denver, USA

Thelma Rose Craig Consultant in Respiratory and Intensive Care Medicine, Antrim Area Hospital, Antrim, UK

Laura Crawford Registered Nurse, Wound Ostomy Consultation Service Rush University Medical Center, Chicago, IL, USA

Mireia Cuartero Senior Intensive Care Medicine Fellow, Imperial College Healthcare NHS Trust, London, UK

Ivonne M. Daly University of Pittsburgh, Pittsburgh, USA

Paul Dark Reader in Inflammation and Repair and Honorary NHS Consultant in Critical Care Medicine, University of Manchester, Salford Royal NHS Foundation Trust, Manchester, UK

Priya Das Northwick Park Hospital, Harrow, UK

Charles D. Deakin Consultant in Cardiac Anaesthesia and Intensive Care, University Hospital Southampton, Southampton, UK

Adam M. Deane Intensivist and Clinical Associate Professor, Royal Adelaide Hospital and University of Adelaide, Adelaide, Australia

Daniel De Backer Head Department of Intensive Care, and Professor of Intensive Care, CHIREC Hospitals and Université Libre de Bruxelles, Brussels, Belgium

Yves Debaveye Associated Professor of Medicine, Department of Intensive Care Medicine, University Hospital Gasthuisberg, Leuven, Belgium

Jason F. Deen Assistant Professor of Pediatrics (Cardiology) and Adjunct Assistant Professor of Medicine, Seattle Children's Hospital, University of Seattle, Seattle, USA

Inneke E. De laet Surgical ICU Consultant, ZNA Stuivenberg Hospital, Antwerp, Belgium

Anthony Delaney Senior Staff Specialist and Clinical Lecturer, Malcolm Fisher Department of Intensive Care Medicine, Royal North Shore Hospital, and University of Sydney and St Leonard's, Sydney, Australia

Candice Delcourt Clinical Research Fellow, The George Institute for Global Health, Sydney, Australia

Giorgio Della Rocca Department of Anaesthesia and Intensive Care Medicine, University Hospital S. Maria della Misericordia, Udine, Italy

Anna Dennis Consultant in Intensive Care Medicine, Heart of England Foundation Trust, Birmingham, UK

Clifford S. Deutschman Professor of Anesthesiology and Critical Care, Philadelphia, PA, USA

Alexander Timothy Dewhurst Department of Intensive Care, St George's Hospital, London, UK

Rajiv Dhand Professor Department of Medicine, University of Tennessee Medical Center, Knoxville, USA

Neal W. Dickert Associate Professor, Emory University School of Medicine, Department of Medicine, Division of Cardiology, Emory University Rollins School of Public Health, Department of Epidemiology and Emory Center for Ethics, Atlanta, GA, USA

Geoffrey J. Dobb Head of Intensive Care and Clinical Professor, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia

Kevin Doerschug Department of Internal Medicine, University of Iowa, Iowa City, USA

Arjen M. Dondorp Professor of Tropical Medicine, Deputy Director and Faculty, University of Oxford, Mahidol Oxford Tropical Medicine Research Unit, and Tropical Medicine Mahdiol University, Bangkok, Thailand

Phua Dong Haur Senior Consultant, Emergency Department, Tan Tock Seng Hospital, Singapore

Jeffrey D. Doyle Associate Clinical Professor, Critical Care Medicine and General Surgery, Niagara Health System and Michael G. DeGroote School of Medicine, McMaster University, Niagara Regional Campus, St Catherines, Canada

Flavie Duc Anaesthesiology and Intensive Care, Pôle d'Anesthésie Réanimation, CHU d'Angers, Angers, France

Abhijit Duggal Assistant Professor of Medicine, Department of Pulmonary, Allergy and Critical Care, Cleveland Clinic, Cleveland, OH, USA

Jacques Duranteau Professor of Anaesthesiology, Associate Professor of Surgery, and Co-Director Cardiothoracic ICU, Duke University School of Medicine, Durham, USA

Charles G. Durbin Jr Professor, Department of Anaesthesiology, University of Virginia, Charlottesville, USA

Claudia Ebm Consultant in Intensive Care and Anaesthesia, WPK Hospital, Vienna, Austria

Michael Eddleston Professor of Clinical Toxicology, Centre for Cardiovascular Science, Pharmacology, Toxicology and Therapeutics, University of Edinburgh, Scotland, UK

Jonathan Edgeworth Consultant Microbiologist and Honorary Reader in Clinical Infectious Diseases, Department of Clinical Infectious Diseases, Kings College London, London, UK

Pierre-Yves Egreteau Service de Réanimation Médicale, Hôpital de la Cavale Blanche, Brest, France

John A. Elefteriades Section of Cardiac Surgery, Yale-New Haven Hospital, New Haven, CT, USA

E. Wesley Ely Professor of Medicine, Vanderbilt University and VA Tennessee Valley, Geriatric Research, Education and Clinical Center (GRECC), Nashville, TN, USA

David Erlinge Professor and Senior Consultant in Cardiology, Department of Cardiology, Lund University, Lund, Sweden

Figen Esen Professor of Anaesthesiology and Critical Care, Istanbul Medical Facility, University of Istanbul, Istanbul, Turkey

Andrés Esteban Post-mortem examination, Intensive Care Unit, Hospital Universitario de Getafe, Madrid, Spain

Timothy Evans Consultant in Thoracic & Intensive Care Medicine and Professor of Intensive Care Medicine, Royal Brompton Hospital and Imperial College London, London, UK

Lorna Eyre Consultant Anaesthetist, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Shawn P. Fagan Department of Anesthesiology, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Vito Fanelli Assistant Professor, Department of Anesthesia and Critical Care Medicine Università degli Studi di Torino, Torino, Italy

David Faraoni Research Associate, Boston Children's Hospital, Boston, MA, USA

Brenna M. Farmer Assistant Professor of Medicine, Division of Emergency Medicine, Weill-Cornell Medical College, and NY Presbyterian Hospital, New York, NY, USA

Abdallah Fayssoil Attending Physician, General ICU at Raymond Poincaré hospital (AP-HP), Laboratory of Cell Death, Inflammation and Infection UM1173, University of Versailles and INSERM, Versailles, France

Colin Ferguson Post-Consultant in Intensive Care Medicine, Derriford Hospital, Plymouth, UK

Niall D. Ferguson Head of Critical Care Medicine and Senior Scientist, University Health Network & Mount Sinai Hospital and Toronto General Research Institute, Toronto, Canada

Simona Ferioli Neurocritical Care Division, Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, OH, USA

Massimo Ferluga Department of Perioperative Medicine, Intensive Care and Emergency, Cattinara Hospital, Trieste, Italy

John Field Cardiologist, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA

Simon Finfer Senior Staff Specialist and Professor in Intensive Care, Royal North Shore Hospital of Sydney, The George Institute for Global Health, University of Sydney, Sydney, Australia

Mitchell P. Fink† Professor of Surgery and Anesthesiology, Vice Chair of Critical Care, Division of General Surgery, UCLA, David Geffen School of Medicine, Los Angeles, CA, USA

Neal Flomenbaum New York Presbyterian Hospital, New York, NY, USA

Oliver Flower ICU Specialist, Royal North Shore Hospital, Sydney, Australia

Carole Foot Staff Specialist Intensive Care Medicine, Royal North Shore Hospital, Sydney, Australia

Paolo Formenti Unità Operativa di Anestesia e Rianimazione, Azienda Ospedaliera San Paolo-Polo , Universitario, Milan, Italy

Robert Fowler Associate Professor, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada

John J. Frank Clinic Assistant Professor and Interventional Cardiologist, St Elizabeth's Hospital, Appleton, USA

Michael Frass Professor of Medicine, Medical University of Vienna, Department of Medicine, Vienna, Austria

Enno Freye KlinikfürGefässchirurgie und Nierentransplantation, Universitätskliniken Düsseldorf, Düsseldorf, Germany

Matthew C. Frise British Heart Foundation Clinical Research Training Fellow, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK

Sara Froio Anaesthesiologist, Dipartimento di Anestesia, Rianimazione (Intensiva e Subintensiva) e Terapia del Dolore, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

Sonja Fruhwald Associate Professor, Department of Anaesthesiology for Cardiovascular Surgery and Intensive Care Medicine, Medical University of Graz, Graz, Austria

Roberto Fumagalli Dipartimento di Medicina e Chirurgia, Università degli Studi Milano Bicocca, Servizio di Anestesia e Rianimazione 1, Ospedale Niguarda, Milano, Italy

James N. Fullerton Intensive Care Medicine, UCL, London, UK

Samson Sujit Kumar Gaddam Department of Neurosurgery, , Baylor College of Medicine, , Houston, USA

Tong J. Gan Professor and Chairman, Department of Anesthesiology, Stony Brook University, Stony Brook, USA

Sanjay Gandhi Director and Associate Professor of Medicine, Endovascular Cardiology, The MetroHealth System, and Case Western Reserve University, Cleveland, USA

Luciano Gattinoni Full Professor of Anesthesia and Chief of Department, Dipartimento di Anestesia, Rianimazione ed Emergenza Urgenza, Fondazione IRCCS Cà Granda – Ospedale Maggiore Policlinico, and Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milano, Italy

Daniël A. Geerse Department of Internal Medicine, Division of Nephrology, Maastricht University Medical Center, Maastricht, The Netherlands

Alistair A. Gibson Specialty Trainee Anaesthesia and Critical Care, South East Scotland Postgraduate Deanery, Edinburgh, UK

Ramyar Gilani Assistant Professor of Surgery and Chief of Vascular Surgery, Division of Vascular Surgery, Michael E. DeBakey Department of Surgery and Ben Taub General Hospital, Houston, USA

Harminder S. Gill Core Medical Trainee, King's College Hospital, London, UK

Jaswinder S. Gill Consultant Cardiologist and Professor of Cardiovascular Medicine, Guy's and St Thomas' Hospitals and Kings College London, London, UK

Mark T. Gladwin Professor and Chair of Medicine, Director, Pittsburgh Heart, Lung, Blood and Vascular Medicine Institute, University of Pittsburgh, Pittsburgh, USA

Lawrence R. Goodman Professor, Diagnostic Radiology and Pulmonary Medicine & Critical Care, Director, Thoracic Imaging, Medical College of Wisconsin, Milwaukee, USA

Josep M. Grau Senior Consultant, Internal Medicine Service and Muscle Research Unit, Hospital Clinic, Barcelona, Spain

Bartley P. Griffith The Thomas E. and Alice Marie Hales Distinguished Professor, Department of Surgery, Division of Cardiac Surgery, University of Maryland Medical School, Baltimore, USA

Dominique Grisoli Staff Cardiac Surgeon, Cardiac Surgery Division, Hospital Timone Adulte, Marseilles, France

Michael P. W. Grocott Professor of Anaesthesia and Critical Care Medicine, Consultant in Critical Care Medicine, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

A. B. J. Groeneveld Professor of Intensive Care, Erasmus MC, Rotterdam, The Netherlands

Michael Gropper Professor and Interim Chair, Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, USA

Danja S. Groves Associate Professor, Department of Anaesthesiology, University of Virginia, Charlottesville, USA

Richard Groves St Thomas' Hospital, London, UK

Guillaume Geri Groupe Hospitalier Cochin- Broca-Hotel dieu, Medical Intensive Care Unit, 27 rue du faubourg St Jacques, Paris, France

Geoffrey C. Gurtner Stanford University School of Medicine, Palo Alto, Stanford, USA

Neil A. Halpern Critical Care Medicine Service Chief, Professor of Clinical Anaesthesiology and Clinical Medicine, Memorial Sloan Kettering Cancer Centre and Weill Cornell Medical College, New York, NY, USA

Scott D. Halpern Assistant Professor, Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medical Ethics and Health Policy, and Leonard Davis Institute Center for Health Incentives and Behavioral Economics, Perelmen School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Naomi E. Hammond Intensive Care Clinical Research Manager, Royal North Shore Hospital, Sydney, Australia

Stephan Harbarth Associate Professor of Medicine, Associate Epidemiologist, and Senior Consultant in Infectious Diseases, Hôpitaux Universitaires de Genève, Service Prévention et Contrôle de l'Infection, Genève 14, Switzerland

Louise Harder Critical Care & Internal Medicine Specialist, Providence Sacred Heart Medical Center, Spokane, WA, USA

Anatole Harrois Anesthesiologist and Critical Care Physician, Anesthesiology and Surgical Intensive Care Unit, Bicêtre Hospital, Le Kremlin Bicêtre, France

Graeme K. Hart Director of Intensive Care and Principle Fellow, Austin Health and Austin Department of Surgery, Melbourne, Australia

Nicholas Hart Clinical and Academic Director, Lane Fox Respiratory Service, St Thomas' Hospital, Guy's & St Thomas' NHS Foundation Trust, London, UK

Yoshiro Hayashi Director of Intensive Care Medicine, Kameda General Hospital, Kamogawa, Japan

Göran Hedenstierna Senior Professor, Department of Medical Sciences, Clinical Physiology, Uppsala University Hospital, Uppsala, Sweden,

Margaret S. Herridge Professor of Medicine, University of Toronto, Toronto, Canada

Liz Hickson Staff Specialist Intensive Care Medicine, Royal North Shore Hospital, Sydney, Australia

Nicholas S. Hill Chief, Division of Pulmonary, Critical Care and Sleep Medicine, Tufts Medical Centre, Boston, MA, USA,

Ken Hillman Professor of Intensive Care & Director of The Simpson Centre for Health Services Research, University of New South Wales, Sydney, Australia

Nicholas Hirsch Consultant Neuroanaesthetist and Honorary , Senior Lecturer, The National Hospital for Neurology & Neurosurgery, London, UK

Vanessa P. Ho Assistant Professor, Department of Surgery, Case Western Reserve University, Cleveland, OH, USA

John Holian Consultant Nephrologist and Lecturer in Medicine, St Vincent's University Hospital, and University College Dublin, Dublin, Ireland

Judd E. Hollander Department of Emergency Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Peter Holzer Professor of Experimental Neurogastroenterology, Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Graz, Austria

Roosmarijn T. M. van Hooijdonk Department of Intensive Care, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Timothy Hooper Consultant in Intensive Care Medicine and Anaesthesia, Defence Medical Services, Southmead Hospital, Bristol, Consultant Great Western Air Ambulance, Bristol, UK

Aluko A. Hope Attending Intensivist, Jay B. Langer Critical Care System, Assistant Professor of Medicine, Division of Critical Care Medicine, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York, USA

Ramona O. Hopkins Psychology Department and Neuroscience Center, Brigham Young University, Center for Humanizing Critical Care, Intermountain Healthcare and Department of Pulmonary and Critical Care Medicine, Intermountain Medical Center, Murray, USA

Catherine L. Hough Associate Professor of Medicine and Director, Division of Pulmonary and Critical Care Medicine, University of Washington and Medical Intensive Care Centre, Harborview Medical Centre, Seattle, WA, USA

Knut Erik Hovda Consultant, National Poisons Information Centre, and Consultant, The Norwegian CBRNe Centre of Medicine, Department of Acute Medicine, Division of Medicine, Oslo University Hospital, Ullevaal, Norway

David T. Huang Associate Professor, Critical Care Medicine, Emergency Medicine, Clinical and Translational Science, Director, Multidisciplinary Acute Care Research Organization (MACRO), University of Pittsburgh School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

Stephen J. Huang Associate Professor & Principal Research Fellow, Intensive Care Medicine, Sydney Medical School, Sydney, Australia

Mark Hull Clinical Assistant Professor, BC Centre for Excellence in HIV/AIDS, University of British Columbia, Vancouver, Canada

Elspeth J. Hulse Centre for Cardiovascular Science, Pharmacology, Toxicology and Therapeutics, University of Edinburgh, Scotland, UK

Beverley J. Hunt Professor of Thrombosis & Haemostasis, and Consultant, Kings College London and Departments of Haematology, Pathology and Lupus, Guy's & St Thomas' NHS Foundation Trust, London, UK

Robert C. Hyzy Professor, Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA

Gaetano Iapichino Medical Director and Professor, Dipartimento di Fisiopatologia medico-chirurgica e dei trapianti, Università degli Studi di Milano, Milan, Italy

Osamudiamen Idahosa Consultant Intensivist, Department of Critical Care Medicine, St Luke's University Hospital, Bethlehem, PA, USA

Can Ince Professor of Clinical Physiology, Department of Intensive Care Medicine, Erasmus Medical Center, s-Gravendijkwal, Rotterdam, The Netherlands

Geoffrey Isbister NHMRC Senior Research Fellow, Clinical Toxicologist, Calvary Mater Newcastle, Professor and Senior Brawn Fellow, University of Newcastle, Newcastle, Australia

Margaret Isaac Assistant Professor of Medicine and Attending Physician, University of Washington and Palliative Care Service and Adult Medicine Clinic, Harborview Medical Centre, Seattle, WA, USA

Theodore J. Iwashyna Associate Professor of Internal Medicine, Pulmonary & Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA

James C. Jackson Assistant Professor of Medicine and Assistant Director, Vanderbilt ICU Recovery Center, Vanderbilt University School of Medicine, Nashville, USA

Dag Jacobsen Director & Professor, Department of Acute Medicine, Division of Medicine, Oslo University Hospital, Ullevaal, Norway, Medical Director, National Poisons Information Centre

Albert Jaeger† Hôpitaux Universitaires de Strasbourg, Strasbourg, France

Shilpa Jain Children's Hospital of Pittsburgh of UPMC, Pittsburgh, USA

Stephan M. Jakob Professor of Intensive Care Medicine, Chief Physician, Department of Intensive Care Medicine, Bern University Hospital and University of Bern, Bern, Switzerland

Rajiv Jalan Department of Hepatology, Royal Free Hospital, London, UK

Stephen James Consultant in Anaesthesia and Critical Care, King's College Hospital, London, UK

Tim C. Jansen Intensivist, Department of Intensive Care, Sint Franciscus Gasthuis, Rotterdam, The Netherlands

B. Jérôme Aboab General ICU department at Raymond Poincaré hospital (Assistance Publique hôpitaux de Paris), and Laboratory of Infection and Inflammation U1173, University of Versailles SQY – INSERM, Garches, France

Donald H. Jenkins Mayo Clinic Hospital, Rochester, USA

Marc G. Jeschke Director, Senior Scientist, Ross Tilley Burn Centre, Sunnybrook Health Sciences Centre, Chair in Burn Research, Professor, Department of Surgery, Division of Plastic Surgery, Department of Immunology, University of Toronto, Toronto, Canada

Ari R. Joffe Clinical Professor, University of Alberta and Stollery Children's Hospital, and John Dossetor Health Ethics Center, Edmonton Clinic Health Academy, Edmonton, Canada

Nicholas J. Johnson Department of Emergency Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Steven B. Johnson Professor and Chairman, Department of Surgery, University of Arizona College of Medicine and Department of Surgery, Banner University Medical Center, Phoenix, AZ, USA

Alison L. Jones Executive Dean Science Medicine and Health at the University of Wollongong, Toxicologist Blacktown Hospital Sydney, Sydney, Australia

Nicola Jones Consultant in Anaesthesia and Critical Care, Papworth Hospital, Cambridge, UK

W. Joost Wiersinga Consultant Infectious Diseases, Department of Medicine, Division of Infectious Diseases, Center for Experimental Molecular Medicine (CEMM), Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Deepak Joshi Consultant Hepatologist, Institute of Liver Studies, King's College Hospital, London, UK

Gavin M. Joynt Professor and Honorary Director of Intensive Care, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China

Marwan F. Jumean Tufts Medical Center, Boston, USA

Jeremy M. Kahn Associate Professor of Critical Care Medicine and Health Policy & Management, University of Pittsburgh, Pittsburgh, USA

Brian P. Kavanagh Professor & Chair and Clinician-Scientist, University of Toronto and Hospital for Sick Children, Toronto, Canada

James Keegan Specialty Registrar, Anaesthesia & Intensive Care Medicine, University Hospital Southampton, Southampton, UK

Didier Keh Associate Professor, Charité - Universitätsmedizin Berlin, Campus Virchow-Klinikum, Department of Anesthesiology and Operative Intensive Care Medicine, Berlin, Germany

John A. Kellum Professor of Critical Care Medicine, Medicine, Bioengineering, and Clinical & Translational Science, Vice Chair for Research, Department of Critical Care Medicine, Director, Center for Critical Care Nephrology, University of Pittsburgh Medical Centre, Pittsburgh, PA, USA

Karina A. Keogh Assistant Professor of Medicine and Consultant in Pulmonary, Critical Care, and Internal Medicine, Mayo Clinic College of Medicine and Mayo Clinic, Rochester, USA

Steven J. Keteyian Director, Preventative Cardiology, Department of Cardiovascular Medicine, Henry Ford Hospital, Detroit, USA

Sean Kiley Assistant Professor, Department of Anesthesiology, University of Florida College of Medicine, Gainesville, USA

Antoine Kimmoun Service de Réanimation médicale Brabois, Institut Lorrain du Cœur et des Vaisseaux, Université de Lorraine, Nancy, France

Sinead Kinsella Clinical Lecturer Department of Renal Medicine, St Vincent's University Hospital, Dublin, Ireland

Eric Kipnis Centre Hospitalier Régional Universitaire de Lille, Lille, France

Thomas Kiss Anesthesiology Specialist, Department of Anesthesia and Intensive Care Therapy, University Hospital Dresden, Technische Universität Dresden, Dresden, Germany

Kelly R. Klein Associate Professor of Emergency and Disaster Global Health, Department of Emergency Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA

Ruth Kleinpell Director, Professor, and Nurse Practitioner, Center for Clinical Research & Scholarship, Rush University Medical Center and Rush University College of Nursing, Chicago, USA

Daniel W. Klyce Assistant Professor and Licensed Clinical Psychologist, Department of Physical Medicine and Rehabilitation, Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA

Leslie M. Kobayashi Associate Clinical Professor of Surgery, University of California San Diego Medical Center, San Diego, USA

Patrick M. Kochanek Safar Center for Resuscitation Research, University of Pittsburgh School of Medicine, Pittsburgh, USA

Joshua Kornbluth Assistant Professor of Neurology and Neurosurgery, Medical Director, The Michael Neely Neurosciences Critical Care Unit, Tufts Medical Centre, Boston, MA, USA

Jan Kornder† Cardiologist, Surrey Memorial Hospital, Surrey, BC, Canada

Andreas Kortgen Center for Sepsis Control and Care, Department of Anaesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany

Jaimal Kothari University College London Hospitals, London, UK

Ferenc Kovari Consultant Anaesthetist and Intensive Care, North Middlesex University Hospital Trust, London, UK

Andrew A. Kramer Senior Research Manager, Cerner Corporation, Kansas City, USA

John P. Kress Professor of Medicine, Director, Medical ICU, University of Chicago, Department of Medicine, Section of Pulmonary and Critical Care, Chicago, IL, USA

Gerhardus J. A. J. M. Kuiper Department of Anesthesiology and Pain Treatment, Maastricht University Medical Center, Maastricht, The Netherlands

John G. Laffey Professor of Anaesthesia and Physiology and Anaesthetist-in-Chief, University of Toronto and St Michael's Hospital, Toronto, Canada

Caroline Landelle University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland

Martin Langer Professor, Anesthesia and Critical Care Medicine, Department of Pathophysiology and Transplantation, Università degli Studi and Fondazione, IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Thomas Langer Consultant, Anaesthesia and Intensive Care Medicine, Dipartimento di Anestesia, Rianimazione ed Emergenza Urgenza, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy

Frédéric Lapostolle Professor, SAMU 93 - UF Recherche-Enseignement-Qualité, Université Paris, Sorbonne Cité, Paris, France

Steven Laureys Coma Science Group, Cyclotron Research Centre and Neurology Department, University and University Hospital of Liege, Liege, Belgium

Gavin G. Lavery Clinical Director and Critical Care Consultant, HSC Safety Forum, Public Health Agency, Northern Ireland, and Belfast HSC Trust, Belfast, UK

Susannah Leaver Consultant in Intensive Care and Respiratory Medicine, St George's Hospital, London, UK

Richard Lee Senior Specialist in Intensive Care, Royal North Shore Hospital, St Leonard's, Australia,

John LeMaitre Cardiologist, Royal Columbian Hospital, New Westminster, British Columbia, Canada

John T. Lemm Assistant Professor, Department of Anaesthesiology, Duke University School of Medicine, Durham, USA

Alain Lepape Critical Care, Lyon Sud University hospital, Hospices civils de Lyon, Pierre Bénite, France

Shaul Lev Institute for Nutrition Research, Rabin Medical Center, Petah Tikva, Israel

Marcel Levi Professor of Medicine, Dean, Faculty of Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Michael Levine Department of Emergency Medicine, Section of Medical Toxicology, University of Southern California, Los Angeles, CA, USA

Andrew Levinson Assistant Professor of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Warren Alpert School of Medicine, Brown University, Providence, RI, USA

Bruno Levy Service de Réanimation médicale Brabois, Institut Lorrain du Cœur et des Vaisseaux, Université de Lorraine, Nancy, France

Jerrold H. Levy Professor of Anaesthesiology, Associate Professor of Surgery, and Co-Director Cardiothoracic ICU, Duke University School of Medicine, Durham, USA

Mitchell M. Levy Brown University, RI, USA

Andrew Lewington Consultant Renal Physician, Honorary Clinical Associate Professor, and Director of Undergraduate Medical Education LTHT, Renal Department, St James's University Hospital, Leeds, UK

William R. Lewis Chief of Cardiology and Director and Professor of Medicine, Endovascular Cardiology, The MetroHealth System, and Case Western Reserve University, Cleveland, USA

Philippe Lheureux Department of Emergency Medicine, Erasme University Hospital, Brussels, Belgium

Gianluigi Li Bassi Attending Physician and Associate Professor, Department of Pulmonary and Critical Care Medicine, Hospital Clinic, and University of Barcelona, Barcelona, Spain

Adamantia Liapikou Sotiria Hospital, Athens, Greece

Alexandre Lima Medical Researcher, Department of Intensive Care, Erasmus MC, University Hospital Rotterdam, Rotterdam, The Netherlands

Mark S. Link Tufts Medical Center, Boston, MA, USA

Jeffrey Lipman Professor and Head, and Adjunct Professor, Anaesthesiology and Critical Care Medicine, School of Medicine, The University of Queensland, and Faculty of Health, Queensland University of Technology, Herston, Australia

Pamela A. Lipsett Johns Hopkins University School of Medicine, Baltimore, MD, USA

Alfredo Lissoni Physician, Dipartimento di Anestesia, Rianimazione ed Emergenza Urgenza, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy

John M. Litell Assistant Professor, University of Michigan Health System, Department of Emergency Medicine, Ann Arbor, MI, USA

David Lockey Consultant in Intensive Care Medicine and Anaesthesia, Southmead Hospital, Clinical Director, Severn Major Trauma Network, Honorary Professor, University of Bristol, Consultant London's Air Ambulance, Bristol, UK

Umberto Lucangelo Department of Perioperative Medicine, Intensive Care and Emergency, Cattinara Hospital, Trieste, Italy

Andrew I. R. Maas Professor and Chairman, Department of Neurosurgery, Antwerp University Hospital, Antwerp, Belgium

Francesco Macagno Professor of Anaesthesiology and Intensive Care Medicine, Catholic University of the Sacred Heart, Policlicnico Universitario

Niall S. MacCallum Consultant in Critical Care Medicine, University College London, London, UK

Neil R. MacIntyre Professor of Medicine, Duke University Medical Centre, Durham, USA

Matthew Mac Partlin Critical Care Physician, Intensive Care Unit, Wollongong Hospital, Wollongong, Australia

Ross D. MacPherson Senior Staff Specialist and Clinical Associate Professor, Department of Anaesthesia and Pain Management, Royal North Shore Hospital, Sydney, Australia

Aline B. Maddux Pediatric Critical Care Fellow, Division of Pediatric Critical Care, University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO, USA

Ulrike Madl Associate Professor of Medicine, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria

Sheldon Magder Professor of Medicine and Physiology, McGill University Health Centre, Montreal, Canada

Jared Magnani Division of Cardiology, Boston University School of Medicine, Boston, USA

Matthew J. Maiden Senior Consultant, Intensive Care Unit, Royal Adelaide Hospital, Adelaide, Australia

Julien Maizel Réanimation Médicale CHU Sud, and INSERM 1088, Amiens, France

Manu L. N. G. Malbrain ZNA Stuivenberg Hospital, Antwerp, Belgium

Atul Malhotra Chief of Pulmonary and Critical Care, Kenneth M. Moser Professor of Medicine, UC San Diego, La Jolla, USA

Jordi Mancebo Director, Intensive Care Medicine Department, Intensive Care Medicine Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

John J. Marini Professor of Medicine, University of Minnesota, Minneapolis, USA

Philip Marino Consultant in Pulmonary Hypertension & Chronic Respiratory Failure, Lane Fox Respiratory Unit, St Thomas' Hospital, London, UK

John C. Marshall Professor of Surgery, Surgeon and Intensivist, University of Toronto and St Michael's Hospital, Toronto, Canada

J. D. Marti Associate Professor of Medicine, University of Barcelona, Barcelona, Spain

Daniel Martich Professor, Critical Care Medicine, Internal Medicine, Biomedical Informatics, and Clinical and Translational Science, University of Pittsburgh School of Medicine, Pittsburgh, USA

Daniel S. Martin Honorary Consultant and Senior Lecturer, Perioperative and Critical Care Medicine, Royal Free Hospital and University College London, London, UK

Greg S. Martin Professor of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Emory University School of Medicine, Atlanta, GA, USA

Rebecca E. Martin Specialist Pain Medicine Physician, Michael J. Cousins Pain Management and Research Centre, Royal North Shore Hospital, St Leonards, Australia

Ignacio Martin-Loeches Vice-Director of Intensive Care Medicine, and Senior Clinical Lecturer, Multidisciplinary Intensive Care Research Organization (MICRO), St James's University Hospital, and Trinity Centre for Health Sciences, Dublin, Ireland

Kenneth L. Mattox Distinguished Service Professor, Baylor College of Medicine, Chief of Staff and Chief of Surgery, Ben Taub General Hospital, Houston, USA

Jeffrey Mazer Pulmonary and Critical Care Medicine, Lovelace Medical Group, Alberquerque, USA

Danny F. McAuley Consultant and Professor of Intensive Care Medicine, Royal Victoria Hospital, Belfast and Centre for Infection and Immunity, Queen's University of Belfast, Belfast, UK

Michael McCormack Assistant Professor, Department of Medicine, University of Tennessee Medical Center, Knoxville, USA

Russell J. McCulloh Physician, Pediatric Infectious Diseases, and Assistant Professor, Children's Mercy Hospitals & Clinics, and University of Kansas, Kansas City, KS, USA

Vickie McDonald Consultant Haematologist, Guy's and St Thomas' NHS Foundation Trust, London, UK

Jean R. McEwan Vice Dean Education and Honorary Consultant Cardiologist, University of Exeter Medical School and Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

John K. McIlwaine Associate in Critical Care Medicine, eICU Program Director, Geisinger Health System, Danville, PA, USA

Stuart McKechnie Consultant in Intensive Care Medicine & Anaesthetics, Oxford University Hospital NHS Trust, Oxford, UK

Anthony S. McLean Director, Intensive Care Medicine, Sydney Medical School, Sydney, Australia

David D. McManus Associate Professor, Departments of Medicine and Quantitative Health Sciences, University of Massachusetts Medical Center, Worcester, USA

Alexandre Mebazaa Chairman of Department, Département Anesthésie-Réanimation, Hôpital Lariboisière, Paris, France

Ravindra L. Mehta Clinical Research Department of Medicine, UCSD Medical Centre, San Diego, USA

Philippe Mercier Paediatric Neurosurgery Fellow, Le Bonheur Children's Hospital, Memphis, USA

Dieter Mesotten Catholic University Leuven (KU Leuven), Department Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium

Emersom C. Mesquita Laboratório de MedicinaIntensiva, Instituto de PesquisaClinicaEvandro Chagas (IPEC), Rio de Janeiro, Brazil

Cristina Mietto Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Universita' degli Studi di Milano, Milan, Italy

Frederick Mihm Professor of Medicine, Codirector, Intensive Care Units, Department of Anesthesiology, Pain and Perioperative Medicine, Stanford University Medical Center, Stanford, CA, USA

Jean-Paul Mira Head of the Medical Intensive Care Unit, Groupe Hospitalier Cochin- Broca-Hotel dieu, Paris, France

Eduardo Mireles-Cabodevila Director, Critical Care Medicine Fellowship and Assistant Professor of Medicine, Clinic Lerner College of Medicine of Case Western Reserve University, Respiratory Institute, Cleveland Clinic, Cleveland, OH, USA

Giovanni Mistraletti Medical Director and University Researcher, Dipartimento di Fisiopatologia medico-chirurgica e dei trapianti, Università degli Studi di Milano, Milan, Italy

Jerome H. Modell Professor Emeritus, Department of Anesthesiology, University of Florida College of Medicine, Gainesville, USA

Francesco Mojoli Anesthesia and Intensive Care Division, Emergency Department, Fondazione IRCCS Policlinico San Matteo, and Anesthesia, Intensive Care and Pain Therapy, University of Pavia, Pavia, Italy

Sean F. Monaghan Assistant Professor of Surgery, Division of Surgical Research, Department of Surgery, Rhode Island Hospital/Alpert Medical School of Brown University, Providence, RI, USA

Hugh Montgomery Professor of Intensive Care Medicine, University College London, London, UK

S. Ramani Moonesinghe Consultant and Honorary Senior Lecturer, Anaesthesia and Critical Care Medicine, Surgical Outcomes Research Centre, Department of Anaesthesia, University College London Hospitals NHS Foundation Trust, London, UK

Ernest E. Moore Professor and Vice Chairman of Surgery, University of Colorado, Denver, co, USA

Rui Moreno Professor da Nova Medical School, Unidade de Cuidados Intensivos Neurocríticos, Hospital de São José, Centro Hospitalar de Lisboa Central, E.P.E., Lisboa, Portugal

Peter Thomas Morley Director of Medical Education, Senior Specialist in Intensive Care, University of Melbourne Clinical School, Royal Melbourne Hospital, Melbourne, Australia

Emma C. Morris Reader in Immunology and Immunotherapy, Consultant Haematologist (BMT), UCL Institute of Immunity and Transplantation, Department of Haematology, University College London Hospitals NHS Foundation Trust, and Department of Immunology, Royal Free London NHS Foundation Trust, London, UK

Linda-Jayne Mottram Critical Care Consultant, Belfast HSC Trust, Belfast, UK

Thomas Muders Senior Attending, Division of Intensive Care Medicine, Department of Anaesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany

Myrna Y. Munar College of Pharmacy, Oregon State University, Corvallis, OR, USA

Claus-Martin Muth Professor of Anesthesiology, Sektion Notfallmedizin, Klinik für Anaesthesiologie, Universitaetsklinikum Ulm, Ulm, Germany

Katie M. Muzevich Division of Pulmonary and Critical Care Medicine, Virginia Commonwealth University Health System, Richmond, USA

John Myburgh Professor of Critical Care, University of New South Wales, Director of the Division of Critical Care and Trauma, The George Institute for International Health, Senior Intensive Care Physician, St George Hospital, Sydney, Australia

Jae Myeong Lee Assistant Professor of Surgery and Critical Care Medicine, Department of Surgery, Ajou University School of Medicine, Chief of the Surgical Intensive Care Unit, Ajou University Hospital, Suwon, Republic of Korea

Monty Mythen Smiths Medical Professor of Anaesthesia and Critical Care, University College London, London, UK

Simon Nadel Adjunct Professor of Paediatric Intensive Care, St Mary's Hospital and Imperial College London, London, UK

Raquel Nahra Assistant Professor of Medicine, Infectious Diseases and Critical Care, Cooper Medical School of Rowan University, Camden, USA

Joseph L. Nates Professor, Deputy Chair, Medical Director Intensive Care Units, Division of Anesthesiology and Critical Care, University of Texas MD Anderson Cancer Center, Houston, USA

Paolo Navalesi Department of Translational Medicine, Università del Piemonte Orientale (UPO), Novara, Anesthesia and Intensive Care, Sant'Andrea Hospital, Vercelli, Moncrivello (VC), Italy

Jeffrey S. Neiger Cardiac Electrophysiologist, University of Illinois, Chicago, IL, USA

Patrick J. Neligan Consultant in Anaesthesia and Intensive Care, Medical Director, Critical Care Services, University College Hospitals, Galway, Honorary Senior Lecturer in Anaesthesia & Intensive Care, National University of Ireland, Galway, Ireland

Catherine Nelson-Piercy Consultant Obstetric Physician and Professor of Obstetric Medicine, Guy's and St Thomas' NHS Foundation Trust, Imperial College Healthcare NHS Trust, and King's College London, London, UK

Judith E. Nelson Associate Chief, Palliative Medicine Service, Attending Physician, Critical Care Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Imran Khalid Niazi Consultant Radiologist, Shaukat Khanum Memorial Cancer Hospital & Research, Lahore, Pakistan

Niklas Nielsen Helsingborg Hospital and Lund University, Helsingborg, Sweden

Sara Nikravan Assistant Professor of Anesthesiology and Critical Care Medicine, Director of Critical Care Ultrasound, Stanford University Hospital and Clinics, Palo Alto, USA

Graham Nimmo Consultant Physician in Intensive Care Medicine and Clinical Education, Intensive Care Unit, Western General Hospital, Edinburgh, UK

Jerry P. Nolan Consultant in Anaesthesia and Intensive Care Medicine, Royal United Hospital, Bath, UK

Muna Noori Consultant Obstetrician and Sub-specialist in Maternal and Fetal Medicine, Queen Charlotte's and Chelsea Hospital, Imperial College Healthcare NHS Trust, London, UK

Ayodeji Nubi Attending, General Surgery, Trauma & Critical Care Medicine, Lancaster General Hospital, Lancaster, USA

Alastair O'Brien Reader in Experimental Hepatology and Consultant Hepatologist, University College London, and The Royal Free Hospitals NHS Trust, London, UK

Michael O'Dwyer Senior Lecturer and Honorary Consultant in Intensive Care Medicine, Barts and The London School of Medicine and Dentistry, London, UK

Ronan O'Leary Consultant in Neurosciences and Trauma Intensive Care Medicine, Addenbrooke's Hospital, Cambridge, UK

Göran Olivecrona Department of Cardiology, Lund University, Skane University Hospital-Lund, Lund, Sweden

Charles M. Oliver Anaesthetic Registrar and Health Services Research Fellow, The National Institute of Academic Anaesthesia Health Services Research Centre, London, UK

Evelien Oostdijk Departments of Medical Microbiology and Intensive Care Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

Steven M. Opal Professor of Medicine, Infectious Disease Division, Alpert Medical School of Brown University, Memorial Hospital of RI, Pawtucket, RI, USA

Efrat Orenbuch-Harroch Physician, Medical Intensive Care Unit, Medical Intensive Care Unit, Hadassah Hebrew University Medical Center, Jerusalem, Israel

David Orlikowski Hôpital Raymond-Poincaré, Garches, France

Marlies Ostermann Consultant in Critical Care, Nephrology and Transplantation, Guy's and St Thomas' Foundation Hospital, London, UK

Ali J. Olyaei Nephrology and Hypertension, Oregon State University/ Oregon Health & Sciences University, Portland, USA

Anand D. Padmakumar Specialist Trainee Registrar ST7 in Anaesthesia and Critical Care Medicine, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Colin Page Clinical Toxicologist & Emergency Physician, Princess Alexandra Hospital, Brisbane, Australia

Pratik P. Pandharipande Professor of Anesthesiology and Surgery, Department of Anesthesiology, Division of Critical Care, Vanderbilt University School of Medicine, Nashville, TN, USA

Preet Panesar Lead Pharmacist in Microbiology, University College London Hospitals NHS Foundation Trust, London, UK

Marianna Parlato Unit of Cytokines and Inflammation, Institut Pasteur, Paris, France

John A. M. Paro Stanford University School of Medicine, Palo Alto, Stanford, USA

Bela Patel Associate Professor, Division Director of Critical Care Medicine, Assistant Dean of Healthcare Quality, University of Texas, Houston, USA

Bhakti K. Patel Section of Pulmonary Clinical Care, University of Chicago Medical Centre, Chicago, USA

Brijesh V. Patel Clinical Lecturer, Section of Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, UK

Mayur B. Patel Assistant Professor of Surgery and Neurosurgery, Section of Surgical Sciences, Department Of Surgery and Neurosurgery, Division of Trauma & Surgical Critical Care, Vanderbilt University School of Medicine, Nashville, TN, USA

Sameer Patel Consultant in Intensive Care, Liver Intensive Care & ECMO, King's College Hospital, London, UK

Gilbert Park North Middlesex Hospital, UK

Michael J. A. Parr Director of Intensive Care, Liverpool Hospital and Macquarie University Hospital, University of New South Wales, Macquarie University, and University of Western Sydney, Sydney, Australia

Joseph E. Parrillo Chairman, and Professor of Medicine, Heart and Vascular Hospital, Hackensack University Medical Centre, and Rutgers New Jersey Medical School, Hackensack, USA

David L. Paterson Professor of Medicine and Infectious Diseases Physician, University of Queensland Centre for Clinical Research and Royal Brisbane and Women's Hospital, Brisbane, Australia

Caroline Patterson Clinical Research Fellow, Imperial College, London, UK

Richard Paul NIHR Research Fellow, Royal Brompton Hospital, London, UK

Paul M. Palevsky Chief of Renal Section, and Professor of Medicine and Clinical and Translational Science, United States Department of Veteran Affairs and University of Pittsburgh School of Medicine, Pittsburgh, USA

Didier Payen Professor in Medicine, General ICU at Raymond Poincaré hospital (AP-HP), Laboratory of Cell Death, Inflammation and Infection UM1173, University of Versailles and INSERM, Versailles, France

Sandra L. Peake Senior Staff Specialist, Department of Intensive Care, The Queen Elizabeth Hospital, Associate Professor, School of Medicine, University of Adelaide, Adelaide, Australia, Adjunct Associate Professor, School of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

Rupert Pearse Professor and Consultant in Intensive Care Medicine, Queen Mary's University of London, Royal London Hospital, London, UK

Giles Peek Chief of Pediatric Cardiacthoracic Surgery, Children's Hospital at Montefiore, New York, NY, USA

Stephen P. Pereira UCL Institute for Liver and Digestive Health, Royal Free Hospital Campus, London, UK

Paolo Pelosi Professor in Anaesthesiology, Department of Surgical Sciences and Integrated Diagnostics, IRCCS San Martino IST, University of Genoa, Genoa, Italy

Frédéric Pène Medical Intensive Care Unit, Cochin Hospital, Assistance Publique-Hôpitaux de Paris and Paris Descartes University, Sorbonne Paris Cité, Paris, France

Paul E. Pepe Professor of Emergency Medicine, Internal Medicine, Surgery, Pediatrics, Public Health and the Riggs Family Chair in Emergency Medicine, Director of Regional Out-of-Hospital Care Systems and Event/Disaster Preparedness Office of Health System Affairs, University of Texas Southwestern Medical Centre, Dallas, USA

A. G. Peppelenbosch Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

Gavin D. Perkins Professor of Clinical Care Medicine, Warwick Medical School and Heart of England NHS Foundation Trust, Coventry, UK

J. Perren Cobb Massachusetts General Hospital, Boston, MA, USA

Jerrold L. Perrott Clinical Pharmacy Specialist – Critical Care (ICU), Royal Columbian Hospital, New Westminster, Canada

Antonio Pesenti Università degli Studi Milano Bicocca, Dipartimento di Scienze della Salute, A.O. San Gerardo, Dipartimento di Emergenza e Urgenza, Via Pergolesi 33, Monza (MB), Italy

David Pilcher Intensive Care Specialist, The Alfred Hospital, Melbourne, Australia

Michael R. Pinsky Professor of Critical Care Medicine, Bioengineering, Cardiovascular Disease and Anesthesiology, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, USA

Tasneem Pirani Advanced ICM and Gastroenterology Registrar, Kings College Hospital, London, UK

Didier Pittet Director, Infection Control Programme and WHO Collaborating Centre on Patient Safety, University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland

Esteban Poch Senior Consultant, Nephrology Department, Hospital Clinic, Barcelona, Spain

Martijn Poeze Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

Tom van der Poll Professor of Infectious Diseases, Department of Medicine, Division of Infectious Diseases, Center for Experimental Molecular Medicine (CEMM), Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Sebastian Pollandt Neurologist, Rush University Medical Center, Chicago, IL, USA

Brian J. Pollard Professor of Anaesthesia, Manchester Medical School, Manchester, UK

Thaddeus M. Pope Director and Associate Professor, Health Law Institute and Hamline University School of Law, Saint Paul, USA

Udaya B. S. Prakash Consultant, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Professor of Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA

Laura Price Consultant Physician, Pulmonary Hypertension Service, Royal Brompton Hospital, London, UK

Susanna Price Consultant Cardiologist & Intensivist, Royal Brompton Hospital, London, UK

Peter J. Pronovost Professor of Anaesthesiology and Critical Care Medicine, Armstrong Institute for Patient Safety and Quality, Johns Hopkins University School of Medicine, Baltimore, MD, USA

John R. Prowle Clinical Senior Lecturer in Intensive Care Medicine, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, Honorary Consultant in Intensive Care & Renal Medicine, Royal London Hospital, Barts Health NHS Trust, London, UK

Christian Putensen Professor of Intensive Care Medicine and Head Division of Intensive Care Medicine, Department of Anaesthesiology and Intensive Care Medicine University Hospital Bonn, Bonn, Germany

Lirong Qu Co-Director, Centralized Transfusion Service, Institute for Transfusion Therapy, Pittsburgh, USA

Alberto Quaglia Consultant Histopathologist, Institute of Liver Studies, Kings College Hospital, London, UK

Michael Quintel Head of Department, Department of Anesthesiology, Center for Anesthesiology, Emergency and Intensive Care Medicine, University Hospital Göttingen, Göttingen, Germany

Peter Radermacher Professor of Anesthesiology, Institut für Anaesthesiologische Pathophysiologie und Verfahrensentwicklung, Universitaetsklinikum, Ulm, Germany

Mohamed Y. Rady Consultant and Professor, Department of Critical Care Medicine and Mayo Clinic College of Medicine, Mayo Clinic Hospital, Phoenix, AZ, USA

Karthik Raghunathan Assistant Professor, Anesthesiology Service Durham VA Medical Center, Duke University Medical Centre, Durham, USA

Tony Rahman Director of Gastroenterology & Hepatology, The Prince Charles Hospital & College of Medicine & Dentistry, James Cook University, Queensland, Australia

Keshava Rajagopal Assistant Professor of Cardiac Surgery and Cardiac Surgeon, Center for Advanced Heart Failure, University of Texas-Houston, Houston, USA

Ram E. Rajagopalan Consultant and Head, Department of Critical Care Medicine, Sundaram Medical Foundation, Chennai, India,

Rajkumar Rajendram Consultant in Anaesthesia, Intensive Care, and Peri-operative Medicine, Royal Free London Hospitals, Barnet General Hospital, Barnet, UK

Raghavan Raju Professor, Departments of Laboratory Sciences and Surgery, Georgia Regents University, Augusta, GA, USA

Navin Ramachandran Consultant Radiologist, University College London Hospitals NHS Foundation Trust, London, UK

Jared Randall Curtis Professor, Pulmonary and Critical Care Medicine, University of Washington, Seattle , USA

V. Marco Ranieri Professor of Anesthesia and Critical Care, Università di Roma 'La Sapienza', Policlinico Umberto I Rome, Roma, Italy

Didier Raoult Director, Unité de Recherche des Maladies Infectieuses et Emergentes (URMITE), Faculté de Médecine, Unité des Rickettsies, France

Raymond Raper Intensive Care Unit, Royal North Shore Hospital, St Leonards, Australia

Michael C. Reade Lieutenant Colonel, Joint Health Command, Australian Defence Force, Canberra, Professor of Military Medicine and Surgery, University of Queensland, Brisbane, Consultant Intensivist, Royal Brisbane and Women's Hospital, Brisbane, Australia

Ugan Reddy Consultant in Neuromedical Intensive Care, The National Hospital for Neurology & Neurosurgery, London, UK

Konrad Reinhart Clinic for Anaesthesiology and Intensive Care, Jena, Germany

Annika Reintam Blaser Intensivist and Scientist, Intensive Care Unit, Lucerne Cantonal Hospital, Lucerne, Switzerland, University of Tartu, Tartu, Estonia

Jordi Rello Professor of Medicine, Vall d'Hebron Institut of Research, CIBERES, Universitat Autonoma de Barcelona, Barcelona, Spain

Andreas Wolfgang Reske Klinik und Poliklinik für Anästhesiologie und Intensivtherapie, Universitätsklinikum Leipzig AöR, Leipzig, Germany

Andrew Retter Intensive Care Consultant, Guy's and St. Thomas' NHS Foundation Trust, London, UK

Steven C. Reynolds Critical Care & Infectious Diseases, Regional Medical Director and Department Head, Critical Care–Fraser Health, Medical Administration, Royal Columbian Hospital, New Westminster Canada

Andrew Rhodes Consultant in Intensive Care and Anaesthesia, Royal Berkshire Hospital, Reading, UK

Jonathan K. J. Rhodes Consultant Intensivist and Anaesthetist, Department of Anaesthesia and Critical Care, University of Edinburgh & NHS Lothian Western General Hospital, Edinburgh, UK

Zaccaria Ricci Department of Paediatric Cardiac Surgery, Bambino Gesù Children's Hospital, Rome, Italy

Saxon Ridley Anaesthetics Department, Glan Clwyd Hospital, Rhyl, Denbighshire, North Wales, UK

Michael A. Rie University of Kentucky, Lexington, USA

Darren M. Roberts Staff specialist, nephrology and clinical pharmacology/ toxicology, The Canberra Hospital, Woden, ACT, Australia, Associate Professor, Medical School, Australian National University, Canberra, Australia

Claudia S. Robertson Professor, Department of Neurosurgery, Baylor College of Medicine, Houston, USA

Stefano Romagnoli Department of Anesthesia and Intensive Care, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

Claudio Ronco International Renal Research Institute (IRRIV), Vincenca, Italy

Matthew R. Rosengart Associate Professor, Departments of Surgery and Critical Care Medicine, University of Pennsylvania Medical Centre, Pittsburgh, USA

Ori D. Rotstein Professor of Surgery, University of Toronto, Toronto, Canada

Charis Roussos Academician and Professor of Medicine, University of Athens and McGill University, Athens, Greece

Sebastian G. Russo Consultant Anaesthesiologist, Department of Anesthesiology, Center for Anesthesiology, Emergency and Intensive Care Medicine, University Hospital Göttingen, Göttingen, Germany

Omar Sabri Consultant Trauma & Orthopaedic Surgeon, Newcastle Upon Tyne University Hospitals and Nuffield Hospital Newcastle, Newcastle, UK

Jonathan B. Salmon Consultant in General Medicine and Intensive Care, Adult Intensive Care Units, Oxford University Hospitals NHS Trust, Oxford, UK

Brett G. Sampson ICCU, Flinders Medial Centre, Adelaide, Australia

Damon C. Scales Associate Professor, Interdepartmental Division of Critical Care, University of Toronto, and Sunnybrook Health Sciences Centre, Toronto, Canada

John R. Schairer Senior Staff, Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, USA

Leslie P. Scheunemann Fellow of Pulmonary and Critical Care, University of Pittsburgh, Pittsburgh, USA

Gregory A. Schmidt Professor, Division of Pulmonary Diseases, Critical Care, and Occupational Medicine, Associate Chief Medical Officer, Critical Care, University of Iowa, Iowa City, USA

Marcus J. Schultz Department of Intensive Care Medicine & Laboratory of Experimental Intensive Care and Anesthesiology, Academic Medical Center at the University of Amsterdam, Amsterdam, The Netherlands

Michael J. Scott Consultant in Anaesthesia and Intensive Care Medicine, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK

Marie Scully Consultant Haematologist, Department of Haematology, University College London Hospital, London, UK

David B. Seder Director of Neurocritical Care and Assistant Professor of Medicine, Maine Medical Center and Tufts University School of Medicine, Portland, OR, USA

Ayan Sen Consultant and Assistant Professor, Critical Care and Emergency Medicine, Mayo Clinic, Phoenix, AZ, USA

Curtis N. Sessler Division of Pulmonary and Critical Care Medicine, Virginia Commonwealth University Health System, Richmond, USA

Jon Sevransky Division of Pulmonary, Critical Care, Allergy, and Sleep, Emory Center for Critical Care, Atlanta, GA, USA,

Shahriar Shahrokhi Assistant Professor, Department of Surgery, Division of Plastic Surgery, University of Toronto, Toronto, Canada, Staff Surgeon Ross Tilley Burn Centre, Sunnybrook Health Sciences Centre

Nathan I. Shapiro Harvard University, Boston, USA

Micha Shamir Anesthesiology and Critical Care, Hadassah Medical Center, Jerusalem, Israel

Tarek Sharshar Professor, Department of Intensive Care Medicine, Raymond Poincaré Teaching Hospital, University of Versailles Saint-Quentin en Yvelines, Garches, France

Andrew Shaw Professor and Chief, Division of Cardiothoracic Anesthesiology, VUMC Department of Anesthesiology, Nashville, TN, USA

Ben Shippey Director of Clinical Skills and Honorary Consultant Anaesthetist, University of Dundee College of Medicine, Dentistry and Nursing and NHS Tayside, Dundee, UK

Andrew F. Shorr Section Director (Interim), Pulmonary and Critical Care Medicine, Director, MICU, Medstar Washington Hospital Center, Washington, USA

Lori Shutter Professor, Critical Care Medicine, Neurology &Neurosurgery, Vice Chair of Education, Critical Care Medicine Director, Multidisciplinary Critical Care Fellowship Program Medical Director, Neurovascular & Neurotrauma ICUs, University of Pittsburgh School of Medicine, Pittsburgh, USA

Henry J. Silverman Professor of Medicine, University of Maryland, School of Medicine, Baltimore, MD, USA

Mervyn Singer Professor of Intensive Care Medicine, University College London, London, UK

Pierre Singer Director, Department and Institute for Nutrition Research, Rabin Medical Center, Beilinson Hospital, Tel Aviv University PetahTikvahIsrael

Jeffrey C. Sirota Division of Renal Diseases & Hypertension, University of Colorado, Denver CO, USA

James R. A. Skipworth Department of Surgery and Interventional Science, University College London, London, UK

Michel Slama Chair of Critical Care Medicine, Head of Medical Intensive Care Unit, Vice President of University of Amiens, Réanimation Médicale CHU Sud and INSERM 1088, Amiens, France

Leigh Ann Slater Johns Hopkins University School of Medicine, Baltimore, MD, USA

Martin Smith Consultant and Honorary Professor in Neurocritical Care, The National Hospital for Neurology and Neurosurgery, University College London Hospitals, London, UK

Jasmeet Soar Consultant in Anaesthesia and Intensive Care Medicine, Southmead Hospital, Bristol, UK

Neil Soni Consultant, Chelsea and Westminster Hospital, Honorary Senior Lecturer, Imperial College Medical School, London, UK

Antoinette Spevetz Professor of Medicine, Cooper Medical School of Rowan University, Cooper University Hospital, Camden, USA

Giulia Spoletini Clinical Fellow in Pulmonary and Respiratory Medicine and Clinical Research Fellow in Pulmonary Medicine, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, IRCCS Fondazione Ospedale Maggiore Policlinico Ca' Granda, and Division of Pulmonary, Critical Care and Sleep Medicine, Tufts Medical Center, Milan and Boston, Italy and USA

Charles L. Sprung Director, General Intensive Care Unit, Department of Anaesthesiology and Critical Care Medicine, Hassadah Hebrew University Medical Centre, Jerusalem, Israel

Nattachai Srisawat Assistant Professor, Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, and King Chulalongkorn Memorial Hospital, Bangkok, Thailand, And Center for Critical Care Nephrology, The CRISMA Center, Department of Critical are Medicine, University of Pittsburgh School of Medicine, Pittsburgh, USA

Bashar S. Staitieh Senior Fellow, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Emory University School of Medicine, Atlanta, GA, USA

Simon Stanworth Consultant Haematologist, Department of Haematology, NHS Blood and Transplant/Oxford University Hospitals NHS Trust, Oxford, UK

Michael Sterling Department of Surgery, Emory University Hospital, Atlanta, GA, USA

Theodore A. Stern Chief, Avery D. Weisman Psychiatric Consultation Service, Director, Office for Clinical Careers, Ned H. Cassem Professor of Psychiatry in the field of Psychosomatic Medicine/Consultation, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Marion Sternbach Associate Professor of Medicine, Faculty of Medicine, Division of Haematology, McMaster University, Hamilton, Canada

Philip Stevens Consultant Surgeon, Glasgow Royal Infirmary, Glasgow, UK

Robert D. Stevens Associate Professor of Anesthesiology Critical Care Medicine, Neurology, Neurosurgery, and Radiology, Johns Hopkins Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Nino Stocchetti Professor, Department of Physiopathology and Transplant, Milan University and Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

Karen K. Stout Professor of Medicine and Director, Adult Congenital Heart Disease Service, University of Washington Medical Centre, Seattle, WA, USA

Jose Ignacio Suarez Department of Neurology, Divisions Vascular Neurology and Neurocritical Care, Baylor College of Medicine, Houston, TX, USA

Kamalakkannan Subhas Clinical Fellow in Neuroanaesthesia, The National Hospital for Neurology and Neurosurgery, University College London Hospitals, London, UK

Anthony F. Suffredini Senior Investigator, Critical Care Department, Critical Centre, National Institutes of Health, Bethesda, MD, USA

Charlotte Summers University Lecturer in Critical Care Medicine, Cambridge University, Cambridge, UK

Ajay Suri Specialist Trainee in Cardiology, Barts Health Centre, St Bartholomew's Hospital, London, UK

Erik R. Swenson Professor of Medicine and Physiology, Attending Physician, University of Washington and Pulmonary and Critical Care Medicine, VA Puget Sound Health Care System, Seattle, WA, USA

Paolo Taccone Department of Anesthesiology, Policlinico Hospital of Milan, Milan, Italy

Sharla K. Tajchman Critical Care/Nutrition Support Clinical Pharmacy Specialist, Division of Pharmacy, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Jukka Takala Professor of Intensive Care Medicine and Director, Department of Intensive Care Medicine, Bern University Hospital and University of Bern, Bern, Switzerland

Sébastien Tanaka AP-HP, Service d'Anesthésie-Réanimation, Hôpitaux Universitaires Paris-Sud, and Hôpital de Bicêtre, Le Kremlin-Bicêtre, Paris, France

Paolo Tarsia Department of Pathophysiology and Transplantation, University of Milan, IRCCS Fondazione Ospedale Maggiore, Policlinico Cà Granda Milano, Milan, Italy

Eva Tejerina Intensive Care Unit, Hospital Universitario de Getafe, and Ciber Enfermedades Respiratorias, Instituto Carlos III, Madrid, Spain

Eric J. Thomas Professor of Medicine, Associate Dean for Healthcare Quality, and Director, Memorial Hermann Center for Healthcare Quality and Safety, University of Texas at Houston, Houston, TX, USA

Peter D. Thomas Colonel, 3rd Health Support Battalion, Australian Defence Force, Adelaide, Australia, Director, Intensive Care Unit, Lyell McEwin Hospital, Adelaide, Australia

Kevin Thornton Associate Professor, Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, CA, USA

Franck Thuny Unit of Heart Failure and Valvular Heart Diseases, Department of Cardiology, University Hospital Nord, Marseilles, France

Isaac Teitelbaum Professor of Medicine, Director, Home Dialysis Program, University of Colorado Hospital, Aurora, CO, USA

Marius Terblanche Honorary Senior Lecturer (Research), Division of Health & Social Care Research, Faculty of Life Sciences & Medicine, King's College London and Department of Critical Care Medicine, Guy's & St. Thomas' NHS Foundation Trust, London, UK

Martin J. Tobin Division of Pulmonary & Critical Care Medicine, Loyola University Medical Centre, Maywood, USA

Ariella Tomasini Department of Anaesthesia and Intensive Care Medicine, University of Trieste, Trieste, Italy

Antoni Torres Department of Pneumology, Hospital Clinic, Barcelona, Spain

William M. Townsend Lymphoma Research Fellow, University College London Hospitals NHS Foundation Trust, London, UK

Darrell J. Triulzi Medical Director, Institute for Transfusion Medicine, Pittsburgh, USA

Richard G. Trohman The Grace DeForest and William Louis Veeck Professor of Cardiovascular Research and Director Electrophysiology, Arrhythmia and Pacemaker Services, Rush University Medical Center, Chicago, IL, USA

David V. Tuxen Senior Intensivist, Department of Intensive Care, The Alfred Hospital, Melbourne, Australia

Hans Ulrich Rothen Professor, Departments of Anaesthesiology and Intensive Care Medicine, Bern University Hospital (Inselspital) and University of Bern, Bern, Switzerland

Franco Valenza Department of Anesthesiology, Policlinico Hospital, University of Milan, Milan, Italy

Benoit Vallet Professor, Lille University Teaching Hospital, Lille School of Medicine, Lille North of France University, Lille, France

Paul Van Buynder Professor Griffith University, Staff Specialist Gold Coast Health, Gold Coast Health Service, Southport, Queensland, Australia

Sophie Van Cromphaut Catholic University Leuven (KU Leuven), Department Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium

Marc Van Nuffelen Department of Emergency Medicine, Erasme University Hospital, Brussels, Belgium

Eduard E. Vasilevskis Assistant Professor of Medicine, Vanderbilt University and VA Tennessee Valley: Geriatric Research, Education and Clinical Center (GRECC), Nashville, TN, USA

Theodoros Vassilakopoulos University of Athens Medical School, 'Evangelismos' Hospital, Department of Critical Care and Pulmonary Services, Athens, Greece

Fabienne Venet Assistant Professor, Immunology Laboratory, Hôpital E Herriot, Hospices Civils de Lyon, Lyon, France

Chethan P. Venkatasubba Rao Department of Neurology, Baylor College of Medicine, Houston, TX, USA, Princess Alexandra and Wesley Hospitals, University of Queensland, Brisbane, Australia

Bala Venkatesh Pre-eminent specialist, Intensive Care Unit, Princess Alexandra & Wesley Hospitals, University of Brisbane, Brisbane, Australia

Paul M. Vespa Professor of Neurosurgery and Neurology, Director of Neurocritical Care, David Geffen School of Medicine at UCLA, Los Angeles, USA

Antoine Vieillard-Baron Professor of Intensive Care Medicine, Head of the Medical and Surgical ICU, University Hospital Ambroise Paré, Assistance Publique des Hôpitaux de Paris, Université Versailles Saint Quentin en Yvelines, Boulogne, France

Laura Vincent ST5 Joint CCT Intensive Care Medicine and Anaesthetics, Oxford University Hospitals, Oxford, UK

Hans-Dieter Volk Chairman, Institute for Medical Immunology and Berlin-Brandenburg Center for Regenerative Therapies, University Medicine Berlin, Berlin, Germany

Peter D. Wagner Distinguished Professor of Medicine & Bioengineering, University of California, San Diego, La Jolla, USA

Carl Waldmann Consultant in Anaesthesia and Intensive Care, Royal Berkshire Hospital, Reading, UK

Allan J. Walkey Assistant Professor of Medicine, University of Boston, Boston, USA

David J. Wallace Core Faculty, Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center, Assistant Professor of Critical Care and Emergency Medicine, University of Pittsburgh School of Medicine, Pittsburgh, USA

Timothy Walsh Professor of Critical Care, Edinburgh University and Edinburgh Royal Infirmary, Edinburgh, UK,

Ruth Y. Y. Wan Expert Pharmacist in Critical Care, Guy's and St Thomas' Foundation Hospital, London, UK

Lorraine B. Ware Professor of Medicine, Professor of Pathology, Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN, USA

David Watson Honorary Professor of Intensive Care Education, Homerton University Hospital NHS Foundation Trust, Barts and The London School of Medicine and Dentistry, London, UK

Andrew Webb Clinical Professor, Faculty of Medicine, University of British Columbia, Vancouver, Canada

Yoram Weiss Director, Hadassah Ein Kerem Medical Center, Hadassah Medical Organization, Jerusalem, Israel

Julia Wendon Clinical Director for Intensive Care and Liver Intensive Care, Institute of Liver Studies, King's College Hospital, London, UK

Jan Wernerman Professor of Anaesthesiology and Intensive Care Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden

Michael Weston Consultant Radiologist and Lead Clinician Radiology, Ultrasound Department, St James's University Hospital, Leeds, UK

Claire Westrope University Hospitals of Leicester NHS Trust, Leicester, UK

Douglas B. White UPMC Endowed Chair for Ethics in Critical Care Medicine, Associate Professor of Critical Care Medicine, and Director, Program on Ethics and Decision Making in Critical Illness, University of Pittsburgh Medical Centre, Pittsburgh, USA

Simon Whiteley Consultant Intensive Care, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Christopher J. M. Whitty Consultant Physician and Professor, The Hospital for Tropical Diseases, London, UK

A. P. R. Wilson Consultant Microbiologist, Clinical Microbiology & Virology, University College London Hospitals NHS Foundation Trust, London, UK

Bradford D. Winters Associate Professor of Anaesthesiology and Critical Care Medicine, Armstrong Institute for Patient Safety and Quality, Johns Hopkins University School of Medicine, Baltimore, MD, USA

S. John Wort Lead Consultant Physician, Pulmonary Hypertension Service and Consultant Intensive Care Physician, Adult Intensive Care, Royal Brompton Hospital, London, UK

Hannah Wunsch Associate Professor of Anaesthesiology, University of Toronto, Toronto, Canada

Sully Xiomara Fuentes Patarroyo The George Institute for Global Health and Neurology Department, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia

G. Bryan Young Emeritus Professor, Department of Clinical Neurological Sciences, Western University, London, Canada

Samuel J. Youssef Cardiac Surgeon, Swedish Heart & Vascular Institute, Seattle, WA, USA

Giovanni Zagli Department of Anesthesia and Intensive Care, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

Walter Zingg Senior Consultant in Infection Control and Infectious Diseases, Infection Control Programme, University of Geneva Hospitals, Geneva, Switzerland

SECTION 1

ICU organization and management

PART 1.1

The intensive care unit

CHAPTER 1

Design of the ICU

Neil A. Halpern

Key points

- The intensive care unit (ICU) design process is complex and time consuming, and needs to balance innovation with practicality, space availability, physical limitations, and cost.
- The ICU patient room is at the core of the ICU patient, family member, and staff experiences.
- All ICU rooms should be similarly designed and equipped, and provide an environment that promotes healing, and infection prevention and control, in concert with supportive spaces.
- An ICU is an autonomous mini-hospital, whose design and functionality must be synchronized with the rest of the hospital.
- Advanced ICU informatics systems seek to electronically integrate the ICU patient with all aspects of care, utilize the data, and monitor the ICU environment.

Introduction

Intensivists are periodically asked to participate in the construction of new intensive care units (ICU) or the renovation of older ones. This chapter explores ICU design through three prisms: concept to occupancy, the patient room and supportive services, and advanced informatics. This chapter is meant to supplement existing ICU and hospital facility guidelines and recommendations [1–5].

Concept to occupancy

Working with the hospital and ICU design team

The ICU design process begins with a shared critical care medicine (CCM) and hospital vision for a new ICU that reflects the desired appearance and feel of the new ICU, and addresses the goals for patient care, workflow, technology, and the environment [3,5]. Two core principles should be appreciated. First, an ICU is an autonomous mini-hospital, whose design and functionality must be synchronized with the hospital. Secondly, the ICU design process is complex, and must balance innovation with practicality, space limitations, healing, and cost restraints.

The core membership of the ICU design team should reflect its broad responsibilities. The CCM clinical chief should chair the project with the hospital's ICU project manager. Only experienced ICU architects should be engaged. Rapid exposure to excellent ICU designs can be gained through the study of ICU design award videos [6] (see Award Winning ICU Designs at http://www.sccm.org) and visits to selected ICUs. Openness to new ideas should be encouraged [3,7].

Several questions must be addressed. Is the ICU project a renovation or a new build? How will the ICU be physically related to other hospital areas? Is the ICU to be a multipurpose or specialty unit? How many ICU beds are planned? How much space is available and how will space be allocated (patient versus supportive areas)? Will the ICU have centralized or decentralized care and support services, or both? Will smart technology be incorporated?

Design timeline

From the start of design to occupancy may take 3–5 years. The ICU design team should meet regularly and utilize continuously updated schematics, computerized design renderings, and full-scale mock-ups.

New construction or renovation

New construction offers greater opportunity than renovation for innovation and the proper location of ICU patient rooms within the rest of the ICU. Once an ICU is completed, it is unlikely that further major changes will be implemented. As most upgrades will be informatic or technological in nature, networking and power capabilities should be expansive to meet future needs.

Technology standardization and purchase

A list of equipment must be developed, finalized, and purchased early in the design process so that the equipment will be available for installation as construction nears completion. Early purchase of technology, however, may lead to the installation of out-of-date devices; therefore, purchases should be protected through 'non-obsolescence' insurance agreements.

Standardizing technologies allows staff to move easily from room to room, minimizes training, simplifies maintenance, limits repair contracts, and permits quantity discounts. Modern devices are really informatics platforms, so the purchase must address software licenses and updates, connectivity, and interoperability. New technologies should also be tested in a simulation laboratory prior to purchase.

Ramifications of the new ICU

The consequences of the new design must be assessed. For example, if additional ICU beds are being added, then more staffing may be required. Similarly, if point-of-care testing is being newly incorporated, the ICU staff will need to be trained and qualified.

Team roles during construction

ICU design team members should monitor the ICU construction and look for problems that may not have been previously anticipated. Changes may be necessary, but they are expensive and time

consuming. The project should be photographed stage by stage to provide a basis for repair or retrofit.

Occupancy, post-occupancy, do-overs, and expectations

A transition team and simulated move will help the changeover to the new ICU, and will minimize moving-in problems and anxieties. A post-occupancy group should address unforeseen surprises. Hopefully, the new ICU will provide a modern workplace, but will not necessarily improve outcomes or correct challenging staff dynamics.

The patient room and supportive services

The ICU patient room

The ICU patient room [1,3,4,6,8] is at the core of the ICU patient, visitor, and staff experience. Each room should function semi-autonomously, be designed similarly, accommodate one patient only to maintain infection control and privacy, and provide a healing environment. ICU rooms have zones (patient, caregiver, and visitor) that are differentiated by room layout; however, the zones must be operationally flexible. The patient's bed should be the room's focal point.

Medical devices, utilities, communications, and room controls are commonly mounted on stationary headboards or columns, or on mobile articulating columns (booms). Booms, although expensive and requiring much maintenance, offer greater flexibility and patient access than stationary units because of their mobility [9]. Core equipment includes an ICU bed, physiological monitor, mechanical ventilator, infusion pump, feeding pump, pneumatic compression devices, webcam, and specimen label printer. Point-of-care testing (POCT) and ultrasonography devices may also be considered to be core technologies, as they speed diagnosis and therapies, and are decreasing in their sizes and costs.

Room environment

The emotional welfare of ICU patients, staff, and visitors is greatly impacted upon by the room's environment [10]. Thus, a healing milieu that controls sound, light, temperature, time, artwork and entertainment, and provides visiting areas and privacy should be developed [3].

Physical noise barriers should be supplemented by control of device alarms and ICU communications. Windows with shades (manual or electric) and multiple lighting configurations help maintain diurnal rhythms. Each room should have artwork (displayed on the walls, curtains, and ceiling tiles, or electronically), televisions or integrated television-computers, thermostat, and clock. Comfortable chairs, Wi-Fi, and electrical and USB outlets should also be available [2,10]. The patient room should include a long-term visiting area if space permits.

Privacy is provided with curtains, double-paned glass with blinds, or electronic glass. Curtains may be more economical than glass solutions, although curtains can become contaminated and must be changed between patients, while glass barriers are easily cleaned.

Room supplies and waste management

Supplies should be stored in secured and non-secured drawers, cabinets, and/or mobile carts or nurse servers (cabinets with bi-directional access—from both outside and inside the room). Resupplying nurse servers from outside the room supports privacy and aids infection control. ICU rooms should have their own bathrooms with automated bedpan macerators or closed bedpan cleaners [8].

Room entry

The ICU room may open directly to or be set back from the hallway. ICU doors may be controlled manually or electronically. The area outside the patient room should include a decentralized staff workstation, computer, sink, storage space, hangers, and a manual or electronic identification or message board.

Supportive services

Centralized work areas

Centralized work areas provide important functions, including greeting desks, and quiet work and conferencing areas. Limited central bed visibility is supplemented with bed-based webcams.

Corridors and central-based storage for medical devices and carts

ICU corridors establish physical and emotional ICU cohesiveness through their lighting, artwork, sound control, and finishings. Local device and cart alcoves near the patient rooms minimize retrieval times. Hallway closets provide access to non-bedside ICU equipment and supplies. Preferably, ICU patients and supplies should enter the ICU via hallways that bypass the waiting room and visitor entranceways.

Floorings and furnishing

Floors should be comfortable to walk on, non-slip, easy to clean, durable, and impermeable [7]. Walls should be impact-resistant and hallway walls should have fixed protective barriers.

The waiting room

A waiting room with soft-lighting, warm colours, artworks, Wi-Fi, power and USB outlets, televisions, vending machines, bathrooms, lockers and coat hangers, and long-term sleeping arrangements, if possible, should be located adjacent to the ICU. Seating arrangements should be configured as small groups of chairs separated by privacy dividers. Consultation rooms and a social worker's office should support family meetings.

Staff lounge

The staff lounge should have a pleasant ambiance with comfortable seating, artwork, ICU communications, televisions, computers, and a food area and refrigerator. There should also be private changing areas, scrub dispensers, lockers, bathrooms, nap alcoves, and storage areas (for coats and footwear).

Staff communications

Telephones, overhead speakers, nurse-call (intercom) systems, and bi-directional transmitters should be integrated into the ICU. Nurse-call systems are capable of point-to-point and global communications, and can be integrated into real time locating systems (RTLS). Similarly, staff assigned bi-directional transmitters can handle point-to-point and global ICU and hospital communications, and convey voice, telephone, pagers, alarms, and e-mail using wireless and cellular networks.

Pharmacy

A fully equipped satellite ICU pharmacy is necessary if the hospital has a decentralized medication system. In contrast, less

support is required if the hospital pharmacy system is centralized. Stand-alone secure medication storage compartments should be strategically positioned in the ICU and linked to the hospital network. Medications may also be stored in secured cabinets at the ICU bedside.

POCT

POCT devices may be positioned in a free-standing laboratory within the ICU, in defined centralized areas, on mobile carts, or at each ICU bedside. POCT models depend on the ICU workflow, testing needs, space available, and resources. All POCT devices should be networked with hospital systems.

ICU logistics

Bulk supplies are usually stored in supply rooms in stationary or track-based shelving, closed supply cabinets, or rolling exchange carts. Optimally, these storage units are fitted with electronic inventory management scanners. The challenge is to 'right-size' the centralized and decentralized supply areas. This process is dependent on accurate projections of ICU occupancy, supply usage, and re-supply patterns.

Infection control

Infection prevention requires good design and a 'culture' of infection prevention. As hand-washing and surface disinfection are the corner stones of infection control, ICUs should have multiple sinks, cleansing fluid dispensers, and easy to clean surfaces [1,2,8]. However, design teams are now supplementing these with automated hand-washing surveillance, surface hygiene monitoring systems, copper or silver antibacterial surface coatings, impermeable, washable, and antimicrobially-coated keyboards and mice, and environmental decontamination (hydrogen peroxide or ultraviolet light) systems.

Conference facilities, on-call suites, and offices

On-call suites, conference facilities, CCM, and respiratory therapy offices should be located within or near the ICU to facilitate staff availability for patient and family matters and meetings. Conference rooms should include advanced informatics, large electronic displays, and video systems, electronic scanners to track attendance, and electronic conference displays to provide notifications of room utilization.

Signage

Signs identify destinations, and provide directions and information. The signage process is facilitated by virtual ICU walk-throughs to simulate patient, staff, and visitor traffic patterns, and maximize hallway efficiencies.

Security

ICU security must be balanced with warmth. Electronic locks with card access should be used to protect and monitor entry to all sensitive ICU areas. Additionally, the ICU should be monitored with a mix of hospital-based video cameras, locally-based webcams, and closed circuit televisions (CCTV).

Advanced informatics

Advanced ICU informatics systems seek to electronically integrate the ICU patient with all aspects of care (devices, data, supplies, caregivers, medical and administrative applications), and the electronic medical record (EMR). These systems should also help utilize the data, and monitor the ICU environment [11].

Connectivity envelope

The creation of a smart ICU requires the construction of a connectivity envelope around the patient. This multistep process starts with the installation of a wired and wireless infrastructure that is integrated with the hospital's network in each patient room. The second step is the attachment of auto-identification (Auto-ID) tags (i.e. bar codes, infra-red, radio frequency identification (RFID), ultrasonic, and/or hybrid tags) on all data sources, and adaptors and/or computers to the data output ports of the medical devices. The Auto-ID tags facilitate the tracking of all tagged sources; the adaptors and/or computers connect the devices to the envelope if the devices do not have their own internal communications. The computers additionally provide 'interoperability' by translating proprietary device data into a standardized language, so that the data can be read and understood by the ICU middleware, and ultimately placed into the EMR [12]. The third step is the installation of data receivers (i.e. access points, readers, scanners, multimode integrators, and multiport concentrators) in each room to track the Auto-ID tagged data sources and capture data from the medical devices. The last step is the placement of ICU middleware on the hospital network to utilize the data originating from the ICU patient room. This middleware stores and transmits data, records and transforms alarms and data to actionable information, develops virtual device communities, promotes RTLS, and prepares data for smart displays.

Advanced ICU informatics design

Three elements are critical to the success of the connectivity envelope. The first is 'association' of all data sources with the ICU patient. This can be achieved through either patient-centric (linked to a unique identifier) or location-centric (linked to the patient's location) approaches [13]. The patient-centric solution is preferable because the data is 'permanently' attached to the patient, regardless of the patient's physical location. The second core element is time synchronization across all bedside devices and systems; this is necessary for maintaining the time integrity of the electronic flow sheet and all data tracking. The third is interoperability or data recognition between data sources, middleware, and the EMR. This process requires data conversion and alignment protocols to synchronize proprietary data output languages of medical devices with industry standards (see http://www.ihe.net/) and the middleware [12].

Alarm and data transformation

ICU device data and alarms will tire the staff mentally [14]. Although alarms can be partially managed at the device level, a systematic approach requires the deployment of network-based alarm applications. Alarm systems capture alarms and convert them into actionable information [15] using 'message delivery' software, which filters and transmits alarms to dedicated receivers or through the use of an 'intelligent' alarm system that combines alarms and patterns, and analyses raw device data and creates its own alarms [16]. Alarm systems can be supplemented by decision support, sniffers that monitor the EMR, and profiling patients at risk of clinical deterioration by fusing alarms, and other preselected data and trends [17].

Virtual device communities

Enterprise-wide views of all devices of a specific genre can be created by ICU middleware that 'looks' at each device and builds

a virtual device community. This application allows global device monitoring (local telemedicine), data uploads and downloads, alarm transmission, and report generation. Device middleware also allows vendors to remotely troubleshoot and update their software.

RTLS

RTLS represents a wide variety of solutions to improve the management and workflow of all types of tagged assets. RTLS may be used in real time or historically [18] to track and locate assets, monitor device utilization, harmonize device distribution, control consumable product inventories, identify products near their expiration dates or subject to recall, and create reports for future purchases and par-level determinations [19]. RTLS can also be integrated with existing systems to improve infection control, personnel location, and patient room management.

Smart displays

ICU middleware supports a variety of smart displays (monitoring, greaseboard, smartboard, and dashboard) that can be used individually or in combination. Smart monitoring enables clinicians to rapidly identify changes in a patient's condition by merging data from bedside devices and the EMR, and processing this data through artificial intelligence algorithms [20]. Electronic greaseboards track ICU bed utilization using hospital bed management middleware or by local ICU data entry. Smartboards provide basic bed information, plus RTLS data to track ICU staff and patient movements. Dashboards sit above EMR and non-EMR applications, and simultaneously display recent patient data from preselected systems.

Telemedicine

ICU design should address the installation of telemedicine solutions if this monitoring process is being considered. The telemedicine technologies include interfaces for the physiological monitoring system, the EMR, the electronic ICU flowsheet, and the computerized physician order entry system. Additionally, high-definition, bi-directional cameras and communication systems should be installed in each ICU room. Bi-directional teleconferencing should also be installed in the ICU waiting room.

References

1. Thompson DR, Hamilton DK, Cadenhead CD, et al. (2012). Guidelines for intensive care unit design. *Critical Care Medicine*, **40**(5), 1586–600.
2. The Facilities Guidelines Institute. *Guidelines for Design and Construction of Hospitals and Outpatient Facilities*, 2014 edn. Chicago: American Society for Healthcare Engineering (ASHE) of the American Hospital Association.
3. Halpern NA. (2014). Innovative designs for the smart ICU: Part 1. From initial thoughts to occupancy. *Chest*, **145**(2), 399–403.
4. Valentin A, and Ferdinande P. (2011). Recommendations on basic requirements for intensive care units: structural and organizational aspects. *Intensive Care Medicine*, **37**(10), 1575–87.
5. Kesecioglu J, Schneider MM, van der Kooi AW, and Bion J. (2012). Structure and function: planning a new ICU to optimize patient care. *Current Opinions in Critical Care*, **18**(6), 688–92.
6. Cadenhead CD and Anderson DC. (2009). *Critical Care Design: trends in award winning designs*. World Health Design 2009. Available at: http://www.worldhealthdesign.com/critical-care-design-trends-in-award-winning-designs.aspx (accessed 3 June, 2013).
7. Bartley J and Streifel AJ. (2010). Design of the environment of care for safety of patients and personnel: does form follow function or vice versa in the intensive care unit? *Critical Care Medicine*, **38**(8 Suppl.), S388–98.
8. Halpern NA. (2014). Innovative designs for the smart ICU: Part 2. The ICU. *Chest*, **145**(3), 645–58.
9. Nestor C. (2005). Critical conditions. A real-world look at features and technologies for the ICU. *Health Facility Management*, **18**(8), 25–9.
10. Davidson JE, Powers K, Hedayat KM, et al. (2007). Clinical practice guidelines for support of the family in the patient-centered intensive care unit: American College of Critical Care Medicine Task Force 2004–2005. *Critical Care Medicine*, **35**(2), 605–22.
11. Halpern NA. (2014). Innovative designs for the smart ICU: Part 3. Advanced ICU Informatics. *Chest*, **145**(4), 903–12
12. Hyman WA. (2010). When medical devices talk to each other: the promise and challenges of interoperability. *Biomedical Instrumentation & Technology*, Suppl., 28–31.
13. Frisch P, Miodownik S, Booth P, Carragee P, and Dowling M. (2009). Patient centric identification and association. *Conference Proceedings of the IEEE Engineering in Medicine & Biology Society*, **2009**, 1722–5.
14. The Joint Commission (2013). *Medical device alarm safety in hospitals. The Joint Commission Sentinel Event Alert 2013*. Available at: www.jointcommission.org (accessed 8 April 2013).
15. ECRI Institute (2007). *Critical Care Safety. Essentials for ICU Patient Care and Technology*. Plymouth Meeting, PA: ECRI Institute.
16. Imhoff M and Kuhls S. (2006). Alarm algorithms in critical care monitoring. *Anesthesia & Analgesia*, **102**(5), 1525–37.
17. Stylianides N, Dikaiakos MD, Gjermundrod H, Panayi G, and Kyprianou T. (2011). Intensive care window: real-time monitoring and analysis in the intensive care environment. *IEEE Transactions on Information Technology in Biomedicine*, **15**(1), 26–32.
18. Poshywak J. (2012). Is RTLS a tipping-point technology? Boost in efficiency gained by real-time capacity management provides significant ROI, better patient care. *Health Management Technology*, **33**(8), 16–17.
19. Frisch PH, Booth P, and Miodownik S. (2010). Beyond inventory control: understanding RFID and its applications. *Biomedical Instrumentation & Technology*, Suppl., 39–48.
20. Kruger GH and Tremper KK. (2011). Advanced integrated real-time clinical displays. *Anesthesiology Clinic*, **29**(3), 487–504.

CHAPTER 2

Staffing models in the ICU

Tim Buchman and Michael Sterling

Key points

- Due to several factors, including an ageing population, retirement, and changing priorities of the newer generations of physicians, there is now and will continue to be a shortage of board-certified intensivists.
- This shortage will require alternative models of critical care delivery in order to meet the demands for critical care in the future.
- Although there are controversies surrounding the training and experience necessary for hospitalists to function as intensivists, hospitalists do currently provide critical care services in some settings where intensivists are not available or where it is impractical to recruit an intensivist.
- Affiliate providers (nurse practitioners (NPs) and physician assistants (PAs)) have proven to be effective in delivering high quality critical care under the direction of a board certified intensivist.
- Tele-intensive care units (ICU) or electronic intensive care unit (eICUs) can be effective in reducing mortality particularly in low acuity patients by helping to prevent their conversion to higher acuity patients, augmenting best practice, and improving financial performance of ICUs.

Alternative provider staffing models in critical care

The team of professionals caring for patients in critical care units can be divided into three large groups:

- Nurses, whose numbers include bedside nurses, administrative and educator nurses, and practical nurses.
- Providers including physicians and advanced care practitioners.
- Allied health personnel, including respiratory therapists, nutrition support specialists, pharmacists, physiotherapists, and social workers.

This chapter examines the evolution of provider staffing.

Three decades ago, provider surplus was forecasted. Projections changed at the turn of the century when the Committee on Manpower of Pulmonary and Critical Care Societies (COMPACCS) report was issued [1]. Demographers, statisticians, and clinicians used population, patient, hospital, and provider data to forecast that supply for critical care physicians would not keep pace with demand, and the shortfall would be around 22% short of demand by 2020, climbing to 35% by 2030. The prediction was subsequently validated by the US federal government. In 2006, the Health Resources and Services Administration (HRSA) similarly forecasted a significant shortage of intensivists by 2020 [2].

The gap between supply and demand can be attributed to at least three factors. The first factor is demographic and predictable—the USA baby boomers have aged to the point that they require critical care services. Over the next two decades, approximately 10,000 Americans each day will reach 65 years of age, an inflection point in the demand for critical care services. The HRSA report estimates that 65–74-year-olds require three times more intensivist care than 45–64-year-olds. Needs increase with each passing decade, amplifying the demand as patients survive previously fatal illnesses.

The second factor is an evolving expectation of increased provider presence. Until recently, provider presence was considered optional during nights, weekends, and holidays. Numerous studies suggest that expanded provider presence reduces mortality and care complications. Such expanded provider presence became an objective advocated by the Leapfrog Group, a consortium of American business leaders created in response to the Institute of Medicine report highlighting medical errors. While, there is ongoing debate over the extent of increase—some studies suggest that daytime presence and immediate off-hour availability might be adequate in some settings—there seems to be a strong general trend towards increasing provider presence as a safety and quality strategy [3].

The third factor is the imbalance between intensivist production and attrition. Although the number of medical schools and their graduates has expanded, neither residency slots nor fellowships appear likely to grow in proportion. The production rate of qualified intensivists is fairly flat, and those qualified have employment options in alternative practice settings that do not require night, weekend, and holiday duty. Given the heightened emphasis placed on work–life balance by many recent medical graduates who are part of the 'millennial generation' and 'Generation Y', it is understandable and not surprising that many choose disciplines with less demanding lifestyles. Alternatively, many who were scheduled to retire during the 2008 global economic collapse postponed their retirement for as long as their retirement accounts took to recover. They continue to work only because of the 2008 economic collapse. Economic recovery is thus something of a double-edged sword, and the projected reduction in physician compensation may well accelerate decisions to retire.

All signs suggest that the COMPACCS prediction is correct—a count of the 'help wanted' advertisements in the professional literature reveals the shortage of intensivist physicians is here and

growing. Three novel strategies by which intensivist expertise can be leveraged to provide care for a larger group of critically ill patients are discussed here. The three strategies include:

- The use of hospitalists.
- Engagement of affiliate providers (nurse practitioners and physician assistants with advanced critical care competencies).
- Investment in tele-intensive care units (tele-ICU) services.

These strategies are complementary and, therefore, can be combined to provide models tailored to local needs and resources.

Hospitalists

The specialty of hospital medicine emerged in response to the changing economic pressures during the managed care era [4]. Generalist practice, and its ideals of comprehensiveness and continuity confronted a need to create efficiency in care delivery, leading to a new division of internist labour. Primary care providers focused on ambulatory practice, while 'hospitalists' have multiplied to provide in-patient care. There are now more than 30,000 hospitalists nationwide and, in a recent survey, more than 75% of them report caring for patients in intensive care units [5].

Hospitalists integrate into the ICU workforce in a collaborative model utilizing a supervising intensivist- or a hospitalist-only model generally used in lower acuity ICUs where intensivists cannot be recruited. All models require knowledge, skills, and attitudes appropriate for the local cohort of critically-ill patients. While hospitalists must be able to recognize and treat acute physiological derangements, and perform basic procedures, such as central/arterial line placement, their comfort surrounding intubation, management of mechanical ventilation, and other advanced life supports varies widely.

Recently, a controversial position paper issued by the Society of Critical Care Medicine (SCCM) and the Society of Hospital Medicine jointly endorsed a conceptual model in which practicing hospitalists with at least 3 years' experience of clinical practice would be eligible for a 1-year critical care fellowship programme, which would lead to competency, as well as to eligibility for specialist certification in critical care medicine [6]. Immediate objections to the proposal surrounded the adequacy of training time and experience to acquire the necessary competencies. For comparison, 6 years of training are required to attain critical care expertise in Australia and New Zealand.

Despite this controversy, there is wide agreement that the standardization of care for common and acute critical situations is mandatory. Such standardization can be enhanced through the use of standard courses, such as Fundamental Critical Care Support (FCCS). The FCCS course was developed by the SCCM, and uses both didactic lectures and skill stations in a 2-day format to provide a framework for assessing and managing critically-ill patients outside tertiary referral centres. The FCCS course can broaden the knowledge base and skill set of hospitalists in both community and rural hospitals. FCCS is emphatically not a substitute for in-depth training, but can serve as a strong foundation for critical care training.

Hospitalists will increase their presence and responsibilities as critical care providers as a consequence of the unmet demand for critical care services. It will be important to ensure that patient needs are matched with verified provider competencies, while avoiding divisive distinctions based solely on board certification.

Affiliate providers

At the Emory Center for Critical Care, we coined the term affiliate provider (AP) to describe our 63 nurse practitioners and physician assistants, who have received special training and demonstrated additional competencies in intensive care. We believe this term provides a more accurate description of the ICU nurse practitioner (NP) and physician assistant (PA) roles and responsibilities, when compared with the more traditional names that include 'mid-level' or 'physician extender'. We further believe that this collective term emphasizes the idea that both NPs and PAs can be trained to be effective, efficient, compassionate providers of critical care.

Certification for NPs in acute and ICU care began in 1995 [7]. The American Association of Critical-Care Nurses recognizes acute care NPs as having the appropriate training and education to manage acute and critically-ill patients. Importantly, recent changes to the scope of practice recommendations and legislation will soon exclude other categories of NPs from practicing in the ICU [8]. We expect that a modest number of well-trained and committed acute care NPs will form a cornerstone of ICUs provider workforce. These workers are especially important because they often bring years of bedside critical care experience (as nurses) to their new provider roles.

The shortage of primary care physicians almost 50 years ago was probably the stimulus for the growth in the number of PA programmes in the USA. However, PAs practicing in the ICU and acute care setting have also grown substantially over the years. According the 2010 American Academy of Physician Assistants census, about 2% of all registered PAs are dedicated full time to an ICU/critical care setting, while 21% spend at least some of their time in an ICU/critical care setting. While critical care is an attractive clinical setting for many new graduates, their relative paucity of clinical ICU experience creates special challenges in transitional training to ensure that they acquire and use the competencies needed to provide safe and effective critical care. We expect that recruitment and focused transitional training of PAs will emerge as a common strategy across the USA.

When appropriately trained, verified, and qualified, the NP and PA affiliates extend the existing provider cohort by participating in multidisciplinary rounds, performing procedures such as central/arterial line placements and endotracheal intubations. With progressive training, APs can master even the most complex procedural skills, such as insertion of ventriculostomy catheters.

APs also take on key administrative roles, participating, and even leading development and refinement of care protocols that lead to the removal of unnecessary variance in practice. Outside the clinical arena, affiliate providers participate in quality projects, assisting in the education of nursing staff, residents, medical students, and other health care professionals who are part of the multidisciplinary ICU team. Additionally, affiliate providers engage in or develop research projects related to their areas of expertise and interest [9]. Affiliate providers have been shown to have a positive impact on quality by improving communication and adhering to best practice guidelines [10,11].

With a shrinking federal health care budget, and with ICU costs estimated to be 0.7% of the US gross national product, simultaneous

emphasis on both quality and value in health care is necessary. Measuring productivity of intensivist physicians and their affiliate providers locally has become a key business strategy. Creating a mandatory time-accounting policy and providing all providers with an electronic tool to log and follow their time allocations has been a useful approach to understanding and refining clinical staffing models and assignments [12].

When building a business model for APs, it is worth noting that APs are reimbursed at 85% of the rate of physicians by federal agencies and often 100% by commercial agencies (usually defined contractually). To further improve utilization, APs can also be asked to respond to codes and with rapid response teams. They can provide another pair of hands, perform procedures, and facilitate transfer of the patients to the appropriate ICU postcode or assist in a rapid response evaluation. In our experience, the time-accounting tool is key to understand and improve utilization of their professional services.

Tele-ICU

Tele-ICU, which is branded and trademarked eICU by a major vendor (Philips Healthcare), continues to grow with the technological advancements needed to build infrastructure, as well as with the need to extend the reach of intensive care providers into under-served or rural areas, where hospitals have limited resources. First described in 1982 by Grundy and colleagues [13], tele-ICU was conceived as a way of networking critical care consultants with hospitals lacking critical care expertise. More recently, affordable high resolution two-way audio and video links, coupled with decision support software has allowed a new generation of tele-ICUs to link critical care providers to critically-ill patients in remote locations. At the time of writing, approximately 14% of the ICU beds in the USA are monitored by a tele-ICU system.

Although there are currently several tele-ICU vendors in the USA, their operating principles are similar. Generally a tele-ICU is staffed 24/7 with ICU registered nurses (RNs) or Aps, but this can vary significantly depending on need. The hours of presence of an intensivist in the central (advising) centre varies, but is dependent on the needs of the health care system. Typically, tertiary and quaternary ICUs that have a structured intensivist programme and use tele-ICU will 'sign out' to the tele-intensivist at night. In contrast, smaller ICUs in rural and under-served locations that depend on part-time physician coverage elect around-the-clock tele-intensivist presence to assure a continuous oversight. One tele-intensivist may be associated with up to 125 patients, but 70 patients are more typical. One tele-ICU RN can manage up to 40 patients [14].

High resolution audio and video allows direct interaction between the tele-ICU team and members of the bedside team, including the nurse, clinical pharmacist, respiratory therapist, AP, or physician. Addressing concerns about the patient, facilitating weaning from mechanical ventilation, and writing orders remotely are just some of the tasks that can be accomplished by the tele-ICU team, in collaboration with the bedside team.

The logistics of setting up a tele-ICU system are complex. Start-up costs include finding and leasing space for the command centre, hiring staff, and purchasing licenses and equipment for the number of beds in the system. However, the benefits of a tele-ICU can have a significant positive impact on patient care, improve best practice compliance, and improve the financial bottom line by emphasizing efficiency and decreasing waste. For-profit companies have emerged that offer turn-key tele-ICU services to hospitals. Should a hospital choose to establish its own tele-ICU command centre, some of the costs can be offset by marketing tele-ICU services to small community or rural hospitals on a per occupied bed basis 'at cost', with the benefit of load-balancing critical care across a larger network and channelling appropriate patients to the larger coordinating hospital. Smaller referring hospitals often cannot afford hospitalists or intensivists to oversee their ICUs, but can utilize the expertise of the tele-ICU team to improve patient care.

There are current data supporting the positive impact on mortality of tele-ICUs (up to 29% in one large acuity-adjusted analysis), best practice, and financial performance [15–20]. The benefits seem to accrue significantly in low-risk patients. Effective management can mitigate their conversion to long-stay patients, and prevent complications through close observation and early intervention.

Unfortunately tele-ICU services are not universally billable through either Centers for Medicare and Medicaid Services (CMS) or private payers. However, this seems likely to change in the future, based on proposed CMS payment guidelines and a drive to increase efficiencies of care.

Alternative models of critical care provider staffing internationally

The need for alternative models of provider staffing in critical care is dependent on many factors including, but not limited to the number of critical care beds that need to be staffed, the availability of critical care trained providers, the presence or absence of training programmes, physician staffing ratios, and nurse staffing ratios. In the USA, these factors have combined to drive a robust need for alternative critical care provider staffing models. However, there is evidence that interest has grown in these models internationally. A query placed on the Critical Care Medicine International Internet Group (CCM-L; ccm-l@pitt.edu)) regarding the utilization of physician extenders in critical care, their prevalence, and their responsibilities, yielded a response from members in 14 countries. Of the respondents, two (Australia and the UK) utilized physician extenders in critical care.

Canada, India, Netherlands, Malaysia, Liberia, Haiti, Lesotho, and South Africa all use physician extenders in their health care systems, but little is currently known specifically regarding their use in critical care medicine.

Conclusion

The decline in supply of board-certified intensivists versus the expanding demand appears inexorable. We have described three core mitigation strategies:

- The use of on-site physicians (hospitalists) who will require additional training in critical care.
- Deployment of critical care trained non-physician providers.
- The use of tele-ICU to expand the benefit of experienced intensivist physicians and seasoned critical care nurses as a second layer of caregivers, who can be spread over large distances.

These three strategies are not exclusive, but are rather complementary, and combinations will probably provide unique solutions to local needs.

References

1. Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J, Jr, for the Committee on Manpower for Pulmonary and Critical Care Societies (2000). Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease; can we meet the requirements of an aging population? *Journal of the American Medical Association*, **284**, 2762–70.
2. Health Resources and Services Administration. (2006). *Report to Congress. The Critical Care Workforce: A Study of the Supply and Demand for Critical Care Physicians*. Available at: bhpr.hrsa.gov/healthworkforce/supplydemand/medicine/criticalcaresupply.pdf (accessed 20 June, 2011).
3. Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, and Young TL. (2002). Physician staffing patterns and clinical outcomes in critically ill patients—a systematic review. *Journal of the American Medical Association*, **288**(17), 2151–62.
4. Wachter RM and Goldman L. (1996). The emerging role of 'hospitalists' in the American health care system. *New England Journal of Medicine*, **335**(7), 514–17.
5. Heisler M. (2010). Hospitalists and intensivists: partners in caring for the critically ill-the time has come. *Journal of Hospital Medicine*, **5**, 1–3.
6. Siegal EM, Dressler DD, Dichter JR, Gorman MJ, and Lipsett PA. (2012). Training a hospitalist workforce to address the intensivist shortage in American hospitals: a position paper from the Society of Hospital Medicine and the Society of Critical care Medicine. *Critical Care Medicine*, **40**, 1952–6.
7. Moote M, Krsek C, Kleinpell R, et al. Physician assistant and nurse practitioner utilization in academic medical centers. *American Journal of Medical Quality*, **5**, 1–9.
8. American Association of Critical-Care Nurses (2006). Scope and standards of practice for the acute care nurse practitioner. American Association of Critical-Care Nurses Website. Available at: http://www.aacn.org/ (accessed 10 June, 2011).
9. Kleinpell RM, Ely EW, and Grabenkort R. (2008). Nurse practitioners and physician assistants in the ICU: an evidence-based review. *Critical Care Medicine*, **36**, 2888–97.
10. Gracias VH, Sicoutris CP, Meredith DM, et al. (2008). Critical care nurse practitioners improve compliance with clinical practice guidelines in 'semiclosed' surgical intensive care unit. *Journal of Nursing Care Quality*, **23**, 330–44.
11. D'Agostino RD and Halpern NA. (2010). Acute care nurse practitioners in oncologic critical care: the Memorial Sloan–Kettering Cancer Center experience. *Critical Care Clinic*, **26**, 207–17.
12. Carpenter DL, Gregg SR, Owens DS, Buchman TG, and Coopersmith CM. (2012). Patient-care time allocation by nurse practitioners and physician assistants in the intensive care unit. *Critical Care*, **16**, R27.
13. Grundy BL, Jones PK, and Lovitt A. (1982). Telemedicine in Critical Care: Problems in Design, Implementation, and Assessment. *Critical Care Medicine*, **10**(7), 471–5.
14. Myers M and Reed KD. (2008). The virtual ICU (vCIU): a new dimension for critical care nursing practice. *Critical Care Nursing Clinics of North America*, **20**, 435–9.
15. Breslow MJ, Rosenfield BA, Doerfler M, et al. (2004). Effect of a multiple-site intensive care unit telemedicine program on clinical and economic outcomes: an alternative paradigm for intensivist staffing. *Critical Care Medicine*, **32**(1), 31–8.
16. Ikeda D, Hayatdavoudi S, Winchell J, et al. (2006). Implementation of a standard protocol for the surviving sepsis protocol 6 and 24 hours bundles in patients with an APACHE II admission diagnosis of sepsis decreases mortality in an open adult ICU [abstract]. *Critical Care Medicine*, **34**(12 Suppl.), A108.
17. Goran SF. (2010). A second set of eyes: an introduction to tele-ICU. *Critical Care Nurse*, **30**(4), 46–55.
18. Ries M. (2009). Tele-ICU: a new paradigm in critical care. *International Anesthesiology Clinics*, **47**(1), 153–70.
19. Forni A, Skehan N, Hartman CA, et al. (2010). Evaluation of the impact of a tele-ICU pharmacist on the management of sedation in critically ill mechanically ventilated patients. *Annals of Pharmacotherapy*, **44**(3), 432–8.
20. Lilly CM, and Thomas EJ. (2010). Tele-ICU: experience to date. *Journal of Intensive Care Medicine*, **25**, 16.

CHAPTER 3

Rapid response teams for the critically ill

Ken Hillman and Jack Chen

Key points

- Like intensive care units (ICUs), rapid response systems (RRSs) are interventions aimed at managing serious illness.
- The implementation of a new system has different challenges to the implementation of a new drug or procedure, both operationally and in its evaluation.
- The implementation of a RRS across an organization requires five elements: standardized triggering criteria; a standard response; organization wide education; support by senior management and clinicians, and involvement of the whole organization; and an agreed way to monitor the system.
- RRS improve over time as the organization adapts, and improves its effectiveness. Currently, the most accurate way of evaluating effectiveness is to monitor the number of calls/1000 admissions that correlates strongly with the reduction of death, and cardiac arrest rates.
- As yet, there is little data to support what are the most appropriate calling criteria or make-up of the response team. The response team must have the skills, knowledge, and experience necessary to match the level of illness of patients that they will be attending.

Introduction

Rapid response systems (RRSs) are based on the simple premise that early intervention in patients with a serious illness is better than neglect. They have in common the early identification of at-risk patients, followed by a rapid response by staff who have the appropriate knowledge, skills, and experience to care for those patients. While the calling criteria used to identify at-risk patients vary, they are all based on severely abnormal vital signs and observations. The systems operate mainly across the general wards in acute hospitals, where the level of care is less appropriate for caring for deteriorating patients compared with patients in environments such as intensive care units (ICUs). Their role has become more important as the population of hospital patients has become older, with an increasing number of co-morbidities and having more complex interventions. In fact, the population of patients subject to RRS interventions is similar to those already being managed in ICUs. Implementing a RRS has different challenges to implementing a new drug or procedure. Successfully implementing a hospital-wide system requires a comprehensive educational programme, support by every level in the organization, and the integration of outcome indicators into the implementation process. For example, the reduction of deaths and cardiac arrests in a hospital is directly related to the number of calls/1000 admissions. RRSs have now been implemented in one form or another in the majority of Australasian, North American, and UK hospitals. Hospitals with a RRS have a significant reduction in cardiac arrest and death rates.

Patients in areas such as operating theatres or ICUs rarely deteriorate without early detection, and can then receive appropriate management. On the other hand, it is the seriously ill or deteriorating patients on general wards who are likely to suffer potentially preventable deaths or cardiac arrests [1]. There are many reasons for this, including low staff–patient ratios, poor monitoring, outdated ways of manually recording vital signs, bedside staff who are not trained in how to recognize and manage serious illness, and rigid silo-based systems that do not encourage a rapid response to at-risk patients. As a result, there are many potentially preventable deaths that occur in acute hospitals [2]. There is a similar slow deterioration in patients who have cardiac arrests [3], and in patients before admission to the ICU from general wards [4]. The situation has been summarized as the wrong people with the wrong skills arriving too late to manage at-risk patients [5].

RRSs were developed in response to a problem. They are aimed at detecting, and responding to the seriously ill, as well as patients who are at-risk of becoming seriously ill. The system is usually implemented across the whole hospital, and has two major features—standardized triggering criteria and an agreed response to patients who conform to those criteria. The objective of RRSs is to identify, and manage serious illness early in order to improve patient outcome, and reduce complications.

Calling criteria

There are many different variations in how we define the threshold level of illness when urgent intervention is required—the triggering or calling criteria [6]. The criteria are usually a combination of abnormal vital signs, such as respiratory and pulse rate, blood pressure, and oxygen saturation, combined with abnormal observations, such as airway obstruction, seizures, and sudden decrease in the level of consciousness. Many criteria also include 'worried' or 'concerned'. This empowers clinical staff to use their clinical judgement, as well as numbers. The rate of 'worried' calls is usually low

when the system is first introduced and then often becomes the single most common trigger as the system matures. This is as a result of nursing staff, gradually feeling empowered to exercise their clinical judgement, confident that they will not be derided for doing so.

The trigger sometimes involves a response when only one of the vital signs or observations fits the calling criteria [7]. Other triggers involve scores that elicit different levels of response, such as the modified early warning system (MEWS) [8]. Potential disadvantages of scoring systems are that they are complex, subject to error, overlook some life-threatening observations, and exclude clinicians from summoning help based on clinical judgement. There may be increasing interest in using RRS-type criteria to predict mortality and prognosis, as well as to investigate even earlier markers of serious illness, such as abnormal biochemistry and the patient's underlying condition. Predictive scores, such as APACHE and SAPS, measure risk and have much in common with calling criteria.

There is little agreement around the balance of sensitivity and specificity needed to identify serious illness without over-burdening the system. As yet, only systems based on single calling criteria have been subject to large patient-outcome studies. It may be that the details of the various triggering criteria are not as important as the effect of simply using a system to identify and respond to serious illness. This, in turn, changes the culture of an organization, increasing the awareness that there are at-risk patients in hospitals and that support to help manage those patients is always available. Supporting this is the observation that the acceptance of the system improves over time [9].

The response

As with calling criteria, there are many different ways to respond to at-risk patients. The overarching principle in determining the nature of the response personnel required is relatively straightforward. First, the type of patient and level of illness of those patients needs to be determined. From that information, the level of skills, knowledge, and experience necessary to match the needs of the patients can be determined [10]. For example, in the largest study on the levels of response, it was found that of the 2376 calls to patients responded to, only five did not require critical care interventions such as central line insertion, inotrope administration, airway control, and ventilation [11]. On the other hand, other hospitals will have a different population of patients with different needs. For example, the usual or admitting team could respond to lower levels of illness, with the back-up of appropriately trained staff, who would also respond to patients with more severe calling criteria [12]. There is no obvious reason why other clinicians, such as nurses, could not be trained to an appropriate level of skills and knowledge. There is also no reason why the usual team could not be trained in all aspects of advanced resuscitation, including critical care skills and knowledge. However, this would probably be extremely expensive and resource consuming. For example, the cost of training staff for relatively simple cardiopulmonary resuscitation intervention is estimated to cost over $600,000/survivor [13]. Another approach would be to organize widespread education to increase awareness of seriously-ill and at-risk patients, so that appropriate triggering occurs and then to respond with a small team of staff, appropriately trained in critical care skills, who operate 24 hours/day [12].

Implementation

Unlike a new drug or procedure, the challenges of implementing a new system are more complex, and require skills, and experience not necessarily familiar to physicians. Acute hospitals operate in professional and geographical silos which is the major reason why so many patients fall through the gaps between the silos, suffering potentially preventable deaths, and serious adverse events [1]. Rapid response systems are unique in being constructed around specific patient needs, and being organization wide, involving all physicians and nurses, as well as being supported by administrative and other hospital staff. There are five main elements necessary to effectively implement a RRS [12]. The calling criteria and the appropriate response have been discussed. However, for optimal implementation, the system also needs clinical and administrative leadership. Usually, several respected senior staff in the hospital are key to successful implementation. An education strategy is also needed. First, all staff in a hospital need to be aware that the system exists and urgent help can be summoned in an easily accessible way. Secondly, the response team needs to have the appropriate skills to manage any emergency. Thirdly, all direct patient care deliverers need to be able to recognize serious illness, and to initiate urgent management before the response team arrives.

Finally, the system needs to be monitored, and the outcome data made available in an easily understood and aggregated fashion to both those monitoring the hospital's performance, but also targeted to hospital departments, and key personnel [14].

One of the more important determinants of the effectiveness of the system's performance is the rate of calls/1000 hospital admissions. This is directly related to the reduction of deaths, and cardiac arrests [15]. Usually, when a system is first implemented, rates can be as low as 3 calls/1000 admissions. More mature and effective systems usually achieve rates of more than 40 calls/1000 admissions. Other outcome data include crude mortality and cardiac arrest rates [12]. A RRS is not aimed at resuscitating patients who are made do-not-attempt-resuscitation (DNAR). The more accurate indicator is probably unexpected deaths and cardiac arrests, i.e. those without an explicit DNAR order. A further refinement is to examine all unexpected deaths and cardiac arrest rates to determine if there were calling criteria in the 24 hours before the event that were not responded to, i.e. 'potentially preventable' [15]. Thus 'unexpected, potentially preventable' become powerful descriptors for monitoring patient safety in a hospital. Measuring and appropriately targeting outcome indicators ensures ownership for those responsible for operating the system, as well as giving information about trends for those monitoring the effectiveness of the system.

Rapid response systems and end-of-life care

An increasing problem in the practice of intensive care is inappropriate admission for end-of-life (EOL) care. There are many possible reasons for this, including the reluctance of doctors to discuss the issue and the increasing specialization of medicine resulting in incremental management. In the process, perhaps we are losing the ability to diagnose dying. Often that task is left to the intensivist in terms of making the decision that further escalation of treatment would be futile. As a result of the failure to diagnose dying, up to one-third of all RRS calls may involve making EOL decisions [16].

This can be frustrating, time-consuming, and resource intensive for intensive care staff. There are early initiatives to define dying and respond more appropriately in systems similar to a RRS, but designed around better EOL care.

Other implications of rapid response systems

Research around RRSs have highlighted major deficiencies in the care of the seriously ill, especially the recording and use of vital signs in general wards. They are often inaccurately and inconsistently measured, especially in the measurement of respiratory rate [17]. This represents a major weak point in any system designed to respond to serious illness. Even when vital signs and observations meet calling criteria, in up to half of all cases, nurses are reluctant to call the response team [18]. Patients in acute hospitals are increasingly older, with co-morbidities, and having more complex drugs and interventions that can result in serious complications. As such, the need for delivering critical care to patients in ICUs can be the same as for patients in general wards. The lack of agreed definitions for defining the need to be admitted to an ICU is blurred by factors such as the nature of the hospital population, the admission and discharge criteria for the ICU, and the number of beds in the ICU. A patient in a general ward in one hospital could easily be a patient in an ICU in another hospital. The level of illness and risk of mortality in patients responded to by a RRS is becoming similar to those in an ICU.

The effectiveness of rapid response systems

Proof that interventions designed to care for the seriously ill in hospitals, such as ICUs, and RRSs is equivocal. Before and after studies of RRSs have shown impressive improvements in serious adverse events [19].

One of the problems in attempting to demonstrate the effectiveness of RRSs and ICUs is that they both need committed staff to make them effective, and thus there would be a large and, indeed, welcome Hawthorne effect necessary in any research attempting to demonstrate effectiveness. The largest study of RRSs was inconclusive for some end-points [17], but did demonstrate a significant reduction in mortality rate in adult hospitals with a RRS [15]. Similarly, the largest meta-analysis on RRSs has demonstrated a one-third reduction of cardiac arrests and deaths in paediatric hospitals, and a one-third reduction of cardiac arrests in adult hospitals [20]. It is hard to imagine many other interventions that are used in the seriously ill that have had a similar impact on mortality and cardiac arrest rates.

References

1. Lundberg JS, Perl TM, Wiblin T, et al. (1998). Septic shock: an analysis of outcomes for patients with onset on hospital wards versus intensive care units. *Critical Care Medicine*, **26**, 1020–4.
2. Hillman KM, Bristow PJ, Chey T, et al. (2001). Antecedents to hospital deaths. *Internal Medicine Journal*, **31**(6), 343–8.
3. Schein RMH, Hazday N, Pena M, Ruben BH, and Sprung CL. (1990). Clinical antecedents to inhospital cardiopulmonary arrest. *Chest*, **98**, 1388–92.
4. Hillman KM, Bristow PJ, Chey T, et al. (2002). Duration of life-threatening antecedents prior to intensive care admission. *Intensive Care Medicine*, **28**, 1629–34.
5. McQuillan P, Pilkington S, Allan A, et al. (1998). Confidential inquiry into quality of care before admission to intensive care. *British Medical Journal*, **316**(7148), 1853–8.
6. DeVita MA, Smith GB, Adam SK, et al. (2010). Identifying the hospitalised patient in crisis—a consensus conference on the afferent limb of rapid response systems. *Resuscitation*, **81**, 375–82.
7. Bellomo R, Goldsmith D, Uchino S, et al. (2004). Prospective controlled trial of effect of medical emergency team on postoperative morbidity and mortality rates. *Critical Care Medicine*, **32**, 916–21.
8. Subbe CP, Kruger M, Rutherford P, and Gemmel L. (2001). Validation of a modified early warning score in medical admissions. *Quarterly Journal of Medicine*, **94**(10), 521–6.
9. Santamaria J, Tobin A, and Holmes J. (2010). Changing cardiac arrest and hospital mortality rates through a medical emergency team takes time and constant review. *Critical Care Medicine*, **38**(2), 445–50.
10. Hillman KM. (2012). Walk don't run. *Critical Care Medicine*, **40**(9), 2712–13.
11. Flabouris A, Chen J, Hillman K, et al. (2010). Triggers for emergency team activation: a multicentre assessment. *Journal of Critical Care*, **25**, 359.e1–7.
12. Clinical Excellence Commission (2007). *Between the Flags. Keeping patients safe*. A statewide initiative of the Clinical Excellence Commission. Sydney. Available at: http://www.cec.health.nsw.gov.au/programs/between-the-flags
13. Lee KH, Angus DC, and Abramson NS. (1996). Cardiopulmonary resuscitation: what cost to cheat death? *Critical Care Medicine*, **24**(12), 2046–52.
14. Hillman K, Alexandrou E, Flabouris M, et al. (2000). Clinical outcome indicators in acute hospital medicine. *Clinical Intensive Care*, **11**, 89–94.
15. Chen J, Bellomo R, Flabouris A, et al. (2009). The relationship between early emergency team calls and serious adverse events. *Critical Care Medicine*, **37**(1), 148–53.
16. Jones D, Bagshaw SM, Barrett J, , et al. (2012). The role of the medical emergency team in end-of-life care: a multicentre prospective observational study. *Critical Care Medicine*, **40**(1), 98–103.
17. Chen J, Hillman K, Bellomo R, et al. (2009). The impact of introducing medical emergency team system on the documentation of vital signs. *Resuscitation*, **80**, 35–43.
18. MERIT Study Investigators (2005). Introduction of the medical emergency team (MET) system: a cluster randomized controlled trial. *Lancet*, **365**, 2091–7.
19. Bellomo R, Goldsmith D, Uchino S, et al. (2003). A prospective before-and-after trial of a medical emergency team. *Medical Journal of Australia*, **179**(6), 283–9.
20. Chan PS, Jain R, Nallmothu K, Berg RA, and Sasson C. (2010). Rapid response teams. A systematic review and meta-analysis. *Archives of Internal Medicine*, **170**(1), 18–26.

CHAPTER 4

In-hospital transfer of the critically ill

Lorna Eyre and Simon Whiteley

Key points

- Critically-ill patients require in-hospital transfer for a variety of reasons.
- Transportation outside of the normal critical care environment can be associated with deterioration and adverse events.
- Wherever possible, patients should be resuscitated and stabilized before transportation.
- Portable monitoring and equipment should be used that are appropriate to the patient's condition.
- Patients should be accompanied by appropriately-trained staff who are able to respond to any changes in the patient's condition and/or critical incidents that may arise.

Introduction

The intensive care unit (ICU) provides a safe environment for the critically-ill patient where optimal standards of critical care can be delivered. However, patients typically develop critical illness outside the ICU, necessitating transport from their point of presentation to the ICU, while those in the ICU frequently need to be transferred out, in order to undergo diagnostic or therapeutic interventions.

The risks and hazards associated with such transfers are often underestimated. This may be because much of the published literature concentrates on inter-hospital transfer, where distance, transport-modality, logistics, and health care economics provide a focus for such attention. Numerically, however, far more in-hospital transfers occur [1]. While these are logistically simpler than inter-hospital transfers, there is evidence that they are associated with a high level of critical incidents, adverse events, and increased morbidity and mortality [2].

The UK Royal College of Anaesthetists National Audit Project 4, for example, reported three serious untoward events relating to airway complications during in-hospital transfer [3]. In another study of incidents occurring over a 6-year period during in-hospital transfer, serious adverse outcomes occurred in 31% of incidents reported, with 2% resulting in death [4]. Of the incidents recorded, 39% related to equipment problems, such as battery failure, while 61% related to poor staff communication, inadequate monitoring, and inadequate positioning of patients.

Many of the adverse cardiovascular and respiratory complications that arise can be related to movement of the non-optimized patient, dislocation of essential life sustaining devices (endotracheal tubes, venous access devices), and equipment failure [5]. One key issue in preventing critical incidents during in-hospital transfer is the training and competence of the accompanying staff. Critically-ill patients should be accompanied by personnel with the appropriate knowledge skills and experience to carry out the transfer safely and to deal with any complications or incidents that arise.

The in-hospital transport of critically-ill patients therefore, deserves the same focus as inter-hospital transfer.

Indications for in-hospital transfer

Indications for the in-hospital transfer of critically-ill patients are shown in Table 4.1.

The in-hospital transfer of the deteriorating patient requiring escalation to a higher level of care can be particularly challenging. Focus on pre-transfer resuscitation and stabilization prior to transfer is mandatory.

Transfer of a patient out of the ICU environment for diagnostic or therapeutic intervention can often be for prolonged periods and to discreet locations some distance away from the ICU. The decision to transfer should be based on the balance between probable benefit of the proposed intervention and potential risk. Observational studies do suggest, however, that the yield from diagnostic intervention in this group is high. Wadyhas et al. [5] noted angiography and abdominal computed tomography (CT) resulted in therapeutic consequences in more than 50% of patients. However, alternative strategies, including the use of bedside investigations such as ultrasound, should be considered.

There is evidence that discharge of patients from intensive care during the night shift hours is associated with increased morbidity and mortality [6,7]. Therefore, unplanned, out-of-hours transfers/discharges should be avoided wherever possible.

Accompanying personnel and training

Critically-ill patients should be accompanied by at least two appropriately trained attendants during transfer. Although not all transfers require a physician; responsible personnel must be able to respond to the individual needs of the patient.

While much of the published data relates to inter-hospital transfers, there is evidence that poor training and performance of staff contribute to the risk during transfer. Beckman et al. [4], for example, examined human factors contributing to critical incidents

Table 4.1 Indications for in-hospital transfer

Indication	Example
Escalation of care	E.g. from ward, operating room, emergency department, following development/recognition of critical illness or deterioration of the patient
Investigation	E.g. for CT or MRI or angiography
Therapeutic	E.g. for definitive surgery, interventional radiology, cardiac catheterization
Planned/emergency evacuation of ICU	E.g. planned transfer from unit to allow essential building/maintenance work or unplanned evacuation, for example, resulting from power failure or fire
De-escalation of care	E.g. step down from ICU (level 3) care to high dependency unit (HDU; level 2)

during transfer, and identified poor knowledge, errors of judgement, delay in problem recognition, failure to follow protocol, and inadequate preparation of equipment as significant factors. All staff involved in the transfer of critically-ill patients should therefore receive appropriate training, and be able to demonstrate the range of skills and competencies required that are appropriate to their role. Detailed competency frameworks have been published by national training organizations and specialist societies [8].

There is growing interest in the use of specialist teams to transfer critically-ill patients. One study has looked at in-hospital transfers and concluded that a specially trained nursing transport team had a reduced rate of complications [9].

Communication

A vital component of all transfers is clear and concise communication between the team responsible for transfer and personnel at the destination. The 'SBAR' (situation, background, assessment, recommendation) structured format for handover is a useful method of conveying relevant information [10]. This should include relevant medical history, indication or reason for transfer and requirements on arrival. The infection status of the patient (e.g. methicillin-resistant *Staphylococcus aureus* (MRSA) status, diarrhoea, etc.) should be provided to enable source isolation if necessary.

Preparation

Except in situations where the transfer is for immediate life-saving intervention (e.g. to the operating theatre or angiography suite to control bleeding), patients should be optimally resuscitated and stabilized prior to transfer. The key elements of this are included in Table 4.2.

Monitoring

The minimum standards of monitoring required during in-hospital transfer are the same as those required for inter-hospital transfer. These are:

- Electrocardiogram (ECG).
- Non-invasive blood pressure.

Table 4.2 Key elements of stabilization prior to transfer

System	Description
Airway	*Either* ◆ Patent and maintained. *or* ◆ Secured by endotracheal intubation. ◆ Indications for intubation include Glasgow Coma Scale. (GCS) <9, actual or impending airway compromise, and facilitation of positive pressure ventilation.
Breathing	*Either* ◆ Spontaneously breathing and maintaining adequate gas exchange, with or without supplemental oxygen, continuous positive airway pressure (CPAP) or bi-phasic positive pressure (BIPAP). *or* ◆ Intubated and ventilated. ◆ Some CPAP and BIPAP systems are portable and where appropriate patients can be transferred on these modalities. If this is not available or appropriate then intubation and positive pressure ventilation should be instituted. ◆ Patients should be stabilized on the transport ventilator prior to transfer and adequacy of gas exchange confirmed by arterial blood gas analysis. ◆ Continuous oxygen saturation and capnography ($ETCO_2$) monitoring is mandatory [3]. ◆ Sedation and paralysis may be required to ensure patient comfort and effective ventilation.
Circulation	◆ Haemodynamically stable. ◆ Hypovolaemia corrected and inotropes/vasopressors used, guided by appropriate haemodynamic monitoring, to optimize cardiac output/perfusion pressure. ◆ Secure venous access is mandatory. ◆ Continuous arterial pressure monitoring should be considered.
Disability	◆ The specific needs of individual patients should be addressed. ◆ For those patients that are not intubated and ventilated (GCS >9) this should include assessment of the individual patient's ability to tolerate the proposed transfer and/or planned procedure (e.g. can the patient lie flat/still for the required length of time).
Exposure	◆ Warm, appropriately wrapped. ◆ Exposure kept to a minimum. ◆ Consider active warming devices if necessary.

- Oxygen saturation.
- Capnography (end tidal CO_2 ($ETCO_2$)) in ventilated patients.
- Temperature.

Invasive blood pressure monitoring has advantages over non-invasive, since it is continuous, less subject to motion artefact, and is less of a drain on the battery life of the monitor. The need for any additional monitoring (e.g. central venous pressure, intracranial pressure, pulmonary artery pressure) will be guided by the patient's condition and ongoing therapy.

Equipment

Equipment required for in-hospital transfer can be divided into four categories. All equipment should meet the relevant national standards, and staff should be familiar with its function and operation.

Basic care

While inter-hospital transfers require the use of a specialized transfer trolley, in-hospital transfers can often be carried out utilizing the patient's own bed. The staff involved must therefore be familiar with the operation of the bed and particularly how to lay the patient flat in an emergency. It is common to place essential equipment on the bed (in proximity to the patient), but this creates a risk of injury to the patient and prevents unhindered access in an emergency. All essential equipment therefore should be carried on portable racking/shelves either attached to the end of the bed or mounted over the bed. A number of systems are commercially available. Some of these also provide housing for portable oxygen cylinders (see Figure 4.1).

Life support

Portable ventilators should be robust, battery powered, and economical with oxygen. As a minimum they require disconnection and high pressure alarms, the ability to supply positive end expiratory pressure (PEEP) variable inspiratory/expiratory (I/E) ratio, and variable inspired oxygen concentration (FIO_2). The provision of pressure controlled ventilation, pressure support, and continuous positive airway pressure (CPAP) is also desirable [7]. A self-inflating bag and mask with oxygen reservoir and tubing should be available in case of ventilator failure.

Sufficient oxygen supply must be available to complete the transfer. Requirements will depend on the patient's minute volume, fractional inspired oxygen and the additional volume required to drive the ventilator (see manufacturers' information sheets). In the UK, oxygen cylinders containing 680 L oxygen (British Oxygen Corporation, size E) are most commonly used and are adequate for most in-hospital transfers. Similar size cylinders are available elsewhere in Europe and North America, although exact size/content may vary with manufacturer. Portable oxygen supplies should be conserved when possible by transfer to a hospital (piped) supply when available.

Syringe drivers/infusion pumps are required to deliver drug and fluid infusions. The concentrations of drug infusions should be optimized to minimize the need to change syringes during transfer.

Monitoring

Portable monitoring equipment should be designed for the purpose with an illuminated screen, the ability to display the minimum monitoring requirements, together with two invasive pressures, and have both audible and visual alarms. Monitor battery failure was common in the Australian ICU Incident Monitoring Study [4] and occurred in 14% of 125 in-hospital patient transfers. Battery life should be conserved by connection to a mains power supply when available.

Dedicated monitoring systems are usually available in magnetic resonance imaging (MRI) suites. If not, staff must be aware of the limitations of standard monitoring systems.

Treatment

Equipment required to both deliver ongoing ICU management (e.g. additional syringe drivers/infusion pumps, underwater seal drains, etc.) and to respond to a potential emergency caused by physiological deterioration or equipment failure.

Where present, underwater seal drains add complexity to the transfer process due to the risk of dislodgment or compromise of drain integrity (e.g. allowing water/air to entrain back into the chest.) Drains should not, however, be clamped during the transfer process, due to the greater risk of re-accumulation of the collection (particularly tension pneumothorax). Drains should be kept below the level of the chest at all times. Disposable one-way 'flutter valves'

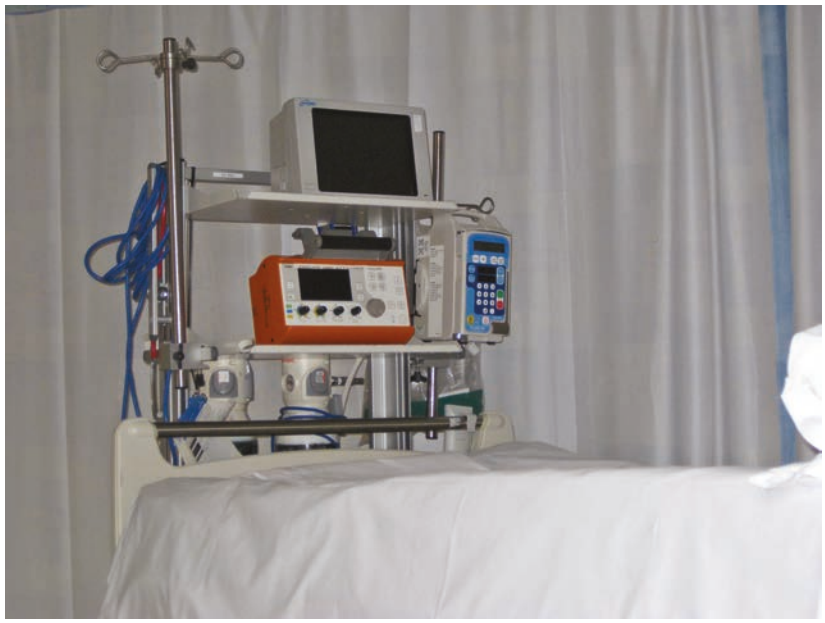


Fig. 4.1 Typical end of bed 'stack system' to facilitate the transport of equipment during in-hospital patient transfer, with mountings for portable ventilator, infusion pumps syringe drivers, and monitoring and secure housing for oxygen cylinders.

Table 4.3 Emergency equipment and drugs for use during in-hospital transfer

System	Items
Airway	Oral and nasopharyngeal airways
	Suction device, and suction catheters
	Laryngeal masks
	Endotracheal and tracheostomy tubes
	Laryngoscopes
	Endotracheal tube introducers (stylet and bougie)
	Magill's forceps
	Tape for securing tracheal tube
	Stethoscope
Ventilation	Fixed performance oxygen masks and tubing
	Self-inflating bag and mask with oxygen reservoir and tubing
	Airway filters/heat moisture exchange (HME) filters
	Nasogastric tubes (assorted sizes) and drainage bag
Circulation	Needles/syringes assorted sizes
	Alcohol and chlorhexidine skin preparation
	Intravenous/arterial/central venous catheters
	Aseptic line insertion packs (including gown and gloves)
	Suture/fixation devices and dressings
	Intravenous fluids and administration sets
	3-way taps/access devises

(e.g. Heimlich valves) may be used as an alternative, but are prone to blockage and malfunction.

A list of emergency equipment and drugs for use during in-hospital transfer is included in Tables 4.3 and 4.4. All equipment should be checked and tested prior to use.

Care, documentation, and audit

The standard of care during transfer should be the same as that delivered within the critical care environment, accepting that some treatment modalities may be suspended for the duration of the transfer (e.g. renal replacement therapy).

The indications for transfer, and communications with other health care professionals and/or family members should be documented. Physiological variables and changes in the patient's treatment or condition should be recorded. Any critical incidents should be reported via the standard local reporting mechanisms. In addition, there should be continuous prospective audit of in-hospital transfers to promote quality improvement, ensuring the highest possibly standards of care.

Common pitfalls

Studies of both in- and inter-hospital transfer consistently report critical incidents resulting from communication failures, poor knowledge and training of staff, (particularly in relation to familiarity with equipment), and equipment failure. Common pitfalls include:

- Dislodgement or obstruction of endotracheal tube.
- Accumulation of airway secretions.

Table 4.4 Drugs potentially required during in-hospital transfer

Type of drug	Drugs
Sedatives/analgesics	Midazolam
	Diazepam
	Propofol
	Thiopental
	Remifentanil
	Fentanyl
	Alfentanil
	Morphine
Neuromuscular blocking agents	Succinylcholine (suxamethonium)
	Rocuronium
	Atracurium
	Vecuronium
Cardiovascular	Dopamine
	Dobutamine
	Norepinephrine
	Epinephrine
	Amiodarone
	Labetalol
	Glyceryl trinitrate (GTN)
	Furosemide
Bronchodilators	Salbutamol
	Aminophylline

List provided is indicative of the range of drugs that may be required and is in addition to drugs required for emergency cardiopulmonary resuscitation. Choice of agent(s) will be dictated by clinical circumstances, and local policies and practice.

- Incorrect setting of ventilation parameters.
- Oxygen supply failure.
- Inadequate correction of hypovolaemia (prior to transfer).
- Kinking of infusion lines.
- Depletion of infusion drugs.
- Failure of syringe pumps.
- Failure of other portable equipment (e.g. monitors).
- Logistic issues, including beds not fitting into lifts or doorways, or being difficult to manoeuvre.

Planned and unplanned evacuation of ICU

The planned decant or evacuation of patients from ICU (e.g. to allow building works or maintenance) is not uncommon. Unplanned emergency evacuation (e.g. as a result of power failure or fire within the vicinity) is a much rarer event, but can occur. All intensive care units should therefore have planned emergency evacuation procedures in place. All staff should be aware of evacuation routes and decant areas. Depending on the circumstances, progressive horizontal transfer within the building may be required to reach a location capable of managing ICU patients. Portable oxygen supplies and basic life support equipment (e.g. self-inflating bag and mask) should be readily available at each bed space to facilitate emergency unplanned in-hospital transfer of this sort.

Conclusion

Safe and effective in-hospital transfer of critically-ill patients can be achieved by adequate staff training, and a systematic approach to the stabilization and transfer process.

References

1. Shirley P and Bion J. (2004). In-hospital transport of critically ill patients: minimising risk. *Intensive Care Medicine*, 30, 1508–10.
2. Warren J, Fromm RE, Orr RA, Rotello LC, and Horst MH. (2004). Guidelines for the inter- and inhospital transport of critically ill patients. *Critical Care Medicine*, 32, 256–62.
3. The Royal College of Anaesthetists (2011). Report and findings of the 4th national audit project of the royal college of anaesthetists. Available at: http://www.rcoa.ac.uk/nap4 (accessed 27 October 2015).
4. Beckmann U, Gillies DM, Berenholtz SM, Wu AW, and Pronovost P. (2004). Incidents relating to the inhospital transfer of critically ill patients. *Intensive Care Medicine*, 30, 1579–85.
5. Wadyhas C. (1999). Inhospital transport of critically ill patients. *Critical Care*, 3, R83–9.
6. Goldfred C and Rowan K. (2000). Consequences of discharges from intensive care at night. *Lancet*, 355, 1138–42.
7. Tobin AE and Santamria JD. (2006). After-hours discharges from intensive care are associated with increased mortality. *Medical Journal of Australia*, 184, 334–7.
8. Intensive Care Society (2011). Guidelines for the transport of the critically ill adult (3rd edn). Available at: http://www.ics.ac.uk/ics-homepage/guidelines-and-standards/ (as accessed 12th April 2015)
9. Stearley H. (1998). Patients' outcomes: inhospital transportation and monitoring of critically ill patients by a specially trained ICU nursing staff. *American Journal of Critical Care*, 7, 282–7.
10. NHS Institute for Innovation and Improvement. http://www.institute.nhs.uk/safer_care/safer_care/situation_background_assessment_recommendation.html (accessed 26 June 2012).

CHAPTER 5

Pre- and inter-hospital transport of the critically ill and injured

Kelly R. Klein and Paul E. Pepe

Key points

- Critical care delivered in the out-of-hospital setting is an integral part of modern health care that can be life-saving when used appropriately.
- Critical care transport systems have special challenges, including logistics, weather conditions, traffic, geography, and strict governmental regulations.
- Many professional societies and governments have developed specific guidelines and regulations regarding critical care transport, with which all personnel involved with transport must be familiar.
- Protocols and policies need to be in place to ensure optimal care and safety for both patients and transport crews with contingencies for weather and altitude challenges.
- Protocols and policies should address issues such as when transport is not safe or not indicated, as well as appropriate crew configurations, specific training, competencies, and equipment.

Introduction

Many elements of intensive care medicine have been brought to the out-of-hospital setting, utilizing specialized pre-hospital care providers (physicians, nurses, paramedics) who can deliver intensive care at the scene, as well as during transport [1–3]. Over the years, facilities were also designated as appropriate transportation destinations for certain critical emergencies, particularly patients with severe injuries, acute coronary syndromes, and stroke [4,5]. Furthermore, to bring such patients to specialized facilities such as trauma centres, cardiac catheterization centres, or other types of tertiary care institutions, both air and ground services have been developed for inter-facility transfer, as well as direct transport from emergency scenes [6–8].

Most emergency medical services (EMS) public safety ambulance responses, including those to motor vehicle crashes and acute illness, do not require critical care. Many of those prehospital care providers are not skilled enough to provide complex critical care support [3,9,10]. On the other hand, specialized critical care transportation vehicles (air and ground) and specialized advanced life support teams still frequently provide critical care transport in the out-of-hospital setting, particularly in terms of inter-facility transfers and specialized support for on-scene providers in distant venues [4,6–8,10–12].

Methods for transporting the critically ill and injured have evolved from the horse-drawn carts and hot air balloons in the 17th and 18th century to station wagon ambulances, fixed wing planes and helicopters in the 20th century [6]. Staffing has shifted from surgeons with amputation saws and hearse drivers with stretchers to cardiologists with portable defibrillators and, eventually, to paramedics, nurses, and accident and emergency physicians with specialized training in out-of-hospital critical care for the very sick and injured [13,14].

Today, critical care transport is considered a necessity in the world of modern health care and has evolved from the original 'scoop and run' mentality to mobile intensive care units capable of supporting care for the most fragile neonate receiving mechanical ventilation, multiple intravenous medications, and intensive monitoring devices [6,7,10, 13,14].

Depending on the distance travelled, weather, geography, environmental challenges, and patient considerations, there are multiple methods of patient transport (Table 5.1), each with relative advantages and disadvantages. Transportation medicine involves the specialized logistics of the mode of travel, and the training and provision of the appropriate health care provider to deliver the high level of care outside of the hospital setting over a period of hours and, in some circumstances, days [7,10,11,13,14].

Patient transfer issues

In many nations, patient transport, particularly those involving inter-facility transfer, are highly regulated. For example, in the United States (USA), the Emergency Medical Treatment and Labor Act (EMTALA) guides such practices [15]. To be compliant with these regulations, the sending (transferring) physician is responsible for the patient's well-being until the patient arrives at the receiving hospital. In terms of determining the mode of transportation, the sending health care provider must take into consideration risks to the patient and crew (Table 5.1).

Independent of the physician, the choice of air medical transport may be excluded for safety reasons by the aircraft pilot who makes the final determination if the flight is safe to take.

Air medical transportation can also involve physiological considerations due to change in altitude. For the most part, the effects of altitude are minimal, particularly for fixed-wing transport with highly-pressurized cabins and helicopter transport involving

Table 5.1 Advantages and disadvantages of various transportation modes

Mode	Advantage	Disadvantage	Range in miles*
Ground	◆ Large interior ◆ Quieter than an aircraft ◆ Can carry larger patients ◆ Can carry more equipment	◆ Limited travel distance ◆ Slower	200–250
Rotor (helicopter)	◆ Speed ◆ Navigates remote terrain	◆ Limited by weather conditions ◆ Expensive ◆ Weight limitations ◆ Close government scrutiny† ◆ Work hour restrictions such as ◆ FAR part 91 and 135‡	150–450
Fixed wing	◆ Speed ◆ Capable of travelling great distances ◆ No weight limitation ◆ Less restricted by weather	◆ Special landing requirements ◆ Expensive ◆ Close government scrutiny and oversight† ◆ Work hours and safety restrictions, such as FAR parts 91 and 135‡	1000–2500

*Depends on the type of vehicle and weather conditions.

†Such as the Federal Aviation Administration (FAA) in the United States.

‡FAR = Federal Aviation Regulations from the United States FAA.

altitudes less than 3000 feet (1000 m) above sea level. Nevertheless, crews should be aware of the potential for certain physiological changes in case cabin pressure is lost or compromised, or altitudes become significantly high due the location of the mission. Some considerations in such circumstances would concern certain patients such as those with:

- A potential or known pneumothorax without a decompression device in place.
- A clamped ventriculostomy tube.
- An endotracheal tube in place and the need to adjust the balloon cuff volume.
- Adjustments in supplemental oxygen in patients with respiratory compromise without closed respiratory support [14].

With proper training and anticipation of these issues with proper monitoring and procedure, these concerns should be minimized.

Staffing considerations for critical care transport

Studies have shown that transport by a specialist retrieval team compared with standard ground ambulance teams resulted a reduction in patient mortality during the first 12 hours of arrival at the receiving hospital (11,12,16). In 1993, the North American-based Society of Critical Care Medicine (SCCM), the American College of Critical Care Medicine (ACCM) and the American Association of Critical Care Nurses (AACN) developed guidelines for the transport of critical patients and recommended that all critical care transport should be performed by a dedicated, specially-trained transport team [17]. Similar guidelines have been promulgated on other continents and are consistent in terms of recommendations (13,18).

Based upon the recommendations, the general consensus is that there should be at least two personnel with critical care training attending the patient at all times during the transfer, regardless of the mode of transportation. Although a three-member team configuration may be used, it is often not necessary and may even be detrimental if space is very limited. The team composition should include a critical care nurse with multiple years of critical care experience, and either a paramedic or respiratory therapist with advanced life support training and experience [6,13,14,16,17,19]. Occasionally, a physician (fully-qualified or in-training) may be used as part of the transport team.

Tables 5.2 and 5.3 annotate crew composition and critical care training requirements for air medical transport adapted from various sources, including the AACN, American Academy of Orthopedic Surgeons (AAOS), Intensive Care Society, National Association of EMS Physicians and SCCM [6,13,14,16,17].

Table 5.2 Crew composition*

Crew	Advantage	Disadvantage
Paramedic	On-scene emergency experience	Limited ICU† experience
Nurse	ICU†/critical care experience	Limited on-scene experience
Respiratory Therapist	◆ Ventilator equipment expert ◆ Airway expertise	◆ Limited on-scene experience ◆ Not able to secure intravenous access or give medications
Physician	Critical care/emergency medicine experience and diagnostic skills	◆ Limited on-scene experience ◆ Expensive

*Or equivalency depending on country, regulatory issues, and national standard of care.

†ICU, intensive care unit.

Table 5.3 Recommended training requirements for the critical care team*

Crew	Required minimums	Additional certifications (recommended)
Paramedic	◆ Over 5 years critical care experience ◆ Advanced cardiac life support (ACLS) ◆ Paediatric advanced life support (PALS) ◆ Neonatal advanced life support (NALS) ◆ Prehospital trauma life support (PHTS) *or* ◆ International trauma life support (ITLS)	◆ Advanced trauma life support (ATLS) (audit) ◆ CCEMT-P certification† ◆ Certified flight paramedic ◆ (PF-C) ◆ Incident command ◆ Disaster life support ◆ Decontamination ◆ Life support
Nurse	◆ Over 5 years critical care experience ◆ Critical care registered nurse (CCRN) ◆ ACLS ◆ PALS ◆ NALS	◆ ATLS (audit) ◆ Paramedic certification ◆ Certified flight registered nurse (CFRN) ◆ Incident command system (ICS) training ◆ Disaster life support ◆ Decontamination ◆ Life support
Respiratory therapist	◆ Over 3 years critical care experience ◆ Critical care respiratory therapist (CCRT) ◆ ACLS ◆ PALS ◆ NALS	Emergency medical technician (EMT)
Physician	◆ Over 1 year post-medical school training ◆ ACLS ◆ PALS ◆ NALS	◆ EMT ◆ Incident command ◆ Disaster life support ◆ Decontamination ◆ Life support

*Or equivalency depending on country, regulatory issues, and national standard of care.

†Critical care emergency medical technician—paramedic certification.

Equipment considerations

Equipment and medication inventories may vary depending on the type of transport vehicle and patient condition (e.g. neonatal versus adult cardiac problem). However, at a minimum, the transport team should have the relevant competencies, appropriate monitoring devices, and capabilities in terms of administering and providing numerous interventions, including the spectrum of advanced cardiac life support medications, vasoactive medication infusions, narcotics, paralytic medications, anti-emetics, and blood products. In addition to ventilators and intravenous pumps for medication drips, the use of point-of-care (POC) testing has proved to be of great assistance for transportation crews. At a minimum, it is generally recommended that POC testing should be available for basic electrolytes, blood gas analysis, complete blood count, lactate, and glucose [20].

Procedural competencies

Recommendations for transportation teams also emphasize that the crews be cross-trained in on-scene/EMS competencies, intensive care unit procedures, advanced trauma care, and a myriad of paediatric/neonatal interventions/monitoring including, but limited to, all applicable levels of:

- Tracheal intubation.
- Surgical airway establishment.
- Needle/pigtail decompression.
- Intracranial pressure (ICP) monitoring.
- Left ventricular assist device (LVAD) monitoring.
- Intra-osseous access.
- Central venous access placement and care.
- Suturing.
- Chest tube placement and care.
- Arterial catheter placement and monitoring.
- Post-mortem caesarean section for trauma patients.
- Escharotomy for severe burns patients.
- Decontamination of contaminated patients.
- Balloon pump operations.

- Isolette operation.
- Splinting and spinal immobilization.
- Transport ventilator operation.
- The ability to appropriately use and analyse an array of monitoring devices ranging from pulse oximetry, end-tidal carbon dioxide and blood gas devices to POC testing tools.
- Experience in landing zone procedures.

Appropriate candidates for transport by critical care teams

Critical care transport teams must be configured in a manner that reliably provides the expertise necessary for the stabilization and care of critically-ill paediatric and adult patients in extraordinary environments and circumstances. It is also important that the referral hospital and the transport service have established a set of guidelines that can help the referring providers make appropriate transfer decisions. These guidelines can best facilitate the transfer, help to save invaluable time, and ensure that the mode of transportation is the appropriate one. Box 5.1 provides an annotated example of guidelines regarding certain non-trauma patients for whom critical care transport is not generally indicated, particularly by air.

Special considerations for protecting the transport team

Guidelines should also be in place for the protection of the transport team as well. Table 5.4 annotates some of these considerations and the handling of special populations for transport.

Conclusion

In summary, numerous guidelines have been established for critical care transport and these include issues such as patient transfer regulatory requirements, staffing competencies, equipment restraints, procedural skills, medical guidelines for non-transport decisions and guidelines for the safety for the crew. Air medical transport also has special considerations in terms of the physiology of altitude and limitations in space and landing zone safety conditions [14]. In all circumstances, appropriate training, guidelines, procedures, and equipment should also be balanced by appropriate continuous quality improvement and expert medical oversight to ensure optimal safety, patient care, and fiscal responsibility [1,10,16,18].

Box 5.1 Sample guidelines regarding non-trauma patients for whom critical care transport generally would not be indicated

- Terminally-ill patients without acute correctable medical problems.
- Patients with do not attempt resuscitation (DNAR) status.
- Patients in a state of cardiopulmonary arrest at the referring institution who cannot be stabilized with restored circulation prior to transport.
- Patients with mental competency not wishing transfer.
- Patients with communicable diseases without necessary precautions established.
- Patient would be transferred to a facility that offers no medical care advantage over the referring institution.

Table 5.4 Safety policies for transport

Type of issues	Things to think about
Agitated patients	Rapid sequence induction and intubation prior to flight with continued sedation as required (if safe for the patient's condition)
Family members	Depending on mode of transport, limit accompanying family members to one or two, and only if there is room, and they are judged to be capable of following safety directions
Hazardous materials incidents with affected patients	Decontamination of the patient so as not as to be a danger for the transport team, particularly considering the necessity to be in an enclosed space during a lengthy transport
Search and rescue missions	Flight operations must make a decision whether or not this will be part of the overall mission statement, and safety considerations for the crew in the environment involved
Transport of patient involving a law enforcement officer with weapons	Having firearms in a pressurized cabin is very dangerous and this consideration must be appraised

References

1. Domeier RM, Hill JD, and Simpson RD. (1996). The development and evaluation of a paramedic-staffed mobile intensive care unit for inter-facility patient transport. *Prehospital and Disaster Medicine*, **11**, 37–43.
2. Pepe PE and Almaguer DA. (1990). Emergency medical services personnel and ground transport vehicles. In: Fromm RE (ed.), *Problems in Critical Care*, pp. 470–6. Philadelphia, PA: J.B. Lippincott.
3. Pepe PE, Roppolo LP, and Cobb LA. (2004). Successful systems for out-of-hospital resuscitation. In: Ornato JP and Peberdy MA (eds), *Cardiopulmonary Arrest*, pp. 649–81. Totowa, NJ: Humana Press.
4. Mechem CC, Goodloe JM, Richmond NJ, Kaufman BJ, Pepe PE, and Writing Group for the US Metropolitan Municipalities EMS Medical Directors Consortium (2010). Resuscitation center designation: recommendations for emergency medical services practices. *Prehospital and Disaster Medicine*,**14**, 51–61.
5. Myers JB, Slovis CM, Eckstein M, et al. (2008) Evidence-based performance measures for emergency medical service systems: a model for EMS benchmarking. A consensus document from the US Metropolitan Municipalities EMS Medical Directors Consortium. *Prehospital and Disaster Medicine*, **12**, 141–51.
6. Judge T, Thomas SH, and Hankins DG. (2009). Air medical services. In: Cone DC, O'Connor RE, and Fowler RL (eds), *Medical Oversight of EMS*, pp. 253–70. Dubuque IA: Kendal Hunt Publishers.
7. Leicht MJ and Kupas DF. (2009). Interfacility transport. In: Cone DC, O'Connor RE, and Fowler RL. (eds), *Medical Oversight of EMS*, pp. 271–80. Dubuque, IA: Kendal Hunt Publishers.
8. Uusaro A, Parviainen I, Takala J, and Ruokonen E. (2002). Safe long distance interhospital ground transfer of critically ill patients with acute severe unstable respiratory and circulatory failure. *Intensive Care Medicine*, **28**, 1122–5.
9. Lippmann MJ, Salazar GA, and Pepe PE. (2012). Prehospital resuscitative interventions: elemental or detrimental? In: Vincent JL. (ed.)

2012 Yearbook of Intensive Care and Emergency Medicine, pp. 483–92. Berlin-Heidelberg: Springer-Verlag.
10. Lehmann R, Oh J, Killius S, Cornell M, Furay E, and Martin M (2009). Interhospital patient transport by rotary wing aircraft in a combat environment: risks, adverse events, and process improvement. *Journal of Trauma*, **66**(Suppl. 4), S31–6.
11. Bellingan G, Olivier T, Batson S, and Webb A. (2000). Comparison of a specialist retrieval team with current United Kingdom practice for the transport of critically ill patients. *Intensive Care Medicine*, **26**,740–4.
12. Ehrenwerth J, Sorbo S, and Hackel A. (1986). Transport of critically ill adults. *Critical Care Medicine*, **14**,543–7.
13. Intensive Care Society (2011). *Guidelines for the transport of the critically ill adult, Standards and Guidelines*, 3rd edn. London: Intensive Care Society. Available at: http://www.ics.ac.uk/EasysiteWeb/getresource.axd?AssetID=482&type=full&servicetype=Attachment (accessed 27 October 2015).
14. American Academy of Orthopedic Surgeons (2011). *Aircraft fundamentals. Critical Care Transport*. Burlington, MA: Jones and Bartlett Publishers.
15. US Department of Health & Human Services (2010). *Emergency Medical Treatment and Labor Act State Operations Manual Appendix V—Interpretive Guidelines—Responsibilities of Participating Hospitals in Emergency Cases* (Revision 60, 07-16-10) §489.24. Washington, DC: US Department of Health & Human Services Centers for Medicare and Medicaid Services. Available at: http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/som107ap_v_emerg.pdf (accessed 14 August 2012).
16. Martins SB and Shojania KG. (2002). *Safety during transport of critically ill patients*. US Department of Health & Human Services, Agency for Healthcare Research and Quality. Available at: http://www.ahrq.gov/clinic/ptsafety/chap47.htm (accessed 12 August 2012).
17. American Association of Critical Care Nurses (AACN) Writing Group (1993). *Transfer Guidelines Task Force. Guidelines for the Transfer of Critically Ill Patients*. Aliso Viejo, CA: American Association of Critical Care Nurses.
18. Duke G and Green J. (2001). Outcome of critically ill patients undergoing interhospital transfer. *Medical Journal of Australia*, **174**, 122–5.
19. Dunn MJG, Gwinnutt CL, and Gray AJ. (2007). Critical care in the emergency department: patient transfer. *Emergency Medicine Journal*, **24**(1), 40–4.
20. Gruszecki AC, Hortin G, Lam J, et al. (2003). Utilization, reliability, and clinical impact of point-of care testing during critical care transport: six years of experience. *Clinical Chemistry*, **49**, 1017–19.

CHAPTER 6

Regional critical care delivery systems

Theodore J. Iwashyna and Colin R. Cooke

Key points

- Scarce resources result in uneven availability of care resources. Regionalization is an effort to manage that scarcity so as to ensure good patient outcomes.
- Regionalized systems concentrate patients in centres of excellence. This can be done using formal (including legal) mechanisms or informal referral patterns.
- Existing models of regionalization often lack effective incentives for moving patients and so often fail to reach many patients who might benefit.
- There is no 'right' number of intensive care unit (ICU) beds; rather bed construction compliments optimized throughput and limiting ICU admission to patients who will benefit most.
- Improving the focus on patient outcomes of regional systems requires hard trade-offs, but there is relevant evidence that should be considered.

Introduction: designing regional systems of care

There is no single 'best' way to design a regional system of care. Any design will require ongoing optimization to local need, and evolving medical technology and practice. Nonetheless, there are both more and less effective ways to reach a given set of systemic goals. This chapter seeks to layout key design decisions in regional systems of care. It focuses on evolving better systems, rather than *de novo* creation in the hope that explicit discussion of decision-makers' key challenges may give rise to more effective patient care.

Problems that require regional thinking

Regional systems of care are a response to fundamental challenges of scarce resources. If there were no scarcity, there would be no need for regionalization; one would simply provide everything everywhere [1]. Instead, even in the USA, there is substantial scarcity of operational finances, capital for big-ticket technology, or perhaps most difficult, of provider labour and expertise. Given such scarcity, hospitals become differentiated, developing different levels of competence to deal with problems.

Differentiation is common. Most prominently, many critical illnesses in the USA exhibit the so-called volume/outcomes relationship [2]. When such a relationship is present, hospitals that see more patients have better clinical outcomes. This is believed to result from learning-by-doing, usually at the systems, rather than practitioner level. High volume systems may respond by hiring dedicated faculty, developing effective protocols, adopting innovations more rapidly, or otherwise investing in human and physical capital. Such a relationship can only persist if there is some reason that new developments do not diffuse to smaller hospitals and are taken up by them. Volume/outcomes relationships have been prominently noted for mechanical ventilation and other high-acuity critical care procedures.

Interestingly, the volume/outcome relationship is not ubiquitous. It has been argued that, as procedures become routine (e.g. percutaneous coronary interventions), the volume/outcomes relationship may become less prominent. While the relationship is quite clear in the US private sector, for patients with non-post-operative mechanical ventilation [3], there is evidence against such a relationship in the integrated health system of the US Department of Veterans Affairs [4]. Similarly, there was little evidence of volume/outcomes relationships in Australia and New Zealand for mechanical ventilation or in the United Kingdom for severe sepsis [5,6]. The absence of such a relationship may be a sign that these integrated systems effectively diffuse new techniques of care throughout their systems.

The volume/outcomes relationship is merely one aspect of the general problem of variability in critical care outcomes. There is wide variation in which patients are admitted into intensive care units (ICUs), the processes of care used once they are there, and the risk-adjusted outcomes obtained. Sometimes that variation is partially explained by a volume/outcomes relationship. However, even when the volume/outcomes relationship is present, it sometimes does little to explain the variability [7].

Nguyen and colleagues have proposed three general approaches to fixing differentiation-induced variability—tiered regionalization, telemedicine, and community outreach [8]. Framed another way, one can move patients to the expertise (interhospital transfer to specialized centres), move the specific clinical expertise to the patients (telemedicine), or build the expertise and systems everywhere (quality improvement). These approaches are not mutually exclusive [1]. This chapter focuses on moving patients to the expertise.

Box 6.1 Key design decisions for regional systems of care

- What criteria are used to designate regional centres?
- Are 'Regional Centre' designations formal or informal, and static or dynamic?
- Can regional centres sustain their performance under increased load?
- What incentives are there to move patients?
- Can the system safely accomplish the physical transport needed?
- What are the consequences for patients at other hospitals?
- How many beds are needed?

Design decisions

We define a regional system of critical care as one in which it is acknowledged that hospitals vary in their care of critically-ill patients, and procedures exist to systematically refer patients to a subset of those hospitals. At least seven challenges shape the design decisions, and these challenges are summarized in Box 6.1.

What criteria are used to designate regional centres?

There are numerous patient-centred options:

- US trauma centres are largely self-designated on the basis of generalized guidelines, which describe the capacity to provide a given level of care defined in terms of key staffing and technologies. Such a system has the virtues of transparency and openness, but may lead to quite uneven availability [9].
- The volume/outcomes literature fostered the hope that volume might serve as a good indicator of high-quality care. Regional centres would then be the highest volume centres.
- One might designate as regional centres those hospitals that actually obtained the best risk-adjusted outcomes [10].
- A planner might choose to define regional centres based not on current performance or population need, but on the anticipated needs some time in the future.

Even in some unplanned systems, patients are systematically (albeit incompletely) referred to centres that provide higher quality of care [11]. Our recommendation is that patients be referred to hospitals that have recently provided the highest quality risk-adjusted outcomes for similar patients. This guided referral system should provide significant disease-specific details on outcomes to guide patient transfers. However, implementing a high-quality profiling system requires substantial investments in a modern information and statistical infrastructure to monitor and publish risk-adjusted outcome. Defraying those costs, such an infrastructure may facilitate ongoing quality-improvement efforts and real-time decision support [12].

Are 'regional centre' designations formal or informal, and static or dynamic?

Most discussions of regionalization focus on formal regionalization—a process by which regional centres are officially designated and patients are directed towards them. In the USA, trauma, comprehensive cancer, and stroke centres operate in this way. However, the absence of a formal system of regionalization does not mean that no regionalization occurs. Informal regionalization has been defined as 'the concentration of select patient populations at specific local centres as a result of selective, historic, or *de facto* referral patterns to those centres by providers and emergency medical services (EMS) systems. Such regionalization is informal primarily because selective referral is based on decentralized decisions by individual providers, and is not mandated by law or other formal administrative organizations [13].

Formal regionalization offers the advantages of transparency. On the other hand, formally regionalized systems may have a tendency towards stasis, ossifying referral patterns based on the criteria of past decades, rather than on current performance. Informal regionalization can incorporate the diverse data sources available to practitioners, and offers the possibility of dynamic reorganization in response to personnel or organizational changes. However, informal regionalization is only likely to succeed in improving care if providers have good information on hospital quality, and are both motivated and able to use it to drive decisions.

Can regional centres sustain their performance under increased load?

Many emergency departments (EDs) show worse patient outcomes when the ED is operating under the stress of acutely high patient occupancy—high volume measured by the hour or day, rather than over years [14]. Existing ED infrastructure appears unable to maintain consistent operations across the range of variability in patient load routinely experienced. In contrast, some, not all, multicentre studies in the USA of ICUs found robust performance across a wide-range of occupancies [15,16].

Thus, an important question is whether the putative regional centres will be able to maintain their excellence under any proposed system of regionalization. This assuredly varies from locale to locale. Kahn and colleagues simulated the regionalization of all patients with non-post-operative mechanical ventilation to high-volume centres. They reported that this would require only a 5.0% (interquartile range 0.9%, 12.7%) increase in total ICU census at the regional centres, suggesting feasibility for many ICUs [17].

Quantitative analysis of the past performance of individual hospitals during periods of acute stress might offer guidance about whether proposed centres could tolerate the stress of a specific regionalization plan. It is worth noting that the US study that found robust patient outcomes across periods of stress examined only ICUs that had invested in the information infrastructure of the APACHE data systems. It has been hypothesized that such data systems support high reliability organization of ICU systems.

What incentives are there to move patients?

The evaluation of a mature trauma system in California demonstrated substantial rates of under-triage, i.e. patients with high Injury Severity Scores who should have been directly transported to trauma centres were instead receiving their care at less capable hospitals. Analyses of USA acute myocardial infarction patients admitted to non-revascularization hospitals showed perverse patterns among non-emergent transports. For example, 27.2% of transferred patients went to a revascularization hospital that was

both further away and had a mortality rate more than 1 percentage point worse than a nearby alternative [11].

Both Italian and USA data suggest that current transfer destinations are selected as a result of organizational priorities and routines other than patient outcomes. This argues that regionalization plans must provide incentives (not necessarily financial) to ensure actual implementation.

Can the system safely accomplish the needed physical transports?

There is embarrassingly little information about the crucial infrastructure of the emergency transport of patients between hospitals necessary for effective regionalization. This leads to wide variation, where some systems have a physician accompany many or most transports, while other systems have only paramedics available to staff any transport. In some well-integrated systems that self-selected to publish their own data, interhospital transfer is remarkably safe [18]. However, the generalizability of such data is unclear. Interviews in community hospitals revealed widespread complaints about the availability and competence of transport, and the ways such problems prevented needed interhospital transfers [20].

The realizable benefits of regionalization depend critically on the balance between the mortality benefit of additional transport to a better facility and the mortality risk of that transportation. In economic terms, transport risk is a 'transaction cost' that prevents patients from being moved fluidly to the places they might best be served. The availability of interhospital transport needs to be examined in each locality. A regionalization plan should evaluate the transport infrastructure's adequacy, and what steps can be taken to insure uniform availability. Rigorous generalizable evidence on what constitutes a cost-effective level of training, staffing, and equipment for safe transport is, as of writing, unavailable, but urgently needed.

What are the consequences for patients at other hospitals?

Regionalization of patients may have external consequences that influence the remaining patients at the hospital from which they are transferred. Interviews with community hospitals suggest that the transfer of high acuity patients is appreciated, as it frees staff resources to focus on their more typical patients [19]. In this sense, regionalization may limit the distraction and overload effects, such as have been noted when trauma patients arrive at EDs [14]. On the other hand, regionalization should lead to reduced volumes of high acuity cases at the community hospitals. This could lead to de-skilling and loss of institutional infrastructure, resulting in significantly worse care for patients who are inadvertently not transferred to the regional centre. There are very little data by which to evaluate the magnitude of these possible effects and so system-specific implementations of regionalization need to evaluate them on an ongoing basis.

How many beds are needed?

The optimal number of beds needed to meet the changing demand for critical care services is a matter of considerable debate. One might naively multiply the number of ICU beds at a referral centre by the expected percentage increase in referred patients. Such a calculation falsely assumes that existing ICU beds cannot be used more efficiently. Optimizing efficiency in use of existing ICU beds requires facilitating the discharge of patients currently in the ICU, improving throughput to relieve 'intensive care unit outflow obstruction'.

Further optimizing ICU use will reserve admission to the ICU for individuals who will benefit most. Such patients are those with **both** an appreciable risk of death or major morbidity **and** an available effective therapy. Perhaps more than one-third of all US ICU patients do not meet these criteria [20]. The beds made available by foregoing admission to the ICU for these low-benefit patients may adequately meet the increased demand at a regional centre. Realizing such efficiency gains in practice may be challenging, given the difficulties of early identification and the potentially disruptive impact of high acuity, but low ICU-benefit patients on non-ICU ward functioning.

Most importantly, we do not yet understand the impact of withholding ICU services for low-benefit patients. In the UK it appears that there is a significant lack of ICU beds. Elsewhere, the optimal bed number seems too contingent on other aspects of the system for a clear recommendation, but it should not be simply assumed that more beds are essential for effective regionalization. Rational bed planning must happen in the context of throughput optimization and frank discussion of what an ICU is to be used for.

Conclusion

Regionalized systems of care are an inevitable result of scarce health care resources. Such systems vary widely in the extent to which this regionalization is formalized, intentionally designed, or focused on patient outcomes. Incremental changes to most systems may significantly improve patient outcomes. For example, transferring non-emergent acute myocardial infarction patients to revascularization hospitals suggested that improved regionalization might reduce 30-day mortality by an absolute 2.7 percentage points, or a 16.5% relative reduction in the USA [11]. While such efforts will not be easy, they offer the hope of dramatic improvements for patients by more effectively using the resources already in place.

Acknowledgements

The opinions presented here are the authors' own and do not necessarily represent the view of the US Government or the Department of Veterans Affairs.

References

1. Iwashyna TJ. (2012). The incomplete infrastructure for interhospital patient transfer. *Critical Care Medicine*, **40**(8), 2470–8.
2. Shahian DM and Normand SL. (2003). The volume–outcome relationship: from Luft to Leapfrog. *Annals of Thoracic Surgery*, **75**(3), 1048–58.
3. Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, and Rubenfeld GD. (2006). Hospital volume and the outcomes of mechanical ventilation. *New England Journal of Medicine*, **355**, 41–50.
4. Cooke CR, Kennedy EH, Wiitala WL, Almenoff PL, Sales AE, and Iwashyna TJ. (2012). Despite variation in volume, Veterans Affairs hospitals show consistent outcomes among patients with non-postoperative mechanical ventilation. *Critical Care Medicine*, **40**(9), 2569–75.
5. Moran JL and Solomon PJ. (2012). Mortality and intensive care volume in ventilated patients from 1995 to 2009 in the Australian and New

Zealand binational adult patient intensive care database. *Critical Care Medicine*, **40**(3), 800–12.
6. Shahin J, Harrison DA, and Rowan KM. (2012). Relation between volume and outcome for patients with severe sepsis in United Kingdom: retrospective cohort study. *British Medical Journal*, 344, e3394.
7. Thabut G, Christie JD, Kremers WK, Fournier M, and Halpern SD. (2010). Survival differences following lung transplantation among US transplant centers. *Journal of the American Medical Association*, **304**(1), 53–60.
8. Nguyen YL, Kahn JM, and Angus DC. (2010). Reorganizing adult critical care delivery: the role of regionalization, telemedicine, and community outreach. *American Journal of Respiratory Critical Care Medicine*, **181**(11), 1164–9.
9. Branas CC, MacKenzie EJ, and ReVelle CS. (2000). A Trauma Resource Allocation Model for ambulance and hospitals. *Health Services Research*, **35**(2), 489–507.
10. Iwashyna TJ and Courey AJ. (2011). Guided transfer of critically ill patients: where patients are transferred can be an informed choice. *Current Opinion in Critical Care*, **17**, 641–7.
11. Iwashyna TJ, Kahn JM, Hayward RA, and Nallamothu BK. (2010). Interhospital transfers among Medicare beneficiaries admitted for acute myocardial infarction at non-revascularization hospitals. *Circulation: Cardiovascular Quality & Outcomes*, **3**, 468–75.
12. Escobar GJ, LaGuardia JC, Turk BJ, Ragins A, Kipnis P, and Draper D. (2012). Early detection of impending physiologic deterioration among patients who are not in intensive care: development of predictive models using data from an automated electronic medical record. *Journal of Hospital Medicine*, **7**(5), 388–95.
13. Glickman SW, Kit Delgado M, Hirshon JM, et al. (2010). Defining and measuring successful emergency care networks: a research agenda. *Academic Emergency Medicine*, **17**(12), 1297–305.
14. Fishman PE, Shofer FS, Robey JL, et al. (2006). The impact of trauma activations on the care of emergency department patients with potential acute coronary syndromes. *Annals of Emergency Medicine*, **48**(4), 347–53.
15. Iwashyna TJ, Kramer AA, and Kahn JM. (2009). Intensive care unit occupancy and patient outcomes. *Critical Care Medicine*, **37**(5), 1545–57.
16. Gabler NB1, Ratcliffe SJ, Wagner J, et al. (2013). Mortality among patients admitted to strained intensive care units. *American Journal of Respiratory and Critical Care Medicine*, **188**(7), 800–6.
17. Kahn JM, Linde-Zwirble WT, Wunsch H, et al. (2008). Potential value of regionalized intensive care for mechanically ventilated medical patients. *American Journal of Respiratory and Critical Care Medicine*, **177**, 285–291.
18. Singh JM, MacDonald RD, Bronskill SE, and Schull MJ. (2009). Incidence and predictors of critical events during urgent air–medical transport. *Canadian Medical Association Journal*, **181**(9), 579–84.
19. Bosk EA, Veinot T, and Iwashyna TJ. (2011). Which patients and where: a qualitative study of patient transfers from community hospitals. *Medical Care*, **49**(6), 592–8.
20. Wunsch H, Angus DC, Harrison DA, Linde-Zwirble WT, and Rowan KM. (2011). Comparison of medical admissions to intensive care units in the United States and United Kingdom. *American Journal of Respiratory Critical Care Medicine*, **183**(12), 1666–73.

CHAPTER 7

Integration of information technology in the ICU

Daniel Martich and Jody Cervenak

Key points

- People, processes, and technology are all essential elements to successfully transforming the critical care environment to meet future demands.
- Five major areas of technology evolution include: workflow automation, information exchange, clinical decision support, predictive modelling, remote monitoring, and data analytics.
- If designed properly, technology can result in doing things differently (better) and doing different things.
- Information exchange is required for quality and efficient critical care information delivery.
- Data analytics will use information for comparative effectiveness, registry reporting, population management, and research study recruiting.

Introduction

International standards mandate that airline pilots run through hundreds of checkpoints every time they sit down in the cockpit. Captains' decisions affect the lives of many individuals. Stock market traders confront a cacophony of noises, while attempting to make split-second decisions, which may result in profit or loss for their organization. Special military forces, often in sleep-deprived states, need to make clear-headed decisions that will determine the success or failure of their mission. What do these three disparate professions have in common with critical care? Similar decision-making complexities and complications are faced in a 'typical' day in the ICU by the busy critical care professional.

Critical care physicians and nurses analyse hundreds of data points to arrive at life-saving decisions. The choices of medications, procedures, and other therapies made by the intensivist, often under emergent conditions, affect not only patients' chances of survival, but also have a great effect on some of the most expensive care provided in medicine. Despite or, perhaps, because of 24/7 ICU coverage, intensivists' sleep–wake cycle can be disrupted enough to potentially cause negative patient outcomes.

The similarities among those professionals and critical care specialists dissolve quickly, however, when considering technology solutions. Pilots have automated workflow and checklists, in addition to a cohort of engineers, to ensure a correctly operating airplane, not to mention auto-pilot to help fly their plane through most of the journey. Busy stock traders have at their command electronic transaction systems, and real-time data input on smart phones and other mobile platforms, as well as remote connection to experts. Navy Seals and Green Berets in the US military use the latest night vision glasses, colleague recognition software, and global positioning equipment to run successful missions.

With an ever-growing number of critical patient volumes, increasing acuity levels, and numerous combinations of complex conditions, our profession requires a quick response to critical situations, whereupon we must be capable of considerable data analysis and rapid decision making. Critical care professionals are faced with the challenge of performing better, faster, and cheaper.

A transformation is needed to manage all of these demands, and it will require improved technology, processes, and skill sets. Yet the health care industry lacks many of the technological advances utilized by the airline, financial, and military industries. This chapter will explore several of the key areas of technology advancement and the critical factors to lead to successful outcomes.

Technology + Process + People = Success

In most instances of information technology (IT) implementation, the focus is on the technology factor of the equation. Technology is important, but should never be the sole factor. Industry examples underscore this point.

For example, at the Children's Hospital of Pittsburgh (CHP), an unexpected increase in mortality was observed when a computerized physician order entry (CPOE) was implemented [1]. Much blame was placed on the technology, but less than 1 year later, the Children's Hospital at the University of Washington implemented the same technology and noted a reduction in mortality. Their conclusions were that careful process design and coordinated team-building mitigated the associated risks even in the ICU [2]. Interestingly, the faculty from the University of Washington was on hand in Pittsburgh during the CPOE deployment at CHP, and privately noted the overlooked people and process elements. The relationship between technology, process, and people is illustrated in Fig. 7.1.

Process is the engine of critical care. It is essential that during an IT implementation, processes be redesigned to identify opportunities to not only do things differently, but also to do different things.

Undertaking the difficult task of mapping out current processes and redesigning future ones requires specific process engineering

Fig. 7.1 Successful technology requires careful process design and good teamwork.

and analytic skills. This leads to the third and most important factor in the success equation—people.

Unless there is engagement and adoption from the people who must follow the processes and utilize the technology, it does little good.

Changes in management and changing culture are two of the more complicated aspects of any transformation project. In the critical care setting, clinicians are called upon to use discretion and judgment in a very intense, time-sensitive environment. Without proper engagement, education, and training, the team is unable to achieve functional and operational success.

To specifically address the people factor, it is important to define the individuals with the right base level skill to be a part of the IT-enabled transformation project team. These skills include organization, analysis, and strong communication abilities. Perhaps the most important attribute to have is an optimistic demeanour. These individuals become the team that informs and drives the rest of the department.

The clinical team should include multiple roles and levels of hierarchy, not simply the least tenured intensivist or youngest respiratory therapist. It is essential that every individual in the critical care environment is well aware of and prepared for the changes involved, and is proficient in the new technology and processes.

Transforming critical care with technology

There are five major areas of technology evolution that will enable an efficient and effective critical care environment.

Workflow automation

Critical care IT solutions can empower a more efficient workflow if designed and implemented properly [3]. A thoughtful and detailed assessment of the current workflow state is a first step for redesigning processes for the future. Start by identifying the current workflow. Then define the opportunities for improvement, identify any gaps in communication or components of the workflow that require reworking or multiple touch points, and observe the way in which the clinical team spends their time.

Many areas will need to be redesigned to fully leverage the technology capabilities. The following are some of the high priority areas:

- **Patient care versus technology care**: minimize the time required to interact with the system and be sure to design the system flow to support efficient care processes.
- **Equipment and computer placement:** ensure clinicians are near the patient as opposed to having to work around the equipment.
- **Mobility**: plan for mobile solutions to improve efficiency in physician's access to information duringconsults, patient visits, and remote patient care.
- **User access**: improve user access through single sign-on, biometrics, and/or proximity-detection technology.
- **Efficient display of information**: consider the intensity and display of critical care data by creating relevant views for clinicians to be able to easily see the information and change parameters on trending the information (e.g. by day, by week).
- **Order sets**: design easy-to-use order sets with minimal clicks.
- **Documentation**: make sure the documentation process models the most efficient and effective data capture at the bedside.
- **Infection control**: incorporate solutions, such as special wall-mounted larger screens with motion sensing input to avoid spread of infection.
- **Ensuring the five rights**: improve patient safety and decrease medication errors by implementing a positive patient identification system (PPID), which ensures the right medication is delivered to the right patient, at the right time in the right dose, and by the right route every time.

Information exchange

Information exchange is required for quality and efficient delivery of information within the critical care setting. There are many levels of information exchange that are important to the care delivery process:

- **Biomedical device integration (BMDI):** sending data directly from biomedical devices into the patient's electronic medical record (EMR) can reduce delays in recording, errors in interpretation and transcription, and delayed or incorrect treatments [4]. Create a rigorous project plan that includes a thorough workflow assessment, engagement of key stakeholders, and tight coordination with the EMR implementation. Ultimately, clinicians need to trust the system, and trust that the data flowing into their record is timely and accurate.
- **Hospital integration:** the next level of information exchange is across the downstream and upstream processes, such as emergency department, operation room, step down, medical/surgical units, etc. This is important for medication reconciliation, transition of care documentation, and ensuring that key elements of the patient medical history and current condition is shared. With an integrated EMR system, the care team shares the same medical record, order sets, documentation tools, and messaging system. Information sharing cannot easily be replicated when the critical care approach is best-of-breed with different vendors' products.
- **Enterprise integration:** many organizations have elected to implement an enterprise EMR system extending the same vendor system beyond the hospital to the ambulatory, home care, rehabilitation, long-term care, and other service lines. This allows for the continuity of patient care across the board. In addition, many health care groups have designed these systems to enable EMS and other community partners' access to the information.
- **Regional/national health information exchange:** many communities have implemented a health information exchange

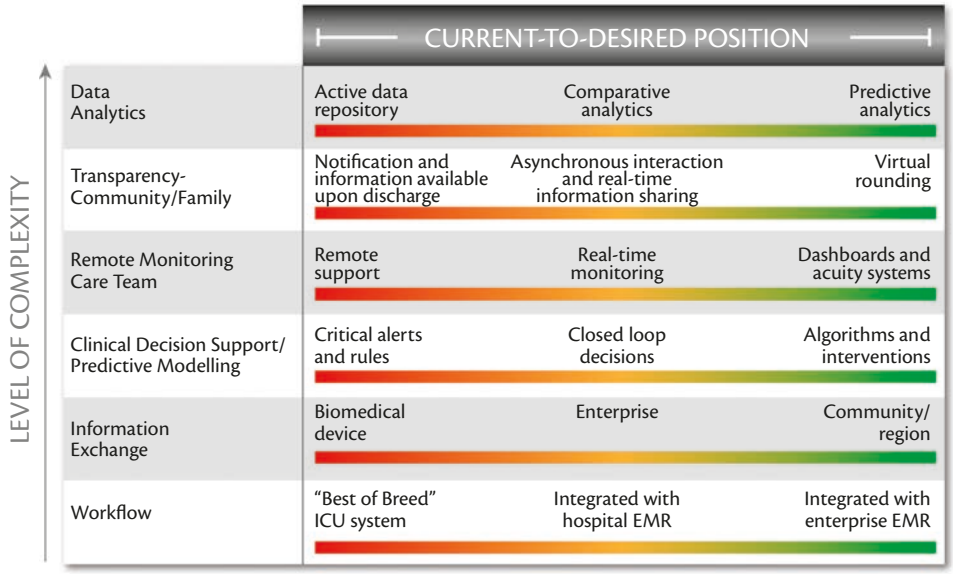


Fig. 7.2 Road map for developing technology, people, and processes in critical care IT.

(HIE) to enable information sharing across regions in order to provide information back to the patient's community physician, hospital, diagnostic centres, home care, rehabilitation, etc. While these exchanges are in a very early stage of data sharing, they provide access to key information as the patient moves across different points of care.

Clinical decision support and predictive modelling

The inherent goal of clinical decision support (CDS) is to anticipate the best care and assist the busy critical care clinician in 'doing the right thing'. CDS is most effective if the rules, which run in the background, stay in the background unless an interruption in workflow with a 'pop-up' alert is essential to avoid harm to a patient. CDS in the ICU falls into one of three broad categories:

- **Alerts:** these generate warnings in response to clinical data. For example, clinicians may want a computerized CDS to alert them (i.e. page, text message, telephone call, etc.) if a patient's heart rate has changed by some preordained percentage. For example, if the cohort of critical care clinicians decide that a 50% change in a patient's heart rate is 'pageable event', then many times the CDS will simply be notifying the intensivist of going from one end of the normal range to another (e.g. 50% increase from baseline of 60/min is only 90/min). For this reason, interruptible CDS needs to be well designed and exceedingly rare. The signal-to-noise ratio of interruptible CDS needs to be as high as possible or else alert fatigue will set in, and no CDS alert is taken seriously. The goal is to minimize the false positive alerts and maximize the clinical appropriateness.
- **Decision modification:** decision modification CDS, or non-closed loop CDS, makes the right thing to do the easy thing to do for the clinician. As an example, the busy intensivist may order Gastrointestinal (GI) prophylaxis for her patient at a standard dose of 150 mg of ranitidine bd. CDS can detect poor renal function and suggest adjusting to an alternative dosing schedule, based on the serum creatinine. These decision modification rules can be written for nearly any laboratory or other standards-based entry (i.e. ICD-10 specific diagnosis, radiological finding, problem, allergy, etc.)
- **Interventions:** CDS tools can also incorporate branched-logic, based on orders or closed-loop CDS. If a combination of sepsis thresholds is achieved for a patient during a given time frame, a set of orders, alerts, and interventions begin. For example, once an ICU patient with fever, leucocytosis, tachycardia, and a mean arterial pressure of less than 65 mmHg experiences that combination in a certain window, then cultures will be obtained, boluses of *in vitro* fertilization (IVF) will be administered, samples for laboratory analysis will be drawn, consultations will be called, the intensivist will be paged, and potentially a clinical trials researcher contacted, all by the CDS system.
- **Predictive modelling:** for the purposes of this chapter, we have combined CDS with the relatively new science of predictive modelling (PM), which leverages the vast amounts of data in an EMR with sophisticated computational data models. PM uses a wide range of clinical variables to quantitatively determine the acuity of a hospitalized patient's condition and make the best possible prediction of whether a patient is at risk of worsening. Modelling is currently based on vital signs and laboratory data, but will soon incorporate structured and unstructured information from nursing assessments and physician documentation.

A growing number of commercial products (i.e. Rothman Index, Predictive Modelling, Oxford Biosigns) tout their ability to trend every at-risk patient and notify clinicians before a life-threatening event occurs. Proving what did not happen is difficult, but increased use of PM software is anticipated because of expected critical care provider shortages and because it will provide the ability to monitor large numbers of patients with fewer bedside clinicians.

Remote monitoring/transparency

Currently, clinicians can remotely monitor critical care, and provide support and consultation to the care team. The future is promising for the provision of portals for referring clinicians, as well as authorized families and friends. This higher level of engagement

with the extended care team and patient guardians will lead to a more informed and transparent environment.

In fact, in discussions with the University of Pittsburgh Department of Critical Care Medicine faculty, early data analysis shows that remote monitoring by critical care physicians can lead to reduced length of hospital stay.

Data analytics

As hospitals, especially ICUs, collect and digitize more data, it will lead to the ability to study diseases and combinations of problems in a manner heretofore impossible. The insights gained from analytics to define operational efficiencies, quality, and performance management are tremendous. However, the real power for the bedside clinicians may reside in their ability to effectively personalize care using historical cases from the EMR in a *de facto* evidence-based medicine (EBM) approach to care.

The critical care IT environment of the future will have the opportunity to utilize information for comparative effectiveness, recruitment for research studies, registry reporting, population management, and multicentre studies. As an example, in the absence of EBM related to anticoagulation, decisions for a critically-ill 13-year-old girl with lupus, renal failure, and pancreatitis, clinicians at the Lucile Packard Children's Hospital at Stanford analysed the data from their EMR repository. Within a short period of time, they found a cohort with matching profiles treated previously, which informed their treatment decisions. As a result, the patient did not have bleeding nor thrombotic problems during her hospital course [5].

Advancing critical care IT

Critical care environments vary widely in terms of adoption and utilization across the IT continuum. As the technology, people, and processes mature, the future of critical care will achieve higher levels of quality, operational efficiencies, and cost effectiveness. The framework outlined in Fig. 7.2 can be used as a roadmap for leading the maturation.

References

1. Han YY, Carcillo JA, Venkataraman ST, et al. (2005). Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. *Pediatrics*, **116**, 1506–12. [A published correction appears in Pediatrics, 2006; 117, 594.]
2. Del Beccaro MA, Jeffries HE, Eisenberg MA, and Harry ED. (2006). Computerized provider order entry implementation: no association with increased mortality rates in an intensive care unit. *Pediatrics*, **118**, 290–5.
3. Ali NA, Mekhjian HM, Kuehn PL, et al. (2005). Specificity of computerized physician order entry has a significant effect on the efficiency of workflow for critically ill patients. *Critical Care Medicine*, **33**, 110–14.
4. Gearing P, Olney CM, Davis K, Loranzo D, Smith LB, and Friedman B. (2006). Enhancing patient safety through electronic medical record documentation of vital signs. *Journal of Healthcare Information Management*, **20**(4), 40–5.
5. Frankovich J, Longhurst CA, and Sutherland SM. (2011). Evidence-based medicine in the EMR era. *New England Journal of Medicine*, **365**(19), 1758–9.

CHAPTER 8

Multiple casualties and disaster response in critical care

Yoram Weiss and Micha Shamir

Key points

- **Definitions:**
  - *Multiple-casualty incident (MCI):* natural or man-made incident at which the number of patients arriving the hospital temporarily strain, but do not overwhelm, hospital resources. *Disaster/mass casualty event (MCE):* natural or man-made scenario at which community resources are overwhelmed mandating allocation of resources from other communities.
- Intensive care unit (ICU) physician should, upon announcement of a MCI or MCE, review the patients in the ICU and determine those that can be transferred.
- Of core importance is proper process control, which is ideally managed by a senior clinician who can assess, prioritize, and ease the transfer of patients.
- Due to the large number of severely injured, the risk of missed injuries is high. A thorough re-evaluation (tertiary survey) is recommended.
- Hospital preparedness for an MCE includes focus areas, such as supplies, communications, security, staff, and utilities to support surge capacity for appropriate clinical activity.

Introduction

Inherent ability to treat multiple casualties is related, among others, to the hospital's certification, number of trauma bays/intensive care unit (ICU) beds, time of day or day of the week. Once the number of casualties arriving at a hospital exceeds the hospital's routine capability, it becomes a **multiple-casualty incident** (MCI) scenario, mandating the allocation of personnel and resources from their routine tasks in order to provide best possible care to the patients. MCIs temporarily strain, but do not overwhelm hospital resources. Larger scenarios can be depicted as an escalating continuum, which may lead to an inability of the hospital and its community to cope. In these later scenarios, there is a need to allocate resources from city to city, from county to county, and from state to state. The smaller events on this continuum are termed '**mass casualty events'** (MCE), while the more devastating incidents are termed '**disasters**'.

There are several definitions of disaster that are related to magnitude. The US Joint Commission on Accreditation of Health Care Organizations (JCAHO) places the term disaster in a spectrum of incrementally worsening emergency events [1]:

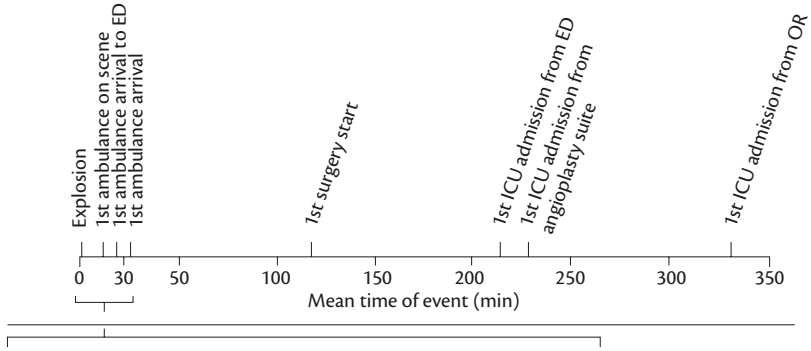
- Level one events are termed emergencies and involve major incidents, such as a suicide bomber explosion on a bus. These constitute short-lived situations (lasting up to 24 hours) that do not disrupt the operations of a hospital.
- Disasters that are defined as a community-wide event, which disrupts the health care system and the infrastructure of the community. The 2005 Katrina hurricane is one recent example of such an event.
- The most severe level constitutes catastrophes, which describe a series of disasters that affect the same community in a short period of time. An example of such a catastrophe was the 2011 earthquake in Japan followed by the huge tsunami wave that caused the leakage of radioactive material from an electric nuclear plant.

All together the continuum consists of MCI, MCE, disaster, and catastrophe. Hence, the reader must understand that concepts described in this chapter should be applied interchangeably on this continuum.

Multiple-casualty incidents

Aschkenasy-Steuer et al. described the sequence of events resulting from 20 terror-related MCIs encompassing an average of four ICU admissions per incident (Fig. 8.1) [2]. In an urban area, it takes at least 20 minutes for the first ambulance to arrive at the hospital and more time is needed for initial resuscitation. The ICU team, supervised by a senior clinician, should use this time to assess the severity of the event, prepare for admissions, determine which patients can be transferred out of the ICU, and call for back-up.

Once survivors begin arriving at the emergency department (ED), a senior intensivist should remain in the ED seeking information. Knowledge of the injuries will provide an estimate of the number of ICU beds required, will help in planning for the best placement of each patient thus enabling efficacious nursing assignments, and allow time to organize special equipment. While screening for potential admissions, knowledge of the treatment plan is important as it provides an estimation of time for admission [3]. In Jerusalem, the mean time for ICU admission was 5.5 hours. Patients arriving from the ED, computed tomography (CT) or angiography suite generally arrive to the ICU earlier, while those arriving from the



Time (min) after explosion	Event	Actions to be taken
0	Explosion	
0–10	Assess incident size and severity	Obtain information from emergency services and media sources Continue life-saving operations Hold elective operations Clear emergency department Send patients from OR waiting area back to departments Consider taking out patients from OR if operation not yet started Notify all anesthesiologists present in the hospital about the event Prepare to call in additional personnel
0–20	Backup and preparation of sites	Recruit additional staff: Head of ICU department, on-call senior physicians, ICU head nurses. Other physicians and nurses as needed Triage patients to be discharged from the ICU and recovery room Send on-call most experienced physicians to the trauma bay and emergency department Prepare trauma bay, two operating rooms and ICU beds (including PACU) for admission

Fig. 8.1 Timeline of events after an incident and actions to be taken.

ED, emergency department; ICU, intensive care unit; OR, operating room; PACU, post-anaesthesia care unit.

Reproduced from Aschkenasy-Steuer G et al., 'Clinical review: The Israeli experience: conventional terrorism and critical care', *Critical Care*, 2005, **9**, pp. 490–9, with permission from BioMed Central.

operating theatre arrive later. Some patients, however, might arrive in the ICU soon after the event because they need extensive stabilization before surgery. These, patients can be temporarily treated in the post-anaesthesia unit (PACU), which provides surge capacity for ICU beds. Additional nurses might be needed and may be recruited from other ICUs or departments, providing that an orientation was completed as part of the hospital's preparedness plan.

In these situations, due to the large number of severely-injured patients, the risk of missed injuries is high. A thorough re-evaluation (tertiary survey) together with the trauma surgeons is therefore recommended. Similar characteristics have been reported for Madrid and New York [4,5]. Activities surrounding a MCI have repercussions for the ICU that can last up to 48 hours or longer. It is recommended to add nurses and physicians to the subsequent shifts to cope with the additional work load. Table 8.1 summarizes ICU statistics following MCI.

Mass-casualty events and disasters

Disasters and MCEs are large-scale destructive events that disrupt the infrastructure and normal functioning of a community. Although semantically these terms can be interchangeable, disasters are commonly attributed to natural causes (earthquakes, tornadoes, hurricanes, floods), while MCEs are attributed to man-made events (industrial spills and explosions, structural collapse, terrorist attacks, etc.). In a large-scale destructive event, the greatest challenge to the medical community is the large number of casualties, out of proportion to the existing health system resources. In these circumstances, it is mandatory to refuse treatment to those unlikely to recover in order to save the maximum number of lives [6]. As true MCEs are rare and there is little opportunity for real-time training and experience, the key for coping with such events is proper preparedness [2,7–9].

Treatment of an enormous number of survivors can be further complicated by damage to the hospital and its infrastructure. In their review, Roccaforte and Cushman counted numerous disturbances that should be anticipated in such situations [10]. For example, the initial information obtained will probably be unreliable, communications may be impaired, transportation may be difficult, the nearest hospital will receive the most patients, but transport from the scene may not be to the designated hospital, up to 72 hours may pass before outside help arrives, volunteers will be numerous, and emergency credentialing may therefore be an issue. Accordingly, JCAHO has listed six focus areas for hospitals aimed

Table 8.1 ICU statistics following multiple casualty incident

	Madrid	Jerusalem
Mean ICU length of stay	10 ± 4	9
ICU mortality	11.1%	8.5%
ICU admissions*	32%	52%
Blast injury	63%	52%
Need for ventilation in ICU patients	80%	86%
Ventilation > 7 days	37%	NR
Injury severity score	34	24
Injury		
Spinal injury	18%	7%
Burns	59%	NR
Head injury	52%	44%
Abdominal injuries	37%	32%
Extremity injuries	62%	85%
Combined injuries	100%	86%
Chest Injuries	82%	NR

*Percentage of hospital admissions admitted to the ICU.

ICU, intensive care unit; NR, not reported.

Reproduced from Shamir MY et al., 'Conventional terrorist bomb incidents and the intensive care unit', *Current Opinion in Critical Care*, **11**(6), pp. 580–4, copyright 2005, with permission from Wolters Kluwer Health.

at developing proper contingency plans and response mechanisms for a disaster (Box 8.1). Also, the ICU must have its plan as a part of the hospital and community plan.

Communications

Communications must be addressed during the preparatory phase (including multiple methods), as this is essential for in-house and home personnel recruitment, and for the provision of material and organizational resources. Ordinary land lines and cell phone reception may become dysfunctional, and flooding may cause electrical failures of systems, including the internet. As walkie-talkies are expensive, messengers appear to be a reliable method for intra-hospital use [11].

Box 8.1 JCAHO focus areas for proper planning and responding to a disaster

- Communications: both internal and external to community care partners and state/federal agencies.
- Supplies: adequate levels and appropriateness to hazard vulnerabilities.
- Security: enabling normal hospital operations, and protection of staff and property.
- Staff: roles and responsibilities within a standard hospital incident command structure.
- Utilities: enabling self-sufficiency for as long as possible with a goal of 96 hours.
- Clinical activity: maintaining care, supporting vulnerable populations, and alternate standards of care.

In the ICU, automatic communication systems sending text messages or Internet-based messages can be used to deliver messages to cell phone users who are included in the MCE response group, thereby replacing traditional emergency phone lists. Cell phones have proven themselves to be more reliable in restoring proper communication faster than cable networks, as illustrated by the 2011 9.1 earthquake in Japan. Hence, a balance must be struck between these two systems [11].

Supplies

'Just-in-time' is an organizational philosophy aimed at reducing inventory to reduce costs [12]. As demonstrated in the wake of Hurricane Katrina and the 2011 earthquake in Japan, hospitals must be prepared for a disruption in their supply chains following a catastrophe and therefore of limited use in disaster medicine. In Israel, hospitals are expected to maintain an in-house inventory that allows for 2–4 weeks of uninterrupted operations. As local suppliers may fail to respond following a catastrophe, a list of vendors outside the region should be created, including contact information. The collection and exchange of information with different suppliers is critical in the responses to changing scenarios. Many hospitals rely on a cooperation plan, whereby neighbouring institutions aim to share supplies and resources. However, in times of catastrophe, these hospitals are likely to fail as well. In the USA, hospitals are expected to be self-sufficient for as long as possible, with a goal of 96 hours, as this has been predicted as the time needed for help from outside the affected area to arrive [13].

Increasing surge capacity

Surge capacity is the ability of a health care facility to expand its operations to safely treat an abnormally large influx of patients in response to an incident [1]:

- **Triage:** if a disaster can be anticipated (an imminent nuclear plant accident, major hurricane, etc.), the ED/trauma bay should be evacuated. Elective activity should be stopped and stable patients should be discharged home. ICU patients should be discharged to step-down units and wards, or transferred to other hospitals. All of the above are part of the process of allocating and prioritizing resources in order to increase **existing** surge capacity [9].
- **Adding facilities:** surge capacity should be **increased** by adding ED, operating room (OR), and ICU spaces together with personnel to operate them [14]. The hospital's disaster plan must identify, prepare, and staff areas in advance for the management of many patients who require augmented care, but do not necessarily meet the criteria for ICU admission [2,8,9]. Preferentially, the augmented care area should be controlled or co-directed by ICU specialists and placed, if possible, in close proximity to the ICU. One possible option is utilizing the PACU, as the nursing staff is trained for the care of unstable and critically-ill patients. Furthermore, it is important to identify in advance personnel who have ED or ICU skills, especially nurses and respiratory therapists who do not practice, but can be routinely updated, so that they may staff critical areas, including the ED, OR, and ICU, in a time of crisis.

Patient flow

During the time of arrival of injured patients to the trauma bay or ED, patient flow is recommended to be uni-directional. Patients

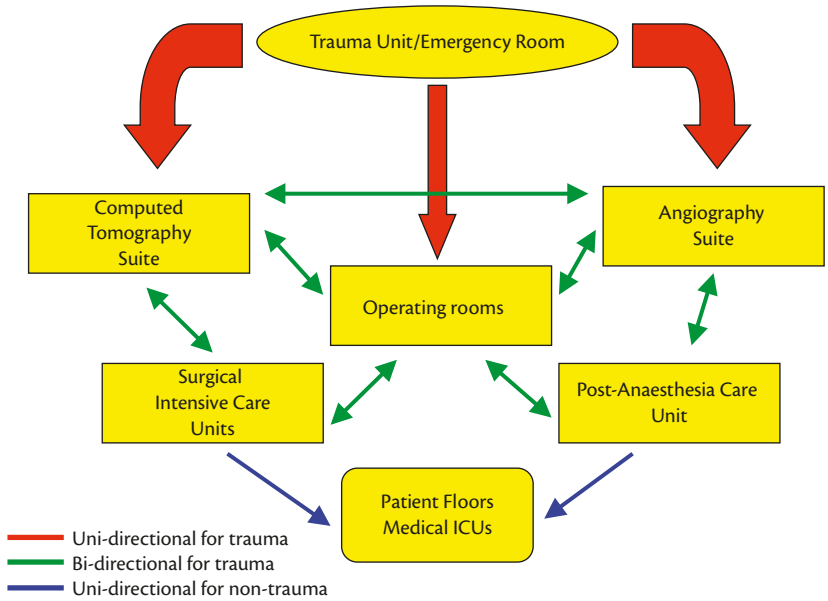


Fig. 8.2 Patient flow during the chaotic phase of an MCE.
Reproduced from Shamir M et al., 'Multiple Casualty Terror Events: The Anesthesiologist's Perspective', *Anesthesia and Analgesia*, **98**(6), pp. 1746–52, copyright 2004, with permission from International Anesthesia Research Society.

move from the ED or trauma bay to imaging (CT/angiography), and then from there to the OR, ICU, or ward (Fig. 8.2). As a rule, injured patients never return to the ED or trauma bay. This policy is of increasing importance as more survivors are expected to arrive from the scene together with secondary transfers from other hospitals.

Medical information gathering

It is nearly impossible to efficiently record all medical information during the initial phases, as both physicians and nurses are overwhelmed. This difficulty is compounded by the multiple surgical subspecialties that may be involved in the preliminary, primary, and secondary surveys in the trauma bay. To remedy this problem, some recommend the assignment of a resident to each severely-injured patient upon admission to the trauma bay. These physicians will follow the patient throughout their entire evaluation and primary care process until their admission to the ICU. Upon arrival, these physicians should record all relevant data in the admission report.

Information technology perspective

Information technologies play an increasingly central role in the provision of medical and logistic services in a modern hospital. Administrators must prioritize the mission-critical information technology systems that must be maintained operational during a catastrophic MCE, together with an expected time frame for their restoration in case of a system crash. The criteria for defining a system as mission critical must include an analysis of the impact of its loss during a MCE on staffing, medical management, etc.

Drills and protocol

It is mandatory to transfer the key elements of disaster response into a hospital protocol that identifies specific action points. Furthermore, dry (desk) and wet (simulation) drills have a central role in maintaining preparedness for a MCE.

Impact analysis

Some advocate that impact analysis is an integral part of preparation for a MCE [15]. After recording the effect of a preparedness drill on manpower and inventories, an impact analysis can be used to determine resources needed by departments and services, and the relationships between them. Impact analyses should be performed at the institutional level and should use hospital-wide input. This analysis, among others, sets the criteria for the closure and/or return of critical service areas to meet patient care needs.

The impact analysis should, among other topics, evaluate the effect of a MCE on increases in staff working hours, changes in routine therapy procedures, or the cancellation of some procedures altogether. The impact analysis should also define an endpoint for the MCE and a timeline for returning to normal operating activities [15]. The definition of 'normal' may be different for each affected department, so some departments may be able to return to normal activity faster than others.

Debriefing

Recording problems in flow and process cannot be performed during a MCE, as the focus is to provide medical care to the injured in a situation when the system is overwhelmed [15]. However, we must not overlook valuable lessons and analyse mistakes. Hence, it is of key importance to perform interdepartmental and hospital-wide reviews soon after the event for all medical and support staff who participated in the MCE. The United States Department of Homeland Security has provided a website with information about lessons learned, best practices, and after-action reports (US Department of Homeland Security. Lessons learned: information sharing. https://www.fema.gov/lessons-learned-information-sharing-program) [16].

Conclusion

Hospital preparedness for a MCE begins long before the event itself occurs, and includes:

- Defining the modus operandi during a MCE by creating hospital, department, and unit protocols.
- The creation of in-hospital working rules.
- Establishing communication alternatives.
- Preparation and storage of emergency equipment, medical supplies, and medications in accessible places (an in-house inventory that would provide for more than 2 days).
- A list of vendors outside of the region should be created and scenarios relevant to the hospital should be routinely practiced.

When an MCE occurs, the first step is to assess its size and severity, and accordingly activate a surge capacity plan and implement the proper process control procedures supervised by a senior intensivist, who can assess and prioritize patient care. The preparation and utilization of an auxiliary area for patients who need additional care outside of the ICU also assists in the treatment of survivors.

References

1. Bonnet CJ, Peery BN, Cantrill SV, et al. (2007). Surge capacity: a proposed conceptual framework. *American Journal of Emergency Medicine*, **25**, 297–306.
2. Aschkenasy-Steuer G, Shamir M, Rivkind A, et al. (2005). Clinical review: the Israeli experience: conventional terrorism and critical care. *Critical Care*, **9**, 490–9.
3. Almogy G, Mintz Y, Zamir G, et al. (2006). Suicide bombing attacks: can external signs predict internal injuries? *Annals of Surgery*, **243**, 541–6.
4. Peral-Gutierrez de Caballos J, Turegano Fuentes F, Perez Diaz D, et al. (2005). Casualties treated at the closest hospital in the Madrid, March 11, terrorist bombing. *Critical Care Medicine*, **33**(Suppl.), S107–12.
5. Kirschenbaum L, Keene A, O'Neill P, et al. (2005). The experience at St. Vincent's Hospital, Manhattan, on September 11, 2001: preparedness, response, and lessons learned. *Critical Care Medicine*, **33**(Suppl), S48–52.
6. Burkle FM, Jr (2002). Mass casualty management of a large scale bioterrorist event: an epidemiological approach that shapes triage decisions. *Emergency Medicine Clinics of North America*, **20**, 409–36.
7. Born CT, Briggs SM, Ciraulo DL, et al. (2007). Disasters and mass casualties: I. General principles of response and management. *Journal of the American Academy of Orthopaedic Surgery*, **15**, 388–96.
8. Shamir M, Weiss YG, Willner D, et al. (2004). Multiple casualty terror events: the anesthesiologist's perspective. *Anesthesia and Analgesia*, **98**, 1746–52.
9. Shamir MY, Rivkind A, Weissman C, Sprung CL, and Weiss YG. (2005). Conventional terrorist bomb incidents and the intensive care unit. *Current Opinions in Critical Care*, **11**, 580–4.
10. Roccaforte JD and Cushman JG. (2002). Disaster preparation and management for the intensive care unit. *Current Opinions in Critical Care*, **8**, 607–15.
11. Mahoney EJ, Biffl WL, and Cioffi WG. (2008). Mass-casualty incidents: how does an ICU prepare? *Journal of International Care Medicine*, **23**, 219–35.
12. Shigeo Shingo and Dillon AP. (1989). *A study of the Toyota Production System*. Boca Raton, FL: Productivity Press.
13. Joint Commission of Accreditation of Healthcare Organizations (2005). Standing together. An emergency planning guide for America's communities. Available at: http://www.jointcommission.org/assets/1/18/planning_guide.pdf (accessed 30 July 2012).
14. Joint Commission of Accreditation of Healthcare Organizations (2006). Surge hospitals: providing safe care in emergencies. Available at: http://www.jointcommission.org/assets/1/18/surge_hospital.pdf (accessed 30 July 2012).
15. Nelson SB. (2008). Information management during mass casualty events. *Respiratory Care*, **53**, 232–8.
16. US Department of Homeland Security. Lessons learned: information sharing. Available at: https://www.fema.gov/lessons-learned-information-sharing-program (accessed on 27 October 2015).

CHAPTER 9

Management of pandemic critical illness

Robert Fowler and Abhijit Duggal

Key points

- Pandemic preparedness hinges on the development of appropriately trained staff with well-defined roles.
- A goal of pandemic planning should be to have the ability to manage surge in the number of patients with optimal use of available resources throughout the duration of the disease outbreak.
- A rigorous infection control programme for pandemics should be built upon the existing infection prevention and control practices of the hospital, and based upon modes of transmission for known or suspected agents.
- Triage protocols should be based on equitable distribution of resources and on ethical principles of justice, beneficence, and non-maleficence.
- Research preparedness, with approved protocols, electronic case report forms, and harmonized clinical trials databases afford the best chance at early accurate pandemic descriptive and interventional studies.

Defining pandemics

The World Health Organization (WHO) defines a disease outbreak as 'the occurrence of new cases of a disease process in excess of what is expected in a defined community, geographical area or season' [1]. An outbreak becomes a pandemic if it extends over several countries over a defined period of time, which may be limited to days, weeks, or even years [1]. Unfortunately, pandemic preparedness is based on assumptions, and these cannot account for the uncertainty associated with the nature, magnitude, or timing of these disease outbreaks.

Adequate and appropriate provision of critical care services during pandemics may dramatically alter vital outcomes of patients who develop acute respiratory distress syndrome (ARDS) and critical illness. As a consequence of the 1918–1920 global H1N1 influenza pandemic, it is estimated that approximately 50 million people—3% of the world's population—died [2]. Today, these patients would be admitted to intensive care units (ICUs) and it is likely that the majority would survive. Indeed, the provision of critical care during the severe acute respiratory syndrome (SARS) outbreak and 2009 H1N1 pandemic had a substantial impact on the survival of the sickest patients [3–5].

However, SARS and the 2009 H1N1 pandemic also highlighted the limited capacity for increased provision of critical care, even in well-resourced settings, and the potential for dramatic differences in mortality in under-resourced settings [3]. Thus, pandemic preparedness planning must focus on the most effective utilization of available resources in times of increased need. During the SARS outbreak in particular, we were taught difficult lessons about how inadequate preparation exacerbates shortages in technical capacity and personnel, and can lead to increased risk of illness transmission, the provision of ineffective and potentially harmful therapies, and a research response that is too slow to inform patient care [5,6]. This chapter will focus upon pandemic preparedness, as well as rapid clinical, education, and research responses.

Pandemic preparedness and mitigation

Intensivists frequently are among the first to recognize the most severe presentation of severe respiratory outbreaks. Accordingly, intensivists not only help develop treatment options, but are also intimately involved with developing the case definitions, determining early case fatality rates, transmission prevention, and the challenging task of informing potential triage decisions if demand exceeds capacity.

Pandemic preparedness hinges on the development of appropriately trained staff with well-defined roles in the event of a pandemic [7]. The lack of an organizational structure, and the absence of command and communication have been recognized as key factors in failure to provide appropriate medical services in previous mass casualty events and disease outbreaks [8]. Therefore, newer models focus on defining clearer roles for the individuals involved in pandemic response with a clear line of communication between health systems, and the local and federal authorities [7,8]. The response and preparedness model for disease outbreaks borrows heavily from the incident management system concept [8]. Government authorities in conjunction with health care personnel have developed standard operating procedures for responders during an outbreak using this model [8]. Emphasis is also placed on staff education and regular training to ensure readiness in the event of an outbreak [7].

Systems surge capacity

Pandemics often present with a sudden increase in patients requiring critical care services. [7,8]. The need for resources is

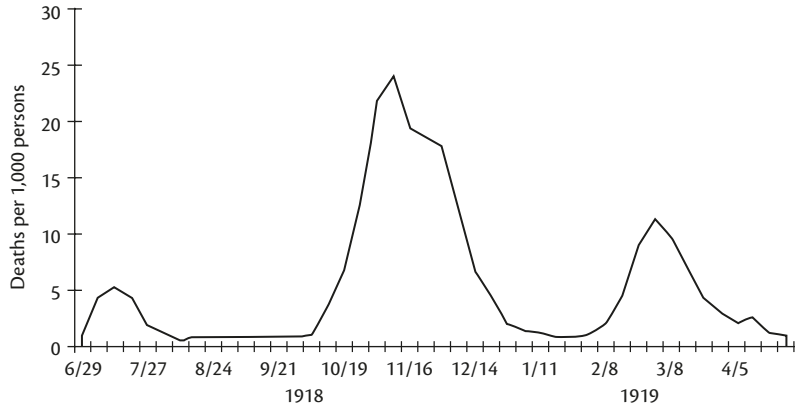


Fig. 9.1 Three waves: combined influenza and pneumonia mortality associated with the three waves of the 1918–1919 influenza pandemic in the United Kingdom.
Reproduced from Taubenberger JK, Morens DM, 1918 'Influenza: the mother of all pandemics', *Emerging Infectious Diseases*, **12**(1), pp. 15–22, 2006, with permission from Centers for Disease Control and Prevention. Data from Jordan E. *Epidemic influenza: a survey*. Chicago: American Medical Association, 1927.

variable, and is dependent on geographical and temporal factors. Pandemic surges typically come in multiple waves, lasting weeks or months at a time, separated by months, and potentially lasting for years [7,9] (see Fig. 9.1) Facilities should be equipped to provide emergency mass critical care (EMCC) services with an ability for a phased expansion to at least double the capacity for critical care beds during a pandemic (Fig. 9.2a, b). However, the scalar is critically dependent upon baseline capacity and the nature of the pandemic, and it is, therefore, impossible to prescribe for a given ICU [7,8]. Increasing ICU needs should also be balanced with other hospitals services—there is a potential for decreasing benefit with a unilateral increase in ICU capacity because of the excess demands on the available resources and health care providers [8].

Critical care staffing

Providing health care during a disaster is stressful and caregivers are at a significant risk of developing compassion fatigue, post-traumatic stress, and anxiety disorders. This results in decreased productivity and team functioning [8,10]. In most cases, there will be a need for expanded roles of non-critical care staff in specific areas in the ICU [10,11]. Members of the health care team from certain acute care areas (for example, post-anaesthetic care units, etc.) might play an important role in helping to care for critically ill patients. A mix of skilled critical care practitioners supervising less experienced health care workers in specified geographical areas may also be effective in pandemic situations [10,11]. Another strategy is to introduce a phased staffing plan where the working

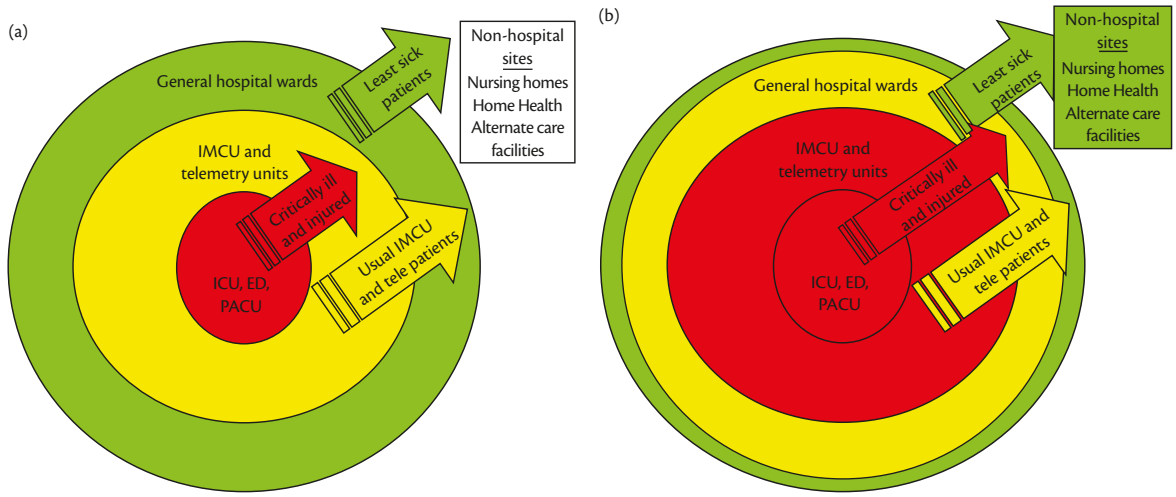


Fig. 9.2 (a) Initial expansion of critical care treatment space during disasters requires expansion into intermediate care units and telemetry spaces. Intermediate care and telemetry patients should be moved to general practice wards. The least sick patients should be discharged or transferred to community care facilities. (b) Expansion of critical care services in sustained catastrophes involves the transfer of all remaining intermediate care and telemetry patients to general hospital wards. Most, if not all, lower-acuity patients on the wards will need to be moved out of the hospital. Critical care patients will now occupy most of the hospital, including some of the general hospital wards.

ICU, intensive care unit; PACU, post-anaesthesia care unit; ED, emergency department; IMCU, intermediate care unit.

Reproduced with permission from the American College of Chest Physicians. Rubinson L et al., 'Definitive care for the critically ill during a disaster: medical resources for surge capacity: from a Task Force for Mass Critical Care Summit Meeting, January 26–27, 2007. Chicago, IL', *Chest*, **133**(5 Suppl.), 32S–50S. American College of Chest Physicians.

Table 9.1 Different levels of precautions in viral outbreaks [12, 13]

	Pandemic H1N1 influenza	SARS	Avian influenza	Seasonal influenza
Level of Precaution	Contact and droplet	Contact, droplet, and airborne	Contact and droplet	Contact and droplet
Duration of infection-control precautions*	5–10 days after onset of symptoms	While the patients are symptomatic	2–3 weeks after onset of symptoms	5–10 days after onset of symptoms
Contact precautions and droplet precautions				
Personnel protective equipment	Gowns, gloves, and eye protection	Gowns, gloves, and eye protection	Gowns, gloves, and eye protection	Gowns, gloves, and eye protection
Masks	Either surgical masks, or N-95 or equivalent masks	N-95 masks, or powered air purifying respirator	Either surgical masks or N-95 masks or equivalent masks	Either surgical masks or N-95 or equivalent masks
Airborne precautions				
Environmental Precautions	Dedicated patient care equipment, private patient room if possible, limit patient transport	Dedicated patient care equipment, private patient room if possible, limit patient transport, negative isolation room, >12 air exchanges/hour through monitored HEPA systems	Dedicated patient care equipment, private patient room if possible, limit patient transport, negative isolation room, >12 air exchanges/hour through monitored HEPA systems	Dedicated patient care equipment, private patient room if possible, limit patient transport
Incubation period*	1–7 days	1–7 days	1–17 days	1–7 days

*Periods are approximate, and may be longer or shorter for certain patients.

SARS, severe acute respiratory syndrome; HEPA, high-efficiency particulate air.

Data from various sources (see references).

hours of care teams are staggered, to overlap individuals from different care teams. This approach is associated with lower rates of fatigue and helps the overall morale of the care team [10].

Infection control

Health care workers and patients are extremely vulnerable to nosocomial transmission of infectious agents during pandemics [10]. A rigorous infection control programme for pandemics should be built upon the existing infection prevention and control practices of the hospital, and based upon modes of transmission for known or suspected agents [12,13]. Infected and exposed patients should generally be physically separated from other hospitalized patients who are susceptible to infection. It is prudent to initiate contact, droplet, and airborne precautions in uncertain pandemic situations and de-escalate accordingly when a fuller understanding of the illness becomes available [12]. Airborne precautions should be instituted for specific pathogens or during certain aerosol generating procedures (see Table 9.1) [12–14].

Health care personnel should receive training in infection control procedures including the need for hand washing, and the implementation of isolation procedures, etc. [12–14]. These personnel should also be trained in the pre-outbreak or inter-pandemic in the use of personal protective equipment, and training such as fit testing for masks, and the use of gloves and gowns in pandemic situations updated and documented regularly [12–14]. Aerosol generating procedures, such as high frequency oscillatory ventilation, non-invasive ventilation, and bronchoscopy, may increase the risk of virus transmission, but there is limited data to implicate particular modes of ventilation, and application of any of these modes may be reasonable, with appropriate health care worker precautions [13,14]. Negative pressure airborne isolation rooms, and high efficiency particulate air (HEPA) filter machines could be considered during procedures such as non-invasive ventilation, high frequency oscillation, etc., but their effectiveness in decreasing transmission rates is still unclear [13,14].

Resource allocation

Pandemic care needs to address the potential for a necessary increase in essential equipment (see Table 9.2) for both the patients admitted as a result of the pandemic, and patients admitted due to other medical problems [7,8,11] A model of a single pool of resources to be accessed by all in a designated health facility is likely to be more effective than numerous stockpiles in various departments [7,11]. Hospitals should establish a pandemic management committee, with representation by personnel from clinical, laboratory, and ancillary health care and administrative departments. Such a group should meet face-to-face on a daily-to-weekly basis to establish effective means of information gathering and dissemination within their area. Ideally, there should be similar local state and national acute care, and public health and governmental communication and coordination of resource allocation. During SARS and H1N1, we learnt that it is common for hospitals, cities, and countries to be differentially affected, and for certain regions to be stretched beyond capacity, while others had yet to experience substantially increased caseloads. A pre-established state and national mechanism to share resources (personnel, ventilators, medication, infection prevention, and control equipment) from small regional stockpiles or from a pre-existing inventory is essential.

Critical care triage

Triage protocols for pandemic situations should only be activated if surge capacity has been maximized across a broad geographic area, calls for aid (personnel, equipment, etc.) have gone out through local, national, and international channels, and there is still

Table 9.2 Equipment and devices to consider during viral respiratory illness pandemics

Essential medical equipment		
◆ Respiratory support equipment including mechanical ventilators ◆ Peripheral, central venous, and arterial catheters for haemodynamic support ◆ Monitoring equipment		
Pharmacologic therapies		
◆ **Antivirals**: neuraminidase inhibitors specifically for influenza outbreaks ◆ **Antibiotics**: for community-acquired pneumonia, secondary bacterial infection after viral pneumonia and hospital-acquired pneumonia ◆ Resuscitation fluids ◆ Vasopressors and inotropes ◆ Sedatives and analgesics ◆ Neuromuscular blocking agents ◆ Enteral nutrition		
Infection control and prevention equipment		
Contact isolation	***Droplet isolation***	***Airborne isolation***
◆ Gloves—sterile and non-sterile	◆ Face shields ◆ Goggles ◆ Face masks ◆ N-95 respirators	◆ Powered air purifying respirators ◆ HEPA Filters
Specific equipment for supportive care in patients with oxygenation failure		
◆ High frequency oscillation ventilators ◆ ECMO ◆ Equipment to support prone patient positioning		

a substantial demand-capacity mismatch that will result in some patients being unable to receive usual care [8]. Timing of critical care triage is very important—too early results in 'over-triage' and waiting too long results in a precipitous decline in the available resources [15]. Equitable distribution based on ethical principles of justice, beneficence, and non-maleficence should drive a triage protocol. Our usual principals of admission to ICU emphasize a 'first come, first served' approach. However, triage systems based upon severity of illness scoring systems have been proposed [8]. Such systems underperform when the pandemic population differs substantially from the derivation group, by younger age, or single organ failure in the H1N1 experience for example [15]. Criteria for triaging should be objective, transparent, easy to apply, and ideally flexible enough to allow a scaled ramping up and down as capacity changes.

Education

Simulation training plays a key role in preparation for pandemics, but cannot anticipate or address the nuances of all possible scenarios, cannot reach all staff, and will not replace targeted and specific intra-pandemic training. Training should begin as soon as possible with demonstrations followed by supervised practice. Subjects to be taught will inevitably include pandemic specific medical management, deployment of personal protection techniques, environmental decontamination, handling of laboratory specimens, alert lists, potential triage systems, visitor restrictions, and stress recognition and management, among others [7,8,10,11,14].

Management

Ventilation and oxygenation

Respiratory symptoms associated with severe hypoxaemia are likely to be common during viral respiratory pandemics and will require supportive care with supplemental oxygen and mechanical ventilation. While a review of effective therapy for ARDS is beyond the scope of this chapter, lung-protective ventilation, with judicious application of positive end expiratory pressure and intravenous fluid management should form the mainstay of lung supportive care. Severe ARDS, as seen during SARS and the 2009 influenza H1N1 pandemic will lead to increased frequency of 'rescue therapies', such as extracorporeal membrane oxygenation (ECMO), prone positioning, high frequency oscillatory ventilation, and inhaled nitric oxide [3,4,16]. While the role of ECMO, high frequency oscillation (HFO), prone positioning and nitric oxide is still unclear, pandemic-specific characteristics, such as young age and single organ failure may increase the likelihood of clinical benefit among therapies proven, thus far, only to improve oxygenation [3,4,16].

Pharmacotherapy

The SARS outbreak was as a result of a coronavirus that led to rapid development of ARDS and may have had an overall mortality of almost 10% [5,6]. Clinicians used ribavirin, steroids, and interferon alpha during the outbreak [5,17]. Subsequent analysis of all these interventions failed to show survival benefit among patients with SARS [6]. So no clear recommendations can be made in regard to the pharmacological treatment options for SARS [6,17]. The 2009 influenza H1N1 pandemic was unique as a severe disease requiring critical care services, which disproportionately affected young, immunologically naïve patients [3,4,15]. In critically-ill patients, the use of neuroaminidase inhibitors (oseltamivir, zamanavir) may have been associated with a lower incidence of death, although true effectiveness is impossible to define outside a properly performed clinical trial [3]. Optimal duration and dose of these therapies is uncertain [3,4,18,19].

There is an extensive prior literature and ongoing debate about the effects of corticosteroids on severe ARDS, and pandemic-associated ARDS. We saw extensive use of corticosteroids during SARS and the 2009 influenza H1N1 outbreak [18]. Although there is suggestive clinical trial data supporting steroid use for severe ARDS, observational studies during the pandemic highlighted worse outcomes among corticosteroid-treated patients. Yet this relationship probably suffers from residual confounding [18]. Currently, there is even less evidence for other agents.

Recent studies have emphasized common bacterial co-infection among patients with severe viral pneumonia [19]. Based on the available literature, early initiation of antibiotics, covering community-acquired organisms and organisms associated with viral infections (e.g. *Staphylococcus aureus*) are probably a very important aspect of therapy [19].

Establishing the means to rapidly deploy effective immunization to the at-risk population (including health care workers) is cost-effective and should be a key component of any pandemic response.

Research

The SARS epidemic highlighted the difficulties associated with developing and implementing studies during pandemic situations [6]. The H1N1 pandemic reaffirmed the need for early clinical and epidemiological data to be developed and implemented in a timely manner to help guide clinical decisions and health policy. During the early phase of the H1N1 (2009) pandemic, a number of critical care groups collaborated with government-affiliated agencies and other funders, and developed sound methodology to study the epidemiology and outcomes of critical illness in pandemic situations [20]. However, clinical trials were still delayed as protocols had not been prepared, regulatory bodies were sometimes slow to assess them, and accruement was limited. In response, the International Forum for Acute Care Trialists (InFACT) [20] evolved, with a vision of improving the quality of care for acute life-threatening illnesses throughout the world, by establishing collaborative networks of critical care societies and research trials groups to develop specific, adaptive studies and trials ahead of subsequent threats. Research preparedness, with protocols prevetted and approved, electronic case report forms and clinical trials databases preconstructed and with internationally harmonized definitions, and placebo/comparator agents well worked out before a pandemic will afford the best chance at early accurate pandemic descriptive and interventional studies [20].

Conclusion

ICUs will play an instrumental part in the care of the sickest patients during a disease outbreak. An appropriate critical care response to disease outbreaks requires preparation for an efficient response, strengthened by regular training of health care staff. The implementation of surge capacity and triage will become important when patient volumes exceed normal limits, and these decisions should always be made based on ethical, humanitarian, and legal principles. Appropriate infection control techniques are critical to saving lives by preventing secondary transmission to health care workers or other patients. Specific anti-viral therapy, antibiotics directed towards probable secondary infections, supportive ventilation and oxygenation, and adherence to multisystem critical care 'best practices' will prevent substantial mortality and morbidity, and lessen the pandemic's impact on global health.

References

1. World Health Organization. (2012). Disease Outbreaks. Available at: http://www.who.int/topics/disease_outbreaks/en/ (accessed 1 June 2012).
2. Morens DM, Taubenberger JK, Harvey HA, and Memoli MJ. (2010). The 1918 influenza pandemic: lessons for 2009 and the future. *Critical Care Medicine*, **38**(4 Suppl.), e10–20.
3. Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, and Lacroix J. (2009). Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *Journal of the American Medical Association*, **302**(17), 1872–9.
4. Davies A, Jones D, Bailey M, Beca J, Bellomo R, and Blackwell N. (2009). Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *Journal of the American Medical Association*, **302**(17), 1888–95.
5. Fowler RA, Lapinsky SE, Hallett D, Detsky AS, Sibbald WJ, and Slutsky AS. (2003). Critically ill patients with severe acute respiratory syndrome. *Journal of the American Medical Association*, **290**(3), 367–73.
6. Levy MM, Baylor MS, Bernard GR, Fowler R, Franks TJ, and Hayden FG. (2005). Clinical issues and research in respiratory failure from severe acute respiratory syndrome. *American Journal of Respiratory Critical Care Medicine*, **171**(5), 518–26.
7. Rubinson L, Hick JL, Curtis JR, Branson RD, Burns S, and Christian MD. (2008). Definitive care for the critically ill during a disaster: medical resources for surge capacity: from a Task Force for Mass Critical Care summit meeting, January 26–27, 2007, Chicago, IL. *Chest*, **133**(5 Suppl.), 32S–50S.
8. Christian MD, Joynt GM, Hick JL, Colvin J, Danis M, and Sprung CL. (2010). Critical care triage. Recommendations and standard operating procedures for intensive care unit and hospital preparations for an influenza epidemic or mass disaster. *Intensive Care Medicine*, **36**(Suppl. 1), S55–64.
9. Taubenberger JK and Morens DM. (2006). 1918 Influenza: the mother of all pandemics. *Emerging Infectious Diseases*, **12**(1), 15–22.
10. Sandrock C. (2010). Manpower. Recommendations and standard operating procedures for intensive care unit and hospital preparations for an influenza epidemic or mass disaster. *Intensive Care Medicine*, **36**(Suppl. 1), S32–7.
11. Devereaux AV, Dichter JR, Christian MD, Dubler NN, Sandrock CE, and Hick JL. (2008). Definitive care for the critically ill during a disaster: a framework for allocation of scarce resources in mass critical care: from a Task Force for Mass Critical Care summit meeting, January 26–27, 2007, Chicago, IL. *Chest*, **133**(5 Suppl.), 51S–66S.
12. World health Organization. (2007). Infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care: WHO Interim Guidelines June 2007. Available at: http://www.who.int/csr/resources/publications/csrpublications/en/index7.html (accessed 1 June 2012).
13. World health Organization. (2008). Infection control strategies for specific procedures in health-care facilities. Available at: http://www.who.int/csr/resources/publications/WHO_CDS_HSE_2008_2/en/ (accessed 1 June 2012).
14. Zimmerman JL and Sprung CL. (2010). Medical procedures. Recommendations and standard operating procedures for intensive care unit and hospital preparations for an influenza epidemic or mass disaster. Intensive Care Medicine, **36**(Suppl. 1), S65–9.
15. Shahpori R, Stelfox HT, Doig CJ, Boiteau PJ, and Zygun DA. (2011). Sequential organ failure assessment in H1N1 pandemic planning. *Critical Care Medicine*, **39**(4), 827–32.
16. Pipeling MR and Fan E. (2010). Therapies for refractory hypoxemia in acute respiratory distress syndrome. *Journal of the American Medical Association*, **304**(22), 2521–7.
17. Stockman LJ, Bellamy R, and Garner P. (2006). SARS: systematic review of treatment effects. *PLoS Medicine*, **3**(9), e343.
18. Brun-Buisson C, Richard JC, Mercat A, Thiébaut AC, and Brochard L. (2011). Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. *American Journal of Respiratory Critical Care Medicine*, **183**(9), 1200–6.
19. Rice TW, Rubinson L, Uyeki TM, Vaughn FL, John BB, and Miller RR, 3rd (2012). Critical illness from 2009 pandemic influenza A virus and bacterial coinfection in the United States. *Critical Care Medicine*, **40**(5), 1487–98.
20. InFACT Global H1N1 Collaboration (2010). InFACT: a global critical care research response to H1N1. *Lancet*, **375**(9708), 11–13.

PART 1.2

Communication

CHAPTER 10

Effective teamwork in the ICU

Peter G. Brindley

Key points

- Without effective teamwork high-quality critical care medicine is largely impossible.
- Traditionally, medicine has focused upon the individual practitioner, not the team.
- Fortunately, practical strategies can be adapted from other high-stakes professions.
- Communication skills are integral to good teamwork and can also be adapted.
- Better teamwork is a prime means to improve patient safety and medical culture.

The importance of teamwork

The modern jet 'is too much for one man to fly' [1]. Similarly, the complexity of critical care medicine means patients are too much for one clinician to manage alone. An Israeli study, publicized by the American surgeon, Atul Gawande, estimated that the average ICU patient required 178 individual actions per-day [1]. Regardless of the exact number, critical care imposes mental and physical demands that exceed even the most seasoned individual [2]. Therefore, without effective teamwork (defined as cooperative efforts to achieve a common goal) high-quality critical care is largely impossible [2].

Research from several high-stakes industries shows human factors to be the commonest reason for preventable errors [2,3] Growing evidence suggests the same during acute medical care [2–8]. Inadequate teamwork (and the intimately-related issue of **suboptimal communication**) is amongst the commonest human error [2–8]. Accordingly, following history's largest aviation disaster, investigators concluded that individuals had simply 'failed to take the time to become a team' [1]. Therefore, teamwork cannot be assumed [2]. Fortunately, it can be taught [2].

In contrast to other professions, medical curricula have rarely addressed teamwork (or communication) during crises [6]. Therefore, this chapter offers strategies from other high-stakes industries and applied to critical care. These ideas are not indigenous to medicine [4,5]. In fact, this may reflect a culture where health care workers have rarely thought in team terms [2]. Regardless, to discuss the medical teams that we want means promoting the medical culture that we need [1].

Many ideas in critical care can be illustrated using the double-headed god, Janus: representing the best and worst of what we do [9]. Teamwork and culture are no different. Western values have bolstered patient-ownership and self-reliance, but this means we highlight individual (rather than team) achievements [2]. We also promote the personal agenda over social cohesion, and equate success with individual efforts (or innate abilities), not the advantages of the community [2,7]. Accordingly, quality care has been linked to how the solo-practitioner performs and remedies centred on individual expertise (longer training, more scholarship) or high-technology assistance for that individual (computers, information technology) [2–6]. In short, it is time that less 'me' and more 'we' became a goal for critical care medicine [2].

There are 'fewer planes crash when the co-pilot is flying' [7]. If we continue to believe that crisis management is an individual endeavour then this is nonsensical, after all, senior pilots have more experience. However, planes are probably safer with co-pilots at the controls because the senior pilot is not afraid to speak up and the subordinate is fully engaged [7]. In short, this way more than one person flies, and a team is created that brings forth collective skills, experience, and wisdom. However, in addition to accepting the importance of teamwork, we must also perfect that team. After all, a team of experts is not the same as an expert team [2].

Good teams and bad

Not all teamwork is good. Milgram's experiments demonstrate our propensity to blind-obedience [10]. Asch's experiments show that people conform to the group, even when not compelled, and even when they know the group is wrong [10]. Moreover, once a majority of team members form an opinion, they usually stick with it, in spite of contradictory information [2]. They will subconsciously alter existing beliefs or add new ones, to reduce 'cognitive dissonance' [10]. Comfort in numbers or 'group think' (if all members agree, then we cannot be wrong) means that teams may follow the majority opinion not the rational argument [2,10]. Therefore, the search for solutions is prematurely abandoned. Groups also amplify individual behaviour for good and bad; tending towards greater risk if an individual's predisposition was to be risky, and towards more caution if individuals were risk averse [2,10]. Overall, the commonest team-failings are the inability to assign roles, to hold members to account, to advocate a position or corrective action, to use check backs, to communicate clearly, to seek usable information (not just data), and to prioritize tasks [2].

There are substantial differences between aviation and critical care. However, a useful principle from aviation is to focus not on **who is right**, but **what is right** [3,4,8] Aviation research also suggests that, in a crisis, 10% of people will lead, 10% will freeze, and 80% will neither lead nor freeze . . . but can be led [11]. To do so, a good leader must establish a 'shared mental model' (a common

understanding, with everyone 'on the same page') [2,3,8]. This allows teams to prioritize, manage information, establish roles, stabilize emotions, and build confidence [2]. If time allows, the leader can invite members to suggest a mental model ('What do you think? What would you do?'). Under time-pressure, the leader has to rapidly establish a model that members will support and amplify ('I believe its septic shock, please do the following . . .') [2,3].

As complexity increases, so does the possibility for harm. Fortunately, a clear team hierarchy can combat confusion and complexity [2,10]. However, hierarchy represents another double-headed Janus. What should be a strength (after all hierachy can provide much-needed order) can be a weakness (after all team members can feel too scared to contribute freely). Aviation crashes are commonly associated with subordinates not speaking up, even with their own lives at stake! [1,7]. On the other hand, without leadership, diffusion of responsibility can occur [2]. Typically, the easiest tasks will be addressed by several people, although one would suffice, while harder tasks remain undone [2]. Inexperienced teams can function well, but typically need more direction and centralized-control [2,10]. Fortunately, physicians are authorized a priori to lead [2]. However, the best teams are dexterous enough to modify structure, hierarchy, and communication norms in response to an individual problem [1,2,7,11].

As teams mature, their members learn to volunteer relevant information, voice concerns, verbalize contingencies, and apportion responsibility (so called 'explicit coordination') [2]. 'Cross-monitoring', or 'mutual-monitoring' also increases the team's cognitive capacity [2]. As teams mature they also anticipate and act with minimal talking ('implicit coordination') [2]. In short, typically, the more unfamiliar the task, and the more unfamiliar the team members, the more that explicit coordination is required. The more routine the task, and the more experienced the members, the less explicit coordination is required [2].

Simulation is another technique adapted from aviation. While useful for teaching individual skills, simulation's real strength is as a 'team laboratory'. Team skills, or **crew resource management** (CRM) skills, have been adapted to medicine as **crisis resource management**, and honed using simulation [4,5]. Of all CRM skills, the most important appears to be communication [3,8]. After all, if communication means to 'share, join, unite, or make understanding common' [2,3], then much of what makes a good team or good leader equates with communication [3]. Accordingly, improving communication may be the single wisest investment in patient safety and 'verbal dexterity' our greatest skill or liability.

Team communication

Team communication is more than just talking: it aids task-execution, information-exchange and relationship-building [2]. It is also more than just what is said—it matters how it is said and how it is understood [2,3,8]. Moreover, non-verbal communication (gesture, posture, eye contact) and para-verbal communication (tone, loudness, pacing, emphasis) are at least as important as verbal communication (potentially more so if there is incongruence) [2,8]. This means that we are unable to **not** communicate . . . even if we do not speak [2]. Following those caveats, we will now focus on verbal communication and will again apply strategies from other high-stakes industries.

Communication during medical crises or aviation disasters is a major source of preventable death [7,8]. Aviation has mandated 'horizontal authority' and 'horizontal communication' to flatten the authority gradient [7,12]. Aviation also demands 'transmitter orientated' communication (i.e. it is the speaker's responsibility to be understood), rather than 'receiver orientated' communication (where listeners are forced to work out what was meant) [7]. This requires a culture that empowers subordinates to speak up and to do so clearly [1,7,8]. It also requires 'active-listening' where others confirm understanding or demand clarification, regardless of seniority or embarrassment. [2–5,8]. In short, all members take responsibility for how messages are delivered, received, understood, and completed [2,3].

'Say what you mean; mean what you say'

Even experienced professionals can be prone to silence during crises [2,3]. In aviation, this means black-box silence for the few minutes before a crash [2]. Similarly, during resuscitation, health care workers may not speak due to stress or uncertainty. Instead, leaders should be taught useful phrases to break the silence ('Still no pulse . . . what am I missing?') [3]. Similarly, the military's situation, background, assessment, recommendation (SBAR) communication strategy offers a communication tool that, while being overly formal for some teams, offers structure for junior staff and unfamiliar situations [8,13]. A simple example would be: Situation: 'I'm Dr X, I need your help with . . .'; Background: '… a 35-year old trauma from today'; Assessment: '… still hypotensive despite blood'. Recommendation: 'You should review him, now' [3,13].

Pilots learn to grade their assertiveness [2–4,7,8,11,14–17]. This includes Besco's archetypal four-step PACE model (probing, alerting, challenging, emergency language) [14]. Others teach up to six steps, but all progress from least to most direct. This includes the 'hint' ('Should things look like this?'), 'preference' ('I would suggest . . .'), 'query' ('What do you think?'), 'shared suggestion' ('You and I could . . .'), 'statement' ('we need to . . .') and 'command' ('Do this now!') [6]. Without instruction, junior members may only hint, and, if ignored, fail to escalate their assertiveness [7]. Senior members may rely too much upon 'commands' as they are not concerned about being blunt [7]. Aviation also teaches a five-step model of advocacy and confirmation [17]. The following has aviation examples with medical corollaries: 'Attention getter' ('Excuse me, captain/doctor'); 'State your concern' ('We're low on fuel/the patient is hypotensive'); 'State the problem as you see it' ('I don't think we can land/I think we need vasopressors now'); 'State a solution' ('Let's re-route to another airport/I'll arrange ICU transfer'); and 'Obtain agreement' (e.g. 'Okay, captain/doctor?' [17].

Ambiguous or non-committal speech (aka 'mitigating speech') is common prior to airline crashes and during medical crises [7]. This is why we must replace comments like 'Perhaps we need a surgeon' or 'We should think about intubating', with 'Get me a surgeon' and 'Intubate the patient, now'. Junior members may mitigate to show deference, when embarrassed or if unsure. If time permits 'mitigating language' can be harmless, and may even aid team building ('If you get a moment could you help me with this patient?'). However, in a crisis, using the wrong communication tool is at least as dangerous as selecting the wrong surgical tool [2]. Regardless, over-cautious language is inappropriate during a crisis, just as overly brusque language is inappropriate during team building.

Crisis communication should still be polite, but also unequivocal and task-focused [3,8].

An aviation adage states that 'You never let a plane take you where your brain hasn't already been' [18]. Therefore, pilots are taught to communicate proactively [8] (i.e. to 'fly ahead of their planes') [18]. The principle could be adapted by both medical team-leaders ('I will be intubating soon, get the difficult airway cart') and subordinates ('The bolus is almost in, how about another?'). Communication must also be addressed to a specific person to avoid diffusion of responsibility [2,4,5]. This is why comments like 'could someone' and 'does anybody' are inappropriate [2]. Closed-loop (or challenge-response) communication means reinforcing instructions by demanding feedback ('John, intubate the patient, and tell me when it's done') [3–5,8,17]. 'Call outs' [17] alert the team to important changes ('He's going back into ventricular fibrillation') [18] and the 'Step back method' [17] means verbally forcing a 'time out' ('Stop compressions and reassess the cardiac rhythm'). The 'Repeat back method' [17] provides a safety check by repeating to confirm mutual understanding ('So that's one milligram of epinephrine?'). Similarly, the 'Read back method' [17] requires confirming an order before processing it.

Team members must speak up [7]. However, contributions must be task-focused and appropriately timed, otherwise it can further exacerbate chaos [2]. Accordingly, aviation's 'Sterile cockpit rule' applies to critical phases, such as take-off and landing [8,19,20]. The team ensures **no** unnecessary talk, and those silenced know not to take offence [19,20]. Similarly, medical practitioners should focus comments during resuscitation. In less-critical situations, we should confirm if others are free to talk. Once the crisis has abated, time should also be provided for more free-flowing communication. This is essential for debriefing, conflict management, stress relief, and to maintain the team for the next crisis [2].

References

1. Gawande A. (2009). The checklist. In: Gawande A (ed.) *The Checklist Manifesto*, pp. 32–48. New York, NY: Henry Holt and Company.
2. St Pierre M, Hofinger G, and Buerschaper C. (2008). *Crisis Management in Acute Care Settings: Human Factors and Team Psychology in a High Stakes Environment*. New York, NY: Springer.
3. Brindley PG and Reynolds SF. (2011). Improving verbal communication in critical care medicine. *Journal of Critical Care*, **26**, 155–9.
4. Gaba DM, Fish KJ, and Howard SK. (1994). *Crisis Management in Anesthesiology*. New York, NY: Churchill Livingstone.
5. Gaba DM. (1992). Dynamic decision-making in anesthesiology: cognitive models and training approaches. In: Evans DA and Patel VI (eds) *Advanced Models of Cognition for Medical Training and Practice*, pp. 123–47. Berlin: Sprinter-Verlag.
6. Aron D and Headrick L. (2002). Educating physicians prepared to improve care and safety is no accident: it requires a systematic approach. *Quality & Safety in Health Care*, **11**, 168–73.
7. Gladwell M. (2008). The ethnic theory of plane crashes. In: Gladwell M (ed.) *Outliers*, pp. 177–223. New York, NY: Little, Brown and Company.
8. Prineas S. (2011). Safety-critical communication. In: Cyna AM, Andrew MI, Tan SGM, and Smith AF (eds) *Handbook of Communication in Anaesthesia & Critical Care: A Practical Guide to Exploring the Art*, pp. 189–200. Oxford: Oxford University Press.
9. Brindley PG. (2010). Patient safety and acute care medicine: lessons for the future, insights from the past. *Critical Care*, **14**(2), 217–22.
10. Heffernan M. (2011). *Willful Blindness: Why We Ignore the Obvious at Our Peril*. Toronto: Doubleday/Random House Canada.
11. Leach J. (2004). Why people 'freeze' in an emergency: temporal and cognitive constraints on survival responses. *Aviation, Space, and Environmental Medicine*, **75**, 539–42.
12. Helmreich RL and Merritt A. (2000). Culture in the cockpit: do Hofstede's dimensions replicate. *Journal of Cross-Culture Psychology*, **31**, 283–301.
13. Institute for Healthcare Improvement (2011). SBAR technique for communication: a situational briefing model. Available at: http://www.ihi.org/IHI/Topics/PatientSafety/SafetyGeneral/Tools/SBARTechniqueforCommunicationASituationalBriefingModel.htm (accessed 16 February 2015).
14. Besco, RO. (1994). To intervene or not to intervene? The copilots 'catch 22': P.A.C.E. Probing, Alerting, Challenging, and Emergency Warning; the Integration of Crew Resource Management with Operational Procedures. Available at: http://picma.org.uk/sites/default/files/Documents/Background/Besco%20Co-pilots%20dilemma.PDF. (Accessed August 10 2015).
15. Fischer U and Orasanu J. (1999) Cultural diversity and crew communication. Available at: http://www.lcc.gatech.edu/~fischer/AIAA99.pdf (accessed 16 February 2015).
16. Leonard M, Graham S, and Bonacum D. (2004). The human factor: the critical importance of effective communication in providing safe care. *Quality & Safety in Health* Care, **13**(Suppl.), i85–90.
17. Dunn EJ, Mills PD, Neily J, Crittenden MD, Carmack AL, and Bagian JP. (2007) Medical team training: applying crew resource management in the Veterans Health Administration. *Joint Commission Journal on Quality and Patient Safety*, **33**(6), 317–25.
18. Skygod Quotes. (2002). Great aviation quotes. Cliches. Available at: http://www.skygod.com/quotes/cliches.html (accessed 16 February 2015).
19. Wikipedia. (2014). The Sterile Cockpit Rule. Available at: http://en.wikipedia.org/wiki/Sterile_Cockpit_Rule (accessed 16 February 2015).
20. Sumwait RL. (1993). The Sterile Cockpit Rule Aviation Safety Reporting System (ASRS). Available at: http://asrs.arc.nasa.gov/publications/directline/dl4_sterile.htm (accessed 16 February 2015).

CHAPTER 11

Communication with patients and families in the ICU

Leslie P. Scheunemann and Robert M. Arnold

Key points

- Structured meetings should occur regularly with families of all intensive care unit (ICU) patients.
- Premeetings help to ensure all the appropriate people have been included and that the clinical team has a coherent understanding of the patient's prognosis and treatment options.
- Family meetings should typically follow the format introductions, goal setting, family illness narratives, clinical updates, responses to family emotions and questions, understanding the patient, transitions to decision-making, making treatment decisions, and wrapping up.
- Debriefing allows the team to review how the patient's treatment plan has changed, to reinforce effective communication behaviours, and to troubleshoot places where communication faltered.
- Listening and responding to families' emotions are essential clinical communication skills.

Introduction

Over the past decade, holding regular, structured meetings between clinicians and the families of patients in the intensive care unit (ICU) has been increasingly advocated by leaders in quality improvement, critical care, and bioethics. Their most commonly cited benefits are reduced family emotional distress and reduced time in the ICU for dying patients [1]. Their structure and content has been informed by theoretical models of ethical decision-making for incapacitated patients [2,3].

Although informal meetings should occur continually, formal meetings are indicated:

- Within the first 72 hours of ICU admission [4].
- When conflict occurs among family members, or between the family and the clinical team [5].
- When the clinical team feels that the current goals of care should probably be revised [6].
- When the family or clinical team requests a meeting.
- When the patient's clinical status changes.

Additionally, the clinical team should meet every 5–7 days with families of patients who have longer than average stays. Because accurate prognostication for ICU patients is notoriously difficult, even families of ICU survivors are at increased risk of psychological symptoms compared with the general population, and families of survivors are less satisfied with communication with the ICU team than families of those who die, regular meetings should occur with families of all ICU patients [7].

The purpose of this article is to review the procedures teams can follow and skills they can develop to improve outcomes of care.

Mechanics of the family meeting

Formal family meetings should include short, focused premeetings and debriefing sessions (see Box 11.1) [8].

Premeeting

Before the family meeting, the clinical team should meet to ensure all the relevant people have been invited, ensure an appropriate space is available, and plan a communication strategy.

Inviting attendees

If a previously competent patient has requested that certain people should not be involved in decision-making, the request should be honoured [9]. Otherwise, any family members wishing to attend should generally be allowed to do so, particularly key family support figures and legal decision-makers. The minimal clinical representation is one member of the primary service responsible for the patient's care. Nurses, social workers, primary care providers, and consultants can contribute a spectrum of knowledge about the patient as a person, the patient's medical condition, possible treatments, and the practical aspects of future transitions (e.g. to hospice or a nursing facility, or for a family to make funeral arrangements), and thus should be included [6,7].

Setting

Most families feel uncomfortable discussing potentially sensitive issues about patient care at the bedside, and patient rooms are poorly structured for such discussions. If possible, ICUs should designate a quiet, private, comfortable room for family meetings [10]. Enough chairs should be available for everyone to sit, and clinicians and family members should ideally be interspersed among each other. Clinicians should minimize possible interruptions, put their pagers and phones on vibrate, and bring tissues.

Communication plan

Finally, clinical teams should take time before the family meeting to review the relevant clinical information, and establish their overall

Box 11.1 Generalized structure of the ICU family conference

Premeeting

Attendees

Representatives of all clinical services planning to attend the meeting proper.

Overarching goals

- Ensure relevant individuals have been invited to meeting proper.
- Ensure an appropriate space has been secured.
- Plan the communication:
  - Establish a facilitator for the meeting proper.
- Achieve consensus among the team about prognosis, appropriate possible treatments, where current decisions fall on the spectrum of shared decision-making.
- Plan a communication strategy.

Key suggestions

- Aim for efficiency—should rarely exceed 10 minutes.

Meeting proper

Attendees

- All family who want to attend, especially designated surrogates.
- Physician and nurse representative(s) of primary ICU service.
- Meaningfully involved consultants and primary care providers.
- Social workers.
- Chaplains.
- Interpreters.

Overarching goals

- Variably focus on updates, family support, or decision-making.
- Ensure flexibility in response to family needs.

Key behaviours

- Introductions:
  - Introduce team members and explain their roles.
  - Ask families to introduce themselves.
- Goal setting:
  - Explain the team's goals.
  - Ask the family to suggest other goals.
- Family illness narratives: ask the family what they understand.
- Clinical updates: provide big-picture, jargon-free clinical updates.
- Answer questions and respond to emotions.
- Understanding the patient:
  - Ask about the patient as a person.
  - Ask about previously expressed health care preferences.
  - Reflect on values evidenced by the descriptions of the patient.
- Transitioning to decision-making:
  - Summarize discussion of the patient's values.
  - Ask permission to talk about treatment plans.
  - Explain the principle of substituted judgment.
- Making decisions.
- Wrapping up.

Debriefing

Attendees

- Representatives of all clinical services who attended the meeting proper.

Overarching goals

- Delegate responsibility for items in the treatment plan and for where family support will be needed.
- Review what went well.
- Troubleshoot places where communication faltered.

Key Suggestions

- Keep it brief.
- Keep it action-orientated.

goals and expectations for the meeting [9]. Families are sensitive as to whether the team appears to have internal consensus [11]. Therefore, the team should internally resolve any apparent conflict about the patient's prognosis or potentially appropriate treatments ahead of time.

The meeting proper

Introductions

Families like to know who the people on the clinical team are and what their role is [10]. Introductions also explain who the family members are, and often give insights into their relationships, including hierarchies or conflicts [9].

Goal setting

It can be helpful to ascertain what the family's expectations and goals are for the meeting, and to clarify the goals of the clinical team. For example, 'We wanted to meet today to update you on how your mother is doing, to give you an idea of some things to expect in the short term, and to understand more about who she is, so we can provide her the best care possible. Do you have anything else that you would like to discuss?'

Family illness narratives

Asking the family what other health care providers have told them about the clinical situation targets several goals. First, their descriptions show their understanding of and reactions to the illness. Secondly, clinicians can avoid unintentionally contradicting or seeming to contradict other members of the team who may have talked to the family. Finally, having the family narrate the clinical course can avoid unintentionally and abruptly providing information for which they are unprepared. If the narrative indicates low expectation of bad news, clinicians can give a warning shot, such as, 'We all hope that being more awake than before is a good sign for him . . . Unfortunately, despite being more awake, he has developed new and serious problems this week.'

Clinical updates

Using this foundation, clinicians should explain the diagnosis and prognosis in clear, jargon-free language. Doing this well reduces families' uncertainty, removes barriers to patient-centred surrogate decision-making, and strengthens the relationship between families and providers [12]. It is often helpful to prognosticate in terms of 'hoping for the best, and preparing for the worst', and give specific details about when uncertain prognoses will be clearer [13]. Clinicians should not provide more than three pieces of information without pausing to assess family understanding.

Answering questions and attending to emotions

Families need the opportunity to react to the clinical update. Clinicians should stop and elicit questions and emotional responses by asking something like, 'This must be difficult to hear. What questions do you have?' Clinicians should answer briefly and focus on the big picture—they should continue eliciting questions until all of them have been asked.

Transitioning to decision-making

Decision-making is a common priority in family meetings. Clinicians can signal this transition by summarizing the important information about the patient, then saying, 'Given how her illness is going, and all these important things about her we've discussed, I'd like to talk about the future. Is that okay?' As long as the family accedes, clinicians should explain the goals of decision-making with statements like, 'We want the treatments we provide to honour and respect her. If your mom was sitting here and could hear what we have been talking about, what would she say?'[3].

Understanding the patient

If this question yields little information, it is important to stay focused on the patient as a way of being a good surrogate. Most of the time, ICU clinicians have not met the patient prior to the incapacitating critical illness. Asking, 'In order to make sure our treatments honour and respect her, it is helpful to know more about what she was like. Could you tell me about her?' opens up another avenue to understanding the patient. It allows ICU clinicians to connect to the patient in a more personal way, demonstrates caring to families, and generates a gestalt about the patient's core values that may be relevant for decision-making [14].

Making decisions

The initial approach to making decisions should be to ask whether the patient has any written or oral directives regarding care as above. Absent applicable directives, providers should discuss possible treatment pathways and their expected outcomes in the context of the understanding of the patient they have achieved. They should assess family understanding of and reactions to this information, and be ready to provide a patient-centred recommendation that links the values discussed previously to a treatment pathway [15]. Regardless of the chosen pathway, they should reassure the family that they will not be abandoned and that the patient's symptoms will be minimized [7].

Wrapping up

Before concluding, the next meeting should be scheduled, a family contact person designated, and the family informed about how to reach the team if needed before the next meeting.

Debriefing

Debriefing is an important way to summarize the information exchanged during the meeting, process reactions to it, and identify strategies for improving communication with individual families or in general.

Key skills and behaviours for clinicians

The most effective family communication focuses primarily on listening and responding to emotions (Box 11.2). Especially when complex transitions or conflict are anticipated, palliative care and ethics consultation can provide further specialized skills and support [1].

Listening

Clinicians tend to dominate family meetings, but families are more satisfied if they have greater opportunity to talk [16]. Therefore, clinicians should adopt practices that counteract this tendency. Among the most effective is 'ask-tell-ask,' in which they bookend their own insights with inquiries about the family's perspective or understanding [17].

Allowing silence

Especially after delivering bad news, clinicians should allow families time to digest and react to it. This may involve pauses of more than 15 seconds [14].

Responding to emotions

Families of critically-ill patients experience sadness, anger, guilt, fear, grief, and anxiety, most commonly expressed according to a 'fight or flight or freeze' paradigm. Clinicians should meet expressions of emotion with empathy [18]. Two mnemonics have been developed to organize clinicians' thinking about skills for managing family emotions—NURSE and VALUE (see Box 11.2) [19,20].

Conclusion

Communication with families in the ICU requires essential and unique clinical skills. A systematic approach to communication improves family satisfaction and emotional outcomes, and facilitates patient-centred decision-making. Clinicians should strive to communicate in a timely way that emphasizes emotional support for families, to explain the diagnosis, prognosis, and treatment options in a concise, jargon-free manner, and to help families connect patient values to the most appropriate treatment pathway. When more specialized communication skills are needed, they should collaborate with palliative care or ethics consultants.

Box 11.2 Key behaviours and skills for communicating with families

Listening

Ask-tell-ask

Tell me what you expect will happen? Why? . . .

I hope that he will get better, too. Unfortunately, the most likely thing is that, even if he gets out of the hospital, he will have to live in a nursing home and be dependent for most of his care . . .

How would he feel about that?

Allow silence.

Responding to emotions

NURSE mnemonic

N → Naming the emotion:

'I can see this is upsetting'.

'It sounds like you're frustrated'.

'Your clearly love your brother very much'.

U → Understanding the emotion:

'This must be so overwhelming'.

'I cannot imagine all you're going through'.

R → Respecting the family:

'You are doing an amazing job representing your mother'.

S → Supporting the family:

'Can we help at all?'

'It is so hard to have someone you love in the ICU'.

'Would it be helpful if I made a recommendation based on what we've talked about?'

E → Exploring the feeling:

'Tell me more about why you feel that way'.

'You seem upset'.

'What are you hoping for right now?'

VALUE mnemonic

V → Value family statements:

Reflect the statement back ('I heard you say . . . is that right?').

Try to understand what motivated the statement (e.g. emotions, need to express hope/caring).

A → Acknowledge families' emotions:

'This really has been worrying you, huh?'

'It seems like you feel strongly about this'.

L → Listen to the family:

'Tell me more'.

'Why do you think that?'

U → Understand the patient as a person:

'Tell me about him/her'.

'What did he most like to do?'

'Were there things she was really afraid of, as she got sicker?'

E → Elicit family questions:

'What questions do you have?'

'Does it make sense that we make decisions for people based on what they thought was important?'

VALUE mnemonic: Reprinted from *Journal of Critical Care*, **17**, 3, Curtis JR et al., 'Studying communication about end-of-life care during the ICU family conference: Development of a framework', pp. 147–160, copyright 2002, with permission from Elsevier and World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM) and Society for Complex Acute Illness (SCAI).

Acknowledgements

All work on this manuscript was performed at the University of Pittsburgh. Dr Arnold was supported by Jewish Healthcare Foundation and Arthur Vining Davis Foundations.

References

1. Scheunemann LP, McDevitt M, Carson SS, and Hanson LC. (2011). Randomized, controlled trials of interventions to improve communication in intensive care. *Chest*, **139**(3), 543–54.
2. Charles C, Whelan T, and Gafni A. (1999). What do we mean by partnership in making decisions about treatment? *British Medical Journal*, **319**(7212), 780–2.
3. Buchanan A and Brock D. (1989). *Deciding for Others: the Ethics of Surrogate Decision Making*. Cambridge: Cambridge University Press.
4. Glavan BJ, Engelberg RA, Downey L, and Curtis JR. (2008). Using the medical record to evaluate the quality of end-of-life care in the intensive care unit. *Critical Care Medicine*, **36**(4), 1138-46.
5. Way J, Back AL, and Curtis JR. (2002). Withdrawing life support and resolution of conflict with families. *British Medical Journal*, **325**(7376), 1342–5.
6. Mosenthal A, Murphy P, Barker L, Lavery R, Retano A, and Livingston D. (2008). Changing the culture around end-of-life care in the trauma intensive care unit. *Journal of Trauma*, **64**(6), 1587–93.
7. Curtis JR and White DB. (2008). Practical guidance for evidence-based ICU family conferences. *Chest*, **134**(4), 835–43.
8. Curtis JR and Rubenfeld GD. (2005). Improving palliative care for patients in the intensive care unit. *Journal of Palliative Medicine*, **8**(4), 840–54.
9. Chaitin E and Arnold R. (2007). Communication in the ICU: holding a family meeting. *UpToDate*, 11.
10. Pochard F, Darmon M, Fassier T, et al. (2005). Symptoms of anxiety and depression in family members of intensive care unit patients before discharge or death. A prospective multicenter study. *Journal of Critical Care*, **20**(1), 90–6.
11. Abbott B, Katherine H, Sago JG, Breen CM, Abernethy AP, and Tulsky JA. (2001). Families looking back: one year after discussion of withdrawal or withholding of life-sustaining support. *Critical Care Medicine*, **29**(1), 197–201.
12. Cassell EJ. (1985). *Talking with Patients*, Vols I–II. Cambridge, MA: MIT Press.
13. Evans LR, Boyd EA, Malvar G, et al. (2009). Surrogate decision-makers' perspectives on discussing prognosis in the face of uncertainty.

American Journal of Respiratory and Critical Care Medicine, **179**(1), 48–53.
14. Curtis JR, Engelberg RA, Wenrich MD, et al. (2002). Studying communication about end-of-life care during the ICU family conference: Development of a framework. *Journal of Critical Care*, **17**(3), 147–60.
15. Gries C, Curtis J, Wall R, and Engelberg R. (2008). Family member satisfaction with end-of-life decision making in the ICU. *Chest*, **133**(3), 704–12.
16. McDonagh J, Elliott T, Engelberg R, et al. (2004). Family satisfaction with family conferences about end-of-life care in the intensive care unit: Increased proportion of family speech is associated with increased satisfaction. *Critical Care Medicine*, **32**(7), 1484–88.
17. Back AL, Arnold RM, Baile WF, Tulsky JA, and Fryer-Edwards K. (2005). Approaching difficult communication tasks in oncology. *CA: A Cancer Journal for Clinicians*, **55**(3), 164–77.
18. Selph RB, Shiang J, Engelberg R, Curtis JR, and White DB. (2008). Empathy and life support decisions in intensive care units. *Journal of General Internal Medicine*, **23**(9), 1311–17.
19. Fischer GS, Tulsky JA, and Arnold RM. (2000). Communicating a poor prognosis. In: Portenoy R and Bruera E (ed.) *Topics in Palliative Care*, Vol. 4, p. 75–91. New York, NY: Oxford University Press.
20. Lautrette A, Darmon M, Megarbane B, et al. (2007). A communication strategy and brochure for relatives of patients dying in the ICU. *New England Journal of Medicine*, **356**(5), 469–78.

CHAPTER 12

Telemedicine in critical care

Bela Patel and Eric J. Thomas

Key points

- The majority of critically-ill patients are admitted to hospitals that do not have physician intensivist coverage, despite the strong evidence that clinical outcomes are improved with intensivist staffing.
- Telemedicine can leverage clinical resources by providing critical care expertise to patients in intensive care units (ICU) by off-site clinicians using video, audio, and electronic links. Telemedicine in critical care has seen tremendous growth in the number of ICU patients being supported by this care model across the USA.
- The impact of ICU telemedicine coverage on ICU outcomes has been studied rigorously in only a few studies over the last 15 years, and the outcomes have been mixed and inconsistent.
- Telemedicine studies show improved adherence to best practices for the prevention of deep venous thrombosis, stress ulcers, cardiovascular protection, prevention of ventilator-associated pneumonia, and catheter-related bloodstream infections.
- Further research in ICU telemedicine is required to understand the variability of outcomes among the telemedicine programmes studied, and to effectively implement the technology to consistently improve outcomes and reduce costs in the critical care environment.

Background and definition of ICU telemedicine

In the United States alone, more than 5 million patients are admitted to the intensive care units (ICUs) every year. A great majority of these patients are admitted to hospitals that do not have physician intensivist coverage, despite strong evidence that clinical outcomes are improved with intensivist staffing [1]. Shortage of skilled critical care professionals combined with increasing health care demands from the ageing population may pose a serious threat to the health care delivery in the intensive care units [2]. Technology-enabled care models have been developed to expand the availability of critical care expertise, regardless of the location of the patient over the last few decades. Telemedicine is the use of medical information exchanged from one site to another via electronic communications to improve health [3]. Telemedicine in critical care is care provided to patients in ICUs by off-site clinicians using video, audio, and electronic links to leverage clinical resources. Telemedicine in critical care was first described in the late 1970s and has subsequently seen tremendous growth in the number of ICU patients being supported by the technology [4,5].

Classification: care models, structure, technology

A lexicon was recently designed and described to facilitate communication, comparison and evaluation of ICU telemedicine. Based on this lexicon, ICU telemedicine care models can be divided based on the delivery of care—continuous care, pre-emptive/scheduled care, or reactive ICU telemedicine care. As the field rapidly evolves, there may be care models that are a combination of these designs [6].

In a continuous care model, care is provided based on different staffing models (8-, 12-, 18-, or 24-hour coverage). Within an institution that initiates a continuous care model, individual attending physicians may still have the liberty to opt-in or opt-out of specific services. In the pre-emptive/scheduled care model, visits occur by the virtual care team at defined intervals, corresponding to morning and afternoon rounds in a traditional ICU model. In the reactive ICU telemedicine care model, the tele-intensivist responds to an issue and/or provides clinical expertise on an as-needed basis.

The organizational structure of ICU telemedicine can be a centralized or a de-centralized model. In the centralized model, which has also been described as a hub-and-spoke model, the centre is an established remote location staffed by intensivists, nurses, and other team members. The comprehensive centres have ICU telemedicine workstations that display clinical information, physiological and laboratory alerting systems, and allow 2-way audio and video communication with the hospitals IT services. In the decentralized model, multiple computers are connected to the site that ICU telemedicine is servicing, and these computers may be inter-connected by tele-providers at multiple locations, such as from homes, offices, etc. [6,7].

Rapid development of technology has been one of the major driving forces behind the robust growth of this field, and such technology has allowed the remote care provider to effectively provide patient care. Such technology can be broadly divided into either technology based on the ICU telemedicine end or at the ICU patient end. The ICU telemedicine end is defined as the site where the remote care provider originates the telemedicine service that may utilize fixed and/or portable technology. Fixed technology at this end relays information from the ICUs that the ICU telemedicine is servicing. Portable technology at the ICU telemedicine end could be a laptop enabled with Internet access, built-in or attached camera, microphone, software, and the required memory space. Mobile technology at the ICU telemedicine end has also seen

growth, through mobile devices that have audio-visual access together with graphic capabilities. Technology that is fixed at the ICU end are devices such as audio-video devices that are permanently attached to some site near the patient. Portable technology at the ICU are systems that are capable of arriving at the bedside, which are capable of having two-way communication. This portability of technology at the ICU end has been further subcategorized as those devices that have dependent portability, semi-autonomous independent portability, or autonomous independent portability. Dependent portability devices, for example, include cart systems dependent on personnel for all activities; these carts have audio-visual access built-in, so the remote clinicians can communicate with on-site providers regarding the ongoing care of the patient. Semi-autonomous independent portability devices are those that are under the direct control of the remote clinical care provider. These devices operate via the wireless environment. Autonomous independent portable devices are currently under development, and these will be programmed to recognize the layout of the ICU and respond to emergencies by automation [6].

Telemedicine ICU outcomes

The impact of ICU telemedicine coverage on ICU outcomes has been studied rigorously in only a few studies over the last 15 years, and the outcomes have been mixed and inconsistent. Initiation of a commercial system installation was first described in Norfolk, Virginia, where the feasibility of utilizing telemedicine as a means of achieving 24-hour intensivist coverage was first reported. This study was an observational study in a 10-bed surgical ICU in a 450-bed, academic-affiliated community hospital. They enrolled patients that presented to the ICU during a 16-week period (n = 201) where the intensivists provided support from home, 24 hours/day. This group was compared with two different baseline periods at the same facility (n = 225, n = 202). The authors reported a 45% reduction in severity-adjusted ICU mortality, and a 30% reduction in hospital mortality and length of stay. ICU costs were also shown to be decreased by 16%. This was one of the first studies that demonstrated the feasibility of continuous intensivist oversight in an ICU by means of computer-based data transmission to obtain clinical information and manage patients remotely [8]. A follow-up study evaluated the outcomes of an ICU telemedicine model in a 10-bed general medical ICU and an 8-bed surgical ICU over a 6-month period. The intervention group received tele-intensivist directed care from 12.00 to 07.00 hours every day from an off-site location. The study demonstrated ICU and hospital mortality reduction during the period by 27% (9.4 versus 12.9%). ICU length of stay was decreased by 16% (3.63 versus 4.35 days). This study also reported a hospital cost savings of 2556 dollars per case due to decreased ICU length of stay [9]. Another study of more than 4000 patients conducted to determine the impact of a telemedicine system in two community hospitals revealed no significant effect on ICU and non-ICU total mortality or hospital length of stay.[10]

An observational study from our medical centre evaluated the ICU telemedicine model in six ICUs in five hospitals, where a total of 2034 patients from the pre-intervention period were compared with 2108 patients in the post-intervention period. Local physicians delegated full authority to the ICU telemedicine for only 655 patients (31.1%) in the study. For the remaining patients, ICU telemedicine intervention required direct communication with the treating physician except for life-threatening events. The hospital mortality rates were 12.0% in the pre-intervention period and 9.9% in the post-intervention period (p = 0.03). However, after adjusting for severity of illness there were no differences between the intervention and control group. Interestingly, in this study, we found that there was a correlation between the ICU telemedicine intervention and severity of illness ($p < 0.001$) [11].

Improved mortality and ventilator use in a study that used the ICU telemedicine staffing model at night times to achieve intensivist coverage 24 hours/day, 7 days/week. This study involved a 727-bed academic community hospital, a total of 954 control patients receiving care for 16 months before the implementation of the model, and a total of 959 study patients received care for 10 months after implementation. Mortality of the control and intervention groups were 21.4 and 14.7%, respectively. The observed mortality for the intervention group was 75.8% ($p < 0.001$) of that predicted by the Acute Physiology and Chronic Health Evaluation IV hospital mortality equations, which was 29% lower than the control group. The intervention patients also had significantly less time on mechanical ventilation (p = 0.001) [2].

A well-established group at the University of Massachusetts found that the implementation of ICU telemedicine was associated with reduced adjusted odds of mortality (adjusted odds ratio (OR), 0.40 (95% CI, 0.31–0.52)). Furthermore, the study showed a higher rate of best practice clinical adherence for the prevention of deep venous thrombosis, stress ulcers, cardiovascular protection, prevention of ventilator-associated pneumonia, and catheter-related bloodstream infections. They reported a shorter hospital length of stay (9.8 versus 13.3 days, respectively) and concluded that their implementation of an ICU telemedicine intervention was associated with reduced adjusted odds of mortality, reduced hospital length of stay, together with changes in best practice adherence [12].

Given the conflicting evidence, a meta-analysis that was conducted in 2011 analysed the combined outcomes of studies in ICU telemedicine, and further focused on 13 studies that met the quality criteria for inclusion in the meta-analysis. Out of the 12 studies that reported ICU mortality, the meta-analysis reported that the ICU mortality among 40,541 patients (15,311 pre-intervention and 25,230 post-intervention), was significantly reduced (pooled OR, 0.80; 95% CI, 0.66–0.97; p = 0.02). Out of these studies, only 10 studies reported in-hospital mortality for patients admitted to an ICU, and the pooled analysis revealed that the ICU telemedicine monitoring was not associated with a statistically significant reduction in in-hospital mortality for patients admitted to an ICU (p = 0.08). Out of the seven studies that reported ICU length of stay, implementation of ICU telemedicine coverage was associated with a significant reduction in ICU length of stay (mean reduction of 1.26 days; 95% CI = 2.21 to –0.30 days; p = 0.01), but was not associated with a reduction in hospital length of stay (p = 0.16) [13].

Implementation and measurement strategies

The inconsistent findings in ICU telemedicine studies are probably due to variable implementation strategies and differences in organizational contexts. A comprehensive plan has to be devised keeping the institution goals and objectives, physician capacity, patient flow, and existing infrastructure in mind. There should be careful consideration given to the kind of care model that will be utilized in

providing care. The technical aspects have to be thoroughly evaluated both at the ICU telemedicine and the ICU end. Both portable and fixed technologies have to be meticulously tested prior to decision endpoints. There are several barriers that organizations have to overcome to implement ICU telemedicine in their hospital environment. There may be a dearth of financial resources for initiation and maintenance of the telemedicine technology and staffing together with competition from IT for other electronic medical record (EMR)-related financial expenses. The ICU telemedicine workstation will have a technical learning curve that needs to be mastered by the ICU telemedicine physicians and nurses. Global acceptance of ICU telemedicine by the bedside physician and staff will require education and development of unit-based support. Physician licensing across states and credentialing at multiple facilities could pose a barrier to initial implementation. Lack of integration of the ICU telemedicine into the hospital medical records may delay care in some instances. Assessment of the programme effectiveness should be incorporated into the overall implementation plan. There are two main methods reported to evaluate an ICU telemedicine programme. The first method is to compare acuity-adjusted hospital, ICU mortality, and/or length of stay between the pre- and post-implementation period. The second method is to compare these standardized ratios over a period of time. This ratio can be compared with a reference population.

Multidisciplinary team

Successful ICU telemedicine is based on a team approach similar to the standard ICU model. The ICU telemedicine multidisciplinary team of intensivists, pharmacists, technicians, and critical care nurses are crucial to the success of the programme. The ICU telemedicine's nurses play a key role in monitoring the patients on a continuous basis and highly-skilled nurses with a vast experience may like providing patient care in a new setting. Those that are excellent at problem solving, and have good communication and computer skills will be assets to an ICU telemedicine model. Implementation of ICU telemedicine is associated with improved teamwork climate and safety climate in ICUs among nurses [14].

Supporting ICU telemedicine

The main argument in favour of telemedicine relates to extending the reach of the short supply of intensivists and improving efficiency of critical care delivery [15]. Based on estimates of current and future requirements for adult critical care physicians in the USA, with the ageing US population, the demand for critical care physicians will grow rapidly, with a projected shortfall of specialists equal to 22% of demand by 2020 and 35% by 2030 [1]. A number of strategies have been suggested to bridge this gap, including organizational changes to incorporate ICU telemedicines, because a single intensivist can manage multiple patients at multiple ICUs that would otherwise not have an intensivist to direct critical care. Furthermore, a recent Agency for Healthcare Research & Quality (AHRQ) report suggests that increasing use of electronic ICUs may have a crucial role in improving patient access to cost-effective and quality care, especially in rural areas [15]. Providing critical care expertise in rural areas that would otherwise not be serviced by an intensivist even during the daytime is not only of benefit to adult populations, but crucial in paediatric populations [16,17].

Utilizing technology to analyse large volumes of objective real-time clinical data leverages the intensivist team in expanding coverage capabilities. Smart alarms can alert the on-call physician and enable them to provide efficient patient care in a time-sensitive manner. Providing cost-effective care by decreasing ICU length of stay will help relieve the burden on leading health care organizations. Utilizing technology to improve adherence to best practice guidelines will further enable physicians to improve overall outcomes in the critical care population with traditionally high mortality rates. The results from the meta-analysis reporting a reduction in ICU mortality and ICU length of stay are important, but more studies are needed to understand the lack of translation to overall improvement in hospital mortality or hospital length of stay [18].

Against ICU telemedicine

General arguments against ICU telemedicine have been centred on the lack of robust evidence that such models improve overall outcomes consistently. Another limitation of remote telemedicine is the lack of bedside presence of the physician in providing appropriate critical care interventions in an unstable patient and lack of the traditional patient–physician relationship. Finally, some of the beneficial studies in ICU telemedicine are industry sponsored, and more independent research should be conducted and validated prior to introducing generalizations.

Conclusion

Implementation of a comprehensive programme in ICU telemedicine can redesign health care delivery in the critical care environment to improve outcomes. Although studies have been conflicting on whether ICU telemedicine improves outcomes, a recent meta-analysis demonstrated a significant reduction in ICU mortality and ICU length of stay, but not in-hospital mortality or hospital length of stay. There are substantial variations in the organization of ICU telemedicine programmes across the USA, and perhaps the greatest value may be in rural areas with limited or no intensivist staffing. Further research into ICU telemedicine is required to understand the variability of outcomes among the programmes studied and advance health care delivery science in telemedicine to effectively improve outcomes and reduce costs in the critical care environment.

References

1. Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J Jr, and Committee on Manpower for Pulmonary and Critical Care Societies (COMPACCS). (2000). Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *Journal of the American Medical Association*, **284**(21), 2762–70.
2. Ewart GW, Marcus L, Gaba MM, Bradner RH, Medina JL, and Chandler EB (2004). The critical care medicine crisis: a call for federal action: a white paper from the critical care professional societies. *Chest*, **125**(4), 1518–21.
3. American Telemedicine Association (2013). ATA Site. Available at: http://www.americantelemed.org/ (accessed 8 November 2013).
4. Grundy BL, Crawford P, Jones PK, Kiley ML, Reisman A, Pao YH, et al. (1977). Telemedicine in critical care: an experiment in health care delivery. *Journal of the American College of Emergency Physicians*, **6**(10), 439–44.

5. Grundy BL, Jones PK, and Lovitt A. (1982). Telemedicine in critical care: problems in design, implementation, and assessment. *Critical Care Medicine*, **10**(7), 471–5.
6. Reynolds HN, Rogove H, Bander J, McCambridge M, Cowboy E, and Niemeier M. (2011). A working lexicon for the tele-intensive care unit: we need to define tele-intensive care unit to grow and understand it. *Telemedicine and e-Health*, **17**(10), 773–83.
7. Reynolds HN, Bander J, and McCarthy M. (2012). Different systems and formats for tele-ICU coverage: designing a tele-ICU system to optimize functionality and investment. *Critical Care Nursing Quarterly*, **35**(4), 364–77.
8. Rosenfeld BA, et al. (2000). Intensive care unit telemedicine: alternate paradigm for providing continuous intensivist care. *Critical Care Medicine*, **28**(12), 3925–31.
9. Breslow MJ, Dorman T, Breslow MJ, et al. (2004). Effect of a multiple-site intensive care unit telemedicine program on clinical and economic outcomes: an alternative paradigm for intensivist staffing. *Critical Care Medicine*, **32**(1), 31–8.
10. Morrison JL, Cai Q, Davis N, et al. (2010). Clinical and economic outcomes of the electronic intensive care unit: results from two community hospitals. *Critical Care Medicine*, **38**(1), 2–8.
11. Thomas EJ, Lucke JF, Wueste L, Weavind L, and Patel B. (2009). Association of telemedicine for remote monitoring of intensive care patients with mortality, complications, and length of stay. *Journal of the American Medical Association*, **302**(24), 2671–8.
12. Lilly CM, Cody S, Zhao H, et al. (2011). Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. *Journal of the American Medical Association*, **305**(21), 2175–83.
13. Young LB, Chan PS, Lu X, Nallamothu BK, Sasson C, and Cram PM. (2011). Impact of telemedicine intensive care unit coverage on patient outcomes: a systematic review and meta-analysis. *Archives of Internal Medicine*, **171**(6), 498–506.
14. Chu-Weininger MY, Wueste L, Lucke JF, Weavind L, Mazabob J, and Thomas EJ. (2010). The impact of a tele-ICU on provider attitudes about teamwork and safety climate. *Quality & Safety in Health Care*, **19**(6), e39.
15. Health Resources and Service Administration. The critical care workforce: a study of the supply and demand for critical care physicians. Available at: http://bhpr.hrsa.gov/healthworkforce/reports/studycriticalcarephys.pdf. (accessed 9 November 2013).
16. Yeo C, Ho SK, Khong K, and Lau Y. (2011). Virtual visitation in the neonatal intensive care: experience with the use of internet and telemedicine in a tertiary neonatal unit. *Permanente Journal*, **15**(3), 32–6.
17. Marcin JP, Ho SK, Khong K, and Lau Y. (2004). Use of telemedicine to provide pediatric critical care inpatient consultations to underserved rural Northern California. *Journal of Pediatrics*, **144**(3), 375–80.
18. Smith AC and Armfield NR. (2011). A systematic review and meta-analysis of ICU telemedicine reinforces the need for further controlled investigations to assess the impact of telemedicine on patient outcomes. *Evidence Based Nursing*, **14**(4), 102–3.

PART 1.3

Training

CHAPTER 13

Clinical skills in critical care

Graham Nimmo and Ben Shippey

Key points

- Some clinical skills are labelled 'basic', such as basic airway management. The derogatory connotations of this label devalue **fundamental** skills, which if correctly applied can be life saving.
- Decision making is likely the most frequently enacted clinical skill in intensive care, yet it is inadequately understood by clinicians and sparsely taught. This needs to be addressed.
- Knowing when **not** to perform a practical procedure is as important as knowing **how** to perform it.
- So-called soft skills involving communication, team working, and situation awareness are actually the hardest. They are harder to do, learn, teach and evaluate than are practical skills.
- No matter how much support we provide a patient, if the diagnosis is wrong and definitive treatment missing, improvement is unlikely. Ensuring the correct diagnosis is a pivotal clinical skill.

Introduction to clinical skills in intensive care

When we think of clinical skills in the context of critical care it is usual to consider practical procedures [1] such as those listed in Box 13.1. These clinical skills are highly visible in clinical practice, can be taught in an easily understood, well-defined sequence (Box 13.2), and can be readily assessed both in the clinical area and in the skills laboratory. A capable critical care practitioner should be able to perform these skills safely and effectively.

However, the performance of even the most fundamental practical skill involves thinking and decision making as detailed by Croskerry [2]. Indeed, the decision on how to perform the skill, or even not to perform the skill at all, may be the most important step in the whole process. Taking central venous access as an example, choices need to be made about the site of access, with the internal jugular the preferred route, but the subclavian or femoral being indicated in certain circumstances. For example, if the patient has a significant coagulopathy, or is to receive thrombolysis, but central venous access is mandatory, the femoral or internal jugular routes are preferable to the subclavian as the related arteries are compressible. In a resuscitation situation, the use of large bore peripheral venous access may be entirely satisfactory, with the use of central access a secondary consideration further down the line.

So a great deal of our clinical time in intensive care is spent in the cognitive domain: thinking, analysing, weighing-up options, making decisions. In addition to this, many of the clinical skills that we practice, particularly as we become more experienced, comprise an amalgamation of a number of different practical, cognitive, and behavioural elements, which need to be coordinated into the final blended skill. Box 13.3 gives some examples of these. The 'emergency intubation checklist' (Fig. 13.1) shows how the different elements can be teased out both as a practical guide for the procedure, but also as a template for teaching the skill. Individual components are learnt in the skills lab and under clinical supervision (e.g. laryngoscopy, confirmation of endotracheal intubation). These are then integrated into the whole process incorporating the non-technical skills, as delineated by Reader [3,4], of decision making, team working and coordination, planning and prioritization, task management, situation awareness, and communication. These skills have been described as 'soft', but this belies the reality. These skills are actually **harder**. They are harder to perform, harder to learn, harder to teach, and harder to assess than practical skills. As we spend most of our time in clinical practice undertaking these non-technical skills, it behoves us to concentrate much more time in understanding and researching them, providing training to, and educating, clinicians than we have previously done. Although these skills were traditionally learnt 'on-the-hoof' in clinical practice they can now also be rehearsed in the simulation situation, in the simulation laboratory or using point-of-care simulation in the ICU, but also under supervision in clinical practice, of course.

Complex clinical skills in intensive care

The blended skills listed in Box 13.3 involve the integration of cognitive, behavioural, and affective components for the successful completion of the process involved.

Thinking

Clinical decision making is a pivotal skill in intensive care. Knowledge of the dual process theory of thinking and decision making is helpful both in the teaching and practice of clinical decision making [2]. There are two main thinking processes involved. System 1 is intuitive, quick, and demands little energy, but is prone to error and emotional influence—this is 'gut' reaction. System 2 is analytical, relatively laborious, but is more reliable and considered. If we know how we have made a decision, e.g. rapid-fire, and realize it could be wrong we can actively toggle between system 1 and system 2, to calibrate and improve our decision making (see Fig. 13.2). The main elements of the dual process model are:

- **The toggle function**: awareness of the processes and how to move from one mode to the other.

Box 13.1 Practical clinical skills

General

- Hand washing.
- **Vital signs**: respiratory rate, pulse, cuff blood pressure, conscious level, temperature.
- Oxygen therapy and nebulizers.
- Basic airway management, basic life support.
- Clinical examination.
- Bedside glucose measurement, urinalysis, pulmonary function tests, occult blood testing, urinary bladder catheterization, gastric tube insertion.
- Venepuncture, blood cultures, cannulation, intravenous fluid and drug administration, injection (subcutaneous, intramuscular), arterial blood gas sampling.
- Pleural aspiration, chest drain insertion, lumbar puncture.

Advanced

- **Airway management**: intubation, ventilation.
- **Advanced life support**: defibrillation, cardiac pacing.
- **Invasive monitoring**: arterial cannulation, central venous cannulation, cardiac output monitoring.
- Intra-osseous access.

Box 13.2 Teaching practical clinical skills

Knowledge

- Indications and contraindications: decision making.
- Consent.
- Safety aspects: e.g. coagulation, allergy, sharps.
- Anatomy and physiology.
- Equipment and technique.
- Complications and treatment.
- Interpretation of results.

Skills

- Preparation.
- Aseptic technique.
- Handling equipment.
- Practice on skills trainer.
- Supervised clinical practice.
- Independent experiential learning.

Box 13.3 Blended complex skills

- Recognition, assessment, management of the critically ill.
- Emergency intubation.
- Echocardiography.
- Handover.
- Brain stem death testing.
- Withdrawal of support.

- **Metacognition**: thinking about how we are thinking can allow us to move from intuitive to analytical thinking and also, in the case of an expert, to go with the intuitive decision, as it is based on experience and repetitive learning, as long as it is remembered that the decision may still be wrong!
- Most errors occur in System 1.
- Repetitive operations of System 2 allow more accurate decision making in System 1. As clinicians gain experience they are able to utilize System 1 more effectively, and also have a greater understanding of when and why this might fail, necessitating a move to a more analytical approach.
- System 2 can override System 1 to make decision making better.
- System 1 can override System 2, particularly when emotion, fatigue, and distractions are present jeopardizing decision making.
- To reduce costs in terms of time and energy, the brain's natural default position is System 1, the so-called 'cognitive miser function'.

Behaviours

Whether you are the trainee doctor, bedside nurse, advanced practitioner, nurse in-charge or a consultant, working in intensive care constantly involves multi-tasking—prioritization of tasks, illness severity assessment and prioritization of patients, juggling multiple clinical problems, managing interruptions as proposed by Nimmo (5), planning admissions and discharges, and coordinating care. The individual non-technical skills involved have been delineated earlier, but there are added levels of complexity. Whatever the nature of the patient's problems and diagnosis are, the intensivist is in the unique position of appreciating how these apply in the context of critical illness and intensive care. In interactions with referring speciality clinicians, it is the place of the intensivist to synthesize an agreed management plan, which may involve accepting or declining specialist advice. This skill requires disciplined listening and sensitive negotiation, as well as knowledge and experience.

Affect

Intensive care can be a high tension environment and emotional elements interweave with the practical and clinical aspects. Particularly in end-of-life care, other aspects of clinical skills are required. In this situation, it may be appropriate to delay decisions, to give more time for the patient, family, and staff. Recognition of our own feelings is an important factor in optimizing these decisions.

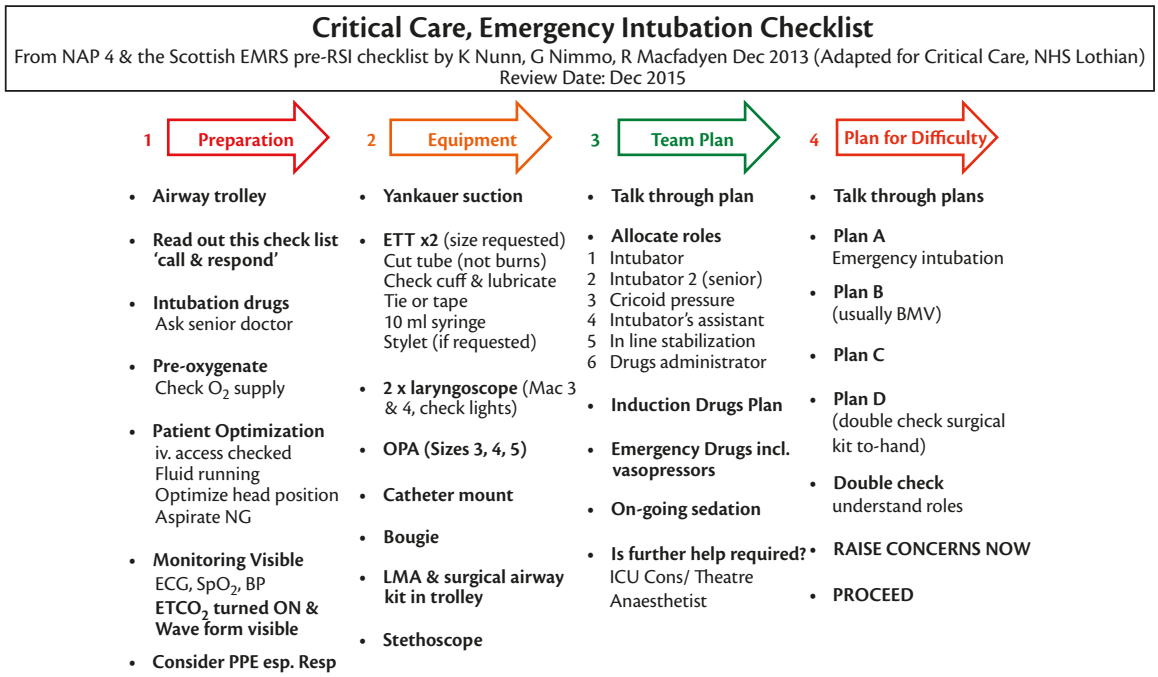


Fig. 13.1 Emergency intubation checklist.

O_2, oxygen; iv, intravenous; NG, nasogastric; ECG, electrocardiogram; SpO_2, pulse oximeter oxygen saturation; BP, blood pressure; $ETCO_2$, end-tidal carbon dioxide; PPE, personal protective equipment; ETT, endotracheal tube; OPA, oro-pharyngeal airway; LMA, laryngeal mask airway; BMV, bag-mask ventilation.

From NAP 4 & the Scottish EMRS pre-RSI checklist by K Nunn, G Nimmo, R Macfadyen Dec 2013 (Adapted for Critical Care, NHS Lothian), review date: Dec 2015.

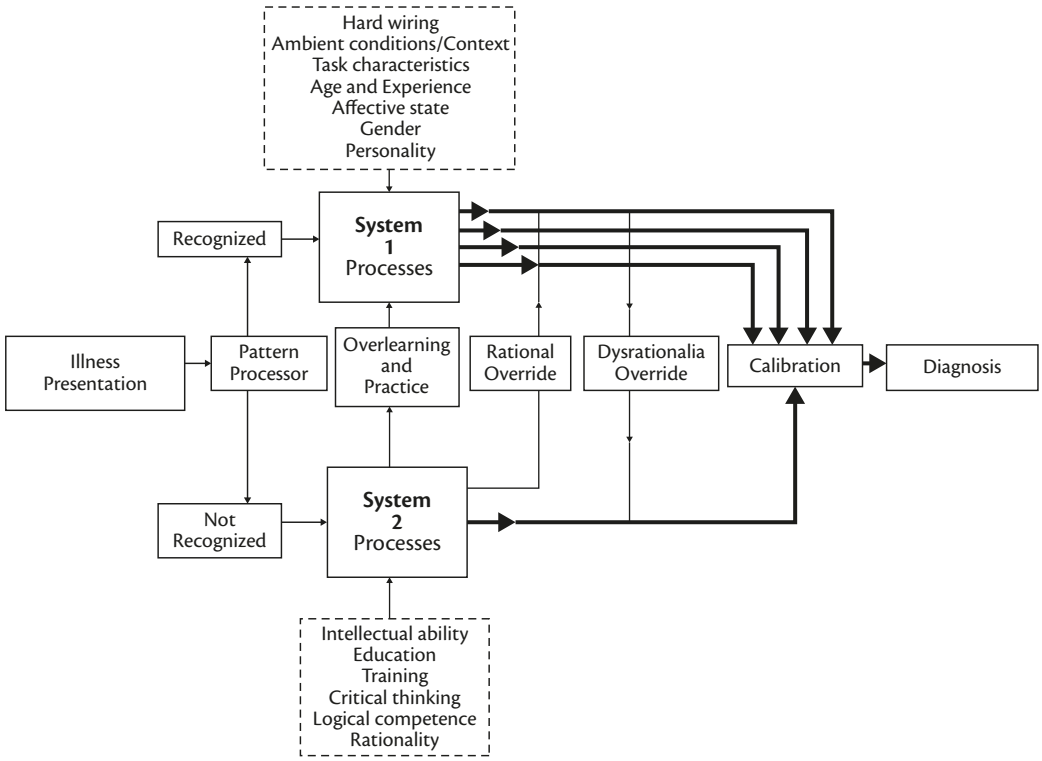


Fig. 13.2 Model for diagnostic reasoning, based on pattern recognition and dual-process theory. The model is linear, running from left to right. The initial presentation of illness is either recognized or not by the observer. If it is recognized, the parallel, fast, automatic processes of System 1 engage; if it is not recognized, the slower, analytical processes of System 2 engages instead. Determinants of Systems 1 and 2 processes are shown in the dotted-line boxes. Repetitive processing in System 2 leads to recognition and default to System 1 processing. Either system may override the other. Both system outputs pass into a calibrator in which interaction may or may not occur to produce the final diagnosis.

Reproduced from Croskerry P, 'A Universal Model of Diagnostic Reasoning', *Academic Medicine*, **84**(8), pp. 1022–8, copyright 2009, with permission from Wolters Kluwer and the Association of American Medical Colleges.

Handover

Handover of care is a bread-and-butter part of everyday emergency and scheduled clinical practice. **Good** handover is said to improve patient safety and reduce error. The risks of poor handover have also been identified and are emphasized by its description as **a perilous procedure**.

Handover is the medium whereby the continuity of patient care can be constructed and assured. An individual patient's clinical course, co-morbidities, diagnoses, and specific therapeutic requirements are just some of the strands which are entwined by their nurse and doctor to construct a **life thread**, which is passed to incoming staff across the potential disrupted space, which comprises a transfer of care, such as a change of shift or a move from one clinical area to another. Handover could also be viewed as a place of concatenation, of linking the chain of events in the patient's journey, and therefore a valuable check point to pick up missed aspects of care or errors.

Thus, in order to minimize risk and to deliver good quality care an acute appreciation of the pitfalls of handover allows those receiving the handover to check that certain elements are indeed accurate—name, date of birth, diagnosis, treatment given so far, relatives, and what they have been told. We are in a particularly vulnerable position, as a diagnosis has often been made prior to transfer to intensive care. The questions we must ask as part of our diagnosis checklist are these:

- Is the diagnosis correct?
- Is the diagnosis complete?
- Is there something else going on?

If we don't get the disease modifying *treatment* right, no matter how much organ system support we apply, the patient will not do well.

Conclusion

Clinical skills range from simple tasks to complex interactions of thinking and doing. Acquisition of knowledge followed by practice of these skills allows the novice to gain experience and become capable of delivering these skills capably in clinical practice. For the more complex skills, the expert will continue to learn and hone these throughout their career, particularly in the light of verbal and non-verbal feedback from patients and their families, and from colleagues.

References

1. Jackson G, Soni N, and Whiten CJ. (2010). *Practical Procedures in Anaesthesia and Critical Care*. Oxford Specialty Training: Techniques. Oxford University Press, Oxford.
2. Croskerry P and Nimmo G. (2011). Better clinical decision making and reducing diagnostic error. *Journal of the Royal College of Physicians Edinburgh*, **41**, 155–62.
3. Reader T, Flin R, Lauche K, and Cuthbertson B. (2006). Non-technical skills in the Intensive Care Unit. *British Journal of Anaesthesia*, **96**, 551–9.
4. Reader T, Flin R, Mearns K, and Cuthbertson B. (2007). Interdisciplinary communication in the intensive care unit. *British Journal of Anaesthesia*, **98**, 347–52.
5. Nimmo GR and Mitchell C. (2008). An audit of interruptions in Intensive Care. *Journal of the Intensive Care Society*, **3**, 240–2.

CHAPTER 14

Simulation training for critical care

Ben Shippey and Graham Nimmo

Key points

- Simulation is an effective, but resource-intensive educational method.
- Simulated educational interventions should be directed by the learning needs of participants and planned around the resources available.
- The simulation faculty should be clear about the intended outcomes for the scenario before it is performed.
- Post-scenario debriefing is needed to promote reflection, and should be undertaken carefully by skilled facilitators.
- While simulation is useful as a formative assessment tool, the value of summative assessment using simulation is unclear.

Introduction

The obvious attraction of training using models that replicate aspects of real patients has led to the development of many different types of simulator, from the simple part-task trainer (venous cannulation, tracheal intubation), to the high-fidelity, physiologically-driven, whole-patient simulator. This chapter will restrict its focus to immersive simulation, using mid- and high-fidelity manikins to train clinicians to manage a clinical situation in its entirety. While there are undoubtedly aspects of technical performance that can be taught in the simulator, there are more efficient ways to do this. Non-technical skills (the raft of interpersonal and cognitive skills involved in effective and safe provision of critical care) are more difficult to observe in other situations, but can be observed and analysed in the simulated environment. Simulation can also be used to test systems and to reinforce emergency drills [1].

The importance of fidelity in simulation is often overstated. The purpose of a simulated environment is to allow the participants to demonstrate behaviours that can be analysed in a constructive manner, usually after the simulation. In order for this to occur, the participants need to put aside their conceptions that the 'patients' are not real, and treat them as if they are. This is often called 'suspending disbelief'. There are many aspects to the simulation experience that aid suspension of disbelief, of which manikin fidelity is only one [2]. Others are the quality of supporting materials, a coherent and appropriate 'story', or clinical course, the environment in which the simulation takes place, and the briefing and support given by the facilitator. The addition of stressors, such as an argumentative colleague or equipment failure can, if done carefully, help the participant to suspend disbelief.

Mid-fidelity simulators are often 'faculty driven'—the displayed physiology being directly controlled by a faculty member—although relatively cheap physiological model-driven mid-fidelity simulators now exist. Perhaps the greatest difference between mid- and high- fidelity manikins is with regard to the lung model, which in high-fidelity manikins is capable of reliably reproducing lung physiology that will allow the simulation of the complex lung mechanics required for many critical care scenarios, but at a cost.

Whole patient simulation is expensive. Space, equipment, and staff time should be built into the simulation budget. At the very least, a permanent simulation centre needs a 'simulator room', ideally with a separate control room, storage space for equipment, and break-out space for debriefing. This space is not required if the simulation is to be performed in clinical areas, but all equipment will need to be easily portable if this is the case. Mid-fidelity simulators cost in the region of £25,000, and that cost rises to £250,000 for a high-fidelity manikin. It is extremely useful to have the ability to record simulated activity, and modern digital recording equipment allows instantaneous replay. Staff costs are more difficult to quantify. It is useful to have a member of staff responsible for the maintenance of the simulation equipment, particularly if a large temporary faculty uses the equipment on an intermittent basis. As activity increases, consideration should be given to administration, centre management, and possibly permanent faculty members.

Planning scenarios

It is almost a *sine qua non* that the scenarios the simulation trainer uses to create the educational experience should be planned with the intended learning outcomes of the participants in mind. Those educational outcomes can be defined by the course or curriculum context in which the simulation experience takes place (adherence to a failed intubation drill in the context of a course designed for novice anaesthetists, for example), in which the scenario can be carefully scripted and programmed well in advance. Alternatively, the simulation facilitator can invite the participants to define their own educational outcomes (aligned to the general trajectory of the simulation experience) in which case the scenario skeleton can be adapted 'on the fly' to enable behaviour, which will allow those intended educational outcomes to be achieved. Other aspects to take into account are the experience and prior knowledge of the participants, and their previous experience of simulation training (which, in the context of 'whole team' training, may be mixed). Considering the environment in which the simulation scenario is to take place allows the scenario

to be tailored to the equipment and facilities that will be available in situ: there is little point in writing a scenario that requires the use of a fibre-optic laryngoscope if there one is not available [3].

It is difficult to facilitate learning around more than two educational objectives in any single simulation scenario, and this should be taken into account when planning the scenario. While it is undoubtedly tempting to create complicated and challenging clinical situations, it is unusual that a complex scenario will succeed in fulfilling educational objectives where a simpler scenario will not, and an over-complex scenario has the potential to disengage with the participants. There seems to be a 'Goldilocks' region where the scenario is neither too simple, where the participants become bored and disengaged, nor too complex, so the participants become over-stimulated and disengaged [4].

Many simulation centres use a template or storyboard to develop scenarios. This has the advantage that all the scenarios that are developed within a centre use a common language and can be delivered by different simulation facilitators—who may not necessarily have been involved in the development process. Many templates exist, but common elements should include a briefing for the participants and faculty members (particularly if one of the faculty members is to be 'planted' within the scenario), the 'set-up', baseline physiology, and subsequent stages in the scenario. The planner should consider the triggers that move the scenario on, the transitions between stages, and prompts that can be used if the participants are struggling. An example is shown in Fig. 14.1.

Running the scenario

The faculty should be clear about the intended outcomes for the scenario before it is performed, and they should have an allocated role or roles. Some roles are:

- **'Observer' (often also the debriefer)**: should watch and mark behaviour within the scenario that can be analysed during the debriefing.
- **'Driver'**: controls the physiology of the manikin, often also providing the patient's voice.
- **'Telephonist/Senior Help'**: controls communication in and out of the simulated environment.
- **'Collaborator'**: a faculty member can be placed within the simulated environment, to introduce physiology not apparent from the manikin and to prompt behaviour if required. He either needs to be very well briefed or in communication with the 'Driver' (usually via one-way radio).

The participants should be briefed immediately before each scenario. The content of this briefing varies between simulation centres, but should include the environment in which the scenario is to take place, the role that is expected of the participants (they should usually be themselves), and their relationships. For example:

> It is 1400 hours on a Saturday afternoon. You are the critical care registrar on call at a level 1 trauma centre. You have been called to the Emergency Department to assist with the management of a young man brought to hospital by paramedics after a motor vehicle collision. Your supervising consultant is not in the hospital, but is available via the hospital switchboard by dialling '0'. Other resources that you would expect in a level 1 trauma centre are available to you.

The scenario should be run according to the script, accepting that the facilitator does not have complete control over the events that occur, and that therefore adjustments (through prompts and interventions) may have to be made to keep the scenario on track, and to allow learning objectives to be achieved.

Debriefing

It is widely accepted among facilitators of simulation-based learning that a debriefing after the simulated scenario is an essential part of the learning process [5]. Certainly, an experiential educational cycle, as described by Kolb [6] or Gibbs [7], contains a stage of reflection on experience, followed by the process of definition of developmental needs, and it is these stages in the learning cycle that the debriefer should be aiming to facilitate. Many debriefing styles exist and there is little evidence for any one style over another, but there are common themes. It is not absolutely necessary for the debriefer and the participant to be different people; the participant may debrief himself, either unguided or using a structured tool to aid reflection and analysis,. More commonly a process of debriefing where a conversation occurs between the debriefer and participants, or a facilitated conversation that takes place between the participants, is used [8].

It is essential that the debriefer creates a supportive environment of mutual trust in which the learner understands that his views will be respected and valued, and the debriefer expects that the input of those learning is offered openly and honestly. This must be achieved before the simulation scenario happens and so the foundations of a good debriefing are made in the prescenario briefing [3]. It is helpful to set the 'Rules of Engagement' in the briefing, in the context of explaining how the simulation experience will be conducted, including a discussion of the aspects of the participant's performance, which will be explored as part of the debriefing process. Many of those learning are apprehensive at this stage in the simulation experience, especially if their performance is to be observed by their peers [9].

At the end of the scenario, if it has been planned and driven well, the participants will be at least engaged with the clinical material, perhaps emotionally affected by the outcome or by their perceived performance. The debriefer should disengage the participant from the situation, and 'decompress' the sometimes emotionally-charged reaction (while acknowledging it as real and valuable), in order to allow the participant to reflect and contribute effectively to the subsequent debrief.

Debriefing should take place away from the simulated environment, partly to allow disengagement, but also to enable the room to be turned round for the next event. The setting should be relatively intimate and comfortable, and be equipped for video playback if this is required. The use of audiovisual aids can be very useful in stimulating discussion leading to the intended learning outcomes, particularly if a video clip is shown that illustrates the behaviour under discussion [10].

Facilitators will have varying input into the discussion, depending on the ability of the participants to analyse their own behaviour. High-level facilitation, paradoxically, implies a low level of intervention, guiding a largely unmoderated conversation towards the intended educational outcomes. Some groups may need a more directed approach, using open questioning, reflective listening, rewording and rephrasing, and structuring analysis (low-level facilitation). Whatever the level of facilitation, there is broad agreement on the characteristics of effective and ineffective debriefing (see Table 14.1) [8].

(a)

SCSC
Scottish Clinical Simulation Centre

Briefing
Patient: Name unknown. Appears c.25 years old. Brought in by ambulance to emergency department after MVC. **Personnel:** Anaesthetist (participant), Emergency Physician (faculty), Emergency department nurse (faculty) **Orientation :** *'It is 1400h on a Saturday afternoon. You are the critical care registrar on call at a level one trauma centre. You have been called to the Emergency Department to assist with the management of a young man brought to hospital by paramedics after a motor vehicle collision. Your supervising consultant is not in the hospital but is available via the hospital switchboard by dialling "0". Other resources that you would expect in a level one trauma centre are available to you.'*

Facilitator's Notes
The patient is semi-conscious and will require tracheal intubation before CT scanning. He will prove impossible to intubate using direct laryngoscopy, and either fibre-optic intubation or tracheostomy will be required.

Environment, Equipment, Essential props
Equipment: Standard ER setting. Long board, stiff collar, sandbags and tape. Failed airway cart including fiberscope. **Drugs :** Standard ER. **Medical Notes & Charts:** Paramedic report form. Blank Emergency Room note. Blank Anaesthetic Form. Blank CT request. **Other:**

(b)

SCSC
Scottish Clinical Simulation Centre

Scenario Storyboard				
Baseline	**Patient** On long board on trolley with stiff collar, blocks and tape. Trauma mask 15 litres. Right arm 18G ivc. Right forehead abrasion *Physiology* 120 SR 140/75 25 bpm Sats 97 E1V2M4 Pupils normal	**Learner Actions:** A- E Assessment/ Primary survey Prepare for intubation Brief assistants Perform RSI	**Trigger:** To Stage 2 on administration of muscle relaxant	**Prompt:** If not planning RSI, EM doctor to ask "His GCS is low. Do you think he'll be safe in CT?" Can drop GCS if necessary. Can drop RR if necessary
2.	**Patient** Activate Tongue swelling /neck stiffness *Physiology* Resp rate 0 BP "blip" to 170/90 HE "blip" to 140 S_pO_2 dropping to minimum 75% over 5 minutes	**Learner Actions:** Declare failed intubation. Release cricoid pressure Follow failed intubation algorithm	**Trigger:** To Stage 3 after fibre optic intubation or tracheostomy.	**Prompt:** ED nurse can ask "Would you like me to call for help?"

Fig. 14.1 (a,b) Example storyboards.
Reproduced from the Scottish Clinical Simulation Centre with permission from Ben Shippey.

Table 14.1 Effective and ineffective debriefing

Effective debriefing	Ineffective debriefing
Open questions	Closed questions
Positive reinforcement	Ridicule or criticism
Cognitive aids	Concentrating on errors
Good audiovisual use	Overemphasis on technical debriefing
Self-debriefing	

Assessment using simulation

Simulation should **always** be used as a formative assessment tool, in so far as the performance of the participants is analysed, and the outcome used to guide future learning. Participants often compare their performance against a standard (even if the standard chosen is self-referenced), and usually in a negative way [9]. It is inevitable that the use of simulation as a summative assessment tool will continue to grow throughout the world. Simulated clinical environments (SCEs) have immediately obvious attractions as an assessment tool. They can be used to recreate rare crises. Reproducibly, they allow the observation of non-technical aspects of medical practice and they seem to test the ability of the candidate to actually practise medicine in a way that a written paper or *viva voce* examination cannot.

Yet there is little evidence of the validity or reliability of simulated clinical environments as assessment tools [11]. Content (face) validity is perhaps self-evident, simulating common presentations or specific emergencies, with clearly-defined interventions, would lend itself to an assumption of content validity. Using a metric based around key actions in emergency treatment algorithms, Murray showed construct validity (experts score more highly than novices) in a series of emergency care scenarios [12], but evidence for criteria-referenced validity (candidates who score highly in SCEs score highly in other assessment modalities) is lacking.

With regard to reliability, inter-rater reliability is probably underestimated, and can be corrected to a large degree by using explicit (checklist style) metrics, norming, and training examiners [13]. Assessment of performance in SCEs using global rating scales (implicit metrics) seems to have a greater degree of inter-rater variability, which is disappointing, as scoring non-technical aspects of behaviour is difficult using explicit metrics [14]. Inter-task reliability is low, perhaps due to the differing clinical content of successive SCEs, and it is estimated that between one and three examiners and 12–15 SCEs are required for acceptable inter-task reliability [15]. This constitutes significant resource usage, and is perhaps too high to be widely adopted.

References

1. Gaba DM. (2004). The future vision of simulation in healthcare. *Quality & Safety in Health Care*, **13**(Suppl. 1), i2–10.
2. Norman G, Dore K, and Grierson L. (2012). The minimal relationship between simulator fidelity and transfer of learning. *Medical Education*, **46**(7), 636–47.
3. Nimmo GR, Shippey BJ, and Fluit L. (2008). Intensive care and simulation—a guide. *Care of the Critically Ill*, **24**(1), 4–8.
4. After Yerkes RM and Dodson JD (1908). The relation of strength of stimulus to rapidity of habit-formation. *Journal of Comparative Neurology and Psychology*, **18**, 459–82.
5. Issenberg B, McGaghie WC, Petrusa ER, Lee Gordon D, and Scalese RJ. (2005). Features and uses of high fidelity medical simulations that lead to effective learning: a BEME systematic review. *Medical Teaching*, **27**, 10–28.
6. Kolb DA. (1984). *Experiential Learning: Experience as the Source of Learning and Development*. Englewood Cliffs: Prentice Hall.
7. Gibbs G. (1988). *Learning by Doing: A Guide to Teaching and Learning Methods*. London: Fell.
8. Fanning RM and Gaba DM. (2007). The role of debriefing in simulation. *Simulation in Healthcare*, **2**(2), 115–25.
9. Savoldelli G, Naik VN, Hamstra SJ, and Morgan PJ. (2005). Barriers to the use of simulation-based education. *Canadian Journal of Anaesthesia*, **52**(9), 944–50.
10. Scherer LA, Chang MC, Meredith JW, and Battistella FD. (2003). Videotape review leads to rapid and sustained learning. *American Journal of Surgery*, **185**, 516–20.
11. Boulet JR and Murray DJ. (2010). Simulation-based assessment in anesthesiology. *Anesthesiology*, **112**, 1041–52.
12. Murray DJ, Boulet JR, Avidan M, et al. (2007). Performance of residents and anesthesiologists in a simulation-based skill assessment. *Anesthesiology*, **107**, 705–13.
13. Savoldelli GL, Naik VN, Joo HS, et al. (2006). Evaluation of patient simulator performance as an adjunct to the oral examination for senior anesthesia residents. *Anesthesiology*, **104**, 475–81.
14. Morgan PJ, Cleave-Hogg D, and Guest CB. (2001). A comparison of global ratings and checklist scores from an undergraduate assessment using an anesthesia simulator. *Academic Medicine*, **76**, 1053–5.
15. Weller JM, Robinson BJ, Jolly B, et al. (2005). Psychometric characteristics of simulation-based assessment. *Anaesthesia*, **60**, 245–50.

CHAPTER 15

Leadership skills in the ICU

Carole Foot and Liz Hickson

Key points

- There is no gold standard definition or tool for measuring leadership, but there are a range of useful theories and assessments.
- The term 'management' refers to a different concept, but this is often incorrectly and interchangeably used.
- Leadership and management skills are both important, but to different degrees in different contexts.
- Poor ICU leadership is associated with adverse patient and clinician outcomes.
- Efforts to incorporate leadership training into doctor's training are progressing.

Definition of leadership and related concepts

Leadership is a concept that can be recognized more readily than described. It is much talked about, written about, studied, valued, needed, and appreciated. There is no universally agreed upon definition and great diversity exists in how it is executed.

Throughout the ages, leaders have influenced the development of individuals, communities, organizations, and humanity. In Table 15.1, key theories of leadership are summarized and examples of each are provided [1–3]. The common themes of all these models are the existence of important specific traits, behaviours, and strategies that are used to influence, facilitate future development, and inspire progress in those being lead.

The ongoing **excellence period** of theories comprises a diverse range of ideas. In addition to the groundbreaking work of McGregor Burns and the Translational–Transformational leadership dichotomy, other contemporary theories have sought to merge aspects of different preceding era concepts.

Emotional intelligence (EI) was popularized by Daniel Goleman in the 1990s, combining aspects of trait and behaviour theories, and correlating excellence in leadership with having high levels of EI, measurable as an emotional quotient (EQ). EI is described as the ability, capacity, or skill to perceive, assess and manage the emotions of one's self, others and groups [4]. His ongoing work has purported neuroscientific links between EI and leadership, and unlike intelligence quotient (IQ), there exists the capacity for individuals to improve their EQ.

The **Substitutes for Leadership theory** is another distinct model that argues that factors can exist within organizations outside the leaders control and so can have an overriding effect on how individuals function within a group. This may be in a positive or negative way [5]. For example, significant resource limitations may reduce the ability of a leader to progress an innovative vision and thwart his/her effectiveness to implement change, thereby losing credibility and influence with followers.

Servant leadership theory states that, to be effective, leaders must place their own needs below all others and by serving these individuals they will be successful in achieving their vision [5].

In contrast with leaders who are focused on the strategic direction and vision of an organization, **managers** are directed towards the co-ordination and stewardship of activities in order to effectively meet predetermined mandates.

The term 'management' is often confused with leadership, and the words associated with both are used interchangeably and incorrectly in many industries including health care.

Management is concerned with current, rather than forward thinking and more focused on order than change, or as Peter Drucker has stated 'Management is doing things right; leadership is doing the right things' [6]. In Fig. 15.1, words that are frequently associated with the term 'leadership', such as inspirational, strategic, innovative, and visionary, are illustrated. In contrast, managers are often described with seemingly more negative terms—bureaucratic, maintaining, administering, regulating, preserving the **status quo**, controlling, system focused, and risk averse [7].

Individuals in positions of responsibility may possess strengths in both leadership and/or management. Incorrectly, such individuals are often labelled as leaders by default, even though they are principally tasked with functions requiring managerial skills. Leaders and managers also share other organizational assets, such as the ability to communicate, make decisions, prioritize, consider goals, and appraise situations. **Power** is the social construct that enables both to get others to do things.

Power has been traditionally described as originating from five bases according to John French and Bertram Raven. **Reward** and **Coercive** power rely on the respective use of enticements and punishments. **Legitimate** power flows from authority inherent to a specific position. **Referent** power originates from respect for an individual's desirable features and **Expert** power from an appreciation of their specific knowledge or experience [2].

The literature suggests that both leadership and management are contextually important to different degrees for entities to flourish, that leaders may be created and grown, and that training in leadership is achievable and measurable [3].

Robert Sutton has recently placed a useful perspective on Drucker's observation stating that 'to do *the right thing*, a leader needs to understand what it takes to *do things right*, and to make sure they actually get done' [8].

Table 15.1 Key leadership theories

Ancient	Trait 1940–50s	Behavioural 1950–60s	Situational 1960–70s	Excellence 1970+
Important lessons on leadership may be gained from leaders of the past	Leaders are born with traits that enable them to lead	Leaders demonstrate behaviours that may be learnt and are of varying utility	Leaders adjust their style to different contexts	Leaders use whatever traits, behaviours, or styles are needed to achieve excellence in their context
Sun Tzu [1] Know yourself and the enemy. Avoid war when possible and when necessary conclude war quickly **Machiavelli** [1] Avoid injuring those critical to your survival; disarm the envious; it is better to be feared than loved; use deception and manipulation in politics	**Stogdill's Great Man theory** [2] Great men are born with certain traits that allow them to emerge and take power (e.g. intelligence, self-confidence, determination, integrity, sociability)	**Blake and Mouton's Managerial grid** [3] Leaders can be classified on a 4 × 4 grid into five types, based on their expressed degree of concern for people versus production issues	**Tannenbaum and Schmidt's Contingency theory** [2] Adjustments in style are needed, with greater or lesser use of authority and control versus freedom for different levels of subordinate	**McGregor Burns and Bass's Translational versus Transformational styles** [2] Translational leaders use reward and punishment compared with Transformational leaders who engage followers, set goals, identify needs, and use charisma, inspirational motivation, intellectual stimulation, and individualized consideration

Data from various sources (see references).

The importance of leadership in intensive care medicine

The need for skills in leadership and management is well established by the medical licensing authorities. There are expectations regarding professional conduct in areas ranging from leading an inter-professional team to contributions within organizations related to patient safety and resource utilization, which are well defined [9].

Studies on career derailment in many professions emphasize the inability to lead a team as a key cause of ineffectiveness and failure to meet career goals [10]. Clinicians who have participated in leadership and management training have been associated with an enhanced ability to negotiate, understand complex systems and be able to effect change [11].

In intensive care medicine, the need for practitioners to function as leaders in multiple contexts is wide (see Fig. 15.2). It should be appreciated that some of these situations, particularly those with clearly delineated expectations may, in reality, require more management than leadership skills. As an example, when considering the non-technical skills associated with improving outcomes for critical care emergencies, using the term leadership may be imprecise, as these situations demand more managerial type skills (see Fig. 15.3 and Box 15.1).

The challenge for leaders in ICU is increasingly to manage a heterogeneous workforce with varied cultural and generational expectations. It is well documented that younger workers (so called **generations X and Y**) have significant differences compared with their older (**baby boomer**) seniors when it comes to what they will respond to. An authoritarian style is generally ineffective compared with a more consensus seeking, flexible, participative approach consistent with more contemporary leadership theories [14].

Qualitative studies have associated poor intensive care unit leadership with various negative outcomes, ranging from adverse patient events related to poor team functioning, to increased clinician burnout, and a reduced ability to attract and retain staff [15].

Fig. 15.1 The essence of leadership.
Image courtesy of Matthew Tinker Photography, available at: www.matthewtinker.com.au

ICU
- Multidisciplinary team leader
- Project lead (e.g. education, echocardiography)
- Subspecialty unit director (e.g. Cardiothoracic surgical patient lead)
- Department head

Regional/National
- Intensive Care Clinical Networks
- Intensive Care Societies
- ICM College Board and regional committee activities (e.g. training programs and examinations, credentialing of practitioners, maintenance of professional standards)
- Course director (e.g. BASICS, ALTS, APLS, ICM Exam preparation programs)
- Multidisciplinary initiatives (e.g. National resuscitation councils, Disaster preparedness, planning for major public events)
- Conference convening

Hospital
- Service head (e.g. MET team)
- Committee chair/representative (e.g. Resuscitation, Patient safety, Ethics)
- Charity/fundraising entities
- Interdisciplinary team meetings (e.g. management of high-risk elective surgical patients)

International
- Humanitarian aid work and disaster response
- Multinational clinical initiatives (e.g. CoBaTrICE, Surviving Sepsis Campaign)
- Journal and textbook editing / subediting
- Major conference organisation

Fig. 15.2 Leadership opportunities in ICM.
Image courtesy of Matthew Tinker Photography, available at: www.matthewtinker.com.au

Fig. 15.3 Crisis Resource Management principles—Leadership or management? See Box 15.1 for an explanation of this image.

Box 15.1 Crisis Resource Management Principles—Leadership or Management?

Fig. 15.3. In the mid-90s David Gaba translated important aviation lessons regarding human factors that influence team effectiveness to health care with development of Crisis Resource Management courses for Anaesthesiologists at Stanford University. These courses are based around Crisis Resource Management principles which include 'leadership' (as well as followership, knowing the environment, calling for help, anticipation and planning, using cognitive aids, using all available information, preventing and managing fixation errors, communicating, distributing the workload, and effective use of resources) [12].

Later the Harvard group introduced their own version of these concepts with their Crisis Event Management principles differing in their recognition that crisis outcomes depend more on having an 'event manager' than a 'leader' [13] and removing the term leadership as a principle. In situations where direction and compliance with recognized clinical interventions and therapies are needed, the individual in charge requires management, rather than true leadership skills if these words are used correctly.

Leadership competencies

The Human Resource Competency Movement has had a profound influence on organizations globally, and health care is no exception. This now engrained concept underpins strategies related to employee recruitment and role delineation, training and development, performance and career development. The underlying idea is attributed to foundation work done by David McClelland in the 1960s; in response to a need to reform education and improve worker competitiveness in the USA market in cold war times. His seminal work emphasized the central nature of competencies as necessary traits and enduring characteristics beyond traditional knowledge and skill frameworks for determining workers' abilities to perform at high levels [16].

Despite ongoing controversy, it seems to have become entrenched, particularly in professional arenas, including medicine, where some argue that ensuring competencies alone does not sufficiently guarantee success in a role. Job descriptions, specialty training programmes and undergraduate medical school degree curriculums all commonly revolve around specific competencies. Such competencies typically define the desirable characteristics, as well as core knowledge and technical skills of prospective doctors. Leadership competencies are being increasingly identified as important components of such lists.

John Zenger and Joseph Folkman have published extensively on the competencies that define extraordinary leaders and emphasize the synergistic effects of possessing combinations [17]. The ability to inspire other individuals appears to be of paramount importance. Other competencies include character, personal capability, a focus on results, interpersonal skills, and the ability to achieve change [18].

Strategies to measure leadership

Management consultancy refers to the process of providing advice and interventions to organizations in order to improve their functionality. Executive coaching and leadership development is an important aspect of this and has driven the market for development of tools that may be utilized by Human Resources departments, supervisors, and educationalists for this purpose. It is also increasingly common for such assessments to form part of a comprehensive selection process for individuals, particularly to executive positions. Examples of such commonly used tools are provided in Table 15.2.

There is no single gold standard tool for measuring leadership, a reflection of the fact that there is no single agreed definition or theory of leadership. Many tools have been developed in conjunction with the developers of individual theories. Other tools examine less specific constructs that can be used to predict or characterize diverse behaviours, including leadership (e.g. Myers Briggs Type Inventory (MBTI), Thomas–Kilmann Conflict Mode Instrument (TKI), BarOn Emotional Quotient Inventory (EQ-i)). Some of these methods rely on self-assessment (e.g. CPI) and others on feedback from followers (e.g. LMX-7) [18].

Measurement of the leadership ability of an individual may be gained from surveys or statistics of quasi-markers, such as employee satisfaction and commitment, staff retention, and productivity outcomes. In multisource or 360-degree appraisals, multiple sources of feedback on selected areas (e.g. from subordinates, supervisors, and clients on items, such as leadership and communication) are typically collated anonymously for the purposes of performance assessment and improvement of individuals [2].

Table 15.2 Leadership coaching tools

Multifactor Leadership Questionnaire	Measures Transactional and Translational leadership behaviours
Leadership Skills Inventory	Aims to identify individuals leadership potential
Leader Member Exchange (LMX-7)	Examines the quality of relationships between a leader and subordinates most relevant to hierarchical organizations
California Psychological Inventory (CPI™)	Generates a leadership coaching report that provides insights into an individual's self-management, organizational capabilities, team building and teamwork, problem-solving, and ability to sustain a vision
FIRO-B™	Quantifies the frequency and number of exchanges with others for the purposes of achieving inclusion, control, and affection
Myers Briggs Type Inventory (MBTI™)	Widely-used personality assessment tool that differentiates individuals based on preferences based on how people perceive and interact with the world
BarOn EQ-i™	Quantifies parameters of emotional intelligence
Thomas–Kilmann Conflict Mode Instrument (TKI)	Defines conflict handling styles and applies it to various aspects relevant to leaders, including leadership style, approach to change, and teamwork

Strategies to improve leadership

There are a myriad of educational resources to assist learning about leadership. In addition to the utilization of leadership measurement tools, a range of other materials that may be used by management consultants and educators are outlined in Table 15.3.

Over the last two decades there has been much written on the importance of leadership and management training for health care professionals, predominantly originating from North America and the United Kingdom.

It has become increasingly common for doctors to complete a Masters of Business Administration (MBA), particularly mid-career to facilitate career development [11], although dual degree programmes in medicine and business management are now increasingly available in some countries. Hard end points in terms of the associated benefits of such programmes and their ability to develop leadership remain unclear. Such programmes do teach leadership as part of organizational behaviour, and would therefore be expected to improve knowledge and highlight the importance of this topic. Shorter courses that introduce individuals to leadership and management topics may be of similar effectiveness.

Efforts to incorporate leadership education into undergraduate medical curriculums are progressing. Teaching about leadership is now generally accepted as important, but there is on-going

Table 15.3 Examples of educational resources to teach leadership*

Classic books that describe theories or perspectives	*The Art of War* by Sun Tzu. Theophania Publishing; 2012 *Leadership* by James M Burns. Harper Perennial Political Classics; 2010—landmark descriptions of transformational leadership *Primal Leadership: learning to lead with Emotional Intelligence* by Daniel Goleman, Richard Boyatzis, and Annie McKee. Harvard Business Review Press; 2004
Books from leadership authorities/ management consultants (usually multiple books)	John C. Maxwell (e.g. *Leadership 101*. Maxwell Motivation; 2002) John Zenger and Joseph Folkman (e.g. *The Extraordinary Leader*. McGraw-Hill; 2002)
Case studies from reputable business management schools	Harvard Business Review Case Discussions, Stanford Case studies, IMD Business School Cases, London Business School
Biographies or studies of famous people to stimulate analysis	*Leadership* by Rudolph Giuliani. Miramax; 2005 *Steve Jobs: Ten Lessons in Leadership* by Michael Essany. eBook; 2012 *In Their Time: The Greatest Business Leaders of The Twentieth Century* by Anthony Mayo and Nitin Nohria. Harvard Business Review Press; 2005
Interactive books that encourage self-development	*Now, Discover Your Strengths* (with on-line assessment) by Marcus Buckingham and Donald Clifton. Free Press; 2001 *The Leadership Challenge Workbook* by James Kouzes and Barry Posner. Pfeiffer; 2003
Fables that stimulate self-reflection and discussion (often with study guides)	Patrick Lencioni has written multiple titles (e.g. *The Five Dysfunctions of a Team*. Jossey-Bass; 2002.) *Squirrel Inc.* by Stephen Denning. Jossey-Bass; 2002
Interactive games (books and kits)	*Leadership games: Experiential learning for Organizational development* by Stephen S. Haagen *Mars Surface Rover Game* from www.hrdqstore.com
Websites that address Leadership in Health care	The King's Fund www.kingsfund.org.uk Centre for Creative Leadership www.ccl.org

*Examples of each category have been selected based on the authors' preferences.

discussion and controversy regarding the best educational methods, as well as core content. It is well described that such education needs to start early and be career long, with a changing focus on the material and variations on how it is contextualized and reinforced [19].

There is an essential need for role modelling and opportunities for real-world, work place experience and exploration of concepts. This may be limited by a lack of educated senior personnel who have not been privy to such an education and became 'leaders by accident' [20]. The potential to rectify this situation by investing in executive coaching initiatives is realistic and being embraced in some hospitals. The material costs, plausibility, effectiveness, acceptance of and perceptions about the value of such initiatives need further evaluation.

Health care systems that do not nurture and support developing leaders may also sabotage what is being taught. The need to drive change in resource-limited, pressured systems may be the greatest obstacle to improving the leadership skills of health care professionals, including intensivists.

References

1. Bolstridge J. (2006). Face off: Machiavelli vs. Sun Tzu. Available at: http://ricenpeas.com/docs/machiavelli%20tzu.html (accessed 15 May 2012).
2. Buchanan D and Huczynski A. (2010). Leadership. In: *Organizational Behaviour*, 7th edn, pp. 595–628. Essex: Pearson Education Ltd.
3. Blake R and Mouton J. (1994). *The Managerial Grid*. Houston, TX: Gulf.
4. Goleman, D. (2005). *Emotional Intelligence: Why It Can Matter More Than IQ*, 10th anniversary edn. New York, NY: Bantam Books.
5. Avolio B, Walumbwa F, and Weber T. (2009). Leadership: current theories, research, and future directions. *Annual Review of Psychology*, **60**, 421–9.
6. Thinkexist.com (2012). Peter Drucker quotes. Available at: www.thinkexist.com/quotes/peter_f._drucker/ (accessed 15 May 2012).
7. Morgan S. (2011). Leadership versus management: What are the differences? Available at: http://www.articlesbase.com/management-articles/leadership-vs-management-what-are-the-differences-4790872.html (accessed 15 May 2012).
8. Sutton R. (2011). True leaders are also managers. Available at: http://blogs.hbr.org/cs/2010/08/true_leaders_are_also_managers.html (accessed 15 May 2012).
9. General Medical Council. (2012). *Leadership and Management for All*, Doctors booklet. London: GMC.
10. Van Velsor E and Leslie J. (1995). Why executives derail: perspectives across time and cultures. *Academy of Management Executive*, **9**(4), 62–72.
11. Parekh S and Singh B. (2012). An MBA: the utility and effect on physician's careers. *Clinical Teaching*, **9**(2), 89–93.
12. Howard S, Gaba D, Fish K, Yang G, and Sarnquist F. (1992). Anesthesia crisis resource management training: teaching anesthesiologists to handle critical incidents. *Aviation, Space, and Environmental Medicine*, **63**, 763–70.
13. Raemer D. (2004). Team-oriented medical simulation. In: Dunn W (ed.) *Simulators in Critical Care and Beyond*, pp. 42–6. Mount Prospect, IL: Society of Critical Care Medicine.
14. McCrindle M. (2009). Leading and managing. In: *The ABC of XYZ: Understanding the Global Generations*, pp. 164–75. Sydney: UNSW Press. .

15. Laporta D, Burns J, and Doig C. (2005). Bench-to-bedside review: dealing with increased intensive care unit staff turnover: a leadership challenge. *Critical Care*, **9**(5), 454–8.
16. Horton S. (2000). Introduction—the competency movement: its origins and impact on the public sector. *International Journal of Public Sector Management*, **13**(4), 306–18.
17. Zenger J and Folkman J. (2006). *The Handbook for Leaders: 24 Lessons for Extraordinary Leadership*. New York, NY: McGraw-Hill Professional.
18. CPP. (2012). Asia Pacific product information. Available at: www.austpsychpress.com.au (accessed 15 May 2012).
19. McKimm J and Swanwick T. (2004). Leadership development for clinicians: what are we trying to achieve? Family Medicine, **36**(Suppl.), S51–6.
20. Ackerly D, Sangvai D, Udayakumar K, et al. (2011). Training the next generation of physician-executives: an innovative residency pathway in management and leadership. *Medical Economics*, **88**(2), 38, 40–1.

PART 1.4

Safety and quality

CHAPTER 16

Patient safety in the ICU

Bradford D. Winters and Peter J. Pronovost

Key points

- Preventable patient harm is probably the third leading cause of death. Despite over a decade of focus, measureable improvement in patient harm is limited to a handful of conditions, such as central line-associated bloodstream infections.
- The delivery of health care should be treated as a science with rigorous methods and metrics.
- Poor outcomes (patient harm) result from flawed health care systems. In order to improve patient safety and quality, we need to take a systems approach to solutions, rather than assuming that individual providers are to blame. Focusing on individual providers only risks further harm to patients.
- To improve safety and quality, we need a standard process to identify and learn from our mistakes. We must transition from a culture of first-order problem solving ('a solution for this patient right now') to second-order problem solving ('an enduring systems solution that protects future patients').
- We must develop a culture of safety that translates evidence into practice, uses the principles of safe design applied to both technical work and teamwork, and relies on the continuous application of the 4 E's—engage, educate, execute and evaluate.

Introduction

The focus on patient safety is often rooted to the 1999 *To Err is Human* report [1]. While a breakthrough publication, the struggle to bring this neglected area of medicine to the public and funding agencies began many years before. Efforts by clinicians and others have raised awareness about medical errors and avoidable harm over the 15 years. Yet, research funding for patient safety or quality improvement still woefully lags behind funding for basic and clinical research [2]. More worrisome, and possibly the result of inadequate funding, is that progress in reducing preventable patient harm has been slow. A recent assessment asking where we stand since the 1999 report [1] found progress in reducing central line-associated bloodstream infections (CLABSI) and intensive care unit (ICU) mortality [3–5], but found little progress overall in improving patient safety and harm [6].

A wide **quality gap** remains between the evidence-based care a patient qualifies for and the delivery of this care. We need to apply the strategies learnt through successful interventions, to areas of urgent need—areas where many people die or are harmed needlessly, including ventilator-associated pneumonia, deep venous thrombosis and pulmonary embolus, diagnostic errors, delerium, surgical site infection, deteriorating general ward patients, and harm from disrespectful and undignified care. The main principle of this chapter is that patient safety and quality improvement are the science of health care delivery, a science that must be rigorous. This chapter describes a framework for developing a culture of safety.

Developing a culture of safety

Understand the science of safety

Systems not individuals

One central tenet of the science of safety is that every system achieves results based on its design, and health care providers work within a health care system. Poor outcomes (e.g. patient harm or indirect harm, such as omitting an evidence-based therapy) result from flawed systems. Fix the systems, and you improve patient safety and quality of care. Historically, patient safety and quality of care were treated as the responsibility of the provider, and when outcomes were poor, individual providers were blamed. This approach drove medical and nursing education, practice, and the tort system for decades. This maladaptive culture encouraged clinicians to blame each other, hide, or downplay errors when they occur, and ultimately led to patient harm. While providers are often the visible connection to medical errors, other latent systems factors, including patient characteristics, task factors, teamwork issues, the work environment (physical space, workload), organizational influences, governmental/regulatory policies, and the economic climate. Learning to transition from individual blame to a systems approach is at the core of creating a culture of safety and quality.

Metrics

A second central tenet is the need to be rigorous in our methodology. Too often, patient safety and quality interventions are developed without a clear goal or valid metrics to evaluate performance. They also often lack a clear theory about how the intervention will lead to improved outcomes or processes. For example, many health care organizations believed that implementing the electronic health record would magically lead to improved quality and reduced costs. Without rigorous metrics, we present a disservice to patients by implementing interventions that we cannot confidently conclude have made care safer and waste time and resources in the process.

There are several types of metrics we can use in our pursuit of improved patient safety and quality. One is an outcome measure, such as infection rates. Outcome measures are preferred, especially by the public and regulators, because measurement on performance is straightforward, more easily understood,

and more directly answers the pressing question, 'is care safer?' Unfortunately, there are few valid outcome measures or it takes too long to collect enough data to determine if the intervention was effective. Wrong-sided surgery is a good example of such a rare, but devastating outcome. This is so uncommon that it would take many years of data collection to measure any statistically significant improvement. In combination with outcome measures, or as an alternative, is to use process measures such as a surrogate for the outcome. In this case, we assume that adherence to specific evidence-based practices (the processes) should reduce the harm and then measure how well we consistently adhere to those practices. While this is an indirect measure of harm, it is sometimes the most feasible approach. This approach taps into the theory that improving the quality of health care delivery through adherence to evidence-based best practices will close the quality gap, thereby improving outcomes. Nonetheless, it is most desirable to measure both processes and outcomes, providing evidence for the relationship between an intervention and improved outcomes.

Implement the comprehensive unit-based safety programme

The foundation for building and maintaining a safety-centric culture is the Comprehensive Unit-based Safety Programme (CUSP) [7]. This programme evolved from the understanding that culture is local, the unit is a powerful component of improvement, and frontline staff possesses the wisdom to identify and mitigate hazards. Yet staff often feel disempowered. The programme is built on five principles:

- Understanding the science of safety.
- Partnering with an executive.
- Identifying and learning from defects.
- Implementing teamwork tools.
- Technical tools to improve safety and quality.

A unit-based multidisciplinary CUSP team has been the cornerstone of some of the most successful patient safety and quality improvement programmes to date [4,8,9]. This programme reverses the traditional top-down one-size-fits-all approach to hospital quality and safety. Although hospital-level safety and quality officers have value in coordinating hospital-wide efforts, the work of improving patient safety and quality must be owned by frontline staff.

The reasoning for a bottom-up approach is the known variation in local culture and patient safety threats across units, differences only frontline staff will know and appreciate. Top-down institution-wide interventions often fail because they are imposed on providers and do not account for the local culture and wisdom. Institution-wide interventions may not realize that a patient safety problem in one clinical unit may not exist or be minimal in other units. For example, central lines are used by many units; yet, their use is greatest in the ICU, where CLABSI is a deadly threat. On the general ward, falls are probably the greater threat to patient safety than a CLABSI. Thus, the ICU may focus on CLABSI, while the general ward might instead focus on falls.

A CUSP team can identify the greatest threats to their patients and devise locally relevant interventions with few implementation barriers, making success more likely. Despite the strong local focus of CUSP, the team needs a hospital executive partner to help the team prioritize interventions and to remove institutional barriers. The executive is the liaison between hospital management and frontline staff, providing resources when necessary and demonstrating commitment. The executive should attend the regular (usually monthly) CUSP team meeting and be an active partner in the process. They also have the central role of ensuring accountability for the CUSP team to collect metrics and demonstrate improvement and to help align local and institution-wide goals.

Identify and learn from defects

In order to improve safety and quality, we need a process to identify and learn from defects. This is perhaps the most important CUSP element. Defects are anything with the potential to cause patient harm or waste. Ideally, this process does not wait for adverse events to occur, but is proactive in identifying problems before they even rise to the level of causing harm. While there are other sources of data to identify defects, such as sentinel events, these defects tend to surface after the harm has occurred. Proactive strategies, such as asking frontline providers how the next patient will be harmed and how to prevent it [7] taps into wisdom and tacit knowledge long before actual harm takes place. There are several strategies to learn from defects, including root cause analysis, failure mode effects analysis [10], sense making [11], and learning from defects (LFD) [12].

Frontline providers use LFD to identify defects in their unit and develop solutions that are suited to workplace practices. Understanding the principles of problem solving is essential to learn from defects. Problem solving is often first order, meaning the problem gets fixed with a plaster not with a permanent solution. First-order problem solving focuses on recovering from the immediate mistake, yet does not learn, thereby not reducing the risk that the same harm will happen to a future patient. These fixes are often viewed as heroic but may have unintended consequences. For example, a nurse borrows a drug from one patient's supply to provide another patient with urgent need. This fixes the immediate need, but it does not prevent the problem from recurring, and it may even endanger the patient whose supply was depleted. The challenge is to move beyond first-order problem solving to a systems-based solution that prevents the problem, thereby protecting future patients. This is second-order problem solving, and the core of LFDs and other learning strategies. A second-order solution for the medication borrowing issue would develop a restocking system to ensure that critical medications were available.

The LFD process asks four straightforward questions:

- What happened (or could have happened)?
- Why did it happen?
- What will you do to reduce the risk of this defect?
- How will you know the risk was reduced?

The question of what happened is addressed by making a timeline of the events, taking the perspective of those involved as the event was unfolding, trying to understand what they were thinking, and the reasoning behind their actions/decisions.

Answering why the event occurred requires a system perspective to understand how latent factors in the system led to the event. Damaging consequences may not become evident until a *triggering event* occurs, but the latent factors that set it up have often long been present, but not appreciated. James Reason described this

concisely, 'Rather than being the main instigators of an accident, operators tend to be the inheritors of system defects . . . Their part is that of adding the final garnish to a *lethal brew* that has been long in the cooking' [13].

Evaluate what happened and what should be done by 'walking the process'

This could be done in the unit where the event occurred or in a simulation environment, recreating the event to analyse what factors led to the event. The goal is to understand why clinicians made their decisions, not to judge those decisions. Answering why creates opportunities to answer the third question, 'What will we do to reduce the risk?'. First, prioritize the most important contributing factors to consider when developing interventions, noting any mitigating factors, as these may be leveraged to prevent harm.

Finally, select appropriate metrics to determine if the risk is reduced. Importantly, measure a baseline for comparison. Too often safety and quality improvement efforts never measure the baseline metric, resulting in an unclear understanding of whether the efforts have improved care. This undermines the science of safety.

Reduce harm by ensuring patients receive recommended therapies

The CUSP is effective at identifying and mitigating local risks, risks with limited empirical evidence, which generally cannot feasibly be measured as a rate. While these risks represent one type of harm, another type of harm occurs when patients fail to receive evidence-based therapies. Efforts to reduce the omission of therapies require different theories and methods, and given the burden of developing programmes, are often developed among multiple units.

Developing these interventions relies on the model of translating research into practice (TRIP) [14]. Start by summarizing both explicit (medical literature) and tacit evidence (e.g. frontline provider experiences) that supports likely interventions. Next, prioritize the interventions based on the strength of the evidence, probable impact, barriers to implementation, and costs. Barriers to implementation are best understood by walking the process to examine the workflow and understand how the intervention will be best implemented in the local unit.

As we develop interventions or redesign systems to reduce harm, we need to focus on the principles of safe design. These principles are to standardize what we do, create independent checks, and make it visible. An example of technical safe design is the engineering of incompatible connectors to avoid infusion of intravenous medications into epidural catheters. Applying safe design principles to technical work often involves better engineering and product design. Historically, manufacturers have performed this work, although those who do an admirable job of creating safe medical products are in the minority.

Recently, there has been a push to partner clinicians and industry to apply human factors engineering (HFE) during the conceptual phase to develop safer medical products. HFE studies the interaction of people, technology, and workflow to identify potential problems in a system and offer solutions. Without HFE, clinicians will develop workarounds if the product does not integrate well in the workflow, potentially endangering patients by bypassing manufacturer-created safety features.

Safe design is applied to teamwork through tools to standardize processes, improve communication, create redundancies, and develop a culture that supports safe practices. Teamwork tools make the work visible and behaviours unambiguous. For example, rounds in an ICU are often subject to distractions, competing patient care issues, and provider fatigue. A daily goals checklist standardizes the plan of care for patients and allows the care team to clearly understand the goals for the day [15,16]. Checklists act as a cognitive tool to close the quality gap [17], creating an independent check/redundancy to ensure nothing is forgotten.

Use the four Es

Finally, ensuring patients reliably receive the recommended practices rely on having a culture of safety and the continuous application of the four Es: engage, educate, execute, and evaluate. Each of the four Es encompasses different parts of the science of safety, learning from our mistakes and the activities of the CUSP. Engagement emphasizes and explains the importance of the problem and the interventions designed to address it. Education is sharing with the staff the evidence that supports the interventions and the results of the interventions. Execution puts the interventions into place and strives to anticipate and overcome barriers. Evaluation ensures that the metrics are collected, analysed, and disseminated, with the process circling back to engagement and starting again. In this way, developing a culture of safety and quality becomes an iterative ingrained part of health care.

Both the CUSP intervention and the TRIP model are informed by the change management literature, wherein interventions done to professionals, rather than with them, are highly resisted, are usually never implemented locally, but if implemented, are not effective. To be effective, safety efforts must engage the wisdom of clinicians.

Future directions

While efforts have focused on reducing a preventable harm, patients remain at high risk. In the Armstrong Institute for Patient Safety and Quality, transdisciplinary research teams are examining harm clusters and developing systems of care to reduce all harms, including harm from undignified care [18]. This integrates the perspectives of all relevant disciplines (patients, health services research, social science, medicine, economics, HFE, biostatistics, device manufacturers, and informatics) to develop a comprehensive approach [19], in this case to create systems to prevent all harms. As the science matures, the vision is an integrated system, wherein medical technologies are linked to clinical analytics systems to support patients, their families, and clinicians. The ICU of the future should be like an iPad®; a device-integrating hardware, software, and content.

References

1. Kohn L, Corrigan J, Donaldson M (eds) (1999). *To Err is Human: Building a Safer Health System*, Institute of Medicine report. Washington DC: National Academies Press.
2. Boat TF. (2010). Insights from trends in biomedical research funding. *Journal of the American Medical Association*, **303**(2), 170–1.
3. Pronovost PJ, Marsteller JA, and Goeschel CA. (2011). Preventing bloodstream infections: a measurable national success story in quality improvement. *Health Affairs (Millwood)*, **30**(4), 628–34.
4. Pronovost PJ, Goeschel CA, Colantuoni E, et al. (2010). Sustaining reductions in catheter related bloodstream infections in Michigan

intensive care units: Observational study. *British Medical Journal*, **340**, c309.
5. Lipitz-Snyderman A, Steinwachs D, Needham DM, Colantuoni E, Morlock LL, and Pronovost PJ. (2011). Impact of a statewide intensive care unit quality improvement initiative on hospital mortality and length of stay: retrospective comparative analysis. *British Medical Journal*, **342**, d219.
6. Shojania KG and Thomas EJ. (2013). Trends in adverse events over time: why are we not improving? *British Medical Journal Quality Safety*, **22**(4), 273–7.
7. Timmel J, Kent PS, Holzmueller CG, Paine LA, Schulick RD, and Pronovost PJ. (2010). Impact of the comprehensive unit-based safety program (CUSP) on safety culture in a surgical inpatient unit. *Joint Commission Journal on Quality and Patient Safety*, **36**(6), 252–60.
8. Sexton JB, Berenholtz SM, Goeschel CA, et al. (2011). Assessing and improving safety climate in a large cohort of intensive care units. *Critical Care Medicine*, **39**(5), 934–9.
9. Berenholtz SM, Pham JC, Thompson DA, et al. (2011). Collaborative cohort study of an intervention to reduce ventilator-associated pneumonia in the intensive care unit. *Infection Control and Hospital Epidemiology*, **32**(4), 305–14.
10. Dean FB, Shebl NA, and Barber N. (2012). Failure mode and effects analysis: too little for too much? *British Medical Journal Quality Safety*, **21**(7), 607–11.
11. Battles JB, Dixon NM, Borotkanics RJ, Rabin-Fastmen B, and Kaplan HS. (2006). Sensemaking of patient safety risks and hazards. *Health Service Research*, **41**(4 Pt 2), 1555–75.
12. Pronovost PJ, Holzmueller CG, Martinez E, et al. (2006). A practical tool to learn from defects in patient care. *Joint Commission Journal on Quality and Patient Safety*, **32**(2), 102–8.
13. Reason JT. (1990). *Human Error*. New York, NY: Cambridge University Press.
14. Pronovost PJ, Berenholtz SM, and Needham DM. (2008). Translating evidence into practice: a model for large scale knowledge translation. *British Medical Journal*, **337**, 963–5.
15. Holzmueller CG, Timmel J, Kent PS, Schulick RD, and Pronovost PJ. (2009). Implementing a team-based daily goals sheet in a non-ICU setting. *Joint Commission Journal on Quality and Patient Safety*, **35**(7), 384–8.
16. Pronovost P, Berenholtz S, Dorman T, Lipsett PA, Simmonds T, and Haraden C. (2003). Improving communication in the ICU using daily goals. *Journal of Critical Care*, **18**(2), 71–5.
17. Winters BD, Gurses AP, Lehmann H, Sexton JB, Rampersad CJ, and Pronovost PJ. (2009). Clinical review: checklists—translating evidence into practice. *Critical Care*, **13**(6), 210.
18. Pronovost PJ and Bo-Linn GW. (2012). Preventing patient harms through systems of care. *Journal of the American Medical Association*, **308**(8), 769–70.
19. Stokols D, Hall KL, Taylor BK, and Moser RP. (2008). The science of team science: overview of the field and introduction to the supplement. *American Journal of Preventive Medicine*, **35**(2 Suppl.), S77–89.

CHAPTER 17

Policies, bundles, and protocols in critical care

Jeffrey Mazer and Mitchell M. Levy

Key points

- Checklists, protocols, bundles and guidelines decrease variability in care and enhance the translation of evidence-based medicine to bedside care.
- Patient safety and minimizing variability is central to the quality movement.
- Performance measurement using audit and feedback systems is essential to help physicians bridge the gap between perceived care and the actual care provided.
- The tools that are central to quality improvement to aid in decreasing variability, include checklist, protocols, guidelines, and bundles.
- Quality improvement projects need to be shaped and guided to meet the needs of patients, staff, units, and hospitals, where they are implemented.

Introduction

Quality and Safety have become central issues in health care as systematic errors and deficiencies in the way health care is delivered have been identified. Prior to this 'quality care' was assumed to be the norm in medical care. Mistakes were thought to be isolated errors and anomalies, rather than routine and widespread. They were the cost of the complexity of care. Errors that made it to the public attention were considered outliers. Several studies have shown that errors are not isolated events. One such intensive care unit (ICU) study found an average of 1.7 errors per day; 37% of them due to miscommunication [1]. Patient safety is now central to both individual physician's daily practice and broad-based institutional initiatives. Central to this transition to safer health care delivery systems is an increased commitment to the identification and maintenance of quality care. Quality care is the application and tracking of best practices, based on best-known evidence for the purpose of limiting practice variability, and thus providing the highest likelihood of patient safety and optimal outcomes.

Should practice variability be limited? Several large studies have demonstrated that clinical care is often quite variable and not necessarily in line with guidelines [2]. In a classic study by McGlynn et al., only 54.9% of 6712 patients in the USA received care that was compliant with recognized best practices for preventative care [3]. This variability in performance may be due to the complexity of patient care, individual patient physiology, professional values, cost, or other important processes. When deviation is due to knowledge deficits, oversight, or the faulty application of knowledge, it is unacceptable. Variability linked to poor outcomes has been demonstrated in the ICU. Adherence to IDSA guidelines for the treatment of severe community-acquired pneumonia (CAP) was only 57.8% in a cohort of 529 ICU patients [4]. Mortality was higher in the guideline non-adherent population. Other deviations are frequently linked to worse outcomes [5].

Limiting variability is central to the quality movement, but has been met with resistance. Standardization of care is seen as an attack on physician and patient autonomy, and a minimization of the importance of physician experience [6]. Some feel that the experience garnered cannot be replaced with quality metrics. Reliance on clinical experience has been called into question. In a systematic-analysis of 62 published studies, the majority of these studies suggested a steady decline in both physician competency and patient-centred clinical outcomes after completion of training [7]. Thus, dependence on accrued knowledge, i.e. 'experience', alone may not be in the best interest of patients.

Performance measurement

Essential to the quality movement is the process of measuring performance. Audit and feedback have been demonstrated to be a key aspect in any intervention targeting change in clinical practice behaviour [8]. Often there exists a gap between clinician-reported perception of practice patterns and audit of actual practice. This 'perception/practice gap' is well described, and supports the potential need for monitoring and reporting practice performance. Physicians have unrealistic expectations around their own competency and performance when compared with external assessments, but also inflated views around the adequacy of care they provide [9]. A survey of ICU directors comparing perception of care provided versus actual care delivered demonstrates this gap. Perceived adherence to low tidal volume ventilation and tight glycaemic control was 79.9 and 65%, while actual adherence was 2.6 and 6.2%, respectively [10]. Physician reporting and clinical experience can play a role in patient care, but evidence suggests that outside evaluation provides a better assessment of practice patterns, and therefore a better basis for informing high quality and reliable care.

Protocols, bundles, checklists, and guidelines

Checklists, protocols, bundles and guidelines are the tools of quality improvement. These tools decrease variability in care and

enhance the translation of evidence-based medicine to bedside care. Checklists are the least complex and have been shown to facilitate efficient, high quality care. Checklists are simple reminders to facilitate routine care patterns, like the provision of deep vein thrombosis (DVT) prophylaxis. Protocols are precise detailed plans to guide a regimen of therapy and provide a guide to clinicians to a default therapy. Protocols are of varying complexity and drive behaviour towards a common standard. Their prescriptive nature facilitates use in both routine bedside care and clinical research. Guidelines are systematic statements of policy, rules, or principles, which serve to capture the rules of clinical judgment, but provide little direct assistance in clinical decisions. Often less proscriptive, they serve as general guides for clinical management.

Bundles are a set of interventions, distilled from evidence-based guidelines, and target specific disease states. The assumption underlying the development of bundles is that 'bundling' proven interventions, together should result in better outcomes than when implementing them individually. Monitoring compliance is a key to the successful utilization of care bundles to drive change in behaviour [11,12]. It is important to emphasize that these tools serve to enhance, not replace the skills of the bedside clinician. They aid in bridging the gap between the discovery and publication of new knowledge with clinical implementation. This path of knowledge translation can help lead to a broad-based application of best practices for appropriate patients.

Two examples of multifaceted interventions in the ICU to improve care include the Michigan experience with an intervention to reduce catheter-related blood stream infections (CR-BSI) and the Surviving Sepsis Campaign's (SSC's) performance-improvement initiative for sepsis management [13,14]. These projects used local interdisciplinary teams, introduced education, and monitored performance using checklists (CR-BSI) or bundles (SSC). Local commitment allowed for large scale implementation. In Michigan, the median CR-BSI rate dropped from 2.7/1000 catheter days to 0 at 3 months and over the next 18 months. In 15,022 patients with severe sepsis and septic shock worldwide over a 2-year period, the SSC initiative demonstrated improved compliance with bundled management strategies leading to a 6.2% decline in mortality.

Conflicting results

Despite these and other quality metrics successes, not all of the results have been positive. Decreased time from knowledge acquisition to bedside care may lead to unintended consequences. The first example of this is the story of tight glucose control. In 2001, Van den Berghe reported that normalization of glucose in critically-ill cardiac patients, i.e. tight glucose control, was associated with decreased mortality. This was rapidly translated into clinical practice in medical and surgical ICU's worldwide. Over the next 9 years studies suggested these findings may be less pronounced in the medical patients, culminating in the NICE-SUGAR trial, which demonstrated harm to these patients [15].

A second example of the potential deleterious effects of widespread application of quality metrics is in treatment of CAP. The Joint Commission established a 4-hour goal for antibiotic administration in response to two large retrospective studies, demonstrating improved outcomes with earlier antibiotics administration [16]. As an unintended consequence, the accuracy of a clinical diagnosis for CAP declined, leading to excessive antimicrobial use and misuse [17]. The Joint Commission has since added a diagnostic category of 'diagnostic uncertainty' and increased the time goal to 6 hours. These stories serve to remind that ongoing evaluation is central to the quality movement. When rapid translation of evidence into clinical practice is associated with unintended consequences detection and response is essential.

Establishing a quality improvement programme

Hospitals and ICUs worldwide have embraced the field of quality improvement (QI). QI includes four essential phases: development, implementation, evaluation, and maintenance. Each phase has key features. The first step of the first phase is to establish a collaborative interdisciplinary leadership group. This group is central to the success of the QI project and so members need to be selected thoughtfully. Members from all parties affected by the potential intervention should be represented, this may include local experts. This team guides the process and needs to have shared commitment to both QI and a collaborative approach.

Understanding the target environment is important for the initiation of a QI project. Characteristics of the target ICU, size, hospital and ICU type, regional culture, and other factors, are essential in the success of a QI initiative. A mature and high functioning ICU with prior QI experience may perform differently to a QI-naive ICU. This will determine the size and scope, as well as dictate the type of data collection and/or feedback systems. Pre-existing systems can decrease the project costs and help ensure sustainability. Goals should be achievable, thus understanding baseline practices is essential. Projects should target low functioning metrics to achieve change [18].

After establishing the scope and goals, a plan for implementation is made. Understanding the target environment will aid the process, utilizing existing assets and targeting potential barriers shape implementation. Cook et al. demonstrated that barriers to implementation are not necessarily complex, but easily overlooked [19]. Poor communication between the bedside nurse and physician was one of the main reasons for inconsistent use of semi-recumbency. Through an understanding of process and barriers, solutions may be identified to improve compliance.

Multifaceted-interventions are more effective than single interventions for influencing behavioural change. Guidelines and education alone are unlikely to make substantial changes, so the addition of audit and feedback systems is important [11]. While designing an audit and feedback system, both outcome (long-term) and process (short-term) measures should be considered. There are arguments both for and against the use of either one, so that understanding the benefits of each become important. Examples of outcome measures include incidence of ventilator-associated pneumonia (VAP), CR-BSI, ICU length of stay, or mortality. Tracking and reporting outcomes data is easier as most institutions collect this data, but demonstrating change may be more difficult. Process measurement, i.e. a marker of 'what we do', such as time to antibiotics, is more difficult to track, may require new systems/people and often a financial investment, but is more likely to show change/success, over a short period of time. Outcomes measures are often better accepted, because they are more obvious measures of patient care. Linking process measures to patient outcomes may facilitate acceptance of specific performance metrics and lead to improved compliance.

The final piece of a QI programme is sustaining the effort. Depending on the complexity of the intervention and level of success, sustaining the initial process may require variable work.

Balancing cost in terms of manpower and financial resources with value, or impact is essential. Augmenting or a downscaling of the audit and feedback system will depend on success in measured outcomes. Not all achievements will decay at the same rate, so the maintenance phase has to be dynamic, and institution-specific, similar to implementation [12].

Running a successful QI project requires sustained, but incremental interdisciplinary teamwork. At the heart of its success and maintenance is leadership and perseverance—continuous pursuit of improvement and sufficient resource allocation to allow it to succeed and persist over time. A full review QI implementation is beyond the scope of this chapter, a useful resource is the 'how to' guide published by Curtis et al. [20].

Conclusion

The ICU is a complex environment, in which multiple teams and care processes operate simultaneously in an environment of intricate physiological derangements that expose patients to the risk of highly variable care. Variation in care is common, even in areas where evidence supports standardized interventions. Variation potentially exposes patients to unnecessary risk. Given the growing demands of critical care practice, physicians in the ICU are challenged to consistently deliver reliable, evidence-based care. The push for quality measures using checklists, protocols, guidelines, or bundles is an important to limit this variation and provides feedback mechanisms to clinicians about actual clinical practice and behaviour. Although a call for respecting and maintaining physician autonomy has been made, it is clear that we can and must do better. QI initiatives are one way to achieve our ultimate goal of enhancing patient safety and quality.

References

1. Donchin Y, Gopher D, Olin M, et al. (1995). A look into the nature and causes of human errors in the intensive care unit. *Critical Care Medicine*, **23**(2), 294–300.
2. Pham HH, Schrag D, Hargraves JL, and Bach PB. (2005). Delivery of preventive services. *Journal of the American Medical Association*, **294**(4), 473–81.
3. McGlynn EA, Asch SM, Adams J, et al. (2003).The quality of health care delivered to adults in the United States. *New England Journal of Medicine*, **348**(26), 2635–45.
4. Bodí M, Rodríguez A, Solé-Violán J, et al. (2005). Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Diseases Society of America guidelines on survival. *Clinical Infectious Diseases*, **41**(12), 1709–16.
5. Peterson ED, Roe MT, Mulgund J, DeLong ER, Lytle BL, and Brindis RG. (2006). Association between hospital process performance and outcomes among patients with acute coronary syndromes. *Journal of the American Medical Association*, **295**(16), 1912–20.
6. Reinertson JL. (2003). Zen and the art of physician autonomy maintenance. *Annals of Internal Medicine*, **138**(12), 992–5.
7. Choudhry NK, Fletcher RH, and Soumerai SB. (2005). Systematic review: the relationship between clinical experience and quality of health care. *Annals of Internal Medicine*, **142**(4), 260–73.
8. Sinuff T, Cook D, Giacomini M, Heyland D, and Dodek P. (2007). Facilitating clinician adherence to guidelines in the intensive care unit: a multicenter qualitative study. *Critical Care Medicine*, **35**(9), 2083–9.
9. Davis DA, Mazmanian PE, Fordis M, Van Harrison R, Thorpe KE, and Perrier L. (2006). Accuracy of physician self-assessment compared with observed measures of competence. *Journal of the American Medical Association*, **296**(9), 1094–102.
10. Brunkhorst FM, Engel C, Ragaller M, et al. (2007). Practice and perception—a nationwide survey of therapy habits in sepsis. *Critical Care Medicine*, **36**(10), 2719–25.
11. Wensing M, van der Weijden T, and Grol R. (1998). Implementing guidelines and innovations in general practice: which interventions are effective? *British Journal of General Practice*, **48**(427), 991–7.
12. Ferrer R, Artigas A, Levy MM, et al. (2008). Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *Journal of the American Medical Association*, **299**(19), 2294–303.
13. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related blood stream infections in the ICU. *New England Journal of Medicine*, **335**(26), 2725–32.
14. Levy MM, Dellinger RP, Townsend SR, et al. (2010). The Surviving Sepsis Campaign: results of an international guideline based performance improvement program targeting severe sepsis. *Critical Care Medicine*, **38**(2), 367–74.
15. Nice-Sugar Study Investigators. Intensive versus conventional glucose control in critically ill patients. *New England Journal of Medicine*, **360**(13), 1283–97.
16. Houck PM, Bratzler DW, Nsa W, Ma A, and Bartlett JG. (2004). Timing of antibiotic administration and outcomes for medicare patients hospitalized with community acquired pneumonia. *Archives of Internal Medicine*, **164**(6), 637–77.
17. Kanwar M, Brar N, Khatib R, and Fakih MG. (2007). Misdiagnosis of community-acquired pneumonia and inappropriate utilization of antibiotics: side effects of the 4-h antibiotic administration rule. *Chest*, **131**(6), 1865–9.
18. Krishnan JA, Moore D, Robeson C, Rand CS, and Fessler HE. (2004). A prospective controlled trial of a protocol-based strategy to discontinue mechanical ventilation. *American Journal of Research: Critical Care Medicine*, **169**, 673–8.
19. Cook DJ, Meade MO, Hand LE, and McMullin JP. (2002). Toward understanding evidence uptake: semi-recumbency in the prevention of pneumonia. *Critical Care Medicine*, **30**(7), 1472–7.
20. Curtis JR, Cook DJ, Wall RJ, et al. (2006). Intensive care unit quality improvement: a 'how-to' guide for the interdisciplinary team. *Critical Care Medicine*, **34**(1), 211–18.

CHAPTER 18

Managing biohazards and environmental safety

Ferenc Kovari and Gilbert Park

Key points

- Washing hands is the key to reducing biological hazards.
- Wearing appropriate protective gear minimizes the risk of chemical hazard.
- Complying with safety rules, attending regular training help avoiding risks resulting from handling dangerous materials, electronic equipment.
- Protect your back—lift, handle, and move patients with care.
- If stressed get help early.

Introduction

The intensive care unit is a dangerous place full of potential harm, not only for the patients, but also for the team members. Excessive sound, electromagnetic fields, radiation, chemicals, moving patients, dealing with infectious materials, slips, falls, and stress are just a few. Safety is often considered to be a first step in achieving health care quality. The challenge for the ICU practitioners is to optimize benefits and minimize the occurrence of risk [1]. This chapter covers the key concepts in the hazard control process and environmental hazards.

Hazards

Identifying hazards helps to determine the consequences and the probability of occurrence, and allows the risks associated with them to be minimized. The categories most present in the critical unit are biological and chemical.

Biological hazards

Biological agents can be classified as:

- **Live agents**: including bacterial, viral, fungal, chlamydial and rickettsial.
- **Toxins**: a toxin can be considered to be a chemically-active agent of biological origin. Toxins generally have a shorter latency period (hours–days) than the live agents, which may take days or weeks, or even months to exert their effects. Biological agents can be injected (inoculated), ingested, inhaled, or transmitted by contact with an infected patient [2]. The most common cause of health care-associated infectious diarrhoea in industrialized countries is caused by the toxin of *Clostridium difficile*.

Health care workers hands and clothing frequently become contaminated with nosocomial pathogens capable of colonizing the intestinal tract. It is probable that small numbers of these pathogens are intermittently ingested. However, intestinal colonization with detectable levels of antimicrobial-resistant pathogens and *C. difficile* diarrhoea remain uncommon among health care workers, because the indigenous microflora inhibit growth of these organisms [3].

Chemical hazards

Disinfectants

Common disinfectants include isopropyl alcohol, ethyl alcohol, quaternary ammonium compounds, sodium hypochlorite, and iodine. Exposure to these agents can cause irritation of the skin, eyes, and dermatitis. Some of the chemicals can act as carcinogens. Cancers caused by environmental agents frequently occur in tissues with the greatest surface exposure to the agents—lung, gastrointestinal tract, and skin. This process often takes years [4]. Exposure to these materials should be kept to a minimum, and personal protective equipment, including respirators when necessary, should be worn.

Toxic substances are poisonous and can have other qualities, such as being inflammable, combustible, corrosive, or irritant. When evaluating the toxicity of a substance, several factors should be considered—concentration of the chemical agent, duration of exposure, and available ventilation. Absorption happens through the skin or breaks in the skin (cuts, sores), inhalation of contaminated air through the nose and mouth, or by ingesting the substance through eating and drinking.

Substances that can be inhaled in the ICU setting include dust, smoke, aerosols (for example during ventilator disconnection), and gases. The most commonly used chemicals are:

- **Isopropyl alcohol:** a widely used antiseptic and disinfectant. It is used to disinfect thermometers, critical care equipment, and other instruments. Workers should use appropriate protective clothing, such as gloves and face shield, or splash-proof safety goggles.
- **Ethyl alcohol (ethanol)**: most hospitals use 70% ethyl alcohol as a topical application for local skin disinfection. It is highly inflammable in all dilutions when vapour may come in contact with an ignition source. When used topically, it dries the skin and care is needed to avoid dermatitis.

- **Iodine:** used as a general disinfectant and can be mixed with alcohol for use as a skin antiseptic or with other substances for general disinfecting purposes. Exposure can include irritation of the eyes and mucous membranes, headaches, and breathing difficulties. Protective clothing such as gloves and face shields should to be worn.
- **Phenol-based disinfectants:** generally used against a wide range of bacteria and for intermediate level disinfection for tuberculoidal infections. Contact with skin or mucous membranes should be avoided. Characteristic of phenol poisoning are burns of the mucous membranes, weakness, pallor, pulmonary oedema, seizures, and respiratory, circulatory, cardiac, and renal failure. Workers should use protective clothing, including gloves and face shields to avoid skin or eye contact.

Medical waste and sharps

Waste is now classified on the basis of its hazardous characteristics and the point of production. Segregation of waste at the point of production into suitable colour-coded packaging is vital to good waste management. There are hazardous (i.e. infectious waste, cytotoxic and cytostatic medicinal waste, health care chemicals, and other hazardous properties) and non-hazardous waste products (bottles, syringes, unused, but expired vials). There is clear guidance on labelling, disposing, storing, segregating, and handling of these waste products [5]. For example, in the UK there is a strict colour-coded waste disposal system, which is implemented by the health care facility according to the Department of Health regulations. The use of colour-coded receptacles is key to good segregation practice. Clear information, instruction, and training on categorizing waste needs to be provided for everyone working in areas where health care waste arises. It is helpful if posters showing the different waste pathways and types of waste are displayed at appropriate locations.

Chemotherapeutic substances

Some chemotherapeutic drugs pose a potential health risk to health care workers who may be exposed during their preparation or administration. Such drugs require special handling because of their inherent toxicities. Their actions are not specific to tumour cells and normal cells may also be damaged [4]. Health care workers who have been exposed to hazardous drugs have reported acute symptoms, such as skin irritation, sore throat, cough, dizziness, headache, allergic reaction, diarrhoea, nausea, and vomiting [6]. Safe handling of these agents is regulated by the Health and Safety Executive [7].

Radiation

Radiation hazards exist in areas where therapeutic radiology is used. Radiation sources in the ICU arise from bedside imaging procedures, such as radiographs, fluoroscopic placement of enteral feeding tubes, and insertion of vena cava filters. Primary radiation should always be pointed at the patient. No untrained health care worker should hold the patient during the procedure as the lead aprons, although they protect against secondary radiation, offer little protection against the primary beam. Secondary radiation exposure usually results from the scatter of the X-ray beam caused by reflection or deflection from the main beam. Generally, the intensity of scatter radiation 1 m from the patient is approximately 0.1% of the intensity of the useful or primary beam seen at the patient's position [8]. Staff are often anxious about portable X-rays done at the patient's bedside. However, if the X-ray is pointing at the patient and the staff member is downstream from the X-ray beam, 6 feet away from the X-ray source, and wears the appropriate protective apparel, the occupational exposure should be minimal. The 6-foot rule states that, by law, the exposure cord for any portable X-ray unit must be no less than 6 feet in length, in order to give the radiological technologist a minimal safe distance from the radiation source although it is advisable for the health care workers to stay as far away from the patient as possible during the actual procedure time [9]. Natural radiation results in the average person receiving about 125 mrem per year. Workers in health care and the nuclear industry, are typically monitored and restricted to effective doses of 100 mSv every 5 years (i.e. 20 mSv per year), with a maximum of 50 mSv allowed in any given year [10]. There are no reports of radiation sickness in ICU workers regarding acute radiation syndrome.

Radiation: pregnant and breast-feeding employees

The vast majority of medical X-rays do not pose a critical risk to a developing child; there may be a small likelihood of causing a serious illness or other complication. The actual risk depends on how far along the pregnancy is and on the type of X-ray. Most standard X-ray examinations of the abdomen are not likely to pose a serious risk to the child. Some abdominal and pelvic studies such as CT deliver greater amounts of radiation to a developing pregnancy [11]. Scattered radiation resulting from diverse radiological interventions are not posing significant risk to the breastfeeding employee, although exposure should be kept at a minimal level.

Ergonomics

Health care ergonomics is the science to fitting the job to the workers. There is scientific evidence linking the physical environment to staff performance effectiveness, and error reduction [12]. It improves patient safety by reducing staff fatigue. There are several hazards resulting from an inappropriate working environment or failure to provide appropriate equipment. Modern ICU design has shifted from traditional crowded environments with little or no natural light, to large single room units with windows and natural light. Single rooms enhance family presence, staff communication, and patient privacy. Designing exposure to nature through posters, pictures, or windows looking upon natural scenes improves outcomes and reduces costs [13].

Back-related injuries

One of the most common occupational injuries among health care workers is back injury. Only about 5% of back injuries result from a single accident; most are the result of long-term wear and tear on the back. This can lead to disc degeneration and nerve damage [14]. In the critical care setting there are countless ways of damaging the back. These include bed-to-stretcher and bed-to-wheelchair transfer, pulling the patient up in bed, turning the patient over, and transferring to the CT scanner table. In the UK, the Manual Handling Operations Regulations Act 1992 states that employers should provide mechanical assistance—a trolley or hoist for example—to employees when doing heavy lifting wherever reasonably practical. All health care workers need to regularly attend safe lifting and patient handling training.

Slips and falls

Slips and falls are some of the most common patient-related occurrences in health care facilities. Identifying risks, tailoring the hospital environment, i.e. better lighting and better flooring, can reduce risk. Splashed fluids on the floor are major sources of slips. Clear sign-posting of a wet surface is essential. Provide all employees with training related to slip, trip, and fall prevention [15].

Equipment and electrical safety

Injuries related to electrical equipment are mostly avoidable if compliance with the safety measures is observed. The human body responds in several ways to electrical current flowing through it. The sensation of shock is only one such effect and this can be extremely painful. The passage of electric current may cause muscular contractions, respiratory failure, and fibrillation of the heart, cardiac arrest, or injury from internal burns. In the UK, the 1989 Electricity at Work Regulations requires every employer and employee to comply with the provisions of the regulations in so far as they relate to matters that are within his control.

Psychological hazards

Stress

Health care workers on shift work or doing overtime can develop stress and burn-out syndrome. Epidemiological studies suggest a link between stress at the job and cardiovascular disease, with a stressful and demanding job doubling the risk of death from these condition [16].

Dealing with life-threatening injuries and illnesses, even with death, complicated by overwork, understaffing, paperwork, tight schedules, and demanding and dependent patients often leave health care workers feeling lonely, isolated, angry, or frustrated.

Stress contributes to apathy, lack of confidence, and absenteeism. Stress has been associated with loss of appetite, mental disorders, migraines, sleeping disorders, and emotional instability [16,17]. According to Coomber et al., self-reported risk factors include a sense that the responsibility is too great, lack of peer recognition, worry about compromising standards, the effects of stress on home life, distressed relatives, and the pressure to keep up to date with the literature [18].

Preventing stress in the ICU is critical for patient safety. Making the workplace a pleasant environment with natural light, windows, posters, or pictures, and having an appropriate place to take breaks is crucial. Positive thinking, good time management, and interacting and sharing problems with colleagues or friends can improve stress management. Also avoiding unhealthy habits and engaging in regular exercise will reduce some of the emotional intensity by clearing the thoughts and enabling the individual to deal with the problems more calmly.

Noise

Exposure to high levels of noise in the workplace is a common job hazard that is much more serious than it was originally thought. The World Health Organization (WHO) guidelines stipulate a limit of 35 decibels (dB(A)) equivalent continuous sound level (LEq) during the day and 30 dB(A) LEq at night in patients' rooms.

Noise may trigger changes in cardiovascular, endocrine, neurological, and other physiological functions, and hinders communication among workers. One potentially useful strategy when building an ICU is to create a quieter facility by installing high-performance sound absorbing ceilings [19]. Other strategies include reducing noise sources (e.g. providing noiseless paging) and converting to single-bed patient rooms.

Conclusion

Through the chapter we aimed to point out the most common elements causing biohazard risk in an everyday intensive care unit. Safety is equally important not only for the patients, but to the team members as well. We hope to improve that by putting special emphasis on the health care ergonomics and raising attention to factors sometimes less obvious like stress or the noise.

References

1. Stockwell DC, and Slonim AD. (2006). Quality and safety in the intensive care unit. *Journal of Intensive Care Medicine*, **21**, 199–210.
2. Poutanen SM and Simor AE. (2004). *Clostridium difficile*-associated diarrhea in adults. *Canadian Medical Association Journal*, **171**, 51–8.
3. Donskey CJ. (2004). The role of the intestinal tract as a reservoir and source for transmission of nosocomial pathogen. *Clinical Infectious Diseases*, **39**(2), 219–26.
4. Loeb LA and Harris CC. (2008). Advances in chemical carcinogenesis: a historical review and prospective. *Cancer Research*, **68**, 6863–72.
5. Department of Health (2006). *Health Technical Memorandum 07-01: Safe Management of Healthcare Waste*. London: Stationary Office.
6. Harrison BR and Kloos MD. (1999). Penetration and splash protection of six disposable gown materials against fifteen antineoplastic drugs. *Journal of Oncology Pharmacy Practice*, **5**, 61–6.
7. Health and Safety Executive. (2014). *Safe Handling of Cytotoxic Drugs*, HSE Information Sheet MISC61. London: HSE.
8. Statkiewicz-Sherer MA. (2013). *Radiation Protection in Medical Radiography*, 2nd edn. Maryland Heights, MI: Mosby.
9. Bushong SC. (1993). *Radiologic Science for Technologists: Physics, Biology, and Protection*, 5th edn. St Louis, MO: CV Mosby.
10. International Commission on Radiological Protection (2007). The 2007 recommendations of the International Commission on Radiological Protection, ICRP publication 103. *Annals of the International Commission on Radiological Protection*, **37**, 1–332.
11. (2012). Radiation Exposure in X-ray and CT Examinations Safety-Xray. RadiologyInfo.org
12. Ulrich RS and Zimring C, with Quan X, Joseph A, and Choudhary, R. (2004). The Role of the Physical Environment in the Hospital of the 21st Century. Available at: http://www.healthdesign.org/sites/default/files/Role%20Physical%20Environ%20in%20the%2021st%20Century%20Hospital_0.pdf.
13. Ulrich RS. (1991). Effects of health facility interior design on wellness: theory and recent scientific research. *Journal of Health Care Design*, **3**, 97–109.
14. Waddell G and Burton AK. (2001). Occupational health guidelines for the management of low back pain at work: evidence review. *Journal of Occupational Medicine*, **51**(2), 124–35.
15. Tweedy JT. (2005) *Healthcare Hazard Control and Safety Management*, 2nd edn. Boca Raton, FL: CRC Press.
16. Rosengren A, Hawken S, Ounpuu S, et al. (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case control study. *Lancet*, **364**, 953–62.
17. Coomber S, Todd C, Park G, Baxter P, Firth-Cozens J, and Shore S. (2002). Stress in UK intensive care unit doctors. *British Journal of Anaesthesia*, **89**(6), 873–81.
18. Matejovic M, Chvojka J, Sykora R, et al. (2011). A 24-h work shift in intensive care personnel: biological pathways between work stress and ill health. *Journal of Internal Medicine Research*, **39**(2), 629–36.
19. Haskins N and Soldan J. (2010). Noise in the critical care environment. *Critical Care*, **14**(Suppl. 1), P450.

CHAPTER 19

Managing ICU staff welfare, morale, and burnout

Gavin G. Lavery and Linda-Jayne Mottram

Key points

- The intensive care unit (ICU) environment exposes staff to stressful and emotionally-demanding situations, which places them at high risk for burnout.
- Risk factors for burnout can be found at both individual and organizational levels.
- Consequences of low morale and burnout include personal distress for clinicians, poor quality of care for patients, and higher health care costs for organizations and society.
- Staff engagement is emerging as the antithesis of burnout.
- We need to promote a wider recognition among ICU staff regarding risks of burnout and the consequences for both them and the patients in their care.

Introduction

Low morale, stress, and 'burnout syndrome' have been identified as risks for staff working in health care. There is also a link between staff dissatisfaction and poor performance by health care organizations [1]. In the clinical environment, poor performance translates to increased frequency of adverse events, patient harm, and suboptimal outcomes.

Clinical staff are prone to work-related stress for many reasons, including the emotional demands of the job, limited resources, ethical conflicts, and excessive clinical workload. In the critical care environment, treatment is complex, patients' needs change rapidly and 'end-of-life' decisions are relatively common. This represents a working environment that can generate significant stress for staff and, potentially, lead to burnout.

Definitions and terminology

Our aim should be to develop a workforce and a working environment that guards against low morale, stress, and burnout. These are diverse concepts that are linked, but not in a simple cause-and-effect relationship.

Morale

Morale is readily detected in the workplace, but is difficult to define. Workplace morale can be defined as;

- The level of staff satisfaction (based on how they see or value their job).
- Attitudes to the work environment.
- Buy-in regarding the aims and objectives of the organization.

Morale is a measure of staff 'happiness' within an organization. When morale is high, the long-term goals of the department or parent organization become merged with the goals of individual staff members—a high degree of 'buy-in'. High morale leads to increased productivity in an appropriate environment and will support similar performance even when working conditions are difficult. In contrast, poor or low morale is associated with inefficiency and poor quality even when the work environment is optimized. Studies have concluded that care delivered by unsatisfied health care employees (low morale) is negatively affected and this adversely affects patient satisfaction [2]. One would expect that increasing the engagement, satisfaction, and morale of employees may benefit a health care organization, and result in improved patient care and higher patient satisfaction.

Stress

Stress at work occurs when there is an imbalance between the demands of the job, and the worker's capacity and capability to cope with such demands. The latter may be due to lack (or perceived lack) of organizational support. It is interesting to note that, compared with airline pilots, intensive care unit (ICU) doctors are much more likely to report themselves as being able to perform effectively during critical phases of care when they are fatigued and are also less likely to acknowledge the effect of personal problems upon performance at work [3]. However, the symptoms caused by stress are often obvious to the individual affected and/or those around them; over engagement, a sense of urgency, and hyperactivity accompanied by overactive emotions—a state of 'too much of everything'. While stress may lead to burnout, most stressed individuals do not suffer burnout. Indeed, finite exposure to some stressors may enhance performance [4].

Burnout

Burnout is a colloquial term, describing a state of work-related mental exhaustion. The burnout syndrome was first defined by Freudenberger as, 'the extinction of motivation or incentive, especially where one's devotion to a cause or relationship fails to produce the desired results' [5]. By the late 1990s the definition had been expanded [6] to 'a persistent, negative work-related state of mind in "normal" individuals that is primarily characterized by exhaustion, which is accompanied by distress, a sense of reduced

effectiveness, decreased motivation, and the development of dysfunctional attitudes and behaviours at work. This psychological condition develops gradually but may remain unnoticed for a long time for the individual involved. It results from a misfit between intentions and reality on the job. Often burnout is self-perpetuating because of inadequate coping strategies that are associated with the syndrome'.

While burnout is often associated with absenteeism and poor performance at work, it may also lead to 'presenteeism', where the clinician is physically at work, but displays little desire to be there. Thus, in contrast to stress, the hallmark of burnout is 'too little of everything', although prior to exhibiting such hallmarks, individuals may show behaviour such as increased intensity at work, with ideas that no one else (except them) is dedicated (or talented enough?) to provide services/care.

Depression is a separate entity from burnout and pervades all areas of life, not merely professional aspects. Depressed individuals experience affective symptoms (low mood, worthlessness, and guilt), behavioural changes (social withdrawal, agitation, and psychomotor retardation) and cognitive symptoms (difficulty with decision-making or concentration). There may also be somatic features, such as change in appetite, fatigue, and sleep pattern. Depression can follow as a consequence of burnout, but in burnout the dysphoric and behavioural features predominate over somatic symptoms. Depression is common in ICU physicians with a reported prevalence of between 12 and 24% [7].

Burnout: recognition

Burnout is most frequently detected and quantified using the Maslach Burnout Inventory (MBI), a questionnaire covering 27 items within three subscales [8]. MBI scores the presence of the three hallmarks of burnout—emotional exhaustion, depersonalization (cynicism and negativity towards patients, clients, or others), and low personal accomplishment (characterized by feelings of professional insufficiency). Freudeberger proposed the existence of 12 phases within the syndrome of burnout [5], although some suggest that this description is overly focused on personal characteristics, rather than the wider social and organizational factors contributing to burnout [9]. Some, but not necessarily all, of these phases may be identifiable on the journey towards burnout (Box 19.1).

Box 19.1 Potential phases of burnout [3]

- **The need to prove oneself:** often occurring in highly motivated and ambitious individuals.
- **Working harder:** high personal expectations emerge as further work commitments are undertaken.
- **Neglecting personal needs:** no time or energy is reserved for activities or relationships outside the workplace.
- **Displacement of conflict:** the individual is unable to identify the cause for their difficulties.
- **Revision of values:** isolation from family and friends with a solely job-related value system.
- **Denial:** cynicism, aggression, and intolerance of others emerge, leading to isolation.
- **Withdrawal:** social contact at a minimum. May seek respite in alcohol or drugs.
- Behavioural **changes become more apparent to others:** e.g. conflict.
- **Depersonalization**: loss of appreciation for self and **self-worth**. Cannot appreciate future success.
- **Inner emptiness:** may seek an activity to fill the void such as eating, drugs, etc.
- **Depression:** typical affective, cognitive and somatic features are present.
- **Burnout ensues:** complete physical and emotional collapse.

Data from Sexton JB et al., 'Error, stress and teamwork in medicine and aviation: cross sectional surveys', *British Medical Journal*, 2000, **320**, pp. 745–9.

Burnout: frequency

It would appear that severe burnout, as measured with the MBI is present in about half of critical care physicians [10] and one-third of critical care nurses [11] in France. These figures match the findings from studies across Europe in anaesthesia and critical care medicine, which suggest a point-prevalence for moderate or severe burnout (as determined with the MBI, of 30% among nurses and approximately 40–50% among physicians.

While the ICU environment appears psychologically challenging, burnout may be a significant problem other clinical environments. A study of 564 UK general medical practitioners (GPs) found that 46% had high levels of emotional exhaustion, 42% had depersonalization characteristics, and 32% had low levels of personal accomplishment [12]. However, differences in methodology prevent direct comparison. In a study of 351 ICU and general nurses from three US hospitals [13], more ICU than general nurses showed evidence of post-traumatic stress disorder (24% versus 14%).

Burnout: contributing factors or risk factors?

Intrinsic factors

Burnout can occur at any age, but is more likely in younger workers and may be quite common in doctors-in-training [14]. It would appear that maturity and experience are protective. The influence of gender is complex. Many physician studies have suggested that females are more likely to suffer from burnout, but this may reflect differing ability to demonstrate empathy. Women suffering burnout tend to display more emotional exhaustion and men experience more depersonalization, or a cynical attitude to co-workers or patients. Demographics such as single status, childlessness, and personality characteristics such as neuroticism and low self-esteem can increase risk [14].

Extrinsic factors

Six key influences, within the working environment and external to the individual, contribute to burnout.

Workload

The profile/case mix of the ICU may influence levels of reported stress. Larger units, typically those in teaching hospitals, with a more diverse and complex case mix, and higher mortality rates, have higher reported rates of burnout. French intensivist physicians with severe burnout [10] tended to be those with hours of work as a stressor (number of night shifts, and time since last vacation). However, while workload can be stressful; conversely, frustration and stress may arise when workers do not get the opportunity to use their specialist skills or to make appropriate progress in their career.

Choice and control

Working patterns for nurses and junior doctors (length of shifts, breaks between periods of working, and flexibility in working) are all known to affect staff morale. When work–life balance is eroded by rigid rostering, staff turnover and sickness increase. The autonomy of many physicians and the ability of nurse empowered to contribute to clinical decision-making would be expected to have some protection from stress and burnout [15].

Recognition and reward

The belief that one's work is important and appreciated can buffer against low morale and burnout. Staff development and training initiatives demonstrate to workers that they are valued. However, the satisfaction from successfully treating critically-ill patients may not be reward enough for ICU staff, since without critical care follow-up, physicians and nurses may not see the full effects of their care in terms of recovery of function or well-being by the patient.

Work community

There is often a positive sense of community between those working in ICU. However, it is also an enclosed community in which it is difficult to escape from (unresolved) conflict. This may erode workplace relationships, even between individuals who are not part of the problem. Junior staff, faced with stressful clinical situations, will experience significant distress, which may progress to burnout if they are poorly supervised and supported by seniors [14].

Fairness and justice

This relates to fairness in areas, such as rostering and opportunities for training or advancement, or may involve deeply-held beliefs about unfair treatment at work. Effective strategies for conflict resolution and an open ICU culture can promote justice.

Values

Incongruence between the stated values of an institution and cultural practices may the genesis of burnout. Practices that appear to promote cost-saving over high quality care can erode staff commitment, especially when the corporate view does not acknowledge a compromise between resources and cost. Moral distress is a key cause of burnout for critical care nurses. This arises when the ethically right course of action is known, but staff are unable to follow it—for example, the continuation of aggressive, but futile treatment, particularly when there is a perception that patients who are more likely to survive are not being admitted at the appropriate time due to bed pressures.

In the study by Poncet and colleagues [11] of almost 2400 French ICU nurses, four domains were associated with severe burnout:

- Age.
- Organizational factors, such as the ability to choose days off or participation in an ICU research group.
- Quality of working relations.
- End-of-life care related factors.

We should think of these factors as contributing to, or being associated with, burnout, rather than being risk factors, linked by cause and effect.

Burnout: effects

The relationship between burnout and outcomes is complex. Does burnout lead to bad outcomes or do bad outcomes lead to burnout? Can they be due to other influences, e.g. inadequate staffing levels or skill mix? Job demands related to burnout (e.g. long working hours) are known to heighten the chance of junior doctors making serious medical errors [16] and this may provide us with a key insight. It would appear that good outcomes are hampered by the presence (or co-existence) of burnout and/or its risk factors. The search for cause and effect is not only very difficult, but also misses the point. The presence of factors known to promote burnout or evidence of burnout among staff should be tackled—both for the benefit of staff, and the quality and/or experience of care for patients

Burnout: prevention

Established burnout appears to be difficult to treat and has serious long-term potential for further harm. Thus, we require strategies that prevent burnout (or that aid early detection), although there is no consensus on what to do [17]. Health care workers also have a responsibility to manage their own risks for burnout. This includes avoiding personal behaviour that may adversely affect themselves or colleagues, and fully engaging with workplace initiatives designed to improve the environment and reduce avoidable stresses.

While redesigning the working environment and providing training in areas such as stress and time management, relaxation, and assertiveness have been suggested to reduce burnout, there is little supportive evidence. More research is required into the causes of burnout, the interventions that might reduce the frequency of burnout, and the coping strategies that ICU staff use on a day-to-day basis that may protect them. Most pressing is the need to assess the effect of burnout on patient safety and the quality of care.

Despite the lack of certainty, sufficient plausibility exists for the causative factors. As with many intensive care strategies, it is unlikely that one magic bullet will cure the problem. It would seem prudent to pursue interventions targeting both the individual and the workplace (Table 19.1). The greatest early advance might be a wider acceptance of the risk of burnout by ICU staff and recognition of the potential consequences for them and for patients.

Worker wellness and employee engagement

Quality indicators in critical care usually focus on outcomes such as infection rates or compliance with processes. However, high quality care must be patient-centred which encompasses patient satisfaction with their experience of care. The experiences of patients and relatives depend heavily on the attitudes and demeanour of the staff providing care. Some have argued that the well-being of health care staff is a missing quality indicator [18]. Staff suffering from burnout and low morale are less productive, more prone to error and less likely to deliver high quality care. Thus, preventative measures and

Table 19.1 Cross-organizational interventions that may reduce the risk of burnout

Individual	Unit	Organizational
Stress management	Flexible working/rostering	Staff engagement
Involvement in research	Leadership development	Resource provision
Assertiveness training	Collaborative decision making	Policy development
Time management skills	Employee mentorship	Promoting a learning culture
Coping strategies	Teambuilding and social support	Organizational values
Interpersonal skills	Improved end-of-life care	Hospital management style

interventions to reduce burnout should improve efficiency, safety, and motivate the workforce for quality improvement. Health care institutions are increasingly recognizing that quality of care and patient safety are partly dependent on the employee well-being [19].

Many health care organizations have moved beyond prevention of burnout to focus on employee engagement. Indeed, burnout could be viewed as the erosion of engagement [20]. Engaged workers are **energized** not exhausted, **involved** not cynical and **work effectively** as opposed to underachieving. Engagement captures the spirit of 'going the extra mile' in order to improve quality of care and patient safety.

Conclusion

In ICU, failure to provide 'care for the carers' may have unwelcome consequences, not least the risk of adverse events, suboptimal care, and poor outcomes. An unsatisfied and exhausted workforce is less effective both individually and collectively. Assessment of critical care performance should encompass more than survival, infection rates, and process measures. As important as these indicators are, reliable high quality care will remain elusive if the health of the carers is not viewed as important. Failure to adopt such an approach will almost certainly result in increased turnover of the workforce, and the financial burden of training and orientating new staff. Recognition and prevention of burnout in ICU may emerge as an important tool in reducing variability and promoting high quality care.

References

1. Montgomery A, Panagopoulou E, Kehoe I, and Valkanos E. (2011). Connecting organisational culture and quality of care in the hospital: is job burnout the missing link? *Journal of Health Organization and Management*, **25**, 108–23.
2. Atkins, PM, Marshall, BS, and Javalgi, RG. (1996). Happy employees lead to loyal patients. *Journal of Health Care Marketing*, **16**(4), 14–23.
3. Sexton JB, Thomas EJ, and Helmreich RL (2000). Error, stress and teamwork in medicine and aviation: cross sectional surveys. *British Medical Journal*, **320**, 745–9.
4. Schoofs D, Pabst S, Brand M, and Wolf OT. (2013). Working memory is differentially affected by stress in men and women. *Behavioural Brain Research*, **241**, 144–53.
5. Freudenberger H. (1974). Staff burn-out. *Journal of Social Issues*, **30**, 159–65.
6. Schaufeli WB and Enzmann D. (1998). *The Burnout Companion to Study and Practice: A Critical Analysis*. London: Taylor & Francis.
7. Embriaco N, Hraiech S, Azoulay E, et al. (2012). Symptoms of depression in ICU physicians. *Annals of Intensive Care*, **2**, 34.
8. Maslach C, Schaufeli W, and Leiter M. (2001). Job burnout. *Annual Review of Psychology*, **52**, 397–422.
9. Schaufeli WB. (2003). Past performance and future perspectives of burnout research. *South African Journal of Industrial Psychology*, **29**(4), 1–15.
10. Embriaco N, Azoulay E, Barrau K, et al. (2007). High level of burnout in intensivists. *American Journal of Respiratory and Critical Care Medicine*, **175**, 686–92.
11. Poncet MC, Toullic P, Papazian L, et al. (2007). Burnout syndrome in critical care nursing staff. *American Journal of Respiratory and Critical Care Medicine*, **175**(7), 698–704.
12. Orton P, Orton C, and Pereira Gray D. (2012). Depersonalised doctors: a cross-sectional study of 564 doctors, 760 consultations and 1876 patient reports in UK general practice. *British Medical Journal Open*, **2**, e000274.
13. Mealer ML, Shelton A, Berg B, Rothbaum B, and Moss M. (2007). Increased prevalence of post-traumatic stress disorder symptoms in critical care nurses. *American Journal of Respiratory and Critical Care Medicine*, **175**, 693–7.
14. Ishak WW, Lederer S, Mandili C, et al. (2009). Burnout during residency training: a literature review. *Journal of Graduate Medical Education*, **1**, 236–42.
15. Joiner TA and Bartram T. (2004). How empowerment and social support affect Australian nurses' work stressors. *Australian Health Review*, **28**, 56–64.
16. Fahrenkopf AM, Sectish TC, Barger LK, et al. (2008). Rates of medication errors among depressed and burnt out residents: prospective cohort study. *British Medical Journal*, **336**, 488–91.
17. van Wyk BE and Pillay-Van Wyk V. (2010). Preventive staff-support interventions for health workers. *Cochrane Database Systems Review*, CD003541.
18. Wallace J, Lemaire J, and Ghali W. (2009). Physician wellness: a missing quality indicator. *Lancet*, **374**, 1714–21.
19. Azoulay E and Herridge M. (2011). Understanding ICU staff burnout: the show must go on. *American Journal of Respiratory and Critical Care Medicine*, **184**, 1099–100.
20. Maslach C, Schaufeli W, and Leiter M. (2001). Job burnout. *Annual Review of Psychology*, **52**, 397–422.

PART 1.5

Governance

CHAPTER 20

ICU admission and discharge criteria

Julian Bion and Anna Dennis

Key points

- The decision to admit or discharge a patient is the responsibility of the intensive care specialist.
- Decisions will be based on the severity of the illness, chronic health and physiological reserve, and therapeutic susceptibility, and will be informed by the patient's wishes.
- Admission and discharge decisions involve balancing the needs of individual patients against those of society.
- Wide variations in admission and discharge practices between centres and countries probably reflect differences in resources, cultures, and clinician beliefs.
- Outcomes of intensive care are affected by the timing of admission and discharge, and the quality of care outside the ICU.

Background

The decision to admit patients to intensive care or discharge them to a hospital ward (or even directly back home) is a daily task for intensivists, a life-changing event for patients and families, and in aggregate a major strategic issue for health care systems worldwide [1]. Decisions must often be made rapidly in conditions of uncertainty involving substituted judgements about relative risks and benefits, framed by sociocultural factors that are not well characterized. The outcomes of the decision are strongly influenced by available resources, staffing, and skills throughout the patient pathway.

Intensive care developed in response to the polio epidemics in the early 1950s. Survival rates were transformed by concentrating technology and expertise in one location, substituting invasive mechanical ventilation for the iron lung, and introducing the science of physiological measurement. With the progressive eradication of polio, the criteria for admission to intensive care shifted to ventilatory support for other causes of acute respiratory failure, and then to the support of other failing organ systems. Single-speciality high-dependency units (HDUs) were established for patients with isolated non-respiratory organ failures (cardiac, renal, neurological, burns), while intensive care was reserved for those with, or at risk of, multiple organ failure or requiring invasive mechanical ventilation. Over the years, the hospital case mix has become more elderly, complex, and dependent, driven by a combination of demographic changes, cost-containment, and technological advances. As the number of hospital beds has diminished, intensive care has expanded in response to the growing demand for multiple organ support. Additional demands come from elective high-risk elective surgery and, more recently, from the transplant community, for the admission of potential organ donors. One of the most important roles for the intensivist, therefore, is in managing this diverse and competing demand to greatest effect through informed and patient-focused decisions about admission and discharge.

Intensive care is a package of interventions, which consists of specific therapies for the disease, technologies for physiological monitoring and organ system support, and integrated multidisciplinary decision-making. Organ system support is not, in itself, therapeutic. Part of the art of intensive care lies in minimizing its burdens. Admission to intensive care implies that the benefits will outweigh these burdens, and that the potential lost opportunity costs for other patients and society are justifiable. Therefore, the intensivist functions as custodian of a scarce resource, balancing a fiduciary duty to individual patients against the interests of wider society. The manner in which this duty is expressed is influenced by the context in which admission and discharge decisions are taken.

Determinants of admission and discharge decisions

Context

Admission and discharge processes and outcomes vary widely between hospitals and between countries. For example, half of all deaths in England and one-third in the USA occur in hospital, but in England only 10.1% of hospital deaths involve intensive care unit (ICU) admission compared with 47.1% in the USA. Of the ICU deaths, patients over the age of 85 accounted for 1.9% of non-operative and 8.5% of operative deaths in England, but 31.5 and 61%, respectively, in the USA [2]. The USA has 5.7 times the number of ICU beds *per capita* that of the UK [1] and makes greater use of chronic ventilator units outside acute hospitals, facilitating 'discharge', but not necessarily improving outcomes [3]. Patients admitted to ICUs in the UK have a much higher severity of illness, are more likely to be intubated, and those with sepsis are less likely to be admitted directly from the emergency department (ED) [4], transiting instead via the ordinary wards. These different admission pathways impact on mortality. Emergency hospital admissions transferred to a ward and, subsequently, to an ICU have a higher mortality than those admitted directly to ICU from the ED, as do

high-risk surgical patients admitted from a surgical ward, instead of directly from the operating theatre.

Both admission and discharge involve a change of location with the potential for gaps in communication and loss of continuity of care. There is growing research evidence showing that the outcomes of intensive care are affected by the timing of admission and discharge decisions, which in turn are influenced by resource availability in the ICU and probable inexpert care on the ordinary wards. Admission to the ICU from 00:00–07:00 hours, and at weekends is associated with a higher mortality, as is discharge from the ICU to the ordinary ward at night [5]. Readmission to intensive care is associated with a hospital death rate 2–10 times that of non-readmitted patients [6], and can be mitigated by intensive care outreach in the form of intensivist-led rapid response teams [7]. Of high-risk surgical patients admitted to intensive care in 28 European countries, 43% of deaths occurred after discharge to the ordinary ward [8], suggesting substantial opportunities for improving discharge planning and post-discharge care. Unintentional discontinuation of chronic medications is also common following discharge from the ICU, and is associated with adverse patient outcomes [9].

Patient factors

Decisions to admit patients to ICU or discharge them to the ward are determined by the severity of their illness. Severity of illness is a composite of the magnitude of the acute disease, the patient's physiological reserve, and the concurrent level of treatment and organ system support. Of these three variables, physiological reserve is the most difficult to quantify and modify. It is generally assessed using functional capacity, co-morbid disease, and age. Loss of functional capacity is an important predictor of frequent hospitalization and death, and co-morbid disease impacts on ICU and hospital outcomes [10]. The benefits of intensive care for very old patients are uncertain, although there may be an increased risk of disability for the elderly when compared with younger patients [11]. However, chronological age is a poor substitute for 'biological age' when deciding on who to admit to intensive care.

Diagnosis and prognosis are intimately linked to therapeutic specificity, and advances in treatment will alter prognosis. Diagnoses that would once have justified non-admission to intensive care are now much more treatable. Patients with AIDS-related critical illness have better outcomes because of antiretroviral therapy [12]; those with haematological malignancy now have much improved survival rates [13]; and outcomes are improving generally across ICUs.

Patient preferences are fundamental determinants of ICU admission and discharge decisions, and in setting levels or limits on intensity of care. However, loss of capacity caused by critical illness means that substituted decision-making is common and this may contribute to substantial variation in practice between centres. Failure by physicians to understand patient preferences to forego life-sustaining treatments, and failure of the health care system to offer alternatives to hospitalization, result in excess burdens and costs of care. The challenge lies in early identification of patients at risk of critical illness to permit informed discussions with intensive care staff, while the patient still has capacity. With a rapidly ageing population, opportunities should be taken to discuss advance planning in the community; doing so reduces unwanted medical treatment (including ICU admission), and stress and depression in family members.

Decision support

Scoring systems

Physiological severity scoring, in particular the Acute Physiology and Chronic Health Evaluation (APACHE) system, was a transformational concept, introduced as a tool to characterize patient populations and to inform decision-making about individual patients. Physician experience may be a valuable tool for contextualizing population-based prognostic estimates for individual patients, but it is an unreliable device for constructing those population estimates for which large observational databases are far better. Scoring systems based on very large patient numbers capture more population information than the individual clinician can acquire in a lifetime, but the clinician will know more about the individual patient than any scoring system can. For this reason, predictive systems may inform clinical judgement, but cannot replace it. Triage protocols to maximize use of scarce resources in pandemics have been modelled prospectively and retrospectively, demonstrating theoretical value in releasing intensive care beds by denying admission to those categorized as being too well or too sick to benefit.

Several models have been developed to inform safe and timely ICU discharge decisions. Simple univariate risk factors include prolonged length of stay, unstable vital signs including tachypnoea or tachycardias, and poor pulmonary function [6]. Badawi and Breslow [14] have modelled post-ICU mortality and ICU readmission, using data from more than 700,000 patients, incorporating admission diagnosis, severity of illness, laboratory values, and physiological variables in the last 24 hours of the ICU stay. The Stability and Workload Index for Transfer score [15], and a model developed in France [16], have similar predictive precision for ICU readmission. Others have identified the potential for important reductions in mortality had triage models been used to avoid premature ICU discharge. All methods need prospective validation.

Guidelines for ICU admission and discharge

The UK guidelines on admission to and discharge from ICUs and HDUs [17] were developed in response to adverse publicity surrounding the lack of intensive care beds. The working party chose simple criteria based on dependence on organ system support linked to intensive care (level 3) or high dependency care (level 2) (see Table 20.1). The classification has stood the test of time, perhaps because it is permissive, rather than constraining.

The guidelines provided by the Society of Critical Care Medicine in the USA [18] offer four alternative classifications:

- A prioritization model with four categories based on different sets of patient characteristics.
- A diagnosis model.
- An objective parameters model based on physiology or investigations.
- Discharge Criteria linked to physiological stability.

This guidance is currently under review with the publication in 2015 of the Guidelines on the Provision of Intensive Care Services by the UK Faculty of Intensive Care Medicine and the Intensive Care Society [19]. Night-time discharge in particular should be avoided, and if it occurs should be treated as a critical incident, accompanied by measures to protect patient safety [20].

Table 20.1 UK Guidelines on admission to and discharge from intensive care and high dependency units [19]

Intensive care is appropriate for:	High dependency care is appropriate for:
Patients requiring or likely to require advanced respiratory support alone	Patients requiring support for a single failing organ system, but excluding those needing advanced respiratory support
Patients requiring support of two or more organ systems	Patients who can benefit from more detailed observation or monitoring than can safely be provided on a general ward
Patients with chronic impairment of one or more organ systems sufficient to restrict daily activities (co-morbidity) and who require support for an acute reversible failure of another organ system	Patients no longer needing intensive care, but who are not yet well enough to be returned to a general ward
	Post-operative patients who need close monitoring for longer than a few hours

Decision processes

Admission and discharge decisions should be made by the specialist intensivist, and taken in collaboration with the referring team, and the patient and family where circumstances permit. Early involvement of the intensivist permits more effective planning, e.g. rapid response teams (intensive care outreach) have an important role in facilitating end-of-life care discussions in order to avoid futile and burdensome treatments.

The provision of futile care is usually driven by family expectations and lack of agreement among the treating team. Discussions involve value judgements—clinicians should be aware of biases based on their own personal views, family requests, or inadequate resources. While caring for the family is an essential component, the primary duty is to the patient. Outcomes are strongly affected by the degree of trust that can be established between the intensivist, family, and referring team. Decisions not to admit a patient to the ICU on grounds of futility or to discharge a patient for palliative care, should be taken by senior staff following a broad consensus, the reasons clearly documented, and with a support plan in place both for the patient and the family.

In conditions of uncertainty about the best course of action, a formal second opinion should be obtained, and for admission to intensive care, a trial of treatment may be offered with explicit and agreed limits, including the withdrawal of support if no improvement occurs. Trials of intensive care discharge is more problematic, as de-escalation involves a loss of process control, if discharge involves an abrupt change in both location and quality of care. Longer-term ICU patients need a planned and supervised trajectory for progressive restoration of physical and psychosocial independence, to realize the investment of intensive care resources in full. Premature discharge from intensive care carries a significant increase in mortality [5], which cannot be acceptable to a modern health care system.

Outcomes

Effective admission and discharge processes will minimize avoidable morbidity, mortality, and ICU readmissions, and maximize family and patient satisfaction and cost-efficacy. However, reaching the most effective level of practice involves balances and compromises—a permissive admissions policy and conservative discharge policy will increase ICU bed occupancy with the potential for refused admissions and lost opportunity costs elsewhere in the health system. Given the uncertainties that surround decision making, and the balance between sensitivity and specificity of decision-support tools, experienced clinical judgement remains a key element in defining suitability of individual patients for ICU admission and discharge.

Objective benchmarked comparative data linking suboptimal processes, such as night-time discharge [5] or unintentional medications discontinuation [9], with undesirable outcomes (ICU readmission rates or post-ICU mortality [6] should be used to determine the quality of local practices, and from this to identify the changes required in resources or processes of care. These changes will be located along the patient pathway, not just in the ICU, and will include senior involvement in decision making, engagement of intensivists with community care and palliative care medicine, earlier identification of critical illness and involvement of intensive care staff, electronic prescribing and compilation of patient records to bridge changes in patient location, and engagement of families in decision making and the provision of care.

References

1. Adhikari NK, Fowler RA, Bhagwanjee S, and Rubenfeld GD. (2010). Critical care and the global burden of critical illness in adults. *Lancet*, **376**(9749), 1339–46.
2. Wunsch H, Linde-Zwirble W, Harrison D, Barnato AE, Rowan KM, and Angus DC. (2009). Use of intensive care services during terminal hospitalizations in England and the United States. *American Journal of Respiratory and Critical Care Medicine*, **180**, 875–80.
3. Kahn JM, Benson NM, Appleby D, Carson SS, and Iwashyna TJ. (2010). Long-term acute care hospital utilization after critical illness. *Journal of the American Medical Association*, **303**(22), 2253–9.
4. Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T et al. (2012). Outcomes of the surviving sepsis campaign in intensive care units in the USA and Europe: a prospective cohort study. *Lancet Infectious Diseases*, **12**(12), 919–24.
5. Goldfrad C and Rowan K. (2010). Consequences of discharges from intensive care at night. *Lancet*, **355**(9210), 1138–42.
6. Rosenberg A and Watts C. (2000). Patients readmitted to ICUs: a systematic review of risk factors and outcomes. *Chest*, **118**(2), 492–502.
7. Al-Qahtani S, Al-Dorzi HM, Tamim HM, et al. (2013). Impact of an intensivist-led multidisciplinary extended rapid response team on hospital-wide cardiopulmonary arrests and mortality. *Critical Care Medicine*, **41**(2), 506–17.
8. Pearse RM, Moreno RP, Bauer P, et al. (2012). European Surgical Outcomes Study (EuSOS) group for the Trials groups of the European Society of Intensive Care Medicine and the European Society of Anaesthesiology. Mortality after surgery in Europe: a 7 day cohort study. *Lancet*, **380**(9847), 1059–65.
9. Bell CM, Brener SS, Gunraj N, et al. (2011). Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. *Journal of the American Medical Association*, **306**(8), 840–7.
10. Esper AM and Martin GS. (2011). The impact of comorbid conditions on critical illness. *Critical Care Medicine*, **39**(12), 2728–35.
11. Barnato A, Albert S, Angus D, Lave J, and Degenholtz H. (2011). Disability among elderly survivors of mechanical ventilation. *American Journal of Respiratory and Critical Care Medicine*, **183**, 1037–42.

12. Turtle L, Vyakernam R, Menon-Johansson A, Nelson MR, and Soni N. (2011). Intensive care usage by HIV positive patients in the HAART era. *Interdisciplinary Perspectives in Infectious Diseases*, **20011**, 847835.
13. Bird GT, Farquhar-Smith P, Wigmore T, Potter M, and Gruber PC. (2012). Outcomes and prognostic factors in patients with haematological malignancy admitted to a specialist cancer intensive care unit: a 5 yr study. *British Journal of Anaesthesia*, **108**(3), 452–9.
14. Badawi O and Breslow MJ. (2012). Readmissions and death after ICU discharge: development and validation of two predictive models. *PLoS One*, **7**(11), e48758.
15. Gajic O, Malinchoc M, Comfere TB, et al. (2008). The Stability and Workload Index for transfer score predicts unplanned intensive care unit patient readmission: initial development and validation. *Critical Care Medicine*, **36**(3), 676–82.
16. Ouanes I, Schwebel C, Français A, et al. (2012). A model to predict short-term death or readmission after intensive care unit discharge. *Journal of Critical Care*, **27**(4), 422.
17. UK Department of Health (1996). *Guidelines for Admission and Discharge to Intensive Care*. London: DoH.
18. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. (1999). Guidelines for intensive care unit admission, discharge, and triage. *Critical Care Medicine*, **27**(3), 633–8.
19. Guidance on the Provision of Intensive Care Services. (2015). UK Faculty of Intensive Care Medicine, London. Available at: www.ficm.ac.uk (accessed 30 April 2015).
20. Gantner D, Farley K, Bailey M, Huckson S, Hicks P, and Pilcher D. (2014). Mortality related to after-hours discharge from intensive care in Australia and New Zealand, 2005–2012. *Intensive Care Medicine*, **40**(10), 1528–35.

CHAPTER 21

Resource management and budgeting in critical care

Jukka Takala

Key points

- Budgeting should cover short-, mid-, and long-term planning of resources, as well as the continuous monitoring of actual resource use.
- Consider separately the two main production lines of intensive care—unplanned (emergency) intensive care unit (ICU) admissions and planned (elective) ICU admissions.
- Patient turnover rate is a major determinant of resources needed. Increasing resources to reduce the length of stay can reduce the total costs without compromising quality.
- Costs and charges are fundamentally different and should not be mixed—there is no fixed relationship between them.
- The key information needed for budgeting includes the number of patients needing intensive care, their expected length of stay, typical treatments needed for the specific case mix, the number, structure, and costs of personnel needed, and the average material and medication costs.

Introduction

Planning, acquisition, and allocation of resources are core management tasks for the leader of an intensive care unit (ICU). Budgeting should optimize resource use and cover short-, mid-, and long-term planning of resources, as well as the continuous monitoring of resource use. Short-term budgeting focuses on operational planning, whereas mid- and long-term budgeting should have a strategic perspective.

Assessment of resource needs

There is no absolute, quantifiable amount of intensive care services needed. As most developed health care systems have a strong public health care component, a major determinant is political: the health care policy makers (state, regional, and local governments, public health officials, health insurance stakeholders) determine the level of health care financing. The regional and local availability of health care services rarely depends on rational or objective factors alone-rather, structural, historical, cultural, and other 'soft' factors have a major influence. Accordingly, health care resources use *per capita* is highly variable. For example, in the USA, Medicare reimbursement varies several-fold across regions [1]. The use of ICU resources also varies widely between countries of comparable wealth and similar population death rates. In the USA, almost half of all hospital deaths involve an ICU stay, whereas in the United Kingdom, intensive care is involved in one out of five hospital deaths [2].

The need for and spectrum of intensive care services in a specific hospital depend on that hospital's characteristics and role within the health care system. It is useful to estimate the needs for intensive care for the population of the main referral area of the hospital. The presence and resources of other intensive care providers, and the role of other hospitals in the area should be taken into account. The structure of the local health care system and probable changes during the strategic planning period should also be considered when determining the resource needs for an individual hospital and ICU.

It is helpful to consider the two main components of intensive care separately:

- **Unplanned (emergency) ICU admissions:** patients with either acute, potentially reversible, life-threatening organ dysfunction(s) or a high risk of developing such.
- **Planned (elective) ICU admissions:** patients undergoing complex surgical or other procedures that require treatment or monitoring of vital organ function.

The resources needed for emergency admissions within a population are relatively constant as long as the indications for intensive care do not change, or new treatments do not alter the indications for ICU admission. For example, new treatments for cerebrovascular emergencies have increased the need for ICU resources. The local culture and religion can have a fundamental impact on indications for emergency ICU admissions and the resources needed. Key issues include how many resources are allocated to treat patients with little chance of meaningful survival or for patients with very small risk of organ dysfunction or the need for treatment.

In both emergency and elective intensive care, the ICU is part of a multidisciplinary, horizontal care process or production line involving other clinical specialties. The resource availability at any step can be rate limiting. Delays in discharging patients from the ICU due to lack of beds in the intermediate care units or wards may substantially reduce the capacity to admit new patients to the ICU. The impact of lack of resources ('reverse bed pressure') is not limited to actual emergency admissions, but it influences the care of all patients potentially benefiting from an ICU admission. The amount and level of care that can be provided in all the participating units should therefore be considered. As ICU patients often continue to need increased nursing care, monitoring, or both after

ICU discharge, limited availability of resources in the recipient ward may delay discharge. 'High dependency', 'intermediate care', or 'step-down' units provide less intensive monitoring and treatment than the ICU, but more than normal wards. Integration of such beds or units in the ICU may enhance flexible resource management.

The need for emergency ICU admissions fluctuates markedly over short periods of time. Insufficient resources are a serious problem for the whole hospital. Either intensive care must be acutely rationed or unstable patients must be transferred to other institutions—both scenarios increase the risk of suboptimal care and poor outcome. Alternatively, planned intensive care admissions could be cancelled. Although frequently used, this should be considered a failure of resource allocation and an indicator of poor process quality. It does not necessarily indicate insufficient resources in the whole production line—an imbalance of resources (e.g. too much interventional capacity in relation to ICU or ward bed capacity), or a problem in resource utilization (e.g. delayed extubation of ICU patients) is also possible. Cancelling elective operations disrupts a complex production line with interlinked support processes (diagnostics, anaesthesia, etc.) and is a disproportionate waste of resources. If this must be done frequently, care process analysis with ICU involvement is mandatory. Patients needing intensive care must be admitted without delay and, after a sufficient recovery period, discharged without delay.

Patient turnover rate (length of ICU stay), has a major impact on the number of beds needed. Increased ICU capacity may be achieved by more beds, but with a concurrent investment and additional staff. In contrast, reducing length of stay without compromising quality of care can be cost effective. If a smaller increase in staff or a different staff profile can reduce the length of stay, an increase in ICU capacity can be achieved without investment costs and with smaller recurring salary costs, as presented in Table 21.1.

Table 21.1 How to acquire the capacity for 600 further ICU admissions in an ICU with 30 beds (the numbers shown are based on a real example from the author's own institution)

	Option 1	**Option 2**
Average length of stay	3.5 days	2.5 days
Intervention	Additional beds with current number of staff/bed	Increase efficiency by process optimization and adding 24-hour, 7 days a week, in-unit specialist coverage
Admissions produced per bed/year (70% effective occupancy)	73	102
Admissions produced with 30 beds	2190	3060
Additional beds needed to produce 600 admissions	8.2	None—additional capacity for 870 admissions achieved
Investment costs	High, depending on the amount of construction and new equipment needed	None
Additional staff	For 8.2 additional beds: five full-time-equivalent nurses to cover 1:1 nurse:patient ratio for three shifts per day per bed = 41 nurses. 3.5 Full-time-equivalent doctors to provide 1 intensivist and one resident for one shift per day	Additional intensivist staff to cover 24 hours, 7 days a week for two additional shifts = 3.5 full-time-equivalent intensivist salaries
Running costs (salaries)	~2.5 Million euros/year	~0.4 Million euros/year

Cost accounting and budgeting

Costs and charges are fundamentally different and should not be mixed [3]. There is no fixed relationship between costs and charges. In profit-driven systems, the charges include the profits. In public health care systems, charges are typically based on political decisions and do not necessarily represent true service production costs. The relationship between costs and charges can be further distorted by cost-accounting efficiency and charging policies, and cross-subsidization within the hospital. Cross-subsidization can be used, for example, to reduce the costs of low-volume, expensive therapies by assigning part of their costs to high-volume, less expensive interventions—a policy that distorts the costs of both. Unintended cross-subsidization may typically result from insufficient differentiation between costs needed for elective (planned) and emergency (unplanned) interventions. An institution performing mainly elective surgery is likely to have lower average costs per intervention compared with an institution that must treat emergency patients as well, since the latter institution needs to maintain capacity for the emergencies. A fair comparison of costs for elective interventions between such institutions can only be made if the costs of resources for elective interventions versus maintaining emergency capacity can be clearly differentiated. In many reimbursement schemes, lumping together the elective and emergency services puts public institutions at a disadvantage compared with private institutions, which have no obligation to provide emergency services.

The economic costs and accounting costs should be differentiated. Economic costs are the marginal costs for additional services, e.g. the costs of additional resources to perform more renal replacement therapy, which may include disposables, more staff, or an additional device. In contrast, accounting costs takes into account all the costs, including a share of all the equipment costs (depreciation) and other relevant infrastructure costs. These approaches provide distinctly different, but relevant cost perspectives.

Cost finding comes first in cost accounting. From the accounting perspective, the ICU should be a cost centre, where at least all the costs directly created in the ICU can be appropriately allocated. These direct costs typically include all salary, material, and medications costs. The indirect costs represent services provided by others for the ICU, e.g. laboratory, radiology, operations, housekeeping, laundry, etc. Three different approaches to handle these costs include:

- Exclusion from the budget of the requesting unit, and budgeting by the producing unit as their direct costs.

- Expected volume of requested services belongs to the budget of the requesting and producing units.
- Internal billing of services, as part of the budgets of both the requesting and producing units.

For example, the ICU needs radiology services. In the first scenario, the radiology carries the risk of fluctuations in demand and changes in production costs. If the demand increases, their budget may not be sufficient for producing the services. If the demand declines, the resulting overcapacity causes inefficiency (which may go undetected, unless the budget is linked with an expected volume of production) and unnecessary hospital costs.

In the second scenario, the producing unit and the requesting unit agree on the level of services needed, and deviations from this (within an agreed tolerance range) will have budgetary or operational consequences for both units. In this case, the two units share the risk—the absence of a direct financial link makes intervention in case of a relevant deviation difficult.

In the third scenario, an internal 'market' is created. Internal prices are defined for the budgeting period, and the budget contains both the direct and the indirect costs. The mechanisms to control the budget include direct monetary equivalents. The disadvantage is that the internal market often contains monopoly service production, but not true market prices. Free outsourcing with market prices is usually only possible for services without strategic importance for the hospital.

From the perspective of the whole hospital, all costs are equal, i.e. the direct and indirect costs for each department and other services cause costs that need to be met by the specific financing system used, from direct public sector financing to the hospital carrying the full consequences of its finances, selling services at the market price—the latter is rather an exception, since some regulation of the charges is established in most systems. Regardless of the system, each service within the hospital has characteristics of either a 'cost centre' or a 'profit (revenue) centre'. Cost centres typically produce services that are not directly charged from third-party payers, e.g. housekeeping, laundry, and information technology. Some clinical services, e.g. radiology and clinical laboratory, can be regarded as cost centres. The profit centres (e.g. surgical departments) charge directly from the third-party payers, and their charges also include the costs of the cost centres. The ICU can function either as a cost centre, billing internally, or a profit centre charging directly, or a mix of the two. In the latter case, some but not all costs are charged directly, e.g. patients admitted primarily for intensive care and/or discharged directly to other institutions. All costs within the hospital must finally be assigned to profit centres to provide total costs and revenues. The cost and profit centre structure, and internal billing are tools to distribute hospital resources. The calculated profit or loss per department or service tells us nothing about the financial efficiency of a particular service; it reflects the combined effects of the tariffs, production costs, internal allocation of costs, and finally, the efficiency of service production.

ICU cost structure

The ratio between direct and indirect ICU costs can only be estimated roughly due to problems related to the costs and charges of internal services. Approximately 50–60% of the total ICU costs are direct costs. Most of the direct costs, up to 90%, are personnel costs. Accordingly, around half of the total ICU costs are personnel costs. Some costs are fixed, i.e. independent of activity level (e.g. costs of floor space), whereas others are variable depending on the volume and content of care (e.g. costs of materials and medications). Personnel costs are often considered as fixed costs; however, if flexible use of staff depending on the patient load can be achieved, part of the staff costs can be transformed to variable costs, with relevant cost savings.

Cost assignment methods

Once the costs of the ICU have been determined, they need to be assigned to individual patients or groups of patients, in order to help in planning budget and cost consequences of changes in ICU activities.

Two common approaches are using time as a proxy (the *per diem* method, the hourly rate method) and the weighted procedure method [3]. Both these methods can be used for the direct costs only, for the total costs, or for part of the costs in combination with separate costing for specific (usually particularly expensive or uncommon) procedures or products.

The *per diem* method and the hourly rate method

These methods divide the costs of the ICU by, respectively, total patient days and patient hours in order to obtain the cost per unit of time in the ICU. Time as a proxy for costs can function relatively well, assuming that all patients require roughly similar therapeutic interventions and procedures. When the need for time-independent resources (e.g. specific materials or interventions) varies widely between patients, more cross-subsidization between patients will result from using these methods.

The weighted procedure method

This assigns a relative weight for the resource consumption of common procedures and therapeutic interventions. The relative weight should consider the need for supplies, equipment, and personnel. The costs assigned for material and equipment should include the direct costs of material usage, purchase price and depreciation, and the personnel costs related to training, supervision, and maintenance. Once the total costs for all procedures and therapeutic interventions have been determined, a relative value is assigned to each of them. The total costs, including those from the use of other services, are then divided according to the number and relative weight of the procedures and interventions performed.

Several standard methods exist to assign the relative weight for ICU interventions [4–6]. The earliest and perhaps most used is the Therapeutic Intervention Scoring System (TISS) [4]. The original TISS consists of 76 individual therapeutic interventions and monitoring tasks with a weight from 1 to 4, based on the relative intensity of nursing and physician effort required. A shorter version with 28 items has subsequently been developed [5]. Using the TISS score, common ICU interventions can be summarized to a single sum score, which gives a surrogate measure of the cost, including both the material and labour costs—the contribution of each cost component to the cost per TISS score can also be calculated. The weighted procedure method using the TISS or other similar instruments provides robustness at the expense of some cross-subsidization, since the direct relationship between individual interventions and costs varies, and since no such scoring covers all the relevant ICU activities. The scoring per se also requires some effort.

Practical steps in budgeting

The budgeting and financing (reimbursement) systems of ICUs vary widely [7,8]. Regardless of the system used, the same basic information is necessary to estimate the resources needed or, conversely, what can be done with the available resources:

- The number of patients needing intensive care.
- Their expected length of stay.
- Typical treatments for the specific case mix.
- The number and structure of personnel needed.

The average length of stay per patient and the average number of staff needed per patient care day can be used to calculate the personnel costs. For an estimation of material and medication costs, data from the preceding budgeting period and the expected changes in practice need to be considered. Using care day or daily TISS score normalized cost equivalents helps to predict the costs. These cost predictions need to be matched with the resources available from the specific financing system, regardless of whether the financing is primarily revenue or cost-orientated.

Conclusion

Resource management and budgeting are core ICU management tasks and cover optimizing resource use, planning for future needs, and continuous monitoring of actual resource use. The main steps include assessment of resource requirements, acquisition of the resources, cost finding, understanding the cost structure, cost assignment, and cost accounting. Costs and charges should not be mixed.

References

1. Skinner JS, Gottlieb DJ, and Carmichael D. (2011). A new series of Medicare expenditure measures by hospital referral region: 2003–2008. In: Bronner KK (ed.), *The Dartmouth Atlas*. Lebanon, NH: Dartmouth College Press. www.dartmouthatlas.org/downloads/reports/PA_Spending_Report_0611.pdf
2. Wunsch H, Linde-Zwirble WT, Harrison DA, Barnato AE, Rowan KM, and Angus DC. (2009). Use of intensive care services during terminal hospitalizations in England and the United States. *American Journal of Respiratory and Critical Care Medicine*, **180**, 875–80.
3. Finkler SA. (1082). The distinction between cost and charges. Annals of Internal Medicine, **96**, 102–9.
4. Cullen DJ, Civetta JM, Briggs BA, and Ferrara LC. (1974). Therapeutic intervention scoring system: a method for quantitative comparison of patient care. *Critical Care Medicine*, **2**, 57–60.
5. Miranda DR, de Rijk A, and Schaufeli W. (1996). Simplified therapeutic intervention scoring system: the TISS-28 items—results from a multicenter study. *Critical Care Medicine*, **24**, 64–73.
6. Sznajder M, Leleu G, Buonamico G, et al. (1998). Estimation of direct cost and resource allocation in intensive care: correlation with Omega system. *Intensive Care Med*icine, **24**, 582–9.
7. Vincent JL, Takala J, and Flaaten H. (2012). Impact of reimbursement schemes on quality of care: a European perspective. *American Journal of Respiratory and Critical Care Medicine*, **185**, 119–23.
8. Bekes CE, Dellinger RP, Brooks D, Edmondson R, Olivia CT, and Parrillo JE. (2004). Critical care medicine as a distinct product line with substantial financial profitability: the role of business planning. *Critical Care Medicine*, **32**, 1207–14.

CHAPTER 22

Costs and cost-effectiveness in critical care

David J. Wallace and Derek C. Angus

Key points

- Overall health care costs and the proportion dedicated to critical care are increasing.
- Cost-effectiveness analysis allows the costs and benefits of different therapies to be directly compared.
- Within a constrained budget, cost-effectiveness analysis can identify the optimal therapies for funding.
- Policy informed by cost effectiveness should improve public health.
- Critical care, with its inherent complexity, frequent innovations, and high cost, is well suited for cost-effectiveness analysis as a basis for improving health care quality.

Introduction

In the USA in 2005, Medicare and Medicaid critical care costs were estimated to be 81.7 billion dollars, representing 4.1% of national health expenditures and 0.7% of the gross domestic product. Compared with only 5 years prior to that, this was a relative increase of 13.7% and a 44.2% increase in absolute spending [1]. Therefore, not only is critical care expensive, but costs are growing. Furthermore, during the same years, the overall number of critical care beds in the USA increased 6.5%, the number of critical care inpatient days increased 10.6% and the proportion of critical care beds to hospital beds increased 5.2% [1]. The shift in physical resources and use comes at a time when the first of the baby-boomer generation is reaching age 65, foreshadowing further demand on a health care system already under strain. These pressures have increased attention on finding the optimal balance between cost and quality for new procedures, protocols, programmes, and therapies, and the methods of cost-effectiveness evaluation.

Definitions

There are four main types of cost studies—cost-minimization, cost-benefit, cost-effectiveness and cost-utility.

Cost-minimization analysis

Cost-minimization studies consider only expenditures and are essentially evaluations of comparable medication costs. Each product is assumed to be equally effective and to equally affect all other aspects of treatment. Medication benefits, such as reduced length of stay, reduced need for other therapies, or improved quality of life after illness, are not considered. The preferred therapy is simply the one that costs less per unit of treatment.

Cost-benefit analysis

For cost-benefit analysis, all costs and benefits are converted into monetary units. Summary costs are then subtracted from summary benefits, resulting in a summary difference. If the result is positive, the benefits outweigh the costs, and the programme or intervention under evaluation is attractive. The difficulty with this approach is that human lives must also be assigned a financial amount, a valuation that is inherently controversial. For this reason, this type of analysis has fallen out of favour in health care cost evaluations.

Cost-effectiveness analysis

Cost-effectiveness analysis is the most common method for health care cost and outcome evaluation. In this analysis, the ratio of net cost difference to net effect difference is calculated for two interventions. The numerator is the marginal cost in dollars between the comparisons, while the denominator represents the change in health status (e.g. number of additional survivors, cases of disease averted, life-years gained, etc.). The expression takes on the form of cost per unit of benefit (e.g. dollars per additional survivor, dollars per case of disease averted, dollars per life-year gained, etc.). This metric is called the **incremental cost-effectiveness ratio**. Alternatively, a simple **cost-effectiveness ratio** can be calculated, which is the cost per unit of benefit for a given therapy or programme, without reference to a comparator.

Perhaps surprisingly, neither the incremental cost-effectiveness ratio nor the cost-effectiveness ratio necessarily indicates whether a therapy or programme under consideration either saves money or is actually cost-effective. The incremental cost-effectiveness ratio of a new therapy may indicate that a new therapy is more expensive than standard care, yet improves outcome. Deciding if this therapy is cost-effective then requires a value judgment regarding how much the patient or society is willing to pay for the additional benefit. At a given cost threshold, the therapy might be considered cost-effective by one person and not by another. This spending threshold varies by health care system. In the USA, its value is somewhere between $50,000 and $100,000 per life year gained, whereas in the United Kingdom it lies in the range of $33,000–50,000. (It is worth noting that in the USA, the Centers for Medicare and Medicaid Services does not formally consider cost-effectiveness in medical coverage decisions, whereas in the United Kingdom the National

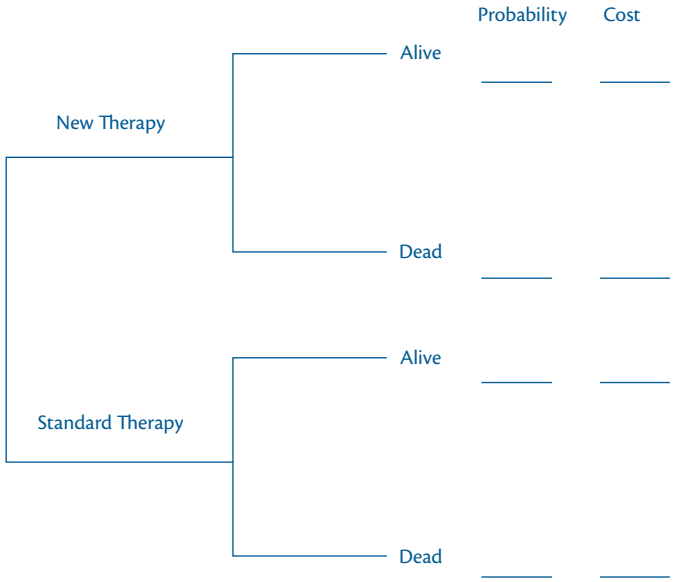


Fig. 22.1 Simple decision tree comparing outcome for patients treated with new therapy versus standard therapy. In order to calibrate the tree, we must estimate: (1) the probability for a given patient to live or die, given whether they received the new therapy or not; and (2) the average costs associated with each of the four branches.

Institute for Health and Clinical Excellence explicitly relies on these analyses to make recommendations regarding medical coverage to the National Health Service.)

A typical cost-effectiveness analysis requires collecting detailed information on costs and effects for both standard care and the new intervention. Based on the complexity of the cost and benefit streams, a **decision analysis model** may be needed to show progressive clinical decisions and outcomes. Branching trees represent these models, where each successive limb has a probability of occurrence and a cost. At its simplest, the tree will contain only branches for treatment allocation (e.g. new or standard therapy) and outcome (e.g. alive or dead). To calibrate the tree, we need to know the probability of living or dying based on each therapy, and the average cost of care for survivors and non-survivors in the two treatment arms (Fig. 22.1).

We could expand this model to include other elements that affect morbidity and cost, or sequela other than death. The new therapy, while expensive alone, may offset its own expense with a reduced need for other supportive care, and may therefore be comparatively more cost-effective than standard therapy. As additional elements are incorporated in the decision analysis model, additional branches must be added to the tree. For each branch, we must know a patient's likelihood of entering a particular branch and the average costs (Fig. 22.2).

Cost-effectiveness analysis is endorsed by both the United States Public Health Service Panel on Cost-Effectiveness in Health and Medicine (PCEHM) and the American Thoracic Society (ATS) as the primary method by which to measure the costs and effects of health care programmes and medical therapies [2,3].

Cost-utility analysis

Cost-utility analysis is a special case of a cost-effectiveness analysis, where benefits are represented as the number of years lived in full health by beneficiaries. These **quality-adjusted life years** (QALYs) are calculated by calibrating the number of years of survival for the 'quality' of that survival. A person living for 1 year with a quality-of-life score of 70% would be 'awarded' 0.7 years of quality-adjusted survival. An advantage of this approach is that it allows comparison of different interventions for different diseases through a common metric. On the other hand, QALYs are more difficult to measure than the monetary summaries of cost-effectiveness analyses. An additional criticism of cost-utility analyses is the implicit bias against older patients, who are will generally have fewer QALYs, as they have fewer overall years of life to live.

Perspective

Each cost-effectiveness method employs cost accounting and adopts a cost-accounting perspective. This perspective is fundamental to the interpretation of the results, as it is the viewpoint from which costs are measured. For example, consider the implications of adding a non-cardiac step-down unit to a hospital that previously had general hospital beds and intensive care beds. One can imagine that, from the perspective of the intensive care unit (ICU), having a step-down unit could reduce ICU length-of-stay, as some patients would be discharged sooner to the step-down unit, rather than waiting until they were well-enough for a general hospital bed. A portion of what would have been the patient's ICU length-of-stay is replaced with presumably less expensive step-down length-of-stay. If outcomes were equivalent, an administrator may be eager to approve implementation of step-down units on these grounds alone. From the perspective of the hospital, however, step-down units may not be associated with clear cost-savings. In fact, unless ICU beds are closed after admissions are diverted to the step-down unit, the overall operating cost of care in the hospital **must** increase. Depending on case mix and payer mix, this **may** be advantageous to the hospital from a financial standpoint, but it is unlikely that it results in a reduced incremental cost-effectiveness ratio from the perspective of society. In other conditions, the costs of care may be transferred out of the hospital itself, such as in the case of long-term acute care hospitals. In that setting, the use of long-term acute care hospitals may lower the costs of care for a transferring facility, but that does not guarantee that the overall cost or quality of care is better for the transferred patient [4]. Both the PCEHM and ATS recommend using the societal perspective for cost-effectiveness studies.

Included costs and cost savings

Accounting for and measuring all cost streams associated with an intervention may appear to be a daunting task. Fortunately, only costs that differ between treatment groups are included in the incremental cost-effectiveness ratio. For example, although PCEHM guidelines identify pain and suffering as relevant costs, they can be omitted from calculations if pain and suffering are equivalent in the two treatment branches. Only unbalanced costs are compared, a feature of the analysis that simplifies the accounting considerably.

Cost savings are also included in cost accounting, although downstream resource use reductions require cautious interpretation. As noted in the step-down unit example, a seemingly intuitive line of reasoning is that if a therapy results in a shorter length-of-stay, it will have a significant reduction in the overall cost of care. Cost perspectives aside, there is also accounting for the actual savings recaptured by reducing the length of intensive care stay to take

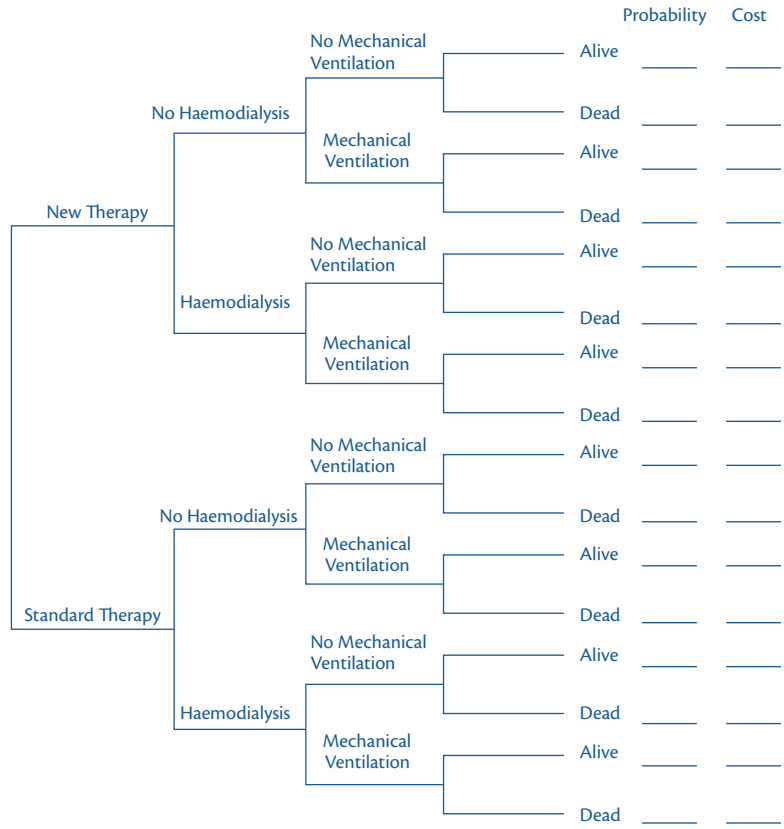


Fig. 22.2 Decision tree comparing outcomes for patients treated with new therapy versus standard therapy, which incorporates the potential to undergo mechanical ventilation and receive haemodialysis. In order to calibrate the tree, we must estimate the probabilities and average costs for 16 separate trees.

into account. Importantly, every day in intensive care is not equivalent to the cost of an 'average' intensive care day. This is because patient costs are usually disproportionally concentrated in the first few hours to days of admission. By the time the patient is transferred out of intensive care, there is a lower intensity of procedures, monitoring, and therapies being performed. Length-of-stay reductions come from this side of the admission, the tail, where costs are inherently lower [5].

Discounting costs and effects

Future costs and benefits are both discounted in health economics, making them worth less than current costs and benefits. As an example, $100 today is worth more than the guarantee of $100 1 year from now. The discount is rooted in uncertainty, economic inflation, and a general preference for immediate gains over those in the future. Likewise, the benefit of one person living 10 additional years is not equivalent to 10 persons each living one additional year. Failure to discount future effects incurs the **Keeler–Cretin procrastination paradox**, wherein we would always favour health care programmes that take place some time in the future [6]. Worldwide economic growth is occurring at approximately 3% per year, and therefore the PCEHM and ATS recommend that costs and effects be discounted at a 3% rate per annum.

Sensitivity analysis

To determine how sensitive a cost-effectiveness analysis is to cost or effect estimates, the completed model may be exposed to a **sensitivity analysis**. Here, cost and effect estimates are iteratively included across the range of plausible values to demonstrate the impact of estimation precision. These values are compared with the **base case**, which uses the best point estimates of cost and effect. As long as the estimates have little effect on the overall conclusions, imprecise estimates are acceptable and the finding is considered robust.

The sensitivity analysis can also be used to determine which model parameters need to be measured most accurately. For example, the cost-effectiveness ratio may be particularly sensitive to estimates of medication costs, but relatively insensitive to expected costs of post-discharge resource use. In this situation, medication costs need to be measured carefully, while post-discharge resource use can be estimated less rigorously. Finally, a sensitivity analysis can be pinned to a cost-effectiveness threshold and then vary other parameters to show the ceiling of costs under which a given therapy would still be considered cost effective. An example of this approach was used in the evaluation of lung-protective ventilation for acute lung injury. Even at an investment level of $9482 per patient with acute lung injury, an intervention that increased adherence to lung-protective ventilation from 50 to 90% would be considered as cost effective [7].

Interpretation

The PCEHM and ATS endorse standardized reporting in cost-effectiveness studies. Studies must generate a reference case, indicate the perspective chosen, determine costs and effects, define the study time horizon, provide measurements of uncertainty,

Table 22.1 League table showing the range of cost-effectiveness ratios for a variety of medical or preventive interventions

Intervention	More favourable scenario	$/QALY	Less favourable scenario	$/QALY
Statins [11]	For secondary prevention with stepped care versus niacin	1600	For primary and secondary prevention versus secondary only	48,000
Neonatal intensive care [8]	Versus standard neonatal care for infants 1–1.5 kg	7100	Versus standard neonatal care for infants 0.5–1 kg	49,000
CABG [12]	For left main vessel disease versus medical management of angina	7100	For one-vessel disease versus medical management	56,000
tPA for AMI [9]	For anterior myocardial infarction versus streptokinase	18,000	For inferior myocardial infarction versus streptokinase	60,000
Air bags [14]	For driver side only versus no air bag	28,000	Dual air bags versus driver-side air bag only	72,000
Implantable defibrillators [10]	ICD-only regimen versus amiodarone to ICD regimen	40,000	Amiodarone to ICD regimen versus amiodarone only	157,000
Lung transplantation [13]	Versus standard care, assuming 10-year survival	44,000	Versus standard care, assuming 5-year survival	204,000

Data from various sources (see references).

and include a sensitivity analysis. This standardized approach allows for comparisons of results across studies. The reference case allows us to make inferences about the cost-effectiveness of lung protective mechanical ventilation compared with a therapy for multidrug-resistant pneumonia. When compiled, these comparisons can be sorted by incremental cost-effectiveness in league tables (Table 22.1). These tables can include interventions against specific disease states (e.g. myocardial infarction, stroke, lung transplantation) [8–13] and interventions designed to prevent injury or illness (e.g. airbags) [14].

Policy implications

To support comparative effectiveness research, the Patient Protection and Affordable Care Act established a non-profit Patient-Centred Outcomes Research Institute (PCORI) [15]. The goals of the Institute were to identify research priorities and fund research that compared the effectiveness of medical treatments. Specifically included were, 'health care interventions, protocols for treatment, care management, and delivery, procedures, medical devices, diagnostic tools, pharmaceuticals (including drugs and biologicals), integrative health practices, and any other strategies or items being used in the treatment, management, and diagnosis of, or prevention of illness or injury in, individuals' [15]. PCORI was fiercely debated throughout its development and, unfortunately, became politically linked to rationing and government restriction on care. In the end, the final version of the bill prohibited the use of QALYs as a metric for comparing therapies. The language was specific, stating that PCORI, 'shall not develop or employ a dollars-per-quality adjusted life year (or similar measure that discounts the value of a life because of an individual's disability) as a threshold to establish what type of health care is cost effective or recommended' [15].

Under the current tax and spending structure, Medicare inpatient and related care funds will be exhausted in the year 2024 [16]. Best evidence from comparative effectiveness is necessary, but not sufficient to improve the quality of the USA health care system. Robust **economic** evaluations of new therapies, procedures, protocols, and interventions are crucial, especially in the complex world of critical care. Currently, the policy debate has focused on effectiveness without cost, while the insurance market has focused on cost without effectiveness. Future directions should look to incorporate incentives that will beneficially influence physician practice, patient preference, and manufacturer investment—directions navigated by careful cost-effectiveness analyses.

Conclusion

The health care industry must improve its return on investment. Critical care, with its inherent complexity, frequent innovations, and high cost, is well suited for cost-effectiveness analysis as a basis for improving health care quality. While cost-effectiveness analyses cannot tell us what proportion of overall resources should be spent on health care, they can tell us what should be considered within a given budget. Ultimately, cost-effectiveness analyses should promote better choices, and in turn, improve the overall public health.

For a more detailed discussion of economic analysis in health care, the reader is referred to texts by Gold and Drummond [17,18].

References

1. Halpern NA and Pastores SM. (2010). Critical care medicine in the United States 2000–2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. *Critical Care Medicine*, **38**, 65–71.
2. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, and Russell LB. (1996). Recommendations of the panel on cost-effectiveness in health and medicine. *Journal of the American Medical Association*, **276**, 1253.
3. Understanding costs and cost-effectiveness in critical care: report from the second American Thoracic Society workshop on outcomes research. *American Journal of Respiratory and Critical Care Medicine*, **165**, 540–50.
4. Kahn JM, Benson NM, Appleby D, Carson SS, and Iwashyna TJ. Long-term acute care hospital utilization after critical illness. *Journal of the American Medical Association*, **303**, 2253–9.
5. Kahn JM, Rubenfeld GD, Rohrbach J, and Fuchs BD. (2008). Cost savings attributable to reductions in intensive care unit length of stay for mechanically ventilated patients. *Medical Care*, **46**, 1226–33.
6. Keeler EB and Cretin S. (1983). Discounting of life-saving and other nonmonetary effects. *Management Science*, **29**, 300–6.
7. Cooke CR, Kahn JM, Watkins TR, Hudson LD, and Rubenfeld GD. (2009). Cost-effectiveness of implementing low-tidal volume ventilation in patients with acute lung injury. *Chest*, **136**, 79–88.
8. Boyle MH, Torrance GW, Sinclair JC, and Horwood SP. (1983). Economic evaluation of neonatal intensive care of very-low-birth-weight infants. *New England Journal of Medicine*, **308**, 1330–7.

9. Kalish SC, Gurwitz JH, Krumholz HM, and Avorn J. (1995). A cost-effectiveness model of thrombolytic therapy for acute myocardial infarction. *Journal of General Internal Medicine*, **10**, 321–30.
10. Owens DK, Sanders GD, Harris RA, et al. (1997). Cost-effectiveness of implantable cardioverter defibrillators relative to amiodarone for prevention of sudden cardiac death. *Annals of Internal Medicine*, **126**, 1–12.
11. Prosser LA, Stinnett AA, Goldman PA, et al. (2000). Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Annals of Internal Medicine*, **132**, 769–79.
12. Weinstein MC and Stason WB. (1982). Cost-effectiveness of coronary artery bypass surgery. *Circulation*, **66**, III56–66.
13. Ramsey SD, Patrick DL, Albert RK, Larson EB, Wood DE, and Raghu G. (1995). The cost-effectiveness of lung transplantation. A pilot study. University of Washington Medical Center Lung Transplant Study Group. *Chest*, **108**, 1594–601.
14. Graham JD, Thompson KM, Goldie SJ, Segui-Gomez M, and Weinstein MC. (1997). The cost-effectiveness of air bags by seating position. *Journal of the American Medical Association*, **278**, 1418–25.
15. Patient Protection and Affordable Care Act (2010). *Public Law*, 111–48. Washington, DC: US government.
16. USA Social Security Administration (2012). *A Summary of the 2012 Annual Reports. Social Security and Medicare Board of Trustees*. Available at: http://www.ssa.gov/OACT/TRSUM/index.html (accessed 26 May 2012).
17. Drummond M, Sculpher M, and Torrance G. (2005). *Methods for the Economic Evaluation of Health Care Programmes*. Oxford: Oxford University Press.
18. Gold M, Siegel J, Russell L, and Weinstein M. (1997). Cost-effectiveness in Health and Medicine. Oxford: Oxford University Press.

PART 1.6

Research

CHAPTER 23

Evidence-based practice in critical care

Marius Terblanche and Damon C. Scales

Key points

- Evidence-based practice (EPB) integrates the best available evidence with individual clinical expertise.
- EBP ensures that patients receive up-to-date care proven to be efficacious, safe, and cost effective.
- EBP benefits patients by introducing new treatment approaches where appropriate, by reducing the harm associated with necessary treatments, and by questioning the continued use of ineffective or harmful treatments.
- To practice EBP, clinicians should become acquainted with techniques to stay current with new publications and research findings.
- When high quality evidence is unavailable to answer specific clinical questions, practitioners of EBP still rely on clinical judgment and expertise to decide upon the best treatment strategies for their patients. However, they are wary of the potential harms of unproven therapies.

What is evidence-based practice?

Evidence-based practice (EBP) refers to the integration of the best available evidence with clinical expertise to make decisions about the care of individual patients [1]. EBP seeks to equip clinicians with tools to overcome incorrect decision making by relying on the highest quality empiric evidence. It is not 'cookbook' medicine, since research evidence informs, but does not replace, clinical expertise [1].

In practice, EBP is a process that starts with the identification of a clinical problem or question, and then involves a search and critical appraisal of the literature. The validity and applicability of the available evidence is assessed and, if appropriate, it is then applied to clinical practice. The process concludes with an evaluation of the individual's performance [2].

Generally speaking, the randomized controlled trial (RCT) provides the most rigorous and reliable evidence to inform practice, and the highest level of evidence is achieved if multiple large, well-conducted trials have similar results and reach concordant conclusions [3]. In situations where RCTs are not feasible, for example, when studying uncommon critical illnesses or where ethical issues prevent conducting an individual patient RCT, other research designs can still help inform EBP. These include observational cohort studies, case-control studies, and even case reports. However, EBP practitioners appreciate that these study designs are more vulnerable to problems with confounding and bias, especially when seeking to establish causal relationships, rather than simply describing associations.

Why is EBP important?

EBP is important because all medical treatments, effective or otherwise, have associated risks. Clinical practice entails weighing the risk of a treatment against its perceived benefits. Good clinicians have always tried to make accurate diagnoses and formulate treatment plans using the best available information, guided by their judgment and experience. Unfortunately, clinical experience and judgment alone are vulnerable to heuristics and cognitive biases, in particular the availability heuristics (e.g. estimating the likelihood of a condition based on how easily we can recall similar conditions), base rate neglect (e.g. failing to appreciate the true incidence of a condition), framing (e.g. avoiding options that pose risks, even if such options offer small, but certain gain), overconfidence (e.g. failing to recognize what we do not know), and hindsight bias (e.g. believing we can deduce all the signs and events that led to a particular outcome) [4,5]. Such biases can undermine clinicians' abilities to make a correct diagnosis or develop an effective treatment plan for individual patients. A solid understanding of the true benefits of a potential treatment requires information from research designs like the randomized controlled trial that adequately protect against sources of error, including findings resulting from chance, bias, and confounding [5]. By considering these principles, EBP aims to ensure that patients receive up-to-date care shown to be safe and effective.

EBP is also increasingly important because of the rising cost of health care. The Cochrane collaboration states: 'Because resources would always be limited, they should be used to provide forms of health care which have been shown in properly designed evaluations to be effective'[6]. Pressure towards adopting EBP now often comes from public and private health insurance providers, which in some jurisdictions have even refused coverage of practices lacking in systematic evidence of usefulness. In the future, adherence to EBP may be targeted by pay-for-performance initiatives, although the cost-effectiveness of these schemes has not been adequately studied in critical care [7].

In practice, EBP benefits patients by introducing new treatments or treatment approaches where appropriate, by directly reducing

Table 23.1 How does EBP benefit patients?

Introducing new treatment approaches	*Example: Lung protective ventilation for Acute Respiratory Distress Syndrome (ARDS)* Mechanical ventilation is a cornerstone of ICU treatment approaches for patients with ARDS. In 2000, The ARDS Network demonstrated that using lower instead of higher tidal volumes reduced mortality (31.0% versus 39.8%, $p = 0.007$) and ventilator-free days [9] *Example: Neuromuscular blockers for ARDS [17]* Neuromuscular blockers may help improve oxygenation in patients with ARDS, but may also cause muscle weakness. In a recent RCT, which enrolled 340 patients with ARDS, a 48-hour cisatracurium infusion (compared with placebo) was associated with improved 90-day survival (HR 0.68, 95% CI 0.48–0.98, $p = 0.04$)
Preventing harm associated with necessary treatments	*Example: Central venous catheters* Central venous catheters are ubiquitous in ICUs, but are also associated with serious infections and consequent harm. A study involving all ICUs in Michigan demonstrated that introducing five recommended procedures (hand washing, using full barrier precautions during the insertion of central venous catheters, cleaning the skin with chlorhexidine, avoiding the femoral site if possible, and removing unnecessary catheters) sustainably reduced the incidence rate ratio of catheter-related blood stream infections from 0.62 (95% CI 0.47–0.81) at baseline to 0.34 (95% CI 0.23–0.50) at 16–18 months [18] *Example: Sedation during mechanical ventilation* Sedation practice and approaches to weaning from mechanical ventilation vary widely. Concerns about patient anxiety and discomfort, and uncertainty about the safest approach to wean may introduce unnecessary delays in extubation, thus increasing the risk of complications associated with sedatives and mechanical ventilation. A RCT conducted in four hospitals showed that pairing a daily spontaneous awakening trial with a spontaneous breathing trial increased the time of breathing without assistance compared with an approach in which patients received spontaneous breathing trials alone (14.7 days versus 11.6 days; mean difference 3.1 days, 95% CI 0.7–5.6; $p = 0{\cdot}02$) [19]
Question the continued use of a current treatment or approach	*Example: Aprotinin to prevent bleeding in cardiac surgery patients* Bleeding after cardiac surgery can be a serious and even fatal complication. The antifibrinolytic aprotinin was commonly used to minimize both the risk of bleeding and the use of blood products. A large RCT with three arms compared aprotinin with tranexamic acid and aminocaproic acid. The rate of bleeding was similar comparing the three groups, but aprotinin was associated with a higher risk of 30-day mortality than the other two agents (relative risk 1.53, 95% CI 1.06–2.22) [20]. These findings suggest that aprotinin should no longer be used for this indication *Example: Synthetic colloids for resuscitation* Hydroxyethyl starch (HES) solutions are commonly used resuscitation fluids. Several recent RCTs highlighted the risks associated with these solutions and raise questions about their continued use. In Australia and New Zealand, a large 7000-patient RCT showed that mortality was similar in both groups, but patients receiving HES required renal replacement therapy more frequently than those receiving saline (7.0 versus 5.8%, relative risk 1.21; 95% CI, 1.00–1.45; $p = 0.04$). These findings reinforced the findings of earlier, but smaller RCTs, and suggest that the use of HES should be curtailed

Data from various sources (see references).

the harm associated with necessary treatments, and by questioning the continued use of ineffective or harmful existing treatments (Table 23.1).

The evidence–practice gap

Considering the high mortality of critically—ill patients, it is especially important that eligible patients receive interventions that are known to improve outcomes. Yet the lag between identification and publication of potentially helpful interventions, and their adoption into clinical practice has been well described. For example, a study examined 439 indicators of quality of care for 30 acute and chronic conditions in 12 metropolitan areas in the USA, and found that only about half of patients received recommended care [8]. In critical care, a compelling example of the delayed uptake of research evidence into clinical practice is the slow adoption of lung protective ventilation using lower tidal volumes for patients with the acute respiratory distress syndrome (Table 23.1) [9]. Although this landmark trial was published in 2000, several investigators have shown that many eligible patients still do not receive this treatment, even in academic centres with ample resources [10]. EBP seeks to reduce these practice gaps by ensuring that eligible patients receive timely, appropriate, and up-to-date therapy.

How to implement EBP into a practitioner's clinical setting

We suggest the following strategies to implement EBP into your own practice:

- **Stay current:** despite the challenges of attempting to remain current and up-to-date in a world where information overload is a common challenge, electronic resources have also made it easier to keep abreast of new developments. It is suggested that all practitioners of EBP subscribe to email alerts of table of contents from the leading journals in their field as an initial strategy for keeping up-to-date. This simple task will allow users of electronic devices, e.g. cell phone and laptop computers, to remain current with minimal additional effort.
- **Take advantage of other experts' summaries of existing EBP:** there are many resources that are available to EBP practitioners to help synthesize the existing literature. For example, guidelines from professional societies, including the American Thoracic Society (www.thoracic.org), European Society of Intensive Care Medicine (www.esicm.org), and the Society for Critical Care Medicine (www.sccm.org), have covered a wide range of topics in critical care medicine. These should not simply reflect a summary of experts' opinions, but should be created using recommended

approaches to ensure transparent explanations for the guidelines' recommendations (for example, the GRADE framework of guideline reporting) [11].

- **Learn how to review and critically-appraise the literature:** becoming familiar with the principles of evidence-based medicine and critical appraisal should be considered an essential part of EBP [3]. There are fortunately many resources available to help clinicians without formal graduate training or a degree in Clinical Epidemiology or Public Health. This chapter directs readers to the excellent series entitled 'Users' Guides to the Medical Literature' from the *Journal of the American Medical Association* (http://jamaevidence.com) or 'Critical appraisal check lists' (http://clinicalevidence.bmj.com) from the *British Medical Journal*. Finally, we believe that all clinicians should receive training to conduct a search on a clinical topic using PubMED or Medline (most health libraries provide training resources), and should familiarize themselves with the Cochrane Collaboration topics collection (www.cochrane.org).
- **Evaluate your own EBP:** an important aspect of EBP involves objectively assessing your own practice to ensure it is current and up-to-date. This can pose a challenge, since it involves time and effort and also an appreciation that there may be aspects of one's own clinical practice—unbeknown to the individual—that no longer represent EBP!

Controversies

The current generation of trainees may find it difficult to comprehend that EBP has not always been the dominant philosophy. However, the adoption of EBP principles has been a controversial movement. In a particular, the following areas have generated debate about the limitations and unintended consequences of adopting EBP; we believe these are derived largely from either a misunderstanding of the principles behind EBP or are reactions to their overly rigid application.

What to do when evidence is lacking to inform EBP?

Unfortunately, there are many specific clinical situations for which no evidence exists to guide clinical practice. For example, should patients with cervical spinal cord injury and ARDS receive low tidal volume ventilation? While there is convincing evidence that ICU patients in general should receive mechanical ventilation with low tidal volumes, there are also recommendations that patients with spinal cord injury should receive larger tidal volumes to prevent atelectasis [12]. In situations such as these, a lack of evidence supporting low tidal volume ventilation from RCTs conducted specifically in patients with spinal cord injury obviously does not imply there is no net benefit or harm; the clinician must rely on his/her own interpretation and judgment to arrive at the best treatment approach for an individual patient. This still comprises EBP, but incorporates the ability of the clinician to decide when to generalize treatment approaches. Another challenging situation arises when there is insufficient high quality evidence available to suggest whether a treatment should be adopted, for example, using statins to prevent sepsis. While it may seem that there may be potential benefit based on preliminary research findings for such treatments [13], clinicians should be wary about broadly applying promising, but unproven treatments because many side effects or harms cannot be predicted or evaluated until high-quality RCTs or even population-based surveillance studies are completed.

Does EBP imply clinicians cannot think for themselves?

That is to say, does EBP leave clinicians practicing 'cookbook medicine'? Some critics have raised concerns that the dogmatic application of guideline or research suggestions may have unintended consequences and potentially cause harm [14]. The authors agree, but feel that these concerns are overstated because EBP also requires that clinicians continually re-evaluate their own practice and are able to recognize when research findings may not be generalizable to their own patients.

Are EBP recommendations transparent and free of bias?

Much controversy has arisen surrounding the process for developing guidelines for EBP. In particular, concerns have been raised about industry-sponsored guidelines, especially when these have been guided largely by expert opinion or funded by industry, and without transparent critical appraisal of the literature [15]. The GRADE approach to guideline creation has evolved to help deal with these concerns and enhance the transparency of guideline creation [11], but critics have raised concerns that even this approach itself has not yet been adequately scrutinized [16]. The authors believe guidelines that are created using a comprehensive and systematic search of the literature combined with transparent procedures for developing recommendations are important if these are to guide EBP. However, EBP implies that clinicians critically appraise all sources of information, including guidelines and the processes used in their development, to ensure that they are using the best-available evidence to guide clinical care.

Conclusion

EBP implies that clinicians make clinical decisions and treat patients using principles and therapies that are based on sound scientific research. There is an obligation to patients to provide treatments that are proven to be effective (and are not harmful), and that our own practices should continue to be evaluated to ensure current, up-to-date, provision of EBP.

References

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, and Richardson WS. (1996). Evidence based medicine: what it is and what it isn't. *British Medical Journal*, **312**, 71–2.
2. Health Science Library. (2013). Evidence-Based Practice Resources. Hamilton, Ontario: McMaster University. Available at: http://hsl.mcmaster.ca/resources/topic/eb/ (accessed 2 May 2013).
3. Haynes RB, Sackett DL, Guyatt GH, and Tugwell P. (2004). *Clinical Epidemiology: How to do Clinical Practice Research*, 3rd edn. Sydney: Lippincott Williams & Wilkins.
4. Kahneman D, Slovic P, and Tversky A. (1982). *Judgement under Uncertainty: Heuristics and Biases*. Cambridge: Cambridge University Press.
5. Delgado-Rodriguez M and Llorca J. (2004). Bias. *Journal of Epidemiology & Community Health*, **58**, 635–41.
6. Cochrane AL. (1989). *Effectiveness And Efficiency: Random Reflections on Health Services*. Oxford: Wiley-Blackwell.

7. Khanduja K, Scales DC, and Adhikari NK. (2009). Pay for performance in the intensive care unit—opportunity or threat? *Critical Care Medicine*, **37**, 852–8.
8. McGlynn EA, Asch SM, Adams J, et al. (2003). The quality of health care delivered to adults in the United States. *New England Journal of Medicine*, **348**, 2635–45.
9. (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *New England Journal of Medicine* **342**, 1301–8.
10. Needham DM, Colantuoni E, Mendez-Tellez PA, et al. (2012). Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. *British Medical Journal*, **344**, e2124.
11. Schunemann HJ, Jaeschke R, Cook DJ, et al. (2006). An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *American Journal of Respiratory and Critical Care Medicine*, **174**, 605–14.
12. Consortium for Spinal Cord M. Respiratory management following spinal cord injury: a clinical practice guideline for health-care professionals. *Journal of Spinal Cord Medicine*, **28**, 259–93.
13. Terblanche M, Almog Y, Rosenson RS, Smith TS, and Hackam DG. (2007). Statins and sepsis: multiple modifications at multiple levels. *Lancet Infectious Diseases*, **7**, 358–68.
14. Tobin MJ. (2008). Counterpoint: evidence-based medicine lacks a sound scientific base. *Chest*, **133**, 1071–4; discussion 1074–7.
15. Eichacker PQ, Natanson C, and Danner RL. (2006). Surviving sepsis—practice guidelines, marketing campaigns, and Eli Lilly. *New England Journal of Medicine*, **355**, 1640–2.
16. Kavanagh BP. (2009). The GRADE system for rating clinical guidelines. *PLoS Medicine*, **6**, e1000094.
17. Papazian L, Forel JM, Gacouin A, et al. (2010). Neuromuscular blockers in early acute respiratory distress syndrome. *New England Journal of Medicine*, **363**, 1107–16.
18. Pronovost P, Needham D, Berenholtz S, et al. (2006). An intervention to decrease catheter-related bloodstream infections in the ICU. *New England Journal of Medicine*, **355**, 2725–32.
19. Girard TD, Kress JP, Fuchs BD, et al. (2008). Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): a randomised controlled trial. *Lancet*, **371**, 126–34.
20. Fergusson DA, Hebert PC, Mazer CD, et al. (2008). A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *New England Journal of Medicine*, **358**, 2319–31.

CHAPTER 24

Research ethics in the ICU

Neal W. Dickert and Scott D. Halpern

Key points

- Barriers to informed consent are unavoidable features of many intensive care unit (ICU) studies and must be recognized and addressed in a context-sensitive manner. This may include alterations to consent processes, the use of surrogates, or exception from informed consent.
- Assessments of equipoise can be complicated in the ICU context. Adequate review and assessment of clinical uncertainty and risk is particularly essential to this determination.
- Choice of control group in ICU trials can be difficult in the context of heterogeneous or non-data-driven practice patterns, but this choice must always be driven by the goal of producing data that will answer the clinical question and have a meaningful impact on clinical practice.
- Quality improvement activities and clinical research can at times be difficult to distinguish. Both should always be evaluated regarding their potential impact on patients and the need for informed consent.
- Improving the ethics of clinical research in the ICU requires innovative, context-sensitive analysis of individual studies and empirical research to determine optimal ways of overcoming ethical challenges.

Introduction

Clinical research in the intensive care unit (ICU) is essential. Patients are at considerable risk for death and disability, and critical care consumes enormous resources (estimated 0.66% of US GDP) [1]. Clinical trials have improved outcomes for many severe illnesses and systems-based research has reduced mortality. However, treatments for many conditions remain inadequate or lack adequate evidence.

Critical care research also presents ethical challenges [2]. Some, such as conflict of interest, are generic to research. Others are more specific, arising from a combination of patient acuity, practice variability, lack of evidence, and consent-related challenges. This chapter focuses on issues with unique manifestations in critical care that warrant specific attention and research.

Challenges to informed consent

Although involving patients in decisions is central to respecting autonomy, many barriers can prevent ICU patients from participating in decisions. Patients are often unconscious, delirious, or in distress or pain, and many require medications that cloud mental status. Mechanical ventilation may complicate communication. Additionally, decisions must often be made quickly. Surrogates are regularly employed in situations of impaired mental status, but time constraints and distress affect surrogates too.

These barriers probably hinder involvement in research decisions even more than in clinical decisions. Clinical trials, particularly in acute settings, are poorly understood. They depart from the norms of clinical medicine prioritizing individual interests, involve complicated concepts such as randomization, involve risks not justifiable by direct benefit, and foster conflation of research with care. For those same reasons, informed consent has an important role in research enrolment decisions when 'stakes are high' in the ICU. Consent is thus most difficult when it seems most important

Although surrogate consent for ICU research is widely employed [3], studies have demonstrated that surrogates' decisions may not reflect patients' choices. Indeed, one recent study found surrogates' predictions were no better than chance [4]. The implications of these findings are unclear. It may, for example, be that patients care more about **who** makes decisions than the '**accuracy**' of substituted judgment [5]. If so, surrogate consent might be justified as a patient-centred process, even if it results in different decisions from what patients themselves may choose. Further research is needed.

There are other challenges with surrogate consent. First, surrogates are typically non-neutral observers (often family), and their distress may degrade decisional capacity. Secondly, surrogates may feel uncomfortable making decisions regarding research. Some investigators have noted, for example, that consent for participating in potentially therapeutic trials is often refused initially, but later granted if the patient fails to improve. This reflects indecision and conflation of research with clinical care. It also may introduce bias by preferentially selecting sicker patients. Finally, it is unclear when patients want surrogates involved. In acute myocardial infarction research, for example, many participants feel capable of making enrolment decisions and often want to do so, despite poor understanding [6].

Barriers to consent in ICU research are thus significant, numerous, and unavoidable. Unfortunately, current regulations continue to require complex documentation that does little to promote informed consent. Shorter, simpler consent materials have been suggested but have not been widely employed or evaluated.

When time constraints are significant (e.g. septic shock, ST-elevation myocardial infarction, or gastrointestinal bleeding), the maximal attainable goal may be to learn whether patients generally accept research enrolment, and a process of informed refusal may be more appropriate [7]. Seeking full consent seems

disingenuous and may delay treatment. However, there is a need for empirical evaluation of the impact of innovative approaches on enrollment decisions, and patients' and surrogates' perceptions of procedural justice.

Exception from informed consent

In the USA and many other countries (including Australia and Canada), regulations allow an exception from informed consent (EFIC) in certain emergency settings. Notably, there is significant heterogeneity across Europe. While the European Clinical Directive contains no provisions to allow for EFIC in emergency settings, many European countries explicitly permit it [8].

The principal requirements in US EFIC regulations are that consent is impracticable within the necessary timeframe, that existing treatment is inadequate, and that studies pose a reasonable risk–benefit ratio. Additionally, there are requirements for community consultation and public disclosure [9]. These regulations have facilitated pivotal studies in conditions including cardiac arrest, status epilepticus, and shock, typically conducted in out-of-hospital and emergency department settings. They may also be appropriate for in-hospital studies of resuscitation or other unpredictable conditions where consent is impracticable. How community consultation processes might differ in inpatient settings warrants exploration. Importantly, EFIC is not appropriate when patients or surrogates can make enrollment in decisions.

Equipoise and critical care

Another set of ethical challenges in ICU research involves study design. Core design elements, such as choice of control, decisions about randomization, and tests or procedures done purely for research purposes, all influence a study's ethical acceptability. These factors determine study risks, the extent to which study care differs from routine care, and the extent to which a study will impact on practice. Given consent challenges and high patient acuity, these issues can be daunting.

Most design issues arise in randomized trials. The prevalent standard for acceptability of randomization is clinical equipoise [10]. Clinical equipoise does not require that individual clinicians be agnostic about which treatment arm they prefer, only that the relevant medical community be sufficiently uncertain. There has been debate about whether this standard is appropriate, but the basic requirement for uncertainty within a field and reasonable risk are intuitively sensible and widely applied. The devil in operationalizing this concept, of course, is in the details.

High acuity clearly raises the stakes. Given that mortality is often a primary outcome measure and not rare in ICU studies, the relative harm of being assigned to an inferior treatment is potentially enormous. Of course, if investigators knew which arms were superior at the outset, the trial would be unethical, but varying levels of evidence may exist to support different treatments. What level of evidence is sufficient to disturb equipoise is a matter of debate. For example, a randomized control trial comparing epinephrine with epinephrine plus vasopressin in cardiac arrest was acceptable because there was significant experience using both drugs, but no evidence of superiority [11]. A study comparing epinephrine with a new compound with encouraging preclinical data, but limited clinical data, may pass a test of uncertainty, but there may be insufficient experience to justify randomization in cardiac arrest. By contrast, a new intervention may have such strong face validity, or accumulated experience may suggest such profound benefits, that some are reluctant to allow randomization to standard interventions. Adaptive designs have at times been employed to minimize the number of patients exposed to inadequate treatment, but these designs require careful consideration of methodological limitations [12].

Although these considerations are not conceptually distinct from similar dilemmas in other contexts, the potential 'costs' of randomization to inferior therapy, coupled with challenges to consent, impose especially rigorous requirements for scientific review. Many institutional review boards (IRBs) are ill-equipped to assess risks of specific comparisons. At a minimum, IRBs should seek confirmation from experts unaffiliated with the trial that comparison arms are reasonable and do not present excessive risks, just as they should seek statistical confirmation that trial designs will answer the clinical question. In large, multicentre trials, review mechanisms may take place centrally, although the locus of responsibility (data safety and monitoring committee versus scientific review committee versus IRBs) can be unclear. The guiding principle of all trials must be to produce evidence that impacts clinical decisions.

Standard of care and control group selection

Another design-related challenge is the choice of control or standard of care. This issue arose, for example, regarding the ARDS Network trial of low versus high tidal volume ventilation for acute lung injury [13]. Investigators chose a 12 mL/kg control, based on available observational data, but critics argued that this control did not reflect community standards and that the trial did not effectively inform practice. They argued that a lower 'high' volume, clinician discretion (no protocol-defined volume), or a three-arm trial should have been employed. While the optimal approach in the context of heterogeneous practices is unsettled, helpful approaches may include systematic surveys of relevant experts to drive a consensus-based choice of comparison [14] or potential inclusion of multiple control groups, one of which does not conform to a particular protocol [15]. The latter, of course, poses logistical hurdles and challenges regarding sample size. These concerns merit careful consideration, because multiple control groups increase cost, and they may delay data production and reduce scientific value if recruitment is insufficient.

Similar dilemmas arise in organizational-level research. For example, one of the authors recently conducted a randomized trial of in-house night-time intensivist staffing versus home-based intensivist availability [16]. Although the latter model was the standard in the ICU where the study was proposed, concerns were raised that it was unethical to randomly assign patients to this model because continuous intensivist coverage had become standard at peer institutions. The trial was ultimately launched after investigators established that this 'standard' lacked evidence, but concerns remained among clinicians who believed the face validity of in-house night-time coverage was sufficiently strong.

System-based studies and quality improvement

Distinguishing between quality improvement and clinical research can be challenging, an issue raised most visibly by a study

evaluating ICU checklists [17]. Investigators did not seek IRB review because their institution considered the study to be quality improvement. Accordingly, informed consent was not sought. The study was eventually halted, as it was determined that it did represent research and prospective consent should have been obtained. However, the study would have been eligible for expedited review and a waiver of consent because of the impracticability of consent and minimal risk involved [18]. The error was thus more in categorization and compliance than in substance. The case nonetheless highlights two key issues. First, it can be difficult to distinguish between quality improvement activities and clinical research, but systematic attempts to generate generalizable knowledge do constitute research and warrant review. More importantly, the ethical acceptability of such activities and standards for consent do not hang on this distinction.

Perhaps the biggest ethical challenge of system-based studies is the inability of individual subjects to decline participation. Informed consent is impractical when randomizing units to checklists or staffing structures; patients cannot choose whether to be admitted to a unit that uses a checklist, and the goal of these studies is to examine the impact of systems. If anything, the absence of consent highlights the importance of review, as significant outcomes are at stake.

Ethical innovation and data-driven research ethics

Two critical elements of advancing understanding of ethics in ICU research are thinking broadly and applying standards of evidence to ethics. A salient example of the former was the first study in humans of glycoprotein IIb–IIIa inhibitors. Because of bleeding concerns, investigators conducted early phase research in brain-dead patients to establish safety before studying the drug in acute myocardial infarction [19]. This approach minimized risk in transitioning new agents into trials in sick patients and represents a model for a context-sensitive approach to critical care research.

Low recruitment is another pervasive problem that delays or prevents important knowledge, and creates inefficiencies in the use of research and health care resources. Incentive payments to patients—long-shunned—have become more accepted in clinical studies as data have suggested that ethical concerns may have been overstated [20]. Broader use of incentives in critical care research, for example, to members of the research team in order to overcome recruitment barriers, may improve enrolment, but these practices raise real ethical concerns. Incentives should thus only be implemented under rigorous empirical evaluation to assess whether beneficial enrol effects can be obtained without adverse consequences. Ethics practices, just like clinical practice, should be data-driven.

Conclusion

ICU research presents unavoidable ethical challenges that must be surmounted to improve care for the sickest patients. This chapter highlighted challenges that are particularly salient or have unique features in the ICU. Approaches to addressing these issues must recognize and be sensitive to the ICU context, maintain commitment to high-quality data, and avoid over-reliance on consent as the *sine qua non* of ethical research. Many of these challenges—and their potential solutions—are amenable to empirical investigation, and it is essential to create a culture of creative thinking and evidence-based research ethics in the ICU.

References

1. Halpern NA and Pastores SM. (2010). Critical care medicine in the United States 2000–2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. *Critical Care Medicine*, **38**(1), 65–71.
2. Luce JM, Cook DJ, Martin TR, et al. (2004). The ethical conduct of clinical research involving critically ill patients in the United States and Canada: principles and recommendations. *American Journal of Respiratory and Critical Care Medicine*, **170**(12), 1375–84.
3. Luce JM. (2009). Informed consent for clinical research involving patients with chest disease in the United States. *Chest*, **135**(4), 1061–8.
4. Newman JT, Smart A, Reese TR, Williams A, and Moss M. (2012). Surrogate and patient discrepancy regarding consent for critical care research. *Critical Care Medicine*, **40**(9), 5.
5. Puchalski CM, Zhong Z, Jacobs MM, et al. (2000). Patients who want their family and physician to make resuscitation decisions for them: observations from SUPPORT and HELP. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. Hospitalized Elderly Longitudinal Project. *Journal of the American Geriatrics Society*, **48**(5 Suppl.), S84–90.
6. Gammelgaard A, Rossel P, Mortensen O, in collaboration with the DANAMI-2 Investigators. (2004). Patients' perceptions of informed consent in acute myocardial infarction research: a Danish study. *Social Science and Medicine*, **58**, 2313–24.
7. Dickert N, Llanos A, and Samady H. (2012). Re-visiting consent for clinical research on acute myocardial infarction and other emergent conditions. *Progress in Cardiovascular Diseases*, **55**(3), 251–7.
8. Lecouturier J, Rodgers H, Ford GA, et al. (2008). Clinical research without consent in adults in the emergency setting: a review of patient and public views. *British Medical Council Medical Ethics*, **9**, 9.
9. US Food and Drug Administration. (2004). Title 21 (Code of Federal Regulations), Part 50.24 Protection of Human Subjects. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24(accessed April 2, 2015).
10. Freedman B. (1987). Equipoise and the ethics of clinical research. *New England Journal of Medicine*, **317**, 141–5.
11. Gueugniaud PY, David JS, Chanzy E, et al. (2008). Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *New England Journal of Medicine*, **359**(1), 21–30.
12. Truog RD. (1992). Randomized controlled trials: lessons from ECMO. *Clinical Research*, **40**(3), 519–27.
13. The Acute Respiratory Distress Syndrome Network. (2000). Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *New England Journal of Medicine*, **342**(18), 1301–8.
14. Truog RD. (2005). Will ethical requirements bring critical care research to a halt? *Intensive Care Medicine*, **31**(3), 338–44.
15. Silverman HJ and Miller FG. (2004). Control group selection in critical care randomized controlled trials evaluating interventional strategies: an ethical assessment. *Critical Care Medicine*, **32**(3), 852–7.
16. Kerlin MP, Small DS, Cooney E, et al. (2013). A randomized trial of nighttime physician staffing in an intensive care unit. *New England Journal of Medicine*. **368**(23), 2201–9.
17. Pronovost P, Needham D, Berenholtz S, et al. (2006). An intervention to decrease catheter-related bloodstream infections in the ICU. *New England Journal of Medicine*, **355**(26), 2725–32.
18. Miller FG and Emanuel EJ. (2008). Quality-improvement research and informed consent. *New England Journal of Medicine*, **358**(8), 765–7.
19. Coller BS, Scudder LE, Berger HJ, and Iuliucci JD. (1988). Inhibition of human platelet function in vivo with a monoclonal antibody. *Annals of Internal Medicine*, **109**, 635–8.
20. Halpern SD. (2011). Financial incentives for research participation: empirical questions, available answers and the burden of further proof. *American Journal of Medical Sciences*, **342**(4), 290–3.

PART 1.7

Medico-legal and ethical issues

CHAPTER 25

Informed consent in the ICU

Henry J. Silverman

Key points

- In recent years, the overemphasis on autonomy that has led patients and family members feel they have to 'make the decision' by themselves has shifted towards a more balanced approach with the participation of both patients and health care providers, a concept termed 'shared decision making'.
- In order to be deemed legally and ethically valid, there needs to be adequate disclosure of information, the individual must have the capacity to understand and make a decision and the decision needs to be free from coercion, i.e. voluntary.
- Advance directives serve as a mechanism for patients to have their previously stated autonomous wishes followed when they lose decision-making capacity to decide for themselves.
- Ethicists, caregivers, and the legal system recommend that standards for surrogate decision making should include substituted judgment and best interests.
- Patient autonomy has assumed an important status in the provision of health care, but it must be recognized that autonomy is largely a Western concept, which might pose challenges in other cultural settings.

Introduction

Informed consent in the medical setting has evolved during the past 50 years. Previously, most major medical decisions were left exclusively to physicians, as society accepted that physicians not only possessed the detailed technical knowledge required to make medical decisions on behalf of patients, but they were also guided by an overriding principle of beneficence. This paternalistic approach had several benefits, as physicians attempted to make the best decisions possible and they spared patients and their families from the emotional burdens associated with these difficult choices. This paternalism emphasized beneficence to the exclusion of other principles, particularly autonomy [1]. By the mid-1980s, the concept of the paternalistic physician was replaced by developments in health care law and ethics that accompanied the rise of the doctrine of informed consent. This doctrine, intended to promote and respect the autonomy of patients [2], 'flows from the recognition that all persons have unconditional worth, each having the capacity to determine his or her own moral destiny' [3].

In addition to this inherent value of autonomy, an instrumental value afforded to informed consent also arose from the realization that it can be difficult for physicians to determine what is in their patients' best interests [4] and to avoid basing decisions on their unintended biases. [1]. As such, in the late twentieth century, the pendulum swung away from paternalism and towards patient autonomy. Unfortunately, many physicians began to act as impartial agents for their patients and withheld any advice, as they strived to avoid exerting what they believed to be inappropriate influences on the patient or family. This overemphasis on autonomy led to patients and family members being made to feel that they have to 'make the decision' by themselves. However, in recent years, the pendulum has begun to swing back from absolute autonomy towards a more balanced approach with participation of both patients and health care providers, a concept termed 'shared decision making' [5].

Elements of informed consent

Typically, in order to be deemed legally and ethically valid, an individual's consent must be properly informed (i.e. adequate disclosure of information), the individual must have the capacity to understand factual information, appreciate the situation he or she is in, make a decision, and the decision must be free from coercion (i.e. voluntary) [2]. The combination of having the abilities to understand, appreciate, and make a decision is sometimes referred to as having 'competence' on the grounds that what is at issue is 'the ability to perform a task' [3]. It is also sometimes referred to as 'capacity', since the task in question involves the capacity to make a decision [6]. In practice, both words are used interchangeably.

Disclosure of information

Patients must have adequate information if they are to make decisions that reflect their own values and preferences, and physicians play a key role as educators in this process. Accordingly, physicians have a basic duty to disclose enough about the proposed treatments (e.g. rationale for the treatment or intervention, risks and benefits, who would carry out the intervention, and alternative recommendations for treatment) so that the patient becomes sufficiently informed to participate in shared decision making. If physicians fail to do their 'due diligence' in this area of patient–physician communication, patient decisions will be based on incomplete and, possibly, incorrect information, which can lead to unwarranted assumptions by the patient. Furthermore, physicians must do more than just tell patients about a proposed procedure or therapy, and its risks and benefits. They must communicate in a way that the patient can understand, including requesting a language translator if necessary and avoiding medical jargon. Physicians must also ask questions of patients to ensure that they demonstrate a deeper understanding of the treatment proposals, not merely prompt the patient to parrot information back.

There is a debate regarding how much information the patient requires, and physicians might find it difficult to strike a balance between too much and too little information. Communicating every detail is neither possible nor practical. Most of the ethics literature and law in this area suggest one of three standards:

- **Professional community standard:** entails that a physician's duty to disclose information to the patient depends on what the majority of physicians in the community would disclose regarding the **intervention**. This standard allows the physician to determine what information is appropriate to disclose. The concern, however, is that the typical physician would tell the patient very little. This standard is also generally considered inconsistent with the goals of informed consent, as the focus is on the physician rather than on what the patient needs to know.
- **Reasonable patient standard:** entails a duty of disclosure based on what the average patient would need to know in order to be an informed participant in the decision. This standard focuses on considering what a patient would need to know in order to understand the decision that needs to be made.
- **Subjective standard**: entails that the physician tailors the information based on **what** a specific patient needs to know and understand in order to make an informed decision. This standard is the most challenging to incorporate into practice, since it requires tailoring information to each individual patient.

The reasonable person standard seems the most practical and achievable, although practice should be guided by local interpretation of the law and professional society's standards.

Decision-making capacity

In order to give valid informed consent, patients must have the following in order to make a decision—the ability to understand factual information, to appreciate their situation and its consequences, to rationally consider information in light of their underlying values, and to commit to a choice.

- **Understanding of information**: once the information provided is deemed adequate, the physician must be assured that the patient understands the basic factual information. A useful technique for assessing understanding is to ask the patient to summarize what has just been said and to correct as needed.
- **Appreciation**: in addition to understanding basic factual information, commentators agree that patients must also have some **appreciation** of the nature and significance of the decision that they are faced with [2]. Appreciation is a term used to refer to the highest degree of understanding, one that grasps more than just the medical details of the illness and treatment. Very basically, patients must recognize that this is **their** decision to make and that it is **their** life and values and future lives that are at stake. Essentially, patients need to demonstrate what has been termed 'insight' into the circumstances of a given decision.
- **Reasoning**: patients must have the cognitive ability to manipulate information rationally, weigh risks and benefits, consider trade-offs of accepting or not accepting the recommended treatment, and evaluating potential consequences. Usually, asking patients to state their reasons for their decision can serve as a 'window' into their reasoning process.
- **Choice**: patients must be able to commit to a decision or a choice. Unless a patient's preferred choice can be expressed to others in some explicit way, it is impossible to know their intended decision. The condition is not trivial, since some patients might defer decisions or authorize others to make decisions for them. This is perhaps the least mental of the sub-capacities that constitute capacity, which may explain why it is not considered an element of capacity by some authors.

Voluntary decisions

A valid informed consent requires that patients' decisions must be free from controlling influences. The institutional setting of the hospital may be a source of subtle or covert coercion, including a fear, justified or not, that they may not receive future care in some way if they do not follow the physician recommendations. Patients may feel they have little choice, but to agree with 'their' doctor who is 'recommending' a treatment. Also, families may exert considerable pressure on patients.

Informed consent and the capacity to consent

Critically-ill patients may have a diminished capacity to make decisions. Studies have showed that patients with acute illnesses may have limitations in their decision making capabilities due to a number of factors, including the presence of delirium, their underlying illness, or the use of sedatives and analgesics [7–12]. The presence of these factors does not necessarily translate into incapacity to provide a valid informed consent. Indeed, two types of errors can occur in the setting of obtaining informed consent from critically-ill patients. One error involves obtaining surrogate consent for patients who are capable of providing consent, thus depriving such patients their autonomous rights to choose for themselves. The opposite error occurs when physicians obtain informed consent from patients who lack decisional capacity. To minimize such errors, it is crucial for physicians to assess the decision-making capacity of their patients.

Methods for assessing capacity

Currently, there are no universally accepted procedures regarding capacity assessment for critically-ill patients.

Physicians may attempt to gauge a patient's ability to make treatment-related decisions through regular communication during the clinical encounter. Such informal capacity assessments consist of using probing questions to assess patient's ability to understand factual information, their appreciation of their situation, and their cognitive ability to manipulate and weigh the information before coming to a decision. Often, physicians rely on 'experts' (e.g., psychiatrists) to determine decision making capacity. Regardless of who does the capacity assessment, one must realize and accept the inherent subjective nature of such judgments regarding the capacity to make decisions. Also, one is often left with the question of how much understanding and rational decision-making capacity is sufficient to make the determination that a patient has capacity. Conversely, how deficient must a patient's decision-making capacity be, before he or she is declared to lack capacity? Rather than selecting a single standard of capacity, commentators have suggested a sliding scale concept, which paternalistically requires an

increasingly more stringent standard (or greater evidence of capacity) as the consequences of patients' decisions embody more risks or more severe consequences to their welfare [3,6]. In other words, if the consequences of a decision for patient welfare are grave (e.g. refusing ventilator support), the greater would be the need to be certain that the patient possesses the requisite capacities. However, if little in the way of welfare is at stake, a lower level of capacity might be required for decision making [3]. This concept of a sliding scale explains why a greater degree of capacity (or greater degree of certainty) is warranted for a patient to refuse treatment, whereas a lower degree of capacity is required to accept treatment recommendations. These concepts can be applied in the following manner. If a patient is critically ill because of an acute illness that is life-threatening and the available treatment is considered to be effective, low in risk, and there are few or no alternatives available, then a physician may accept a low level of decisional capacity from the patient to accept the treatment. That is, the act of consent to such a treatment is considered to be an informed consent as long as the patient is aware of what is going on. Awareness in the sense of orientation or being conscious of the general situation would satisfy the cognitive requirement of informed consent [13].

However, a high level of decisional capacity would be required if the patient refuses to accept the available treatment. Such decisions can be respected as long as the patients satisfy the most demanding standard of capacity. Patients need not conform to what most rational people would do to be considered as having capacity, but patients must be able to give reasons for their decisions. Patients must be able to show that they have thought through the medical issues and related this information to their personal value systems. Patients' personal reasons may derive from a set of religious beliefs (e.g. Jehovah Witness) or from a philosophical view that is shared by only a small minority, but they should not be purely idiosyncratic or incoherent [13]. If the patient is terminally ill, and the treatment carries great risk or is of less definite benefit (or if there are real alternatives to one or another course of action, e.g. hospice care, rather than lingering illness), then the physician should accept a low level of capacity if the patient refuses the treatment.

A problem with the sliding scale strategy is that health care providers may manipulate it to declare patients who consent to a treatment to be competent and those who refuse treatment to be incompetent.

When patients lack capacity for decision making

When patients lack decision-making capacity to provide their own consent, several mechanisms exist by which their autonomy can still be respected.

Advance directives

Advance directives serve as a mechanism for patients to have their previously stated autonomous wishes followed when they lose decision-making capacity to decide for themselves. There are two types of advance directives. One is an instructional directive, or a 'living will', which specifies the patient's preferences to specific care decisions. Often, such directives contain general statements of not wanting life-sustaining interventions or they describe the values that should guide specific terminal care decisions. Such general statements might not be helpful, as they lack specificity for complex decisions that occur in the critical care setting. Some advance directives enumerate different scenarios and interventions for the patient to choose from and others are designed for use by patients with a specific disease, such as cancer.

Alternatively, a person can select a proxy decision maker, sometimes called a durable power of attorney for health care, to make decisions for them when they lose decisional capacity. Individuals choosing a proxy should make sure that the proxy knows their wishes and values well enough to ensure that decisions made are more likely to be reflect the decisions they would have made. Often, a combined directive includes both instructions and the designation of a proxy. In general, advance directives remain a challenge with their clinical implementation [14] and also with its normative justification in different cultural contexts that define varying roles for family decision making, e.g. individualistic vs. relational understandings of autonomy [15].

Surrogate decision making

If a patient has not legally appointed a health care proxy, family members (or in some cases, friends who know the patient well) may still be able to serve as the patients' surrogate decision maker and make health care decisions for patients. US and European standards require such surrogates to be legally authorized to provide such consent under applicable law.

Standards for surrogate consent

Ethicists, caregivers, and the legal system recommend that standards for surrogate decision making include a substituted judgment and best interests. Substituted judgment holds that the surrogate decision makers should attempt to reconstruct the patients' judgment by analysing prior statements, and their overall values and beliefs, and to make the decision that 'would be made by the incompetent person, if that person were competent . . .' . Most surrogates, even close family members, cannot accurately predict what the patient would want. Therefore, in the absence of specific guidance from the patient, substituted judgment involves surmising what a patient would want, rather than a guaranteed fulfilment of the patient's wishes. Of note, patients who were surveyed in one study varied in the extent to which they want families to strictly adhere to their personal wishes in making end-of-life decisions on their behalf [16].

If the patient's wishes cannot be reliably ascertained, then surrogates should resort to a best-interests standard, which entails that the surrogate should base decisions on a balancing of the treatments' benefits and risks, the medical prognosis, and the patient's present and future interests. The term 'best' is used to denote that the surrogate's obligation is to select from those competing treatments the one in which the benefits maximally outweigh the burdens of treatment. This standard can be considered 'objective', only if there is a 'societally-shared criteria' about what constitutes benefits and burdens. This has proved to be problematic, as benefits and burdens transcends a medical calculus (e.g. pain and discomfort), and usually also include patient values, e.g. religion, any beliefs related to life and death, level of rationality, and concepts of dignity. In the absence of an objective best-interests standard, physicians largely rely on families to decide what constitutes a benefit or burden from their estimation of a patient's personal values, and only object if these decisions seem to demand treatments that seem to be not beneficial or futile. Without a perfect solution to the problems

raised by proxy decision making, this approach may be the most reasonable one in difficult circumstances.

A concern with surrogate decision making in general, is that studies have shown high levels of anxiety and psychological distress in family members of critically-ill patients. This consideration might, at times, call into question the ability of surrogates to make morally adequate decisions for incapacitated patients.

Special situations

Critically-ill patients who lack both decision-making capacity and surrogate decision makers

No formal guidelines exist regarding the process that should be involved with decisions regarding the use of limit life-sustaining treatments for adults lacking both in capacity to make decisions and surrogate decision makers. One study demonstrated that such a situation was present in 16% of patients admitted to the intensive care unit of one hospital. Processes to make decisions regarding life supporting treatments include unilateral physician decision making, involvement of an ethics committee, and institutional or judicial review [17]. Further discussions are warranted to develop optimal guidelines for such patients.

Emergency clinical situations

In general, all invasive procedures require informed consent from the patient or the appropriate surrogate. Exceptions occur when emergent, life-saving procedures are required (e.g. endotracheal intubation), and patients lack decision making and surrogates are not available. Under the concept of implied consent, whereby it is implied that such patients would consent to such treatments, if competent, it would be ethically appropriate to provide treatments to such patients. It is the responsibility of individual units and institutions to establish guidelines for which procedures require formal written consent.

Informed consent in the research setting

A major and complex issue regarding informed consent in the research setting involves the inability of potential research participants to distinguish between research and clinical care [20]. Patients and families have a strong tendency to inaccurately attribute therapeutic intent to research interventions. However, the goal of clinical trials is not to provide direct benefits to subjects, but rather, the primary goal of research is to generate generalizable knowledge for future patients [18]. The term 'therapeutic misconception' is used to describe this phenomenon, a term first reported by Appelbaum and colleagues in 1982 during interviews with patients with psychiatric disorders who participated in clinical trials [19]. There are two major ethical concerns with the therapeutic misconception. First, the failure of patients to appreciate correctly the risks and benefits of potential research participation raises concerns regarding the validity of informed consent [20]. Secondly, the presence of the therapeutic misconception reflects the very real possibility that research participants will see the investigator's role as that of the physician and view an invitation to enrol in research as a professional recommendation, intended to serve their individual treatment interests. Such inappropriate enrolment of patients into research reflects a concern with exploitation. Physician investigators should explicitly refute such a 'therapeutic misconception' and should dispel any notion that a clinical trial is designed to or will provide patients with direct benefits, or that the research substitutes for clinical care. Commentators have given further recommendations for informed consent in the critical care setting [20].

Emergency research

Advancing the field of emergency medicine requires research, but, in emergency circumstances, it is often impossible to obtain consent from patients or their families in time. Several ethicists believe that, because the field of emergency medicine simply cannot progress without research, there should be an exception to informed consent requirements, even for such risky trials, combined with additional safeguards to to ensure that exploitation is prevented.

Conclusion

Patient autonomy has assumed an important status in the provision of health care, but one must recognize that autonomy is largely a Western concept that might pose challenges in other cultural settings. For example, full disclosure might be at variances with cultural beliefs about hope and wellness, autonomous decision making may contradict family-centred values, and uncoerced choices may counter cultural norms of obedience to other family members. Cultural competence in the health care setting is recommended to gain sensitivity to cross-cultural encounters in the medical care setting.

References

1. Quill TE and Brody, H. Physician recommendations and patient autonomy: finding a balance between physician power and patient choice. *Annals of Internal Medicine*, **125**, 763–9.
2. Faden RR and Beauchamp, T.L. (1986). *A History and Theory of Informed Consent*. New York, NY: Oxford University Press.
3. Beauchamp TL and Childress, JF. (2001). *Principles of Biomedical Ethics*. New York, NY: Oxford University Press.
4. Schneiderman LJ, Kaplan, R.M., Pearlman, R.A., and Teetzel, H. (1993). Do physicians own preferences for life-sustaining treatment influence their perceptions of patients' preferences? *Journal of Clinical Ethics*, **4**, 28–33.
5. Elwyn G FD, Thomson R, Joseph-Williams N, et al. (2012). Shared decision making: a model for clinical practice. *Journal of General Internal Medicine*, **27**, 1361–7.
6. Buchanan AE and Brock DW. (1989). *Deciding for Others: The Ethics of Surrogate Decision Making*. Cambridge: Cambridge University Press.
7. Schaeffer MH, Krantz DS, Wichman A, et.al. (1996). The impact of disease severity on the informed consent process in clinical research. *American Journal of Medicine*, **100**, 261–8.
8. Hustey FM and Meldon SW. (2002). The prevalence and documentation of impaired mental status in elderly emergency department patients. *Annals of Emergency Medicine*, **39**, 248–53.
9. Smithline HA, Mader TJ, and Crenshaw BJ. (1999). Do patients with acute medical conditions have the capacity to give informed consent for emergency medicine research? *Annals of Emergency Medicine*, **6**, 776–80.
10. Pisani MA, McNicoll L, and Inouye SK. (2003). Cognitive impairment in the intensive care unit. *Clinical Chest Medicine*, **24**, 727–37.
11. Raymont V, Bingley W, Buchanan A, et al. (2004). Prevalence of mental incapacity in medical inpatients and associated risk factors: cross-sectional study. *Lancet*, **364**, 1421–7.
12. Office of Human Research Protections (OHRP) (2000). *Compliance Determination Letters*. London: OHRP.

13. Drane JF. (1984). Competency to give an informed consent. *Journal of American Medical Association*, **252**, 925–7.
14. Gutierrez KM. (2012). Advance directives in an intensive care unit: experiences and recommendations of critical care nurses and physicians. *Critical Care Nursing Quarterly*, **35**, 396–409.
15. Biller-Andorno N and Brauer S. (2010). Advance directives from a cross-cultural perspective. *Bioethics*, **24**, ii–iv.
16. Sehgal A, Galbraith A, Chesney M, et. al. How strictly do dialysis patients want their advance directives followed? *Journal of the American Medical Association*, **267**, 59–63.
17. White DB, Curtis JR, Lo B, and Luce JM. (2006). Decisions to limit life-sustaining treatment for critically ill patients who lack both decision-making capacity and surrogate decision-makers. *Critical Care Medicine*, **34**, 2053–9.
18. Miller FG and Rosenstein DL. (2003). The therapeutic orientation to clinical trials. *New England Journal of Medicine*, **348**, 1383–6.
19. Appelbaum PS, Roth LH, and Lidz C. (1982). The therapeutic misconception: Informed consent in psychiatric research. *International Journal of Law and Psychiatry*, **5**, 3–4.
20. Silverman HJ, Luce JM, Lanken PN, et al. (2005). Recommendations for informed consent forms for critical care clinical trials. *Critical Care Medicine*, **33**, 867–82.

CHAPTER 26

Patient rights in the ICU

Thaddeus M. Pope and Douglas B. White

Key points

- To say that a patient has a 'right' is to say both that the patient has a 'claim' against the clinician for X and that the clinician owes a correlative 'duty' of X to the patient.
- Patient rights are not absolute trumps. They are only *prima facie* (presumptively) valid claims, which must sometimes yield to other sufficiently compelling claims.
- Overriding a right can be either justified (an 'infringement') or unjustified (a 'violation'). Patient rights are sometimes justifiably infringed by distributive justice concerns.
- Patient rights are also sometimes justifiably infringed by clinicians' assertions that the requested intervention violates professional integrity.
- Patient–clinician conflicts can usually be prevented or mediated. When conflict is intractable, it should be resolved through appeal to socially-accepted rules. When this is not possible, the dispute should be managed through a fair process of dispute resolution.

Introduction

This chapter proceeds in seven stages. First, it explains the nature and source of patient rights. Secondly, it analyses the scope of patient rights. Thirdly, it describes five specific patient rights that are particularly relevant to critical care. Fourthly, this chapter turns to discuss several ways in which patient rights might be illegitimately violated. Fifthly, it discusses how patient rights might be justifiably infringed by distributive justice concerns and concerns grounded in professional integrity. Finally, this chapter concludes by describing four leading mechanisms by which patient rights are balanced against clinician rights.

Nature and source of patient rights

The concept of 'rights' is ambiguous, but Wesley Hohfeld [1] famously disambiguated and clarified the concept by distinguishing four types of rights: claim, liberty, authority, and immunity rights. Most relevant, here, are claim rights. To say that a patient has a 'right' is to say both that the patient has a 'claim' against the clinician for X and that the clinician owes a correlative 'duty' of X to the patient. Or one might say that a patient's 'right' is a normative demand, which imposes a constraint on the clinician [2].

Hohfeld's theory of correlative rights concepts has been enormously influential, and it is particularly appropriate in the critical care context. Because of a patient's overwhelming vulnerability and dependency, typically he/she can effectively exercise his/her rights only through or with her clinician. Indeed, the very basis of patient rights (and clinicians' correlative duties) rests to a significant degree on the extreme power imbalance between clinicians and patients. Patient rights are also grounded in the highly-valued principle of respect for autonomy or self-determination.

One need not resort to philosophical axioms to identify patient rights. They are already well-articulated more concretely in state and federal statutes, Medicare conditions of participation, licensing regulations for clinicians and facilities, Joint Commission accreditation standards, professional medical association ethics codes, and international conventions [3–6].

Scope of patient rights

Theoretically, patient rights could be specified in such a way that they would include exceptions and limitations that accommodate competing claims of clinicians and society. With such 'built-in' specification, patient rights would always be absolute. However, anticipating and incorporating all these restrictions would be burdensome, cumbersome, and probably impossible. For example, consider a proposed right to 'treatment within the boundaries of accepted medical practice'. Such a right would be indeterminate, because the boundaries of accepted practice are notoriously fuzzy.

Accordingly, ethicists and political philosophers generally consider rights as only *prima facie* binding. Rather than narrowly defining rights with exhaustive detail, it is better to talk about when a (presumptively broad) right can be 'permissibly infringed' or 'overridden'. Beauchamp and Childress distinguish the 'violation' of a right from the 'infringement' of a right. Violation refers to an unjustified action against a right, whereas infringement refers to justified action overriding a right [7].

Due to the pre-eminence of the principle of respect for autonomy in Western culture, the scope of patient rights is quite broad. Indeed, the claim is basically that medicine should make its skills available to patients to help them achieve their own private vision of the good life. Nevertheless, both through professional standard setting and court rulings, some limits have been established. For example, it is well-settled that patients generally do not have a right to non-palliative treatment in situations of physiological futility, death, anencephaly, or gestation under 22 weeks [8].

Key patient rights

Because some patient rights are human rights, they are inalienable and universal. Other patient rights vary across countries. The

development of patient rights is evolving. We must necessarily generalize across settings with material and minor differences. Still, many patient rights are standard across health care settings. For example, patients typically have the right to privacy and to confidentiality of their health information. They typically have the right to be treated according to the prevailing standard of care. However, particularly notable in critical care are patient rights to informed consent, treatment refusal, non-discrimination, pain management, and non-abandonment.

Informed consent

Patients are usually ethically and legally entitled to informed consent. They have the right to know what their treatment options are and to intelligently participate in decisions about their care. Accordingly, the clinician must provide the patient with information about his/her diagnosis and prognosis, the risks and benefits of proposed procedures and treatments, and the risks and benefits of reasonable alternatives. Furthermore, the clinician must provide all this information in an understandable manner, which is sensitive to the patient's language and cultural needs.

Treatment refusal

A logical corollary of informed consent is the right to refuse treatment. The patient has the right to withhold (not start) treatment that might be offered (e.g. cardiopulmonary resuscitation) and to withdraw (stop) treatment that is already under way (e.g. mechanical ventilation). Moreover, the patient has the right to refuse treatment, even if clinicians regard it as 'medically indicated' and even if such refusal will cause the patient's death. In particular, the patient has the right to have an advance directive with the expectation that clinicians will honour the intent of that directive. However, while patients have the 'negative' right to decline unwanted treatment, it remains less settled whether patients have an 'affirmative' right to demand the initiation or continuation of treatment.

Non-discrimination

Patients are entitled to treatment without regard to their race, sex, colour, ancestry, national or ethnic origin, religious beliefs, sexual or political orientation, marital status, genetic information, age, or disability. While these are the classic grounds of prohibited invidious discrimination, patients are also entitled to treatment without regard to their source of payment, educational background, compliance with social norms, perceived social worth, or, sometimes, even ability to pay.

Pain management

Patients have a right to effective pain management. This includes physical, social, psychological, and spiritual pain management. If requested, clinicians must administer, prescribe, or dispense medications or procedures sufficient to relieve the patient's pain or discomfort, even if that intervention may hasten or increase the risk of death.

Non-abandonment

Clinicians are generally free to choose whom they will serve, but once having undertaken a case, clinicians must not abandon the patient. Clinician-initiated termination of a treatment relationship is particularly serious when the patient is acutely ill. Clinicians must assure the patient's continuity of care. Therefore, clinicians may not discontinue treatment, so long as that treatment is needed, unless adequate care is otherwise available.

Illegitimate violations of patient rights

Unfaithful surrogates

Patient rights are often exercised on the patient's behalf by surrogate decision makers. Because patients in critical care usually lack decision-making capacity, surrogates make most treatment decisions. Accordingly, clinicians usually honour patient rights, such as informed consent and treatment refusal through joint deliberation with the surrogate, rather than with the patient him/herself.

Unfortunately, the very surrogates who are supposed to protect and promote the patient's rights sometimes undermine those rights. For example, surrogates are often unable or unwilling to properly exercise substituted judgment and make the same treatment decisions that the patient would have made for him/herself if he/she had the capacity. Surrogates often do not know the patient's preferences. Moreover, even when they know the patients' preferences, surrogates sometimes fail to follow them faithfully. Sometimes, these are calculated decisions influenced by private gain or personal advantage. Other times, the surrogate lacks the capacity, or is encumbered by emotional or psychological barriers to ideal decision making [9].

Under those circumstances in which the surrogate's decision represents a material contradiction of or a substantial deviation from patient wishes or best interests, it is appropriate for the clinician to remonstrate or even challenge the surrogate. This is not an affront to patient rights. Rather, the clinician actually protects the patient's right to autonomy (informed consent) by challenging a surrogate who seems to be acting inconsistently with the patient's wishes [10].

Poor communication

Patient rights are also threatened by inadequate training or performance at the individual and system-wide level. In particular, poor communication both between team members, and between the team and the family is a common causal factor underlying adverse events. Critically-ill patients and their families have a unique set of issues and concerns that clinicians must address. Unfortunately, effective goals discussions are often confounded by late timing, poor communication, and lack of regularly implemented protocols [11].

Conflicts of interest

Patient rights are also threatened by clinicians' conflict of interest. Different reimbursement models can provide incentives and external pressures that influence the provision of critical care services. For example, a fee for service payment may encourage the overuse of medical procedures relative to patients' actual preferences, while capitated payment models may encourage undertreatment relative to patients' preferences [12].

Misrepresentation and coercion

Sometimes, clinicians engage in misrepresentation or coercion in order to obtain surrogate consent. This can violate the patient's rights to informed consent and treatment refusal. For example, some clinicians intentionally withhold information or prognosticate with varying degrees of certainty [13]. Others write 'slow codes' or 'show codes', the ethical and legal status of which remains unsettled. The risk of infringing patient rights is far greater where

the grounds are not explicit, because unspoken and illegitimate biases may be influencing behaviour.

Personal conscience-based objections

Critical care clinicians are also sometimes faced with situations in which they have a personal, moral objection to providing or disclosing information about a medical service, also known as a conscience-based objection. Such situations may be common in critical care due to the frequency of value-laden decisions with life and death consequences. For example, clinicians may have moral objections to disclosing information about the option of withdrawing nutrition and hydration, to offering or providing palliative sedation to unconsciousness, to participating in organ donation after cardiac death, or to providing advanced life support to patients with a poor prognosis [14].

There are numerous reasons to accommodate clinicians' conscience-based objections, such as by transferring care to an alternate clinician. Doing so allows the objecting clinician to preserve their moral integrity and to avoid moral harm associated with acting contrary to moral beliefs. It may improve medical quality at the population level by allowing a diverse clinical workforce, which is especially valuable in pluralistic society. Moreover, accommodating conscience-based objections may help identify needed changes in professional norms and practices.

However, it would be an illegitimate violation of patient rights if the clinician's CBO resulted in the patient not receiving legal, accepted medical services. Instead, clinicians should continue to provide treatment to the patient until an alternative provider can be found. Although doing so may impose a burden both on the clinician (e.g. feeling complicit in a treatment plan that violates their moral beliefs) and on the patient (e.g. the delays and inconvenience associated with transferring care to an alternate provider), this approach is a compromise that preserves respect for both clinicians' moral integrity and patients' right to legal, accepted medical services [15].

Legitimate infringement and distributive justice

While patient rights are sometimes unjustifiably violated, as mere *prima facie* claims, they are sometimes permissibly infringed. Rationing of critical care is both necessary and unavoidable. For example, it is common to transfer a patient out of an intensive care unit (ICU) when she still might derive some small benefit from ongoing monitoring. Such transfer accommodates the need of sicker patients in the face of a finite number of ICU beds [16].

Distributive justice refers to fairness in the distribution of limited resources. Fairness refers to giving equal treatment to all patients who are similarly situated with respect to relevant characteristics, but there are competing principles to guide such allocation—utilitarian, egalitarian, prioritarian, and the rule of rescue. Because reasonable people may be unable to agree on which principles should guide rationing, these should be determined through a fair process like that described in the section 'Balancing Patient Rights and Clinician Rights'.

Legitimate infringement and clinician rights

Patient rights may be infringed not only by the needs of the community, but also by the rights of clinicians themselves. Clinicians sometimes refuse to comply with patient treatment decisions either on the basis of professional integrity or on the basis of personal conscience-based objections.

Professional objections to medically-inappropriate treatment

Patients sometimes request treatments that either will not work or that clinicians believe are medically inappropriate under the circumstances. Often this is because the clinician judges that the potential benefit is either not probable enough or not great enough to be worthwhile. Clinicians may object to such treatment because they want to avoid patient suffering, to protect the integrity of the medical profession, to avoid moral distress, and/or to promote good stewardship [8,17].

Balancing patient rights and clinician rights

There are four leading mechanisms by which patient rights are balanced against clinician rights—prevention, mediation, established socially-accepted rules, and procedural due process.

Prevention

Clinicians should focus efforts on preventing treatment disputes between clinicians and surrogates, rather than focus on developing policies to manage such disputes once they occur. Most clinician–surrogate disagreements arise not from intractable value conflicts, but from inadequate communication and support in the face of the emotional and psychosocial difficulty of facing death. These conflicts can often be avoided by coordinating effective family meetings, providing family centred communication, and fostering shared decision making.

Mediation

While good preventative efforts can reduce the number of disputes, they will not eliminate conflict altogether. Fortunately, clinician–surrogate disputes are not generally intractable and can be resolved collaboratively through ongoing dialogue. Ethics consultants, social workers, chaplains, ethics committees, legal counsel, ombudspersons, and other hospital resources are quite effective at achieving consensus. Therefore, clinicians should focus on consensus building through counselling, negotiation, and mediation.

Established socially-accepted rules

If a dispute proves intractable, it should ideally be resolved by appeal to established, widely-accepted rules. Such rules (e.g. brain death, prioritization strategies for organ allocation) have normative weight in proportion to the degree that they are:

- Explicit.
- Developed with diverse input.
- Based on explicit, defensible reasons.
- Overseen by groups viewed as legitimate policymakers.

Unfortunately, very few rules have been developed for the types of situations (e.g. critical care for patients in a persistent vegetative state) that commonly produce intractable conflict.

Requests for treatment that the clinician believes is medically inappropriate should not be managed unilaterally, unless the requested intervention is the subject of one of these rules or would

be wholly ineffective at achieving the patient's goals. This is because judging whether a treatment, which could potentially achieve a patient's goals, is nonetheless inappropriate involves complex value judgments at the intersection of medicine, law, and ethics. Individual clinicians may lack the necessary expertise to independently manage such dilemmas. In addition, given substantial diversity in clinicians' attitudes about appropriate treatment near the end of life, allowing individual discretion risks unwarranted treatment variability in which similarly situated patients receive different treatment [18].

Procedural due process

In the absence of a widely accepted rule, when a surrogate requests treatment that the clinician believes is inappropriate, the dispute should be managed through a fair process of dispute resolution. Such a procedural resolution process does not force rigid, predetermined templates onto situations that are often complex and highly nuanced, and may be better addressed in an individualized way.

Such processes should conform to accepted principles of due process. First, the surrogate must be given adequate notice that a process-based resolution procedure has been undertaken, the steps involved in such a process, and the anticipated timeline. Secondly, the review should be undertaken by a multidisciplinary hospital committee that includes representative members of the community as active members. This committee's task is both to evaluate the clinician's judgment about whether the requested treatment is inappropriate and to oversee the remaining steps in the process. This committee should actively elicit the surrogate's input into the process. Thirdly, the clinician and facility should afford an opportunity for transfer to a willing provider. Finally, the surrogate must be afforded the opportunity to appeal the hospital committee's decision to an impartial third party, such as a court or other socially-sanctioned mechanism [19].

Conclusion

The physician charter on professionalism observes that medicine's commitment to patient rights is being challenged by external forces of change within our societies [20]. While patient rights are not absolute, clinicians must not override them without compelling reasons and through fair processes.

References

1. Hohfeld WN and Cooke WW (eds) (1919). *Fundamental Conceptions as Applied in Judicial Reasoning and Other Legal Essays*. New Haven, CT: Yale University Press.
2. Rainbolt G. (2006). *The Concept of Rights*. Dordrecht: Springer.
3. American Hospital Association (2003). *The Patient Care Partnership: Understanding Expectations, Rights, and Responsibilities*. Washington, DC: American Hospital Association.
4. American Medical Association Council on Ethical and Judicial Affairs (2012). *Code of Medical Ethics: Current Opinions and Annotations*. Chicago: American Medical Association.
5. Annas GJ. (2004). *The Rights of Patients: The Authoritative ACLU Guide to Patient Rights*. Carbondale, IL: Southern Illinois University Press.
6. Snyder L. (2012). American College of Physicians Ethics Manual, sixth edition. *Annals of Internal Medicine*, **156**, 73–104.
7. Beauchamp TL and Childress JF. (2008). *Principles of Biomedical Ethics*, 6th edn. New York, NY: Oxford University Press.
8. Pope TM. (2007). Medical futility statutes: no safe harbor to unilaterally stop life-sustaining treatment. *Tennessee Law Review*, **75**(1), 1–81.
9. Zier LS, Sottile PD, Hong SY, Weissfield LA, and White DB. (2012). Surrogate decision makers' interpretation of prognostic information: a mixed-methods study. *Annals of Internal Medicine*, **156**(5), 360–6.
10. Pope TM. (2010). Surrogate selection: an increasingly viable, but limited, solution to intractable futility disputes. *Saint Louis University Journal of Health Law & Policy*, **3**(2), 183–252.
11. Davis H and Hackner D. (2010). Early and effective goals discussions: a critical review of the literature. *ICU Director*, **1**(**3**), 155–62.
12. Dorman T and Pauldine R. (2007). Economic stress and misaligned incentives in critical care medicine in the United States. *Critical Care Medicine*, **35**(S2), S36–43.
13. Brush DR, Brown CE, and Alexander GC. (2012). Critical care physicians' approaches to negotiating with surrogate decision makers: a qualitative study. *Critical Care Medicine*, **40**(4), 1080–7.
14. Pope TM. (2010). Legal briefing: conscience clauses and conscientious refusal. *Journal of Clinical Ethics*, **21**(2), 163–80
15. Lewis-Newby M et al. (2015). An official American Thoracic Society policy statement: managing conscientious objections in intensive care medicine. *American Journal of Respiratory and Critical Care Medicine* **191**(2):219-27.
16. Scheunemann LP and White DB. (2011). The ethics and reality of rationing in medicine. *Chest*, **140**(6), 1625–32.
17. Pope TM. (2011). Legal briefing: medically futile and non-beneficial treatment. *Journal of Clinical Ethics*, **22**(3), 277–96.
18. Cook DJ, Guyatt GH, Jaeschke R, et al. (1995). Determinants in Canadian health care workers of the decision to withdraw life support from the critically ill. *Journal of the American Medical Association*, **273**(9), 703–8.
19. Delgado R, Dunn C, Brown P, Lee H, and Hubbert D. (1985). Fairness and formality: minimizing the risk of prejudice in alternative dispute resolution. *Wisconsin Law Review*, **1985**(6), 1359–404.
20. American Board of Internal Medicine Foundation, ACP-ASIM Foundation. American College of Physicians-American Society of Internal Medicine, and European Federation of Internal Medicine (2002). Medical professionalism in the new millennium: a physician charter. *Annals of Internal Medicine*, **136**(3), 243–6.

CHAPTER 27

Medico-legal liability in critical care

Michael A. Rie

Key points

- Malpractice law arose 1000 years ago from the ethic of fiduciary trust relationships in feudal monarchies of England and Europe.
- This 'Common Law' holds professionals accountable to the trust relationship (doctor–patient or team–patient) and not the beneficiary (patient).
- Legal accountability in democratic nations recognize widely divergent understandings of individual 'rights of consumption' in balance with judicially recognized transparent efficiency and health care outcomes.
- Efficient medical errors management is procedurally changing in 2012 as we move from expensive adversarial legal proceedings to medical disclosure, apology, and preventive settlement offer (Disclosure, apology and offer methodology).
- All critical care medicine (CCM) professionals should educate their respective judiciaries in preserving the ethical integrity of our profession, while preserving public trust in the fiduciary relationship.

Introduction

Contemporary critical care medicine is team-based care. Malpractice accountability and liability (under rule of law) arose from Plato and the Hippocratic tradition. Patient and physician freely met in a relationship of trust for the betterment of the patient's welfare. Neither was obligated to join the endeavour and each could withdraw without external constraint. Although resources were limited, Greek physicians avoided 'rescue' when patients were overmastered by their diseases [1].

To address malpractice negligence and professional accountability we should first ask who is the patient in the eyes of the judicial system, how that image may be changing, and what are the standards of care that society expects, while providing (or failing to provide) necessary resources to produce the care. The past generation has produced a migration of health policy from individual-centred finance and regulation to population-based financial distribution criteria, driven by evidence-based outcomes. Praiseworthy as such goals may be, they will fall short at legal challenge. Much of what we offer patients lacks clear evidence, often requiring unethical clinical trial designs or revision of marginal evidence prior trials [2,3]. The imbalance between the service demand for marginal outcome success and the societal ability to supply services not paid for by individuals produces moral strife of finitude [4,5]. Thus, national policy conflicts of interest are rendered to the patient care delivery level. Within this mayhem, patients and professionals continue to receive and deliver care. We should accept our role in defining limits of individual rights of consumption (under rule of law). Rights require balance with morally prioritized and defined minimal standards of care for those patients cared for by public funds. However, private ownership of money requires ability of the well off to buy more. Such a lawful multi-tiered system of health insurance was created in the Oregon Health Plan in the 1990s [6], and adopted by the Netherlands and other western democracies. Infrastructure for critical care implementation should soon emerge [6–9].

This chapter adopts classical medical ethics [10] as the historical source of judicial authority for professional fiduciary relationships. Developed in medieval times, fiduciary trust relationships define professional duty to the trust relationship and not the beneficiary (patient) [11–13].

Nations differ in judicial enforcement of critical care resource limitation policies when challenged by individual patients [14]. In New Zealand (with few intensive care unit (ICU) beds), the courts have consistently upheld the policies promulgated and adopted by professionals [15]. Such explicit finite resource allocation policies are not developed or codified in the USA or Germany [16] (where more ICU beds exist).

Clarity requires the elimination of politics, religion, national budgets, economic global recession, and other geopolitical sources from Common Law understandings. The English Common Law arose from property law and the creation of contract law (trusts) in the feudal period of absolute monarchy. Preceding creation of the seventeenth-century parliamentary system, the Common Law was retained as to contracts and trusts. Common Law originally applied to nobles responsible for collecting taxes for the King. If a noble died with the oldest son and heir still to be raised to adulthood, 'trustees' were responsible for preserving the estate, raising the future heir (landowner), and collecting the taxes. Failure to do so was held punishable by the King under rule of law. The rise of merchant trades and professions (law and medicine) were incorporated into the laws of contracts and trusts, and continue to the present. It is the courts that interpret the meaning of the patient–doctor relationships, including mutual obligations and limitations. These laws have undergone continuous and slow modification by the

courts as to the definition of obligations owed by physicians to the beneficiary (patient). The present population-based health care methodology remains to be reconciled with the Common Law in all countries that have adopted the Common Law. To better analyse judicial meanings of our fiduciary duties, we begin with the analogy of critical care teams as champion ballroom dancers or Olympic skating pairs. The changing nature of medical care, technology, and drug innovation has led to continuous improvements in the care of patients. What might have been 'standard practice' in year 1 would be obsolete and below the contemporary standard in year 50. However, honest discussions with patients and families would be constant over time eventually including entitlement limits to non-evidence-based service demands. As the ethical and legal foundation of 'professionalism' relies on the trust that individual patients, the public or political and governmental society have in their professionals, all of us and patients must be held to standards of champion ballroom dancers and skaters. We must perform in perfect harmony with patient(s) to achieve the best that can be hoped for and contextually framed by circumstances of resource finitude, innovation and the present state of medical science. However, professionals, health care systems, individual patients, and non-governmental mass demonstrations may not legally disrupt the size of the ballroom, skating rink, or how long the music plays.

This text appears during sustained global economic malaise. Professionals in national health systems (Canada, UK, France, Netherlands, Australia, New Zealand) and the complex American regulated free market all share the necessity to publically articulate intrusions upon professional integrity created by all forces external to fiduciary trust that are not transparent and publically accepted [10].

This ancient principle is clearly enunciated in the Common Law doctrine of the *Parens Patria* ('The State as Parent of the People'). A cornerstone of Common Law predating the American Constitution and British conversion from absolute monarchy to limited democracy, the doctrinal duties are:

- Prevention of homicide.
- Prevention of suicide.
- Protection of innocent third parties (e.g. wards of the state, children of Jehovah Witness parents forbidding necessary blood transfusions to minor children).
- Protection of the Ethical Integrity of the Medical Profession(s).

In this changing world of resources, budgets, and finite funds available for health care, it will be incumbent upon the institutions of health care and our organized medical leadership to articulate our integrity and how it may be threatened by greater societal forces. The need for transparency and the quest of evidence-based truth and its articulation will be the first step [17] necessary to preserve the integrity of medicine and 'critical care rescue medicine' in the coming years. When we lack evidence and rely on 'judgment and experience' in care delivery, it is our moral and legal duty to defend individual and group integrity for all branches of government and the public. When necessary, judicial review and protection may be necessary. Conversely, when we know or should have known that our integrity is threatened by external forces, we should presumably disclose them as a risk management issue beyond our direct control.

While governments differ in payment methodology for drug purchase, hospitals and professionals have experienced widespread shortages of generic injectable drugs that are daily mainstays of our standards of care (e.g. propofol, midazolam, fentanyl, norepinephrine) in the USA, Canada, and other countries, i.e. Greece. Despite obvious disruptions in care delivery procedure, drug errors, and the arrival of underground 'grey markets', professionals, health systems, and health system researchers have not reported the presumed identifiable morbidity and mortality risk, including system inefficiency costs of ongoing shortages. Until such data is disclosed, our professional integrity is at risk; we should have known our patients were at risk, as we passively allowed standards of care to decline.

Case examples over half a century

Case 1

In 1972, a healthy 25-year-old female suffered multi-trauma in a road accident and was admitted to an early trauma centre. Bleeding and intra-abdominal injuries were surgically controlled. Post-operative care for respiratory failure with bilateral chest injury and rib fractures required volume cycled mechanical ventilation with an Emerson Post-Operative Ventilator widely used at the time. Unpredictable and undetected acceleration of ventilator rate resulted in intrathoracic pressurization and bilateral tension pneumothorax with cardiac arrest. Following resuscitation she survived for several years with anoxic ischaemic encephalopathy.

Comment

A lawsuit ensued. Under civil law judicial rules, a breach of the 'standard of care' (legal negligence) requires plaintiffs to carry the burden of proof demonstrating evidence (with reasonable probability) that the defendant was responsible for the injury. An adversarial relationship that previously existed in other areas of negligence law was woven into the culture of medical liability disputes. In this case, causation was attributed to equipment malfunction. No ventilator rate monitors, saturation metres, or pressurization alarms existed. The plaintiff could find nothing in the patient's record mentioning technology failure. Hospital and medical personnel were not forthcoming with explanation of the event. Subsequent plaintiff review discovered an unsigned nurse's note at the cardiac arrest. When located, the nurse divulged that he had been admonished by the trauma surgical director not to come forward with information about what had transpired. When presented to a court of law as evidence, a private settlement followed.

Since the 1970s, the number of malpractice cases has increased with public awareness. In adversarial 'battle of the experts', courts and juries rely on the accuracy and completeness of information supplied by medical experts for either party. The result is costly and prolonged expenses for lawyers, expert witnesses, and insurers before the matters are settled or tried in court. While a minority of cases comes to trial, those privately settled consume vast amounts of resources [18]. Their data suggest that costs of malpractice litigation may be decreased by a new process best described as Disclose, Apologize, and Offer. First developed in Michigan [19], this process is now thought to result in decreased costs of litigation for all parties. Massachusetts (a state moving to system wide value based health care payments) announced a state-wide pilot programme of the non-adversarial approach [20]. The underlying assumption is

to increase patient trust in medical care while decreasing cost and promptly recompensing patients for real errors.

Case 2

In 2008, a 50-year-old woman was admitted to ICU with viral pneumonia. Hypoxaemic respiratory failure followed necessitating intubation and ventilator support. Mentation was stable when not sedated. As weaning was not possible at 2 weeks, a surgical tracheostomy was performed and she returned to the ICU with a stable airway and prior ventilator parameters. That evening, following a bed bath, the patient's nurse noted significant air leak from the tracheostomy and cervical subcutaneous emphysema with decline of tidal volume. A critical care physician examined the patient and ordered a chest X-ray and noted differential diagnoses of airway dislodgement and pneumothorax in the patient's record. The physician's duty shift terminated and he failed to report this patient's precarious situation to the night-time physician. Air leakage continued, the patient became unresponsive and tachycardic with desaturation on pulse oximetry for at least 1 hour. The covering physician was called and arrived during cardiac arrest finding ICU nursing staff bag ventilating the tracheostomy, while performing cardiopulmonary resuscitation. The physician replaced the tracheostomy with an endotracheal tube in a displaced trachea. No breath sounds were heard on the left and subcutaneous emphysema was prominent. A chest tube was placed once oxygenation and vital signs were re-established. The next day the surgeon re-established the tracheostomy within the prior intact tracheal incision. She survived in anoxic ischaemic coma with tracheostomy and gastrostomy in a chronic care centre.

Comment

Extensive review was conducted by experts for both parties. Hospital records showed no available policies and procedures for medical hand-offs in ICU. No policies and procedures consistent with contemporary hospital standards could be identified defining guidelines or parameters for calling physicians when ventilatory or vital function problems developed. Continuous electrocardiographic monitoring station and technician were present, but recordings could not be located for this sentinel event. Evidence was provided explaining the mechanism of airway dislodgement and its necessary re-establishment as the standard of care, which was not followed. One day before trial, the matter was privately settled. Such agreements typically contain non-disclosure secrecy provisions. Little is divulged to shed light on procedural migration to the non-adversarial proposed changes.

Conclusion

Comparing adversarial cases with the evolving disclosure, apology, and offer culture will take time and data. If there has been direct injury from a medical error in a negligence proceeding, the possibilities for improving the efficiency of negligence proceedings (cost containment) and recompensing injured patients promptly may become established. Challenges along the way may go to court by patients. Professionals may also seek court protection when the desired outcomes could not be produced. Resource deficiencies could then be demonstrated as evidence of system-generated invasions of professional integrity. The new frontier of justice is on the horizon.

References

1. Amundsen DW. (1978). The physician's obligation to prolong life: a medical duty without classical roots. *Hastings Center Report*, **8**(4), 23–30.
2. Rie MA and Kofke A. (2013). First critique of the fair and equitable health care act. In: Crippen DW (eds) *A Better Approach to Medical Malpractice Claims?* 1st edn, pp. 251–61. New York, NY: Springer Science + Business Media.
3. Ranieri VM, Thompson BT, Barie PS, et al. (2012). Drotrecogin alfa (activated) in adults with septic shock. *New England Journal of Medicine*, **366**(22), 2055–64.
4. Adamy J and McGinty T. (2012). The crushing cost of care. *Wall Street Journal*, July 7, C1. Available at: http://www.wsj.com/articles/SB10001424052702304441404577483050976766184 (accessed 28 October 2015).
5. Engelhardt HT and Rie MA. (1986). Intensive care units, scarce resources and conflicting principles of justice. *Journal of the American Medical Association*, **255**(9), 1159–64.
6. Rie MA. (1995). The Oregonian ICU: multi-tiered monetarized morality in Health Insurance Law. *Journal of Law, Medicine & Ethics*, **23**(2), 149–66.
7. Strosberg MA, Wiener JM, and Baker, R. (1992). *Rationing America's Medical Care: The Oregon Plan and Beyond*, 1st edn. Washington, DC: Brookings Institution Press.
8. Crippen DW. (2013). *ICU Resource Allocation in the New Millenium: Will We Say No?* 1st edn. New York, NY: Springer Science + Business Media.
9. Rodwin MA. (2011). *Conflicts of Interest and the Future of Medicine: The United States, France, and Japan*, 1st edn. Oxford: Oxford University Press.
10. Truog RD. (2012). Patients and doctors—the evolution of a relationship. *New England Journal of Medicine*, **366**(7), 581–5.
11. Rodwin MA. (1993). *Medicine Money and Morals: Physician Conflicts Of Interest*. 1st edn. Oxford: Oxford University Press.
12. Kofke WA and Rie MA. (2003). Research ethics and law of healthcare system quality improvement: the conflict of cost containment and quality. *Critical Care Medicine*, **31**(3 Suppl.), S143–52.
13. Rie MA and Kofke WA. (2007). Nontherapeutic quality improvement: the conflict of organizational ethics and societal rule of law. *Critical Care Medicine*, **35**(2 Suppl.), S66–84.
14. Wunsch H, Angus DC, Harrison DA, et al. (2008). Variation in critical care services across North America and Western Europe. *Critical Care Medicine*, **36**(10), 2787–93.
15. Streat, S. (2013). Where have we been in New Zealand critical care? In: Crippen, DW (ed.) *ICU Resource Allocation in the New Millenium: Will We Say No?* 1st edn, pp. 65–74, 161–8. New York, NY: Springer Science + Business Media.
16. Crippen DW. (2013). The Fair and Equitable Health Care Act. In: Crippen, DW (ed.) *ICU Resource Allocation in the New Millenium: Will We Say No?* 1st edn, pp. 247–50. New York, NY: Springer Science + Business Media.
17. Mancebo J and Hall J. (2012). Is the doctor in? Views on the deployment of intensivists from both sides of the Atlantic. *American Journal of Respiratory Critical Care Medicine*, **185**(7), 696–7.
18. Studdert DM, Mello MM, Gawande AA, et al. (2006). Claims, errors, and compensation payments in medical malpractice litigation. *New England Journal of Medicine*, **354**(19), 2024–33.
19. Boothman RC, Blackwell AC, Campbell DA Jr, Commiskey E, and Anderson S. (2009). A better approach to medical malpractice claims? *Journal of Health & Life Sciences Law*, **2**(2), 125–59.
20. Beaulieu D. (2012). Disclosure, apology and offer: a new approach to medical liability. *Vital Signs*, **17**(6), 1–3.

PART 1.8

Critical illness risk prediction

CHAPTER 28

The role and limitations of scoring systems

Hannah Wunsch and Andrew A. Kramer

Key points

- Severity of illness scores are frequently used in critical care settings to describe patients.
- The most common severity of illness scores use patient data from the first hour to 24 hours immediately after admission to the intensive care unit (ICU) to predict short-term outcomes, such as hospital mortality.
- Severity of illness scores are extremely useful for comparing risk-adjusted outcomes between ICUs, as well as within an ICU over time.
- The use of severity of illness scores must be tempered by the inherent limitations of current systems, including variable performance outside of derivation cohorts, inability to accurately predict outcomes for individuals, and performance decline over time.
- Future systems may include the prediction of long-term outcomes and assimilation of granular data temporally, and at the molecular level that could result in more personalized severity scores to help guide individual care decisions.

Introduction

The concept of scores that provide information on the severity of illness for critically-ill patients and allow for comparison of outcomes between different cohorts of patients is now over 30 years old. The field of critical care has seen a proliferation of scores since then [1–4]. The majority of these scores use information gleaned from patient status on admission or within 24 hours post-admission to the intensive care unit (ICU). Either the severity score itself, or components of the score, can then be used in multivariable models that predict duration of stay or mortality at the end of the acute hospitalization. This chapter describes the most common general ICU scores that were initially developed to predict short-term mortality, uses of these scores, limitations, and future directions.

Main scoring systems in use for intensive care

General ICU scoring systems are complex to develop and require periodic updating. As a result, there are only a few scoring systems in general use today (see Table 28.1). The oldest system is the Acute Physiology and Chronic Health Evaluation (APACHE) score. Created in the 1980s and updated intermittently, APACHE's main score is made up of three components: the Acute Physiology Score (APS), age, and chronic health items indicative of severe underlying disease. The most current published version is APACHE IV [1]. An earlier version, APACHE II, is still widely used [5], probably due to its free availability, as well as its previous application in determining eligibility for recombinant activated protein C use in US patients with severe sepsis [6]. However, the accuracy of APACHE II for contemporary ICU populations is equivocal [7].

The Simplified Acute Physiology Score (SAPS) was initially developed in Europe as an alternative to APACHE's complexity [2]. While using many of the same data items as APACHE's APS, the SAPS requires the worst physiologic value within the first hour post-admission, rather than the first 24 hours, as in APACHE. The Mortality Probability Model (most recently MPM0-III) was developed using USA ICU data from the Project IMPACT database [3]. Like SAPS, variables used to generate an MPM prediction are captured within the first hour after admission to the ICU. Of the equation's 16 variables, 15 are binary responses to items representing a patient's condition, and one continuous variable (age). The idea behind MPM was to arrive at a predictive model that could easily be implemented. Finally, the United Kingdom has its own severity of illness system (ICNARC score), developed using information from National Health Services ICUs in England, Wales, and Northern Ireland [4]; the ICNARC score is very similar to APACHE.

All of the systems except for MPM rely heavily on physiology. APACHE IV and ICNARC have substantially more diagnostic categories than the other systems. The number and type of outcomes that are predicted also differ; most (APACHE II, SAPS, and ICNARC) predict only hospital mortality; MPM also has an equation to measure weighted hospital days. APACHE IV has equations for predicting hospital and ICU mortality, hospital and ICU length of stay, duration of mechanical ventilation, and need for active therapy. As well as generating a score for general use, SAPS 3 also provides different weights for the equation that can be applied in individual regions of the world.

The majority of scores were developed on very large cohorts (>100,000) of ICU patients. While APACHE, MPM, and ICNARC were all developed on data from a single country, the development of SAPS 3 included admissions from ICUs in 35 countries. Other than APACHE II, each system currently in use was developed within the past 10 years, with fairly similar exclusion criteria (Table 28.2). Most notably, the majority of these scoring systems cannot be applied to cardiac surgery patients or burn patients.

Table 28.1 Selected information collected for APACHE II and the most recent versions of the APACHE, MPM, SAPS, and ICNARC scoring systems

	APACHE II [5]	APACHE IV [1]	MPM_0-III [3]	SAPS III [2]	ICNARC [4]
Age	Yes	Yes	Yes	Yes	Yes
Type of patient (medical/surgical or planned/unplanned)	Yes	Yes	Yes	Yes	Yes
Co-morbidities (#)	Yes (5)	Yes (7)	Yes (3)	Yes (14)	Yes (6)
Location prior to ICU admission	No	Yes	No	Yes	Yes
Length of hospital stay prior to ICU admission	No	Yes	No	Yes	Yes
Cardiopulmonary resuscitation prior to admission	No	No	Yes	No	Yes
Mechanical ventilation within the first hour or first 24 hours	No	Yes, 24 hours	Yes, 1 hour	No	Yes, 24 hours
Disease categories (#)	Yes (50)	Yes (433)	Yes (6)	Yes (39)	Yes (709)
Physiology measurements					
Vital signs	Yes	Yes	HR and MAP	All but RR	Yes
Arterial blood gases	Yes	Yes	No	Yes	Yes
Glasgow coma score	Yes	Yes	Yes	Yes	Yes
Albumin	No	Yes	Yes	No	No
Bicarbonate	Yes	No	No	No	Yes
Bilirubin	No	Yes	No	Yes	No
Blood urea nitrogen	No	Yes	No	No	Yes
Creatinine	Yes	Yes	No	Yes	Yes
Glucose	No	Yes	No	No	Yes
Haematocrit or haemoglobin	Yes	Yes	No	No	Yes
Lactate	No	No	No	No	Yes
Platelet count	No	No	No	Yes	Yes
Potassium	Yes	No	No	No	Yes
Sodium	Yes	Yes	No	No	Yes
Urine output	No	Yes	No	No	Yes
White blood cell count	Yes	Yes	No	No	Yes
Outcomes predicted					
Hospital mortality	Yes	Yes	Yes	Yes	Yes
ICU mortality	No	Yes	No	No	No
Hospital length of stay	No	Yes	No	No	No
ICU length of stay	No	Yes	Modified*	No	No
Duration of mechanical ventilation	No	Yes	No	No	No
Need for active therapy	No	Yes	No	No	No
Daily mortality predictions	No	Yes	No	No	No

*Weighted hospital days: weights ICU days more than days on acute care floor.

HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate.

Data from various sources (see references).

Other scoring systems: organ-specific, therapeutic, and disease-specific

Other types of scoring systems focus on organ-specific information that can be examined as a trend to assess the trajectory of a patient, or number and types of interventions required—either as the predictor or outcome [8–10]. Two scores in particular, the Multiple Organ Dysfunction Score (MODS), and the Sepsis-Related Organ Failure Assessment (SOFA) score, include information that characterizes specific organ dysfunction or failure, and may be assessed at multiple times during the ICU stay [8,9]. The benefit of these scores is that they provide more specific information regarding

individual organ function. However, they were not developed to be used as a general scoring system across all critically-ill patients. The Therapeutic Intervention Scoring System (TISS) first developed in 1974 [11], and then simplified to the TISS-28 [10] takes a different approach, focusing on quantifying nursing activities for patients in the ICU, with the idea that the workload required to care for patients is a measure of the severity of illness. Other types of scores help assess the risk of an event occurring, such as prediction of need for organ support in intensive care [12], or may be disease-focused, such as the Ranson criteria for acute pancreatitis [13].

Model performance and use

Model accuracy can be measured in two ways—discrimination and calibration. The former gauges how well a model predicts mortality. It is usually assessed by calculating the area under the receiver operating characteristic curve (AUROC) [14]. This statistic is based on randomly sampling all pairs of patients in which one patient died and another survived. The percentage of pairs in which the patient not surviving has a higher probability of mortality than the surviving patient is the AUROC. All of the models described had an AUROC value >0.80 (good to excellent) for predicting mortality (Table 28.2) [1–5]. APACHE IV and ICNARC had the highest AUROCs, probably due to using single-country data, inclusion of diagnostic group information, and inclusion of physiology variables gathered from data over 24 hours.

Calibration measures the extent to which a model accurately predicts probability across a population. There are many ways of assessing calibration, including the Standardized Mortality Ratio (SMR), graphs of observed versus predicted probability, the Hosmer–Lemeshow statistic, and the Brier score. All of the models described had acceptable levels of calibration when applied to the patient population in which the model was developed.

Severity of illness scoring systems can be used in a variety of ways. Their most frequent use is as a variable in predictive models, which are then employed in benchmarking efforts. For example, hospital mortality for patients in an ICU may be evaluated by taking the number of deaths over a specific time period and dividing that by the predicted number of deaths over the same period (SMR). The SMR for an ICU can be tracked over time to evaluate an ICU's performance. This kind of analysis is usually used for internal quality initiatives. Alternatively, ICU SMRs can be compared with each other to assess comparative effectiveness.

Scoring systems are also used as a descriptive comparator across patient groups in research studies. Most commonly, the severity of illness scores are then included in multivariable models as a method of adjusting for any differences in the severity of illness between groups in studies. The severity score is usually highly significant and, therefore, in outcomes studies the inclusion of case mix adjustment is strongly advised. Finally, the severity of illness scores have sometimes been used as a stratification variable in randomized clinical trials to ensure balanced groups.

Limitations of scoring systems

Scoring systems have many uses, but they also have limitations that must be recognized. Each scoring system attempts to balance the number and type of variables against the accuracy of the prediction. While addition of variables may improve a predictive model,

Table 28.2 Patient populations used to develop current severity of illness scoring systems

	APACHE II	APACHE IV	MPM-III	SAPS 3	ICNARC
Dates of admission to ICU	1982 primarily	2002–2003	10/2001–3/2004	10/2002–12/2002	12/1995–8/2003
No. of admissions	5815	120,345	124,885	16,784	216,626
Location of patients	United States	United States	United States	35 countries	England, Wales, and Northern Ireland
No. of hospitals	13	45	98	NA	NA
No. of ICUs	19	103	135	303	163
Discrimination accuracy (AUROC)	0.86	0.88	0.82	0.85	0.87
Excluded patients					
Age	<16 years	<16 years	<18 years	<16 years	None
Cardiac diagnosis	CABG patients	None. CABG patients get separate set of predictive equations	Cardiac surgery, acute myocardial infarction	No	No
Burns	Yes	Yes	Yes	Yes	No
Transplants	Yes, except kidney not excluded	Yes, except liver and kidney not excluded	No	No	No
Other	Missing any physiology values. ICU stay <8 hours	ICU length of stay <4 hours	None	None	None

CABG, coronary artery bypass grafting; AUROC, area under the receiver operating characteristic curve.

Data from various sources (see references).

this is offset by the increased data burden necessary to collect that information. All of the scores require accurate data collection on a range of variables associated with an individual patient, which can be a time-consuming process and may require some training [15]. The adoption of electronic medical records may improve the ability to gather these data in a more timely fashion, but this process is still hampered by differences in electronic systems and variations in data input.

Severity scores were initially developed to predict in-hospital mortality. However, changes have occurred in critical care over the past two decades that can affect the measurement of in-hospital mortality as an endpoint. Most prominent is an increase in the discharge of patients to post-acute care facilities [16]. Appreciable mortality occurs well after patients are discharged alive from the hospital and may still be related to the critical illness [17]. For example, in the USA some critically-ill patients—many of whom may still be ventilated and/or requiring vasopressors or inotropes—are now discharged to long-term acute care facilities [16]. These changes in practice may significantly shift reported hospital mortality and SMRs [18].

Current predictive models using severity scores were developed to be applied to groups of patients. Although the accuracy of these systems is quite good at the cohort level, they are not intended for assessing an individual patient's course. This weakness is borne out in head-to-head studies of predictions by clinicians and scores, where the clinicians were equal to or more accurate than the models [19].

The performance of current predictive models on patient populations outside of the cohort used for development (external validity) is modest to poor. Calibration, the accuracy of a model over a patient cohort, usually suffers. As a result the ability to compare risk-adjusted outcomes for patients across different regions or countries is compromised. The SAPS 3 scoring system provides different equations for different regions. While this approach may allow for broader use of the score globally, it still does not address this limitation of comparison between regions.

Finally, even well calibrated models tend to show 'fade' over time [20], most likely due to a combination of changes in case mix and the delivery of care that shift patient mortality. Models, therefore, require recalibration periodically to ensure that the predictions remain robust.

Future possibilities for scoring systems

There are a number of directions that research into scoring systems may move to accommodate changes in the field of critical care. The first is recognition of the continued increased risk of both morbidity and mortality after hospital discharge, leading to new interest in risk prediction models that use end-points such as 6-month mortality, or focus on patient populations that are likely to have high long-term morbidity and mortality. Secondly, current scoring systems implicitly assume that patients are identical in their reaction to physiological distress and response to subsequent treatment. Adding genetic and other molecular markers may result in predictions that are patient-specific in their scope. A final change may be continuous assessment of physiology—incorporation of data from earlier in an illness/hospitalization, updates of predictions as the course of critical illness evolves to allow for adjustment of the original prediction, and assessment of real-time data for overall change and variability across time.

References

1. Zimmerman JE, Kramer AA, McNair DS, and Malila FM. (2006). Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Critical Care Medicine*, **34**(5), 1297–310.
2. Moreno RP, Metnitz PG, Almeida E, et al. (2005). SAPS 3—from evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Medicine*, **31**(10), 1345–55.
3. Higgins TL, Teres D, Copes WS, Nathanson BH, Stark M, and Kramer AA. (2007). Assessing contemporary intensive care unit outcome: an updated Mortality Probability Admission Model (MPM0-III). *Critical Care Medicine*, **35**(3), 827–35.
4. Harrison DA, Parry GJ, Carpenter JR, Short A, and Rowan K. (2007). A new risk prediction model for critical care: the Intensive Care National Audit & Research Centre (ICNARC) model. *Critical Care Medicine*, **35**(4), 1091–8.
5. Knaus WA, Draper EA, Wagner DP, and Zimmerman JE. (1985). APACHE II: a severity of disease classification system. *Critical Care Medicine*, **13**(10), 818–29.
6. Abraham E, Laterre PF, Garg R, et al. (2005). Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *New England Journal of Medicine*, **353**(13), 1332–41.
7. Zimmerman JE and Kramer AA. (2008). Outcome prediction in critical care: the Acute Physiology and Chronic Health Evaluation models. *Current Opinion in Critical Care*, **14**(5), 491–7.
8. Vincent JL, Moreno R, Takala J, et al. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Medicine*, **22**(7), 707–10.
9. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, and Sibbald WJ. (1995). Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Critical Care Medicine, **23**(10), 1638–52.
10. Miranda DR, de Rijk AB, and Schaufeli WP. (1996). Simplified Therapeutic Intervention Scoring System: the TISS-28 items—results from a multicenter study. *Critical Care Medicine*, **24**(1), 64–73.
11. Cullen DJ, Civetta JM, Briggs BA, and Ferrara LC. (1974). Therapeutic intervention scoring system: a method for quantitative comparison of patient care. *Critical Care Medicine*, **2**(2), 57–60.
12. Zimmerman JE and Kramer AA. (2010). A model for identifying patients who may not need intensive care unit admission. Journal of Critical Care, **25**(2), 205–13.
13. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, and Spencer FC. (1974). Prognostic signs and the role of operative management in acute pancreatitis. *Surgery, Gynecology & Obstetrics*, **139**(1), 69–81.
14. Hanley JA and McNeil BJ. (1982). The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*, **143**(1), 29–36.
15. Polderman KH, Jorna EM, and Girbes AR. (2001). Inter-observer variability in APACHE II scoring: effect of strict guidelines and training. *Intensive Care Medicine*, **27**(8), 1365–9.
16. Kahn JM, Benson NM, Appleby D, Carson SS, and Iwashyna TJ. (2010). Long-term acute care hospital utilization after critical illness. *Journal of the American Medical Association*, **303**(22), 2253–9.
17. Wunsch H, Guerra C, Barnato AE, Angus DC, Li G, and Linde-Zwirble WT. (2010). Three-year outcomes for Medicare beneficiaries who survive intensive care. *Journal of the American Medical Association*, **303**(9), 849–56.
18. Hall WB, Willis LE, Medvedev S, and Carson SS. (2012). The implications of long-term acute care hospital transfer practices for measures of in-hospital mortality and length of stay. *American Journal of Respiratory and Critical Care Medicine*, **185**(1), 53–7.
19. Sinuff T, Adhikari NK, Cook DJ, et al. (2006). Mortality predictions in the intensive care unit: comparing physicians with scoring systems. Critical Care Medicine, **34**(3), 878–85.
20. Kramer AA. (2005). Predictive mortality models are not like fine wine. *Critical Care*, **9**(6), 636–7.

CHAPTER 29

Severity of illness scoring systems

Graeme K. Hart and David Pilcher

Key points

- Severity of Illness Scoring Systems enable meaningful comparisons, and identify 'similarities' within patient cohorts or across diverse care settings.
- It is important to understand the strengths and biases of the available models when selecting a model for a given audit or research purpose.
- Worst in 24-hour models have potential for poorly performing units to have higher severity of illness indices and, hence, lower (better) standardized mortality ratios.
- Large 'big data' administrative data sets may prove useful and with accurate data linkage to intensive care unit (ICU)-based datasets can provide cost-effective longer-term (30–90 days or greater) outcomes.
- The use of risk adjustment models by clinical quality registries or government regulators for hospital peer review and quality assurance is important, but must recognize that statistical signals only identify a potential problem and data quality must be carefully validated before conclusions can be reached.

Introduction

Inter-group comparisons are central to medical science in randomized controlled trials, performance comparisons between hospitals and clinicians, or in assessing changes to care processes within an institution. Case mix and severity adjustment is critical for meaningful understanding. No adjustment system is perfect, and understanding their strengths and limitations helps avoid erroneous conclusions.

Severity of illness scoring and outcome modelling of patients in the groups being compared are used to ensure appropriate adjustments. Selecting the correct outcome measure is important as not all measures have equal reliability, ease of measurement, or validity. Comparators used in health care systems include physical or activity metrics such as institutional size, academic role, procedure numbers (oesophagectomy, prostatectomy, whipples, cardiac surgery), uptake of electronic health records, and case mix. Critical care comparators are based more on the characteristics of the patients than those of the institution, although the latter may be relevant when comparing outcomes across international and social system boundaries. In general, all patients with the same illness should receive the same chance of a good outcome, regardless of their socio-economic standing or care setting. To this end, critical illness scoring systems do not contain elements in the models for these parameters. This is to enable research studies or quality improvement activities to be conducted on an international scale and for systems performing less well to 'benchmark' themselves against others. Pragmatically, care settings within each 'region' compare themselves to peers to promote improvement within given constraints.

Severity of illness scoring systems are most commonly applied in three settings:

- **Randomized controlled clinical trials**: internationally validated scoring systems facilitate the balancing of severity of illness between treatment arms to ensure inadvertent bias does not corrupt the study outcome.
- **Clinical quality data registries**: several regional or national registries have been established to provide quality assurance and peer review of critical care unit performance within their jurisdictional governance frameworks (ANZICS CORE, ICNARC, Dutch National Intensive Care Registry, NICE). Registries use risk-adjustment models to provide meaningful comparisons and identify sites where statistical variation may identify outlier performance requiring further investigation.
- **Quality assurance and improvement**: assessment of an intensive care unit's (ICU's) performance over time depends on the ability to adjust for illness severity and, hence, identify other factors impacting outcomes, such as specific quality improvement interventions or structural change.

Severity scoring systems measure only one attribute of unit performance (ICU or hospital mortality) and other measures of quality and performance may be equally important. Current scoring systems do not measure quality of life, or survival past ICU or hospital discharge.

Severity of illness scoring systems

Systems must ensure the population of interest is clearly defined, a statistical sample size in the development model that provides adequate power, model components that are meaningful for the comparisons to be undertaken, and model elements free of potential for systematic bias that are freely available as part of the care process and represent the impact of the illness as distinct from the impact

of treatment. The individual elements must be robust in their measurement and likely to be used over long time periods. In order to be useful, appropriate training and data quality systems must be in place to ensure acceptable and consistent use of the model.

Models must be validated in diverse settings and purposes to which they will be applied. Periodic recalibration ensures that they remain relevant and adapt to the impact of evolving case mix on the calibration of the model [1,2]. Another area of potential bias in the models relates to the scope of the models prediction. Assessment of mortality at ICU discharge (Simplified Acute Physiology Score (SAPSII)), versus hospital discharge (Acute Physiology and Chronic Health Evaluation (APACHE) II, III, IV) versus 3-month outcomes, allows variation in discharge practice to impact measured performance [3]. As ICU resources are scarce and expensive, there are pressures to discharge patients to the lowest cost care location that can manage them. Patients may be discharged from ICU to die on the ward or at palliative care locations. Survivors may be discharged to long-term ventilation facilities in some countries and, hence, survival or length of stay may be improved compared with countries where such facilities do not exist. Determining impact of ICU care on mortality may be significantly affected by these practices, and will change over time and between hospitals, regions, and countries. The impact of disease processes on ultimate survival can be immediate or long term and there is value when determining trial outcomes or cost effectiveness to examine outcome over longer time periods. This is generally expensive to achieve, however, where there is access to state death registries, this is more easily achieved through data linking technologies. Outcomes also vary depending on the primary disease and are predicted by Organ Failure Scores and APACHE [4]. In cardiac surgical cohorts, the hospital discharge mortality and the 30-day mortality were almost identical with only a 0.6% increase in deaths between the two measures. Mortality at 90 days increased further to 0.9% [5].

APACHE (I–IV)

The work of Knaus et al. [6], at George Washington University, pioneered severity adjustment in the critical care environment. Successive iterations of the APACHE model have refined diagnostic classifications, definitions, and process descriptors, and larger samples in the logistic regression models have increased reliability. The initial APACHE system was developed in five hospitals in the USA with 795 patients in the development set. APACHE IV, by contrast, used 110,558 patients in 45 USA hospitals. The APACHE IV model was derived from ICUs using the APACHE III computerized data collection and analysis system acquired by Cerner Corporation of Kansas City, Missouri, USA. Criticisms of the APACHE III and IV models included commercial ownership, continuous computer-based physiology variable acquisition (increases the score by up to 25% [7] and use of 'worst in 24-hour variables'), rather than admission values. Lead time bias refers to treatment-related changes in physiology to bias results. Poorly-performing units, paradoxically, may have 'sicker' patients and an improved Standardized Mortality Ratios (SMR) [8]. Although APACHE II score is still used in many studies, APACHE II risk of death for routine benchmarking of ICU outcomes is inappropriate, not least because of the dramatic increase in minimally-invasive surgery, which is not represented in the classification framework or prediction algorithm, and lack of recalibration. APACHE III was the first version of the model to include cardiac surgery and persisted with worst in 24 hours post-admission physiology variables. There are 78 diagnostic categories and 20 physiological variables. It was derived in 40 US hospitals from 17,440 consecutive patients. APACHE III has had multiple revisions of its prediction algorithm.

APACHE IV

APACHE IV [9], which expanded and modernized admission diagnoses, included additional pre-admission variables and broadened the range of locations and settings (104 ICUs in 45 North American hospitals, 110,558 admissions in 2002–2003). It uses a non-linear regression model with four spline terms.

SAPS 2

The Europeans, led by Jean Roger Le Gall, aimed to develop and validate predictive models for medical and surgical patients with greater international validity [10]. The models are based on the hospital outcome of 13,152 consecutively-admitted adults (65% development and 35% validation). It uses 17 variables—12 physiology, age, admission type, and three co-morbidities. The sample was derived from 137 units in 12 countries. Areas of potential bias relate to the self-selection of the contributing units, although the performance as judged by the area under the ROC curve was 0.86.

SAPS 3

SAPS 3 updated predictive models and increased international validity [11]. Both ICU and hospital outcome models were developed in 2002 from 19,577 consecutively admitted patients, over age 16, from 307 units in 35 countries. Contributing ICUs were self-selected.

Australian and New Zealand Risk of Death Model

The Australian and New Zealand Risk of Death Model [12] was recently published and derived using 450,000 adult admissions at 140 ICUs in Australia and New Zealand. In contrast to other scoring systems, the only patients excluded are those whose reason for admission to ICU is for palliative care or organ donation. It also employs eight separate prediction equations (one for each major diagnostic group), which allow more appropriate weighting of components (e.g. a higher weighting for Glasgow Coma Score in neurological and trauma patients than in post-operative cardiac surgery patients).

Mortality Prediction Model

Mortality Prediction Model (MPM) was introduced in 1985 and was cognisant of the potential for gaming by developing both admission and 24-hour models. It excluded patients <14 years old, and those admitted for cardiac surgery, coronary care, or burns. The development data was collected in one country from 755 consecutive patients. The MPM0 (admission) model uses seven variables. The MPM24 (24-hour) model used data from 458 patients still in the ICU 24 hours after admission.

MPMII

MPMII is the revised 1993 model [13] developed in patients from 12 countries. There were 12,610 in the development, and 6514 in the validation cohorts, which excluded patients <18 years, and those admitted for cardiac surgery, coronary care, or burns.

The $MPMII_0$ (admission) model uses 15 variables, is treatment independent, and avoids single principle diagnosis categorization. The MPM_{24} (24-hour) model was designed to update the prediction for longer-term ICU patients who are 'different' to those being discharged earlier. It contains five of the admission variables and eight additional variables easily ascertained at 24 hours.

Therapeutic Intervention Severity Score

The ability to reduce treatment bias in the first 24 hours post-ICU admission was raised as one of the benefits of the MPM0 scoring system. Poor ICU performance resulting in worsened physiology could increase the severity score and, hence, paradoxically improve the standardized mortality ratio. Some of the earliest work on severity of illness modelling and resource utilization was based on the therapeutic interventions required to maintain physiological stability as markers of severity. If high doses of inotrope were required to maintain blood pressure, a score based on the dose requirement may actually be more reliable than the blood pressure measure in its own right. This premise was used to develop the Therapeutic Intervention Severity Score, TISS-76, in 1974, which was updated in 1983, incorporating newer interventions and its subsequent simpler version TISS-28 [14]. This system has been used not only for outcome prediction, but also for nursing acuity and activity measures, staffing allocation, and predicting the safety and reliability of discharge from the ICU.

Administrative datasets for use in risk prediction and stratification

Dependence on manual data collection and entry carries risk of inter-rater reliability, systematic data collection bias, training overheads, and cost. Clinical information systems enable automated or semi-automated data entry, but may introduce other problems [7] and require vendors to co-operate for submission to regional clinical quality registries, update prediction algorithms and calculations. Non-'ICU specific' data models supplement ICU-based systems. Administrative databases use abstracted medical records coded after discharge. Intensive care risk prediction modelling can be performed on such data with some degree of confidence. The Critical Care Outcome Prediction Equation (COPE) was developed using ICD10-AM codes for hospital admissions with ICU hours recorded in the Victorian Department of Health Administrative Episode Dataset (VAED). The Area under the Receiver Operator Curve ROC Curve for risk adjusted survival is 0.82 after stratification for hospital level (tertiary, community, regional) [15]. Prerequisites for using administrative data include robust governance around data acquisition standards and audit excluding 'gaming' (as these systems are used for hospital funding). Where funding is based on coding, data quality audits by funding authorities ensure reliability. Such data has been used to demonstrate improved system wide outcomes of critical care interventions such as medical emergency teams (MET) over multiyear periods [16]. Administrative data (death register) set linkages can also enrich ICU risk adjustment models by follow-up to specific censor dates/date of death [4].

Cardiac surgery

Linked Veterans Health Administration and New York Cardiac Revascularization Registry data were used to develop multi-logistic regression models for risk-adjusted outcomes [17]. This model examined potential outcome and cost benefits of directing Veterans to 'High volume, Low mortality' hospitals. The Danish Heart Register (DHR) analysed 7 years of administrative information from the DHR (operation type, comorbidities), the Danish National Patient Register (previous 12 months admissions for specific cardiovascular, metabolic, renal, and pulmonary conditions), and the Centralized Civil Register for long-term mortality outcomes. A multilogistic regression model using 20,078 patients was developed. The additive EuroSCORE predictions contained in the DHR were compared with the new model, which was found to be comparable or slightly better [18].

Organ failure scoring

In the early to mid-1990s, more detailed examination of specific organ system dysfunctions were developed for both sepsis research and mortality outcome prediction. In Europe, the Logistical Organ Dysfunction System, in Canada the MultiOrgan Dysfunction Score [19], and subsequently the Sequential Organ Failure Assessment Score (SOFA) from Europe. Each system had some variations in definitions, and SOFA appears to have become the predominant model in current day use.

SOFA score

The SOFA score [20] was developed to enhance the assessment and time course analysis of critical illness organ dysfunction over the course of illness. Derived from 1449 patients in 40 adult ICUs in 16 countries, during May 1995, patients staying less than 48 hours or after elective surgery were excluded. This study assisted in the description of the time course of organ system deterioration or recovery in critical care illness. The median length of stay was 5 days, mortality 22%. Sepsis-based admissions had higher mortality (28.7%) and in the 544 patients with an ICU stay longer than 1 week, the increase of organ failure score predicated higher mortality rates.

Graphical techniques to identify performance trends and statistical outliers

Severity of illness scoring systems facilitate the comparison of mortality outcomes for an ICU. Graphical displays facilitate understanding of complex statistics. For appropriate analysis of the data, the risk adjustment model should be well calibrated, and the graph should be easily understood by the reader and lead to consistent conclusions. There are two broad types:

- **Cross-sectional risk adjusted charts** (e.g. Funnel Plots and League Tables): SMRs (the number of observed deaths divided by predicted deaths derived from a scoring system) of a group of ICUs are plotted.
- **Continuous charting methods** (e.g. risk-adjusted sequential probability ratio test charts and risk-adjusted exponentially weighed moving average charts) Sequential mortality outcomes of patients are plotted and compared with predicted mortality derived from a scoring system.

Common examples are shown in Fig. 29.1.

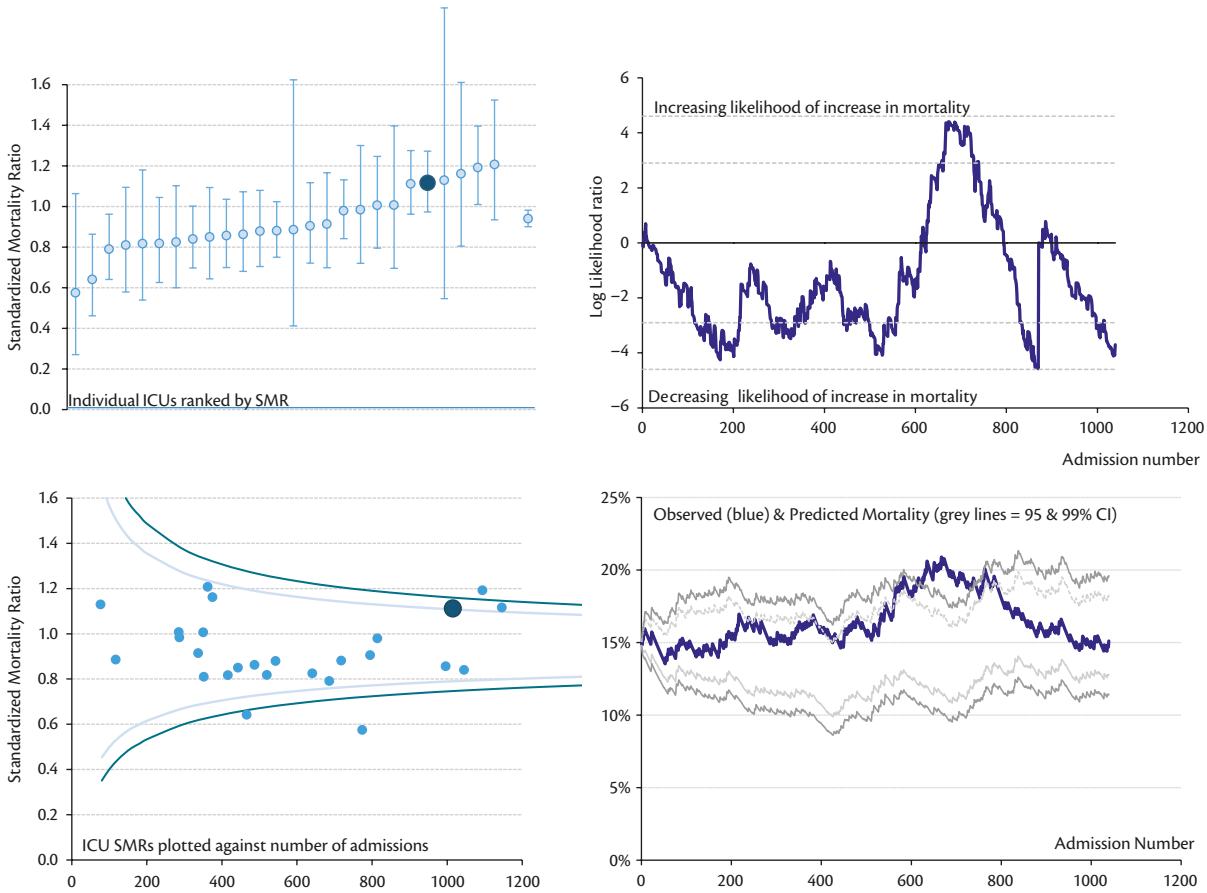


Fig. 29.1 All data from the same hospital showing graphical representation of comparative annual outcomes (SMRs) of one hospital plotted against others on the left of the figure and sequential mortality outcomes monitoring techniques for the same hospital on the right of the figure. This demonstrates a period in the middle of the year when mortality outcomes were above those predicted and thus accounted for the 'relatively high' SMR. (Top left) Caterpillar plot of SMRs arranged as league table. (Bottom left) Funnel plot showing SMRs of the ICUs plotted against number of admissions. (Top right) Risk-adjusted sequential probability ratio test. (Bottom left) Risk-adjusted exponentially weighed moving average chart.

Data from the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database 2011.

References

1. Harrison DA, Brady AR, Parry GP, Carpenter JR, and Rowan KD. (2006). Recalibration of risk prediction models in a large multicenter cohort of admissions to adult, general critical care units in the United Kingdom. *Critical Care*, **34**(5), 1378–88.
2. Kramer JA and Zimmerman JE. (2007). Assessing the calibration of mortality benchmarks in critical care: the Hosmer Lemeshow test revisited. *Critical Care Medicine*, **9**, 2052–6.
3. Baker DW, Einstadter D, Thomas CL, Husak SS, Gordon NH, and Cebul R. (2002). Mortality trends during a program that publicly reported hospital performance. *Medical Care*, **40**, 879–90.
4. Taori G, Ho KM, George C, et al. (2009). Landmark survival as an end point for trials in critically ill patients—comparison of alternative durations of follow-up: an exploratory analysis. *Critical Care*, **13**(4), R128.
5. Nashef S, Roques F, Sharples L, et al. (2012). EuroSCORE II. *European Journal of Cardiothoracic Surgery*, **41**(4), 734–45.
6. Knaus WA, Draper EA, Wagner DP, and Zimmerman JE. (1981). APACHE—acute physiology and chronic health evaluation: a physiologically based classification system. *Critical Care Medicine*, **9**, 591–7.
7. Bosman RJ, Oudermans van Straaten HM, and Zandstra DF. (1998). The use of intensive care information systems alters outcome prediction. *Intensive Care Medicine*, **24**, 953–8.
8. Shann F. (2000). Mortality Prediction Model is preferable to APACHE. *British Medical Journal*, **320**, 714.
9. Zimmerman JE, Kramer A, McNair DS, and Fern MM. (2006). Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Critical Care Medicine*, **34**, 1297–310.
10. Le Gall JR, Lemeshow S, and Saulnier F. (1993). A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *Journal of the American Medical Association*, **270**, 2957–63.
11. Moreno R, Metnitz PG, Almeida E, et al. (2005). SAPS3-from evaluation of the patient to the evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Medicine*, **31**, 13454–5.
12. Paul E, Bailey M, and Pilcher D. (2013). Risk prediction of hospital mortality for adult patients admitted to Australian and New Zealand intensive care units: development and validation of the Australian and New Zealand Risk of Death model. *Journal of Critical Care*, **28**, 935–41.
13. Lemeshow S, Teres D, Klar J, Avrunin JS, Gehlbach S, and Rapoport J. (1993). Mortality Probability Models (MPM II) based on an international cohort of intensive care unit patients. *Journal of the American Medical Association*, **270**, 2478–86.
14. Miranda D, de Rijk A, and Schaufel IW. (1996). Simplified Therapeutic Intervention Scoring System: the TISS-28 items—results from a multicenter study. *Critical Care Medicine*, **24**, 64–73.

15. Duke GJ, Santamaria J, Shann F, Stow P, Pilcher D, and Ernest D. (2008). Critical Care Outcome Prediction Equation (COPE) for adult intensive care. *Critical Care and Resuscitation*, **10**(1), 41.
16. Tobin AE and Santamaria JD. (2012). Medical emergency teams are associated with reduced mortality across a major metropolitan health network after 2 years service: retrospective study using government administrative data. *Critical Care*, **16**(5), R210.
17. Weeks WB, Bott DB, Bazos DA, et al. (2006). Veterans Health Administration patients' use of private sector for coronary revascularisation in New York. Opportunities for improving outcomes by directing care to high performance hospitals. *Medical Care*, 44(6), 519–26.
18. Abildstrom SZ, Hvelplund A, Rasmussen S, Nielsen PH, Mortensen PE, and Kruse M. (2010). Prognostic information in administrative comorbidity data following coronary artery bypass grafting. *European Journal of Cardiothoracic Surgery*, **38**, 573–8.
19. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, and Sibbald WJ. (1995). The multiple organ dysfunction (MOD) score: a reliable descriptor of a complex clinical outcome. *Critical Care Medicine*, **23**, 1638–52.
20. Vincent JL, De Mendonca A, Cantraine F, et al. (1998). Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. *Critical Care Medicine*, **26**(11), 1793–800.

CHAPTER 30

Organ failure scoring

Rui Moreno

Key points

- The most commonly used organ failure scores (OFS) are the Sequential Organ Failure (SOFA) score, the Multiple Organ Dysfunction Score (MODs) and the Logistic Organ Dysfunction (LODs) score.
- Organ failure scores (OFS) are designed to describe organ dysfunction, in a sequential (or repetitive) way, during the entire ICU stay, in patients with critical illness.
- OFSs are designed to dynamically describe the patient with critical illness and not to forecast mortality based on a set of variables collected within the first hours or days in the intensive care unit (ICU).
- All OFSs consider organ failure as a spectrum or continuum of organ dysfunction that exists from very mild altered function to total organ failure, which behaves as a dynamic process.
- All the scores widely used nowadays include six key organ systems—cardiovascular, respiratory, haematological, central nervous system, renal, and hepatic.

Introduction

Organ failure scores (OFSs) are designed to describe organ dysfunction, in a sequential (or repetitive) way, in individual patients with critical illness. In the development of organ dysfunction scores, three important principles need to be remembered [1]. First, organ failure is not a simple all-or-nothing phenomenon, but rather a spectrum or continuum of organ dysfunction exists from very mild altered function to total organ failure. Secondly, organ failure is not a static process and the degree of dysfunction may vary with time during the course of disease, so that scores need to be calculated repeatedly. Thirdly, the variables chosen to evaluate each organ need to be objective, simple, and available but reliable, routinely measured in every institution, specific to the organ in question, and independent of patient variables, so that the score can be easily calculated on any patient in any ICU. Ideally, all these scores should be independent of therapeutic variables [2], but this as proven to be virtually impossible to achieve, as all factors are more or less treatment dependent. For example, the partial pressure of oxygen (PaO_2)/fraction of inspired oxygen concentration (FiO_2) ratio (also known as P/F ratio) is dependent on ventilator conditions and positive end-expiratory pressure (PEEP), platelet count may be influenced by platelet transfusions, and urea and creatinine levels are affected by haemofiltration, etc.

Many different scoring systems have been developed for assessing organ dysfunction, since the early 1980s, differing in the organ systems included in the score, the definitions used for organ dysfunction, and the grading scale used. Nowadays, almost all the scores widely used include just six key organ systems—cardiovascular, respiratory, haematological, central nervous system, renal, and hepatic. The three more widely used OFSs (Table 30.1) will be discussed in the following section.

The Multiple Organ Dysfunction Score

This scoring system was developed based on a literature review from 1969 to 1993 performed by Marshall et al. [2]. Optimal descriptors of organ dysfunction were thus identified and validated against a clinical database. Six organ systems were chosen, and a score of 0–4 allocated to each organ, varying from normality (0 points) to the most severe failure (4 points), with a maximum score of 24. The worst score for each organ system in each 24-hour period is taken for calculation of the aggregate score. A high initial Multiple Organ Dysfunction Score (MODS) correlated with ICU mortality and the delta MODS (calculated as the MODS over the whole ICU stay less the admission MODS) was even more predictive of outcome [2]. In a study of 368 critically-ill patients, the MODS was found to better describe outcome groups than the APACHE II or the organ failure score, although the predicted risk of mortality was similar for all scoring systems [3]. The MODS has been used to assess organ dysfunction in clinical studies.

The Sequential Organ Failure Assessment Score

The Sequential Organ Failure Assessment (SOFA) score was developed in 1994 during a consensus conference organized by the European Society of Intensive Care and Emergency Medicine. It is a score designed to objectively quantify the degree of organ failure over time, organ-by-organ, in individuals or groups of individuals [1]. Initially named the sepsis-related organ failure assessment score, the score was then renamed the sequential organ failure assessment as it was realized that it could be applied equally to non-septic patients. In designing the score, the participants of the conference decided to limit to six the number of systems studied—respiratory, coagulation, hepatic, cardiovascular, central nervous system, and renal. A score of 0 is given for normal function through to 4 for most abnormal (for a maximum total of 24 points), and the worst values on each day are recorded. Individual organ function can thus be assessed and monitored over time, and an overall global score can also be calculated.

Table 30.1 Organ dysfunction/failure scoring systems

Organ system	MODS[a]	SOFA[b]	LODS[c]
Respiratory	PaO_2/FiO_2 ratio	PaO_2/FiO_2 ratio Mechanical ventilation	PaO_2/FiO_2 ratio Mechanical ventilation
Cardiovascular	Pressure adjusted HR	MAP Use of vasoactive agents	SAP HR
Renal	Creatinine	Creatinine Urinary output	Creatinine Urinary output Urea
Haematological	Platelets	Platelets	Platelets WBC
Neurologic System	GCS	GCS	GCS
Hepatic	Bilirubin	Bilirubin	Bilirubin Prothrombin time

HR, heart rate; MAQP, mean arterial pressure; SAP; WBC, white blood count; GCS, Glasgow Coma Score.

Data from (a) Marshall JC et al., 'Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome', *Critical Care Medicine*, 1995, **23**, pp. 1638–52; (b) Vincent J-L et al., 'The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure', *Intensive Care Medicine*, 1996, **22**, pp. 707–10; and (c) Le Gall JR et al., 'The ICU scoring group. The logistic organ dysfunction system. A new way to assess organ dysfunction in the intensive care unit', *Journal of the American Medical Association*, 1996, **276**, pp. 802–10.

Based on this score, several derived scores could be derived, that have been shown to provide additional information about the time-course of the disease [4]:

- The admission SOFA (usually computed with the worst values in the first hour after admission to the ICU).
- The daily SOFA.
- The maximum organ failure score (the sum of the worst scores for each of the components, independently from the day they occurred, because the maximum degree of failure for each organ/system usually occurs in different days).
- The amount of organ dysfunction failure appearing after ICU admission (delta SOFA), computed as the total maximum SOFA score minus the admission total SOFA score.
- The maximum daily SOFA (the day in the ICU stay were the aggregated score was maximum).
- The Discharge SOFA Score (which has been shown to be significantly related to mortality after ICU discharge) [5].

A high total SOFA score (SOFA max) and a high delta SOFA (the total maximum SOFA minus the admission total SOFA) have been shown to be related to a worse outcome [4,6], and the total score has been shown to increase over time in non-survivors compared with survivors [6]. It is by far the most widely used of the OFS scores (Table 30.2).

The Logistic Organ Dysfunction System Score

This score was developed in 1996 using multiple logistic regression applied to selected variables from the database of ICU patients used in 1991 to build the SAPS II score [7]. To calculate the score, each organ system received a number of points according to the worst value for any variable for that system on that day. If no organ dysfunction is present the score is 0, rising to a maximum of 5. As the relative severity of organ dysfunction differs between organ systems, the Logistic Organ Dysfunction System (LODS) score allows for the maximum 5 points to be awarded only to the neurologic, renal, and cardiovascular systems. For maximum dysfunction of the pulmonary and coagulation systems, a maximum of 3 points can be given for the most severe levels of dysfunction and for the liver, the most severe dysfunction only receives 1 point. Thus, the total maximum score is 22. The LODS score was designed (due to the constraints of the database used in its development) to be used as a once-only measure of organ dysfunction in the first 24 hours of ICU admission, rather than as a repeated assessment measure. The LODS system is quite complex and the less used of all.

Table 30.2 The Sequential Organ Failure Assessment (SOFA) Score

SOFA score	1	2	3	4
Respiration PaO_2/FiO_2 mmHg	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation platelets × $10^3/mm^3$	<150	<100	<50	<20
Liver bilirubin, mg/dL (μmol/L)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (>204)
Cardiovascular hypotension[a]	MAP <70 mmHg	Dopamine ≤5 or dobutamine (any dose)	Dopamine >5, or epinephrine ≤0.1, or norepinephrine ≤0.1	Dopamine >15, or epinephrine >0.1, or norepinephrine >0.1
Central nervous system	GCS 13–14	GCS10–12	GCS 6–9	GCS < 6
Renal creatinine, mg/dL (μmol/L) or urine output	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) or <500 mL/day	>5.0 (>440) or <200 mL/day

[a]Adrenergic agents administered for at least 1 hour (doses given are in μg/kg/min). GCS, Glasgow Coma Score.

Reproduced from *Intensive Care Medicine*, **22**, 7, 1996, pp. 707–10, 'The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure', Vincent JL, et al., Table 1, Copyright 1996 Springer, European Society of Intensive Care Medicine, and European Society of Paediatric and Neonatal Intensive Care. With kind permission from Springer Science and Business Media.

Comparison of the described systems

The main difference between the three described models is the method chosen for the evaluation of the cardiovascular dysfunction:

- SOFA uses blood pressure and the level of vasoactive support (maximum amount of vasoactive or inotropic drugs in continuous IV perfusion).
- MODS uses a composed variable, the pressure-adjusted heart rate (PAR, the product of the heart rate (HR) multiplied by the

ratio of the central venous pressure (CVP) to the mean arterial pressure (HR × CVP / MAP)).

- LOD score uses the heart rate and the systolic blood pressure.

A comparison among them, suggests that the MODS and the SOFA scores are both reliable outcome predictors, but the cardiovascular dysfunction/failure is better related to outcome with the SOFA score than with the MODS score [8]. It is also easier to compute.

Several mixed models, integrating a combination of OSF and general severity scores have been published [9,10], but they never gained widespread acceptance.

References

1. Vincent J-L, Moreno R, Takala J, et al. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Medicine*, **22**, 707–10.
2. Marshall JC, Cook DA, Christou NV, Bernard GR, Sprung CL, and Sibbald WJ. (1995). Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Critical Care Medicine*, **23**, 1638–52.
3. Jacobs S, Zuleika M, and Mphansa T. (1999). The multiple organ dysfunction score as a descriptor of patient outcome in septic shock compared with two other scoring systems. *Critical Care Medicine*, **27**, 741–4.
4. Moreno R, Vincent J-L, Matos R, et al. (1999). The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. *Intensive Care Medicine*, **25**, 686–96.
5. Moreno R, Miranda DR, Matos R, and Fevereiro T. (2001). Mortality after discharge from intensive care: the impact of organ system failure and nursing workload use at discharge. *Intensive Care Medicine*, **27**, 999–1004.
6. Vincent J-L, de Mendonça A, Cantraine F, et al. (1998). Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicentric, prospective study. *Critical Care Medicine*, **26**, 1793–800.
7. Le Gall JR, Klar J, Lemeshow S, et al. (1996). The logistic organ dysfunction system. A new way to assess organ dysfunction in the intensive care unit. *Journal of the American Medical Association*, **276**, 802–10.
8. Bota DP, Melot C, Ferreira FL, Ba VN, and Vincent J-L. (2002). The Multiple Organ Dysfunction Score (MODS) versus the Sequential Organ Failure Assessment (SOFA) score in outcome prediction. *Intensive Care Medicine*, **28**, 1619–24.
9. Chang RW, Jacobs S, and Lee B. (1988). Predicting outcome among intensive care unit patients using computerised trend analysis of daily Apache II scores corrected for organ system failure. *Intensive Care Medicine*, **14**, 558–66.
10. Timsit JF, Fosse JP, Troche G, et al. (2001). Accuracy of a composite score using daily SAPS II and LOD scores for predicting hospital mortality in ICU patients hospitalized for more than 72 h. *Intensive Care Medicine*, **27**, 1012–21.

CHAPTER 31

Genetic and molecular expression patterns in critical illness

Anthony F. Suffredini and J. Perren Cobb

Key points

- Global molecular expression patterns have provided important new insights into the host response to critical illness and injury, identifying new genes of interest, key regulation pathways, and novel inflammation paradigms to test.
- The last decade provided tantalizing evidence that omic technology can improve molecular diagnostics, prognostics, and therapeutics, but the promise of clinical benefit for the critically ill and injured has yet to be fulfilled.
- Technological, computational, and expense hurdles have delayed rapid evolution of the field, but the pace of continued advances suggests broader application and improved feasibility for clinical studies.
- Consistency of study design and analysis, in addition to independent corroboration of the major findings, are essential to the success of all omic approaches.
- Analyses of blood are influenced by the composition of cellular populations and the cell phenotype may change with the condition of the patient requiring multiple samples during the course of critical illness. Differences in cell phenotypes in different body compartments (i.e. blood, inflammatory cells within tissues, and parenchymal cells) affect the expression data and may change during the course of an illness.

The omic era

The 1990s brought whole-genome sequencing and microarrays into the clinical domain. These enabling technologies were leveraged first by interdisciplinary collaboratives in the basic sciences that discovered new networks of interacting gene products in single cell organisms. These findings, in turn, fuelled interest in the emerging fields of human systems biology and genomic medicine. Strictly defined, **genomics** describes the potential of the cell to respond to stimuli based on heredity and genetic variation at the level of DNA [1]. **Transcriptomics** describes cellular responses at the RNA level and is used as a proxy for changes in gene transcription or activation (also commonly called 'gene expression profiling') [2]. **Proteomics** studies relative changes in protein abundance and is used to help understand altered gene translation [3]. Finally, **metabolomics** (or metabonomics) characterizes changes in the abundance of metabolites and also reflects aggregate alterations in the transcriptome and proteome [4]. Investigations of critical illness directed at different levels of biological organization provide information that can be integrated horizontally and vertically.

Applying these approaches to a complex critically-ill patient requires an understanding of the technologies and their limitations. Practical assumptions need to be recognized. For example, analyses of circulating blood are influenced by the composition of cellular populations (e.g. leukocyte differential), so that studies often focus on a specific cellular subset, such as monocytes or lymphocytes. The cell phenotype may change rapidly with the condition of the patient, and require multiple sampling during the course of an illness and recovery. Moreover, the phenotype of cells available for sampling (skin, blood, lung airway) may have fundamentally different phenotypes compared with the same type of cells in other organs (i.e. leukocytes or parenchymal cells within tissues). Finally, consistency of study design and analysis, in addition to independent corroboration of the major findings, are essential to the success of omic approaches.

Typically, the output of these investigations are enormous data sets, which cannot be analysed with the statistical approaches familiar to most clinicians [2]. The range of variables analysed—including genes, transcripts, peptides, and metabolites—often number in the tens of thousands multiplied many-fold across patients and the time course of the experiment. In these instances, univariate analysis (e.g. Student's *t*-test) is usually inadequate to find significant results because of the risk of false associations that occur by chance when multiple tests are applied repeatedly to a huge numbers of variables (also known as the 'curse of dimensionality'). One successful analytical method is the reorganization of the data using unsupervised analysis, which makes no assumptions regarding the association of the variables with the patient's clinical state. Examples include hierarchical clustering and principal component analysis. These approaches reorder the data, so that molecules that have similar patterns of expression are depicted near each other. The assumption is that molecules that group similarly are, in some way, biologically related. In turn, these apparent associations must be verified by independent experiments at the molecular level.

This discovery approach is relatively unbiased, but is susceptible to variations in analytical techniques. In contrast, supervised analysis associates variables with a specific medical condition, such as sepsis. While this approach is less sensitive to technical variation, it may be affected by overfitting of the data to match one or more hypotheses.

Transcriptomics

The most illuminating experience with gene expression profiling as a discovery tool in critical care is in the field of sepsis research. For more than a decade, investigators have been motivated by the promise of an accurate sepsis diagnostic, which could determine which patients were infected and which were not, could identify the organism responsible, and could determine the patient's response to therapy. Early advances included pre-clinical data from *in vitro* models and animal experiments that identified a suite of leukocyte RNA markers that could characterize genome-wide cellular response to infectious stimuli. Moreover, it appeared that these changes in leukocyte gene expression could be used to detect the presence of microbes to the point of being diagnostic, differentiating human leukocyte responses to Gram-negative organisms, viruses, and fungi [5]. These discoveries, in turn, fuelled interest in clinical studies, testing the hypothesis that gene expression profiling could be used to diagnose infection.

Because of the novelty, complexity, and expense of human genomic studies, multicentre, interdisciplinary teams were assembled to conduct these investigations, funded by large-scale, collaborative research programmes. Initial studies aimed at addressing a number of theoretical and technical challenges concluded that a national programme for gene expression analysis could reduce unwanted investigative variance present in the clinical setting and enable the detection of gene expression signal reflective of human pathophysiology [6]. Normal human subjects were studied first, testing the ability of circulating leukocyte gene expression profiles to characterize the host response to intravenous bacterial endotoxin, a prototypical inflammatory insult, compared with placebo [7]. The results demonstrated that gene expression profiling could be used not only to track the human systemic inflammatory response, but also to identify inflammation-induced perturbations of highly coordinated gene groups (functional modules), such as leukocyte bioenergetics and gene translation (Fig. 31.1).

Having demonstrated proof of feasibility, attention turned to testing the ability of leukocyte gene expression profiles to diagnose sepsis in patients. Several groups reported that leukocyte gene expression profiles could be used to differentiate the responses of septic patients from those of critically-ill patients that were not septic, both in adults and children [8]. However, in comparing the lists of genes that appeared to be most informational in these studies, little to no overlap was identified, probably due to differences in septic patient cohorts, experimental design, microarray platforms, and analytical methods. The majority of these early investigations compared expression profiles from blood samples drawn at single time points. In contrast, data from longitudinal gene expression studies in septic patients generated a relatively short list of genes associated with ventilator-associated pneumonia (VAP) [9]. Significant heterogeneity of VAP gene expression profiles was observed, associated with differences in patient geographic ancestry, age, and gender. Yet, 85 genes were identified with consistent changes in abundance during the 7 days bracketing the diagnosis of VAP. Consistent with activation of the host response to pneumonia, several of the genes identified were associated with leukocyte pathways related to cellular activation, antimicrobial proteins, and adhesion molecules. Graphs of changes over time in the expression of these 85 genes was used to track the host response to and recovery from infection (Fig. 31.2), similar to the findings from normal subjects treated with endotoxin, as discussed previously. This was the first report demonstrating that disease trajectories derived from microarray expression profiles can be used to quantitatively track the clinical course of acute disease and identify a state of immune recovery. As these graphs are derived from changes in the abundance of ribonucleic acids in circulating leukocytes, these immune trajectory maps are called **riboleukograms** (RLGs) [9].

The ability of RLGs to detect VAP was validated in an independent cohort of 158 severely-injured, intubated patients [10]. Gene expression profiles obtained at frequent intervals up to 28 days after injury validated that 32% of the 85 genes from the initial study were associated significantly with the diagnosis of VAP, but the prediction model based on these 85 genes did not predict pneumonia in this independent patient cohort better than chance. However, a prediction model based on *de novo* analysis of gene expression data from the 158 trauma patients predicted VAP 4 days prior to VAP diagnosis, but the positive and negative predictive values were only 25 and 90%, respectively. Similar results have been reported studying whole-blood gene expression profiles from septic children [11]. Computer-based analysis of gene expression profiles from a derivation cohort of 98 children revealed 100 genes that classified these patients into three sepsis subclasses ('A, B, and C'). A follow-up study of 82 paediatric patients validated these results.

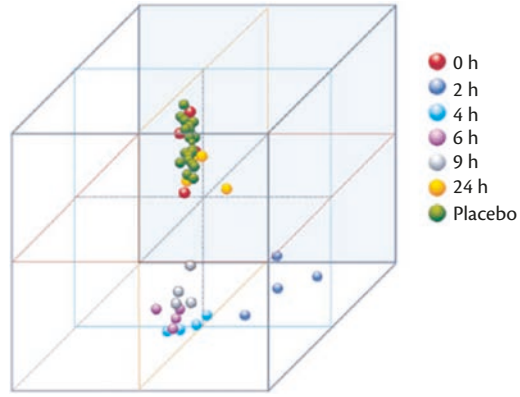


Fig. 31.1 Circulating leukocyte gene expression profiles can be used to track the human systemic inflammatory response. Circulating leukocytes from eight healthy volunteers were tested at baseline (0 hour), and 2, 4, 6, 9, and 24 hours after intravenous administration of endotoxin (four subjects) or placebo (four subjects). Treatment with intravenous endotoxin in this model of systemic inflammation produces flu-like symptoms that resolve spontaneously after 12–24 hours. Significant changes in the expression of 3714 genes were mapped for each sample in three dimensions using principal component analysis. Zero and 24-hour samples in endotoxin-treated subjects mapped similar to samples from placebo-treated subjects at all time points. In contrast, time-dependent changes in the four endotoxin-treated subjects mapped similarly at 2, 4, 6, and 9 hours, returning to baseline at 24 hours.

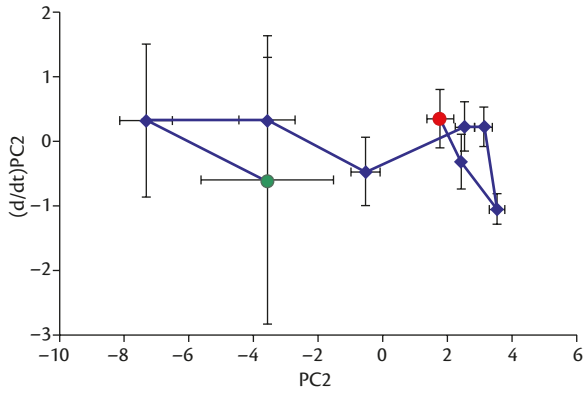


Fig. 31.2 Immune trajectories, called riboleukograms (RLG), from critically-ill patients who developed and recovered from VAP. Buffy coat microarray expression profiles were generated from 11 mechanically ventilated patients every 2 days for up to 3 weeks. Eighty-five genes were found to change in all patients coincident with the development of VAP. Shown is the principal components analysis of these genes. The averaged RLGs appeared to define a general trajectory for the onset and resolution of VAP (the green and red circles indicate where the patients entered and exited the study, respectively). As patients recovered from critical illness complicated by acute infection, the RLGs moved from left to right, converging to a common point concomitant with a decrease in the variance of gene expression (standard deviation of green compared with red circle). These latter findings are consistent with an attractor state of immune health (homeostasis).
PC is principal component, (d/dt)PC is the rate of change of the principal component.
Adapted from McDunn JE et al., 'Plasticity of the systemic inflammatory response to acute infection during critical illness: development of the riboleukogram', *PloS One*, 2008, 3, available at: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0001564. © 2008 McDunn et al. This figure is from an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited [9].

Sepsis subclass A patients were the sickest, based upon higher illness severity scores on average and fewer ICU-free days.

To summarize, gene expression profiling of circulating leukocytes differentiates between the responses of septic and non-septic patients, both in children and adults. Riboleukograms that map changes over time can be used to track the host response to and recovery from septic insults, such as VAP. However, a lack of reproducibility across studies and the number of confounding influences on circulating leukocyte RNA abundance (such as the patient's geographic ancestry, gender, age, and perhaps co-morbidities) have frustrated efforts to date to discover a clinically useful gene expression profile to diagnose sepsis [8]. Reports of human circulating leukocyte gene expression profiles have also raised questions as to the validity of the two-hit model of critical illness and the use of mice to model human disease [12,13]. National efforts to leverage gene expression profiling for clinical benefit should continue as we build on advances in genomic science. For example, the study of enriched populations of circulating leukocytes (granulocytes, monocytes, and lymphocytes), coupled with technical and computational advances (e.g. microfluidics), promise improved signal-to-noise ratios and better discriminatory capabilities that will translate into improved diagnostics.

Proteomics

The proteome encompasses a broad range of molecules that can be classified based on differences in size, post-translational modifications (such as glycosylation), proteolytic cleavage (altering activity), and cellular location. In addition, alternative splicing of mRNA from a particular gene can generate mRNA variants that are translated accordingly into proteins with different amino acid sequences and biological function. Thus, there are far more proteins than there are genes in a genome; for example, there are approximately 21,000 human protein-coding genes, but estimates of the number of human proteins exceeds 100,000. Furthermore, proteins usually found within a cell may leak from a damaged or stimulated cell, and can be found in blood or urine.

The typical approach to identifying proteins in a biological fluid relies on simplifying complex mixtures by sample fractionation—separated typically by size and charge—and then analysing these enriched peptide fractions by mass spectrometry (MS) [3]. Two analytical approaches are typically used [14]. A bottom-up analytical approach simplifies complex mixtures by digesting all the proteins in the mixture and then fractionating them prior to application onto a MS platform. The peptide masses and sequences detected by MS serve as surrogate markers for their respective intact proteins. The thousands of peptide fragments used in this analytical approach create a substantial computational challenge. These peptide sequences are compared with predicted proteins using database searches and the predicted *in silico*-generated fragmentation patterns. An alternative analytical approach is the top-down proteome method in which analysis of intact proteins, their fragments, and post-translational modifications is performed. This approach requires precise, pre-analytic separation of a protein mixture prior to MS, which presents a different set of challenges.

Over the last decade, these approaches have been applied to study critical illness. For example, the application of proteomics to characterize biomarkers is relatively independent of the analytic platform and requires prospective validation in large, independent cohorts [15]. Analysis of the trauma patient plasma proteome exemplifies some of the challenges [16]. The workflow entailed removal of the most abundant plasma proteins, leaving the lower molecular weight proteome for analysis. This fraction was digested and separated into different peptide populations enriched for the presence of cysteinyl peptides and N-glycopeptides. After extensive analysis, over 2000 proteins were identified, including cytokines, chemokines, cell differentiation molecules, and other proteins involved in inflammation and immune responses. The challenges of this type of comprehensive approach include the complexity, throughput, resources, and costs necessary to process and analyse samples. Proteomic analysis of bronchoalveolar lavage is another example that has provided insight into potential biomarkers associated with acute respiratory distress syndrome (ARDS). Patients with ARDS had distinct protein patterns associated with increased levels of apolipoprotein A1 and S100 calcium binding proteins A8 and A9, potentially of use to monitor acute inflammation and the clinical response to therapy [17].

Finally, it is worth emphasizing that the application of mass spectrometry in the microbiology laboratory has revolutionized the rapid identification of microbes. This is based on generating spectral proteomic patterns of the unknown organism and comparing them to a reference database. After relatively simple sample preparation, the results are achieved within minutes, with a high level of accuracy [18].

Metabolomics

Metabolites are small molecules generated as the intermediary products of metabolism, such as signalling molecules, sugars, fatty acids, amino acids, nucleic acids, and vitamins. Metabolomics (the global profiling of metabolites produced in response to different disease states, drugs, or environmental stresses) is an emerging field that complements proteomics and transcriptomics as a means to identify novel biomarkers in critical illness [4,19]. These approaches can be used to identify, in parallel, hundreds of metabolites in biological fluids, utilizing either nuclear magnetic resonance (NMR) spectroscopy or MS coupled to liquid or gas chromatography. NMR has the advantages of a broad interrogation of metabolites with minimal preparation time and high throughput, allowing hundreds of samples to be processed per day. This occurs without destruction of the sample, but this analytical approach is limited by its relative insensitivity due to overlapping metabolite signals and the difficulty of absolute quantification. In contrast, chromatographic separation methods linked to MS have greater sensitivity and reproducibility, but samples are consumed in the process and data analysis is more time consuming [19].

Preliminary work suggests the potential of this approach to define new markers of inflammation in critically-ill patients. Using NMR spectroscopy, plasma from patients with sepsis-induced acute lung injury differed globally from healthy controls, and myo-inositol and glutathione were found to correlate with the APACHE III Acute Physiologic Score [20]. These data confirm the feasibility of this approach in elucidating pathways and potential biomarkers in patient samples.

References

1. Feero WG, Guttmacher AE, and Collins FS. (2010). Genomic medicine—an updated primer. *New England Journal of Medicine*, **362**, 2001–11.
2. Ballman KV. (2008). Genetics and genomics: gene expression microarrays. *Circulation*, **118**, 1593–7.
3. Hawkridge AM and Muddiman DC. (2009). Mass spectrometry-based biomarker discovery: toward a global proteome index of individuality. *Annual Review of Analytical Chemistry (Palo Alto, California)*, **2**, 265–77.
4. Serkova NJ, Standiford TJ, and Stringer KA. (2011). The emerging field of quantitative blood metabolomics for biomarker discovery in critical illnesses. American Journal of Respiratory and Critical Care Medicine, **184**, 647–55.
5. Huang Q, Liu D, Majewski P, et al. (2001). The plasticity of dendritic cell responses to pathogens and their components. *Science*, **294**, 870–5.
6. Cobb JP, Mindrinos MN, Miller-Graziano C, et al. (2005). Application of genome-wide expression analysis to human health and disease. *Proceedings of the National Academy of Sciences, USA*, **102**, 4801–6.
7. Calvano SE, Xiao W, Richards DR, et al. (2005). A network-based analysis of systemic inflammation in humans. *Nature*, **437**, 1032–7.
8. Tang BM, Huang SJ, and McLean AS. (2010). Genome-wide transcription profiling of human sepsis: a systematic review. *Critical Care*, **14**, R237.
9. McDunn JE, Husain KD, Polpitiya AD, et al. (2008). Plasticity of the systemic inflammatory response to acute infection during critical illness: development of the riboleukogram. *PloS One*, **3**, e1564.
10. Cobb JP, Moore EE, Hayden DL, et al. (2009). Validation of the riboleukogram to detect ventilator-associated pneumonia after severe injury. *Annals of Surgery*, **250**, 531–9.
11. Wong HR, Cvijanovich NZ, Allen GL, et al. (2011). Validation of a gene expression-based subclassification strategy for pediatric septic shock. *Critical Care Medicine*, **39**, 2511–17.
12. Xiao W, Mindrinos MN, Seok J, et al. (2011). A genomic storm in critically injured humans. *Journal of Experimental Medicine*, **208**, 2581–90.
13. Seok J, Warren HS, Cuenca AG, et al. (2013). Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proceedings of the National Academy of Sciences, USA*, **110**, 3507–12.
14. Yates JR, Ruse CI, and Nakorchevsky A. (2009). Proteomics by mass spectrometry: approaches, advances, and applications. *Annual Review of Biomedical Engineering*, **11**, 49–79.
15. Anderson NL. (2005). The roles of multiple proteomic platforms in a pipeline for new diagnostics. *Molecular Cell Proteomics*, **4**, 1441–4.
16. Liu T, Qian WJ, Gritsenko MA, et al. (2006). High dynamic range characterization of the trauma patient plasma proteome. *Molecular Cell Proteomics*, **5**, 1899–913.
17. de Torre C, Ying SX, Munson PJ, et al. (2006). Proteomic analysis of inflammatory biomarkers in bronchoalveolar lavage. *Proteomics*, **6**, 3949–57.
18. Drake RR, Boggs SR, and Drake SK. (2011). Pathogen identification using mass spectrometry in the clinical microbiology laboratory. *Journal of Mass Spectrometry*, **46**, 1223–32.
19. Dieterle F, Riefke B, Schlotterbeck G, et al. (2011). NMR and MS methods for metabonomics. *Methods in Molecular Biology*, **691**, 385–415.
20. Stringer KA, Serkova NJ, Karnovsky A, et al. (2011). Metabolic consequences of sepsis-induced acute lung injury revealed by plasma (1) H-nuclear magnetic resonance quantitative metabolomics and computational analysis. *American Journal of Physiology—Lung Cellular and Molecular Physiology*, **300**, L4–11.

SECTION 2

Pharmacotherapeutics

PART 2.1

Respiratory drugs

CHAPTER 32

Oxygen in critical illness

James N. Fullerton and Mervyn Singer

Key points

- Hypoxaemia should be avoided.
- Mortality is increased in intensive care patients with PaO_2 <8–9 kPa.
- Hyperoxaemia is not benign. Observational studies indicate an association with increased mortality in ventilated patients and survivors of cardiac arrest.
- Oxygen is a drug. Commencement and continuation represents a clinical decision. Full prescription, monitoring, and frequent review are required.
- Oxygen therapy may cause hypercapnic respiratory failure in at-risk patients.

Introduction

Oxygen is cheap, widely available, and efficacious in preventing and treating hypoxaemia. Oxygen therapy has long been regarded as integral to the management of critical illness. In the UK, oxygen is administered to over one-third of emergency ambulance patients, while around 15% of in-patients receive oxygen therapy on any given day [1,2]. In critical care, its use is nearly ubiquitous. Despite this, oxygen is a drug. Its use must be accompanied by the traditional stipulations and clinical rigor applied to other therapeutics. However, supplemental oxygen without prescription remains common [2]. In patients with a specified target oxygen saturation range, one-third fell outside [3].

The primary indication for oxygen therapy is actual or suspected hypoxaemia. Sustained hypoxaemia is associated with end-organ damage, most notably to the brain as a result of tissue hypoxia [4,5]. The precise levels of hypoxaemia that are dangerous in given disease states are not known. However, a degree of hypoxaemia may be tolerated in the short term, while gradual acclimatization alters the threshold at which harm occurs [6,7]. Observational studies in mechanically-ventilated patients describe an independent and linear association between hypoxaemia in the first 24 hours after ICU admission and mortality [8,9]. Similar data have been reported in survivors of non-traumatic cardiac arrest [10]. The threshold for harm appears to be around PaO_2 8–9kPa (91–94% SaO_2).

Hyperoxaemia is now recognized as injurious in certain settings. While prolonged exposure to high inspired concentrations of oxygen (FiO_2 > 0.5) has long been known to induce oxygen toxicity with predominantly pulmonary and neurological sequelae [11], more recent research indicates that exposure to lower doses over shorter durations may also be harmful. Data describes an independent association between increasing hyperoxaemia and mortality in both mechanically ventilated patients [8] and survivors of cardiac arrest [10]. Questions remain over whether this contributes to excess mortality after multivariate analysis [9,12]. Harm may arise from cardiopulmonary side effects and deleterious local effects at sites of prior ischaemia or inflammation, e.g. promotion of free radical generation and vasoconstriction (for instance, by promotion of free radical generation and vasoconstriction).

Given the potential for harm, targeted oxygen therapy routinely aiming to achieve normoxaemia and normal tissue oxygen tensions should be the standard of care.

Principles

Oxygen therapy should alleviate both arterial and tissue hypoxia, facilitating aerobic respiration and cellular metabolism. Unfortunately, a simple relationship between FiO_2 and cellular adenosine triphosphate (ATP) generation cannot be assumed.

Maximizing arterial haemoglobin saturation by increasing the FiO_2 represents only one factor that determines oxygen delivery. The oxyhaemoglobin binding characteristics (themselves dependent on pH, 2,3-diphosphoglycerate and $PaCO_2$), haemoglobin concentration, cardiac output, and factors affecting pulmonary gas exchange, peripheral vascular distribution and diffusion from capillary to tissue, also play key roles. A simple dose response relationship (FiO_2 to intracellular PO_2) cannot be expected. To compound the issue, critical illness may also alter or impair mitochondrial aerobic respiration, creating a state of 'hibernation' in organs [13].

Correcting hypoxaemia neither indicates alleviation of tissue hypoxia, nor guarantees oxygen utilization at a cellular level. In the absence of a clinically-relevant measure of intracellular PO_2 and/or mitochondrial function, treatment efficacy must be inferred [14]. Reliance on the correction of arterial oxygen concentration with oxygen therapy, merely because it is achievable and measurable, may not be in the patient's best interests [5]. Modifications of pulmonary physiology, haemoglobin concentration, and a reduction in regional and local barriers to cellular oxygenation (circulatory disturbance, oedema, etc.) may facilitate improved oxygen delivery beyond that afforded by oxygen therapy alone (Box 32.1).

Indications

The main indication for oxygen therapy is documented hypoxaemia (PaO_2 < 8 kPa [60 mmHg], SaO_2 < 92%). Oxygen may also be commenced in emergency situations where hypoxaemia is suspected, but not yet documented. Oxygenation status should be determined as rapidly as possible, a target set, and therapy titrated and/or ceased as necessary. Oxygen is *not* a treatment for dyspnoea.

Box 32.1 Alternative methods to increase oxygen delivery

- Improving and safeguarding the airway: suctioning, manual manoeuvres, airway adjuncts, supraglottic devices or endotracheal tube.
- Optimizing circulating volume to maintain tissue perfusion.
- Enhancing cardiac output.
- Correction of anaemia, increasing oxygen carrying capacity.
- Avoiding or reversing respiratory depressants.
- Establishing and treating the underlying cause of hypoxaemia.
- Non-invasive or invasive ventilation including recruitment manoeuvres.

Adapted from *British Medical Journal*, O'Driscoll R, 'Emergency oxygen use', **345**, 6856, copyright 2012, with permission from the BMJ Publishing Group Ltd.

The normal range for arterial blood oxygen is 11–14 kPa (85–105 mmHg, SaO_2 > 93%). Hypoxaemia is commonly caused by ventilation/perfusion (V/Q) mismatch, resulting in a shunt or dead-space, and hypoventilation. Clinical symptoms of hypoxaemia include restlessness, agitation, confusion, sweating, headache, nausea, paraesthesiae, palpitations, and eventually reduced Glasgow Coma Score (GCS). Signs, are also neither sensitive nor specific, and include cyanosis, tachypnoea, decreased cognitive function and co-ordination, and fluctuating blood pressure (hypertension and subsequent hypotension).

Dosages and monitoring

Hypoxaemia and hyperoxaemia are frequently a result of inappropriate use, dosing, or delivery route of oxygen therapy, in combination with a failure to monitor and titrate therapy. Oxygen commenced out of presumed need is often not reviewed promptly.

Dose

Acutely unwell patients should be prescribed and administered oxygen to achieve target arterial saturations of 94–98% [15]. Patients with risk factors for hypercapnic respiratory failure (Box 32.2) or known chronic hypoxaemia should be set a target range of 88–92% [15]. In specific clinical situations, or if monitoring is unavailable or inaccurate, high-flow oxygen (10–15 L/min) via a reservoir mask may be provided until determination of PaO_2 or SaO_2 can be reliably made with subsequent titration/cessation (Box 32.3). Permissive hypoxaemia may be preferred in certain clinical situations [5].

Box 32.2 Risk factors for hypercapnia

- Chronic obstructive pulmonary disease.
- Chest wall deformities.
- Neuromuscular disorders.
- Morbid obesity.

Adapted from *Thorax*, O'Driscoll BR et al., 'BTS guideline for emergency oxygen use in adult patients', **63**(Suppl. 6), pp. vi1–68, copyright 2008, with permission from the BMJ Publishing Group Ltd.

Prescription

Oxygen should always be prescribed. The delivery device(s) and flow rate range must be specified, along with a target range of saturation or PaO_2.

Box 32.3 Medical emergencies where oxygen is likely to be required

Medical emergencies requiring high concentration oxygen in all cases

- Shock, sepsis, major trauma.
- Cardiac arrest and during resuscitation.
- Anaphylaxis.
- Carbon monoxide or cyanide poisoning.
- Diving and altitude emergencies (specialist input required).

Medical emergencies where patients are likely to need oxygen therapy (ranging from low to high concentration depending on disease severity), with target saturation range 94–98%

- Pneumonia.
- Asthma.
- Acute heart failure.
- Pulmonary embolism.

Medical emergencies where patients are likely to need controlled oxygen, with target saturation range 88–92%

- Acute exacerbation of COPD.
- Acute illness in patients with cystic fibrosis.
- Acute respiratory illness in patients with obesity hypoventilation syndrome or morbid obesity.
- Acute respiratory illness in patients with chronic neuromuscular or musculoskeletal conditions.

Medical emergencies where oxygen is advised only if the patient is hypoxaemic

- Myocardial infarction or unstable coronary artery syndrome.
- Stroke.
- Ongoing management of survivors of cardiac arrest with restored spontaneous circulation.
- Sickle cell crisis or acute anaemia.
- Obstetric emergencies.
- Poisoning (other than above, paraquat is a relative contra-indication).

- Metabolic and renal disorders with tachypnoea due to acidosis (Kussmaul breathing).

Other indications (non-emergency)

- Operations and procedures involving sedation.
- Long-term use in pulmonary disease.
- Assistance in pneumothorax resolution.
- Promotion of wound healing including necrotizing fasciitis.

Adapted from *Thorax*, O'Driscoll BR et al., 'BTS guideline for emergency oxygen use in adult patients', **63**(Suppl. 6), pp. vi1–68, copyright 2008, with permission from the BMJ Publishing Group Ltd.

Monitoring

Documentation of vital signs, including pulse oximetry, is necessary while oxygen is being administered. The delivery device, flow rate, and FiO_2, if known, must be noted. Blood gas sampling (arterial or capillary) is necessary to identify hyperoxaemia and hypercarbia, and to describe hypoxaemia accurately (due to the sigmoid shape of the oxygen dissociation curve). These should be performed routinely in patients at risk of hypercarbic respiratory failure and in ventilated patients (non-invasive and endotracheal). Hyperoxaemia cannot be identified via pulse oximetry or clinical signs so arterial blood sampling is required to facilitate its avoidance.

Routes of administration

Spontaneous respiration

Low-flow devices

The FiO_2 provided by these devices is dependent on the device, mask fit, inspiratory flow rate, and anatomical reservoir. Oxygen is delivered at flows less than the patient's inspiratory flow rate and, due to entrainment and consequent dilution of the oxygen with room air, the concentration delivered to the alveoli will be reduced. FiO_2 >0.8–0.85 cannot be delivered via these devices.

As the inspiratory flow rate rises, the FiO_2 falls. With a constant oxygen flow, a tachypnoeic patient may thus receive reducing and potentially insufficient amounts of oxygen. Equally, with a reduced respiratory rate there is the danger of a rising FiO_2. In patients at risk of hypercapnic ventilatory failure, a vicious cycle may emerge.

Low-flow devices are the most frequently used due to comfort, cost, ease of use and ready availability. They include nasal cannulae or catheters, simple masks (Hudson or MC) and reservoir masks (both partial rebreathing and non-rebreathing). The size of the reservoir (~200 mL with a simple face mask, to 1 L with a dedicated reservoir bag) determines the FiO_2 range that is delivered. Devices with reservoir capacity should be inflated with O_2 prior to use and should neither collapse fully on inspiration nor be utilized at low flow rates. CO_2 re-breathing may occur in this situation secondary to insufficient flushing.

High-flow devices

The FiO_2 supplied is constant (within a range of minute volume) as a prescribed oxygen/air mixture is delivered at flow rates that exceed patient demand.

The most commonly used system is the Venturi valve and mask with either fixed or variable oxygen concentration delivery. The latter is normally linked to a humidification system. The system relies on the Bernoulli principle. Both valve (orifice width) and flow rate must be altered in tandem to provide the desired FiO_2, ensuring the correct amount of room air is entrained.

As inspiratory flow-rate does not alter the FiO_2, these masks represent the first choice in patients who required controlled oxygen therapy.

Mechanically-assisted ventilation

Mechanical ventilation may be used to treat hypoxaemic states, with or without ventilatory failure, that is refractory to standard oxygen therapy. Continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) can be delivered via a tight-fitting mask or hood to the alert, spontaneously breathing patient. FiO_2 may be varied between 0.21 and 1.0, dependent on seal.

Hyperbaric oxygen

This has a role in the management of acute carbon monoxide poisoning, arterial gas embolism, severe decompression sickness, clostridial gas gangrene, necrotizing fasciitis, and acute crush injury. Hyperbaric oxygen therapy can be safely administered to critically-ill patients, but specialized equipment and trained personnel are required to operate in chambers. Risk/benefit analysis should be considered prior to transfer and commencement.

Non-spontaneous respiration

Patients with cuffed endotracheal tubes may be provided with variable, accurate, and often high FiO_2 levels via diverse modes of ventilatory support. Severe hypoxaemia in this setting, often secondary to lung pathology, may prompt consideration of extracorporeal membrane oxygenation (ECMO).

Humidified oxygen

The upper respiratory tract is responsible for humidification of inspired air in normal physiology. Administration of non-humidified oxygen at high flow rates for prolonged periods may compromise the mucociliary elevator and, consequently, secretion and pathogen clearance. This insult will be compounded if pathology or an artificial airway determines that the nasopharynx is bypassed. Humidified oxygen offers one means of ameliorating this insult.

Side effects

Oxygen therapy elicits a fall in cardiac output secondary to a vagal nerve-mediated reduction in heart rate and an increase in peripheral vascular resistance. The latter is seen clinically as a rise in both systolic and especially diastolic blood pressure. Prolonged exposure to high FiO_2 may induce long-lasting or even permanent pathological changes.

Oxygen toxicity—cellular mechanisms

Normal cellular respiration generates reactive oxygen metabolites. From the superoxide anion (O_2^-), formed by incomplete reduction of oxygen in the mitochondrial electron transport chain, multiple other reactive species are generated, including perhydroxyl radicals, hydrogen peroxide, and hydroxyl radicals (via redox cycling in the presence of catalytic iron and copper), and peroxynitrite (via

reaction with nitric oxide). These may cause local damage, engaging in destructive oxidation and reduction reactions with cellular constituents, or diffuse insults further afield.

Usually less than 5% of oxygen used metabolically is incompletely reduced to form the superoxide anion. As the intracellular PO_2 rises the law of mass action dictates that this is proportionally increased. In turn, reactive oxygen species increase in concentration, especially in situations where key intermediaries are present (e.g. nitric acid formed by inflammatory cells at a septic site or iron in circulatory stasis). Under normal circumstances protective antioxidants (including glutathione, vitamin A, ascorbate) and 'antioxidant' intracellular enzymes (including superoxide dismutase, catalase, and glutathione peroxidase) exist to eliminate these toxic products. When production increases, these are consumed or overwhelmed.

Oxygen toxicity—clinical manifestations

The key systems affected are the respiratory and central nervous systems, although ocular, endocrine, and diverse other changes are recognized. Symptomatically, patients may experience cough, chest pain, paraesthesiae, visual changes, tinnitus, vertigo, irritability, anorexia, nausea, and vomiting. Seizures may occur. Pathologically, in the lung, a spectrum is seen dependent on both duration of exposure and concentration [11]. An initial endothelial injury-triggered exudative phase, characterized by inflammatory cell infiltration and thickening of the alveolar interstitium, precedes a proliferative phase. This is typified by septal proliferation, alteration of the cellular balance in favour of type II alveolar cells, and deposition of interstitial collagen, elastin, and fibrin. The end-result is fibrosis, similar to the diffuse alveolar damage arising from other pathologies, e.g. smoke inhalation or influenza pneumonia. Physiological changes include reduced gas exchange, V/Q abnormalities, and alteration in lung mechanics (reduced compliance and forced vital capacity).

Multiple drugs may exacerbate oxygen toxicity via increasing tissue oxygen consumption (e.g. epinephrine, norepinephrine) or free radical production (directly or in their metabolism, e.g. nitrofurantoin, bleomycin), or impairing endogenous antioxidant systems (e.g. cyclophosphamide). Several agents show promise in ameliorating oxygen toxicity in experimental models (often focused around 'boosting' the antioxidant system), yet none have entered routine practice. Steroids may have a role in preventing late complications from extended exposure.

Given oxygen's potential toxicity when given at high concentrations ($FIO_2 > 0.5$) for even short periods (>12 hours, no defined cut-off) a policy of titration to need, reduction (where possible), attention to other modifiable factors determining oxygen delivery, and even permissive hypoxaemia should be considered [5].

Summary of other key side effects

- **Ventilatory depression and CO_2 retention**.
- **Absorption (oxygen) atelectasis**: nitrogen washout occurs. At the alveolar level, as oxygen is readily absorbed by haemoglobin, collapse may occur.
- **Depression of lung barrier function**:
  - Ciliary dysfunction, producing decreased tracheal mucous velocity.
  - Lymphocytic infiltration.
- **Vasoconstriction**:
  - *Local*: cardiac and cerebral circulation is of primary concern.
  - *Systemic:* increased vascular resistance and hence cardiac load.

Cautions

There are no absolute contraindications to oxygen therapy. Clinical risk/benefit analysis should determine the target oxygen saturation range and adoption of alternative strategies to maximize oxygen delivery (see Box 32.1) in parallel with selecting a FIO_2 and oxygen delivery system on a case-by-case basis.

Hypercapnic ventilatory failure

The primary concern regarding oxygen therapy is oxygen-induced hypercapnic ventilatory failure in at risk patients (see Box 32.2). Chronic obstructive pulmonary disease (COPD) represents the most prevalent risk factor. In this population, the use of uncontrolled (>35%) oxygen is associated with mortality and requirement for ventilatory support twice that of those receiving targeted (88–92%) therapy [16,17]. Groups not classically associated with 'at-risk' status have also been shown to be vulnerable, including patients with acute exacerbations of asthma [18] and pneumonia [19], reinforcing the need to monitor, titrate, and target therapy. Transcutaneous CO_2 sensors are neither widely available, nor accurate, and the signs of hypercapnia are non-specific, late, and may not be evident in a sedated, ventilated patient. For this reason, arterial blood gases are recommended in all patients at risk of hypercapnic respiratory failure receiving emergency oxygen therapy.

CO_2 retention secondary to an increased FIO_2 is multifactorial. Physiologically, the Campbell theory is most commonly cited, where reduced central hypercapnic drive (secondary to chemoreceptor tolerance after prolonged hypercapnic exposure) places reliance on hypoxaemia for respiratory stimulation [20]. Supplementation with FIO_2 diminishes this drive leading to a falling respiratory rate, CO_2 narcosis, and eventually apnoea. A further significant contribution may come from V/Q mismatching secondary to the release of hypoxic pulmonary vasoconstriction. The pulmonary circulation, in contrast to the systemic circulation, constricts in response to hypoxia. In at-risk patients, increased FIO_2 results in vasodilation in parts of the lung that are poorly ventilated and/or have impaired gas transfer. CO_2 transported in these vessels will not be excreted. Underlying pathology prevents normal compensatory increases in alveolar ventilation with resultant hypercapnia.

In acutely unwell patients, the explanation for a $PaCO_2$ rise in response to oxygen therapy is more complicated. Acute fatigue (often secondary to increased respiratory muscle load, decreased strength, and reduced chest wall compliance) and atelectasis (secondary to weak cough, poor respiratory efforts, increased sputum production, and failed excretion) compounds the physiological factors described previously. In addition, increased CO_2 production as a result of the underlying pathology (e.g. sepsis) or resulting from treatment (e.g. bicarbonate infusion) exacerbates this. Rarely can oxygen therapy be identified as the sole cause of a $PaCO_2$ rise.

Relative contraindications

In the case of paraquat poisoning, bleomycin-induced lung injury and acid inhalation, oxygen therapy may worsen the insult. The decision to initiate oxygen therapy should be made on an individual basis, often encompassing a strategy of permissive hypoxaemia (e.g. SaO_2 90%).

Risk of fire or explosion

Oxygen promotes combustion and poses a fire risk in specific situations

- **Defibrillation**: oxygen sources should either be removed and turned away from the patient or, if a closed circuit is in place, left sealed prior to an electric current being delivered.
- **Bronchoscopic laser-therapy**: risk of ignition.
- **External risk factors**: naked flame, lit cigarette, etc. These are predominantly associated with domestic oxygen use.

References

1. Hale KE, Gavin C, and O'Driscoll BR. (2008). Audit of oxygen use in emergency ambulances and in a hospital emergency department. *Emergency Medical Journal*, **25**(11), 773–6.
2. O'Driscoll BR, Howard LS, Bucknall C, Welham SA, and Davison AG. (2011). British Thoracic Society emergency oxygen audits. *Thorax*, **66**(8), 734–5.
3. O'Driscoll R. (2012). Emergency oxygen use. *British Medical Journal*, **345**, e6856.
4. Michiels C. (2004). Physiological and pathological responses to hypoxia. *American Journal of Pathology*, **164**(6), 1875–82.
5. Martin DS and Grocott MP. (2013). Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. *Critical Care Medicine*, **41**(2), 423–32.
6. Grocott MP, Martin DS, Levett DZ, McMorrow R, Windsor J, and Montgomery HE. (2009). Arterial blood gases and oxygen content in climbers on Mount Everest. *New England Journal of Medicine*, **360**(2), 140–9.
7. Murphy R, Driscoll P, and O'Driscoll R. (2001). Emergency oxygen therapy for the COPD patient. *Emergency Medicine Journal*, **18**(5), 333–9.
8. de Jonge E, Peelen L, Keijzers PJ, et al. (2008). Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Critical Care*, **12**(6), R156.
9. Eastwood G, Bellomo R, Bailey M, et al. (2012). Arterial oxygen tension and mortality in mechanically ventilated patients. *Intensive Care Medicine*, **38**(1), 91–8.
10. Kilgannon JH, Jones AE, Shapiro NI, et al. (2010). Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *Journal of the American Medical Association*, **303**(21), 2165–71.
11. Kallet RH and Matthay MA. (2013). Hyperoxic acute lung injury. *Respiratory Care*, **58**(1), 123–41.
12. Bellomo R, Bailey M, Eastwood GM, et al. (2011). Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. *Critical Care*, **15**(2), R90.
13. Abraham E and Singer M. (2007). Mechanisms of sepsis-induced organ dysfunction. *Critical Care Medicine*, **35**(10), 2408–16.
14. Ekbal NJ, Dyson A, Black C, and Singer M. (2013). Monitoring tissue perfusion, oxygenation, and metabolism in critically ill patients. *Chest*, **143**(6), 1799–808.
15. O'Driscoll BR, Howard LS, and Davison AG. (2008). BTS guideline for emergency oxygen use in adult patients. *Thorax*, **63**(Suppl. 6), vi1–68.
16. Austin MA, Wills KE, Blizzard L, Walters EH, and Wood-Baker R. (2010). Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *British Medical Journal*, **341**, c5462.
17. Roberts CM, Stone RA, Buckingham RJ, Pursey NA, and Lowe D. (2011). Acidosis, non-invasive ventilation and mortality in hospitalised COPD exacerbations. *Thorax*, **66**(1), 43–8.
18. Perrin K, Wijesinghe M, Healy B, et al. (2011). Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. *Thorax*, **66**(11), 937–41.
19. Wijesinghe M, Perrin K, Healy B, Weatherall M, and Beasley R. (2012). Randomized controlled trial of high concentration oxygen in suspected community-acquired pneumonia. *Journal of the Royal Society of Medicine*, **105**(5), 208–16.
20. Campbell EJ. (1965). Respiratory failure. *British Medical Journal (Clinical Research edn)*, **1**(5448), 1451–60.

CHAPTER 33

Bronchodilators in critical illness

Rajiv Dhand and Michael McCormack

Key points

- Pressurized metered-dose inhalers (pMDIs) and nebulizers are routinely used for aerosol delivery to ventilator-supported patients.
- A complex array of factors influences the efficiency of drug delivery in mechanically-ventilated patients.
- With an optimal technique of administration, drug deposition in the lower respiratory tract of ventilator-dependent patients is comparable with that achieved in ambulatory patients.
- Recommended doses of bronchodilators in mechanically-ventilated patients are higher than in ambulatory patients to compensate for the effects of humidity in the ventilator circuit.
- Despite major impediments to drug delivery during non-invasive positive pressure ventilation (NIPPV), significant responses can be achieved following bronchodilator administration with a jet nebulizer or pMDI.

Introduction

Beta-adrenergic agonists, anticholinergic drugs, and methylxanthines are commonly used in critically-ill patients who are in urgent need of bronchodilation. Beta-adrenergic agonists and anticholinergics are preferably administered by inhalation, whereas methylxanthines can only be administered enterally or parenterally. Intravenous beta-agonists may be used in patients who are refractory to inhaled beta-agonists. The doses of inhaled drugs used in mechanically-ventilated patients are shown in Table 33.1.

Beta-agonists in asthma and chronic obstructive pulmonary disease

Increasing doses of beta-agonists produce greater bronchodilation, but they also increase adverse effects. Usually, 5–10 mg of albuterol produces maximum bronchodilation in severe asthma [1]. Patients who fail to respond to such doses (non-responders) may require hospital admission, whereas responders could be discharged from the emergency department. If pulmonary function does not improve by the end of the first hour of treatment and the asthma attack is severe, continuous nebulization may provide additional benefit [2].

Anticholinergics in asthma and chronic obstructive pulmonary disease

In patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), a pooled analysis comparing fenoterol and metaproterenol with ipratropium found no significant differences in improvement in FEV_1 [3].

Combination therapy is not unequivocally superior to individual drug therapy, but ipratropium can be added when the response to beta-agonists is suboptimal, or if the exacerbation is severe.

Side effects of beta-agonists and anticholinergics

Beta-agonists predictably increase heart rate, and occasional reports of angina and myocardial infarction suggest the potential for myocardial injury. Higher doses of these agents should be used with caution, especially in elderly, hypoxaemic patients. There may be a transient decrease in PaO_2 after beta-agonist inhalation, but not following inhalation of anticholinergic agents. Therefore, a significant fall in PaO_2 can occur during beta-agonist administration and patients with marginal oxygenation should be closely monitored.

Ipratropium and tiotropium do not influence mucus secretion or the rheological properties of mucus, although some reports suggest a decrease in sputum volume. Mucociliary clearance is unchanged with ipratropium use. Dry mouth is the most common side effect, and unilateral mydriasis has been reported with nebulized ipratropium.

Methylxanthines

In acute asthma or COPD, theophylline does not confer additional bronchodilation in patients receiving intensive therapy with inhaled beta-agonists and intravenous corticosteroids [4]. Currently, theophylline is recommended only for patients who fail to respond to beta-agonists, have paradoxical bronchospasm, or have impending respiratory failure. Careful monitoring is required to maintain plasma theophylline levels between 5 and 15 mg/L because these levels could fluctuate with resulting changes in the patient's condition. The frequent occurrence of side-effects with theophylline, especially nausea and vomiting, is a major drawback.

Factors influencing aerosol delivery during mechanical ventilation

In the past, poor efficiency of aerosol delivery to the lungs with pressurized metered-dose inhalers (pMDIs) and nebulizers has meant that much larger doses of drugs than those employed in ambulatory patients are needed in patients receiving mechanical ventilation. With optimized techniques of administration, large increases in the administered dose of a drug may not be necessary to achieve therapeutically meaningful effects [5].

Table 33.1 Doses and duration of action of commonly used bronchodilators in ventilated patients*

Agents	Dose	Time course (onset, peak, duration)	Frequency of dosing
Albuterol (salbutamol)	*SVN*: 0.083% solution, 3 mL (2.5 mg) *pMDI*: 90 mcg/puff, four puffs	5–15 minutes, 30–60 minutes, 4–6 hours	4–6 times daily
Levalbuterol	*SVN*: 0.63 mg or 1.25 mg	15 minutes, 30–60 minutes, 4–6 hours	3–4 times daily
Formoterol	*SVN*: 20 mcg/2 mL solution	1–3 minutes, 1–3 hours, 8–12 hours	2 times daily
Arformoterol	*SVN*: 15 mcg/2 mL solution	1–3 minutes, 1–3 hours, 8–12 hours	2 times daily
Ipratropium	*pMDI*: 18 mcg/puff, four puffs, *SVN*: 0.02% solution, 2.5 mL (0.5 mg)	15 minutes, 90–120 minutes, 4–6 hours	4–6 times daily
Albuterol + ipratropium	*pMDI*: 90 mcg + 18 mcg/puff, four puffs *SVN*: 2.5 mg + 0.5 mg/dose	5–15 minutes, 30–60 minutes, 4–6 hours	4–6 times daily

*Dry powder inhalers are not routinely used in ventilated patients.

pMDI, pressurized metered-dose inhaler; SVN, small volume nebulizer.

Efficiency of drug delivery with pMDIs and nebulizers in laboratory models of mechanical ventilation ranges from 0.3 to 97.5% of the nominal dose depending on the formulation and technique of administration [6]. Obviously, such extreme variability is undesirable and administration techniques that lead to inadequate drug delivery could result in therapeutic failure. Careful attention to several factors is required to achieve consistently efficient drug delivery, including variables related to the aerosol-generating device, the ventilator and ventilator circuit, the inhaled drug or agent, and the patient [6].

With pMDIs, several commercially-available adapters are used to connect the canister to the ventilator circuit, ranging from simple adapters with a port and single nozzle to more complex adapter designs with a chamber and third-party actuator. A pMDI connected to a chamber spacer of about 140 mL volume, placed at a distance of approximately 15 cm from the endotracheal tube provides efficient aerosol delivery in mechanically-ventilated patients, and elicits a significant bronchodilator response [5]. Moreover, pMDI actuation must be synchronized with the precise onset of inspiratory airflow from the ventilator. Even a 1–1.5-s delay between pMDI actuation and ventilator breath can profoundly reduce drug delivery [7]. Furthermore, the pMDI must be appropriately primed before first use or if it has not been actuated for more than 24 hours.

With a jet nebulizer, placement in the inspiratory limb at a distance from the endotracheal tube improves efficiency compared with placement between the 'y' connector and endotracheal tube. The nebulizer brand, nebulizer design, diluent volume, operating pressures and flows, and treatment duration are other factors influencing nebulizer efficiency [8]. Ultrasonic nebulizers are infrequently used for bronchodilator therapy during mechanical ventilation. Likewise, there are limited clinical data with vibrating mesh nebulizers in mechanically-ventilated patients, although bench studies show a 2–4-fold greater efficiency of drug delivery with these nebulizers compared with conventional jet nebulizers [9].

In a ventilator circuit, nebulizers can be operated continuously or intermittently by airflow from the ventilator. The efficiency of some nebulizers is decreased by the lower pressure of gas supplied by the ventilator during intermittent operation compared with continuous operation with gas under higher pressure from a tank or wall outlet at a similar flow rate. Thus, with gas flow from a ventilator, the specific ventilator and nebulizer brand should be tested to determine the aerosol characteristics and efficiency of drug delivery [10].

Other factors that enhance the efficiency of bronchodilator delivery include a tidal volume of 500 mL or more (in an adult), a longer inspiratory time, and slower inspiratory flows [11]. Drug delivery is linearly correlated with a longer duty cycle (T_I/T_{TOT}) for both pMDIs and nebulizers [12].

With jet nebulizers, aerosol delivery is influenced by inspiratory time, pattern of inspiratory flow, and lung mechanics. Delivery is notably lower during pressure-controlled compared with volume-controlled ventilation [13]. Use of flow triggering with a nebulizer could dilute the aerosol and increase aerosol washout into the expiratory limb between breaths.

Circuit humidity reduces drug delivery from both pMDIs and nebulizers by 40% or more compared with a dry circuit [6]. However, removing the humidifier for administration of routine bronchodilator therapy is not recommended. Such a practice would require opening the circuit for each treatment and it may take more than 1 hour after shutting off the humidifier for the circuit humidity to decrease to a level that would enhance drug delivery [14].

A more practical solution is to compensate for the effects of humidity by increasing the bronchodilator dose.

Modifying the density of the gas in the circuit affects aerosol delivery. With helium–oxygen mixtures in the ventilator circuit, drug delivery with a pMDI was 50% greater than with oxygen alone. A practical method to achieve a similar increase in efficiency with a jet nebulizer is to operate the nebulizer with oxygen (6–8 L/min) and to entrain the aerosol into a ventilator circuit containing helium-oxygen [15].

Impaction of aerosol on the endotracheal tube is a major impediment to efficient aerosol delivery, particularly in paediatric ventilator circuits with small endotracheal tubes (internal diameter (ID) 3–6 mm). With larger endotracheal tubes (ID 7–9 mm), the type of aerosol generator and ventilator settings have a greater influence on aerosol deposition within the tube than the endotracheal tube ID per se.

In mechanically-ventilated patients, gamma scintigraphy and measurement of plasma or urinary drug levels also demonstrate that administration technique influences drug delivery.

Bronchodilator therapy

Bronchodilators are among the most commonly used drugs in ventilator-supported patients with acute severe asthma or acute exacerbations of COPD [5,16]. Common indications for bronchodilator therapy in ventilated patients are summarized in Box 33.1. Optimal techniques for bronchodilator administration, based on consideration of various factors influencing aerosol delivery, are shown in Boxes 33.2 and 33.3.

When the technique of administration is carefully executed, the majority of stable mechanically-ventilated patients with COPD achieved near maximal decrease in airway resistance and intrinsic positive end-expiratory pressure (PEEP) following administration of four puffs of albuterol [5]. Patients with acute exacerbations of asthma or COPD may require higher doses of inhaled bronchodilators, but further studies are needed to establish a dosing schedule for such patients. In stable patients with COPD, the bronchodilator effect of albuterol is sustained for 2–3 hours [16]. In ventilator-supported patients with COPD, fenoterol and ipratropium bromide in combination were more effective than ipratropium alone. Although bronchodilators are commonly used in a diverse group of patients receiving mechanical ventilation at considerable additional cost [17], they do not definitely improve clinical outcomes [18].

Box 33.1 Indications for bronchodilator therapy in patients receiving mechanical ventilation

- Severe asthma.
- COPD.
- Acute bronchospasm or wheezing.
- Elevated airway resistance.
- Dynamic hyperinflation/intrinsic PEEP.
- Difficulty in weaning.
- Chronic ventilator-dependence.

Box 33.2 Optimal technique for drug delivery by pMDI in mechanically ventilated patients

- Review order, identify patient, and assess need for bronchodilator.
- Suction endotracheal tube and airway secretions.
- Shake pMDI and warm to hand temperature.
- Place pMDI in space chamber adapter in ventilator circuit.
- Remove heat and moisture exchanger (HME) if used. Do not disconnect humidifier.
- Coordinate pMDI actuation with beginning of inspiration.
- Wait at least 15 seconds between actuations; administer total dose.
- Monitor for adverse response.
- Reconnect HME.
- Document clinical outcome.

This table was published in Egan's *Fundamentals of Respiratory Care*, 8th edn, Wilkins RL et al., p. 795, Copyright Elsevier 2003 [20].

Box 33.3 Optimal technique for drug delivery by jet nebulizer in mechanically-ventilated patients

- Review order, identify patient, and assess need for bronchodilator.
- Suction endotracheal and airway secretions.
- Place drug in nebulizer to fill volume of 4–6 mL.
- Place nebulizer in the inspiratory line 18 in (46 cm) from the 'y' connector.
- Turn off flow-by or continuous flow during nebulizer operation.
- Remove HME (if used) from circuit. Do not disconnect humidifier.
- Set gas flow to nebulizer at 6–8 L/min.
  - Use a ventilator if it meets the nebulizer flow requirements and cycles on inspiration, or
  - Use continuous flow from external source.
- Adjust ventilator volume or pressure limit to compensate for added flow.
- Tap nebulizer periodically until nebulizer begins to sputter.
- Remove nebulizer from circuit, rinse with sterile water and run dry, store in safe place.
- Reconnect HME, return ventilator settings and alarms to previous values.
- Monitor patient for adverse response.
- Assess outcome and document findings.

This table was published in Egan's *Fundamentals of Respiratory Care*, 8th edn, Wilkins RL et al., p. 795, Copyright Elsevier 2003 [20].

Bronchodilator therapy during non-invasive ventilation

Patients receiving non-invasive positive pressure ventilation (NIPPV) for treatment of acute and chronic respiratory failure often require inhaled bronchodilators. Despite several impediments to drug delivery in patients receiving NIPPV, significant bronchodilator responses have been observed after albuterol administration by a jet nebulizer or a pMDI [19].

References

1. McFadden ER Jr, Strauss L, Hejal R, Galan G, and Dixon L. (1998). Comparison of two dosage regimens of albuterol in acute asthma. *American Journal of Medicine*, **105**, 12–17.
2. Rudnitsky GS, Eberlein RS, Schoffstall JM, Mazur JE, and Spivey WH. (1993). Comparison of intermittent and continuously nebulized albuterol for treatment of asthma in an urban emergency department. *Annals of Emergency Medicine*, **22**, 1842–6.
3. Brown CD, McCrory D, and White J. (2008). Inhaled short-acting beta2-agonists versus ipratropium for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Systems Review*, **1**, 1.
4. Siegel D, Sheppard D, Gelb A, and Weinberg PF. (1985). Aminophylline increases the toxicity but not the efficacy of an inhaled beta-adrenergic agonist in the treatment of acute exacerbations of asthma. *American Review of Respiratory Diseases*, **132**, 283–6.
5. Dhand R, Duarte AG, Jubran A, et al. (1996). Dose-response to bronchodilator delivered by metered-dose inhaler in ventilator-supported patients. *American Journal of Respiratory and Critical Care Medicine*, **154**, 388–93.
6. Dhand R, and Tobin MJ. (1997). Inhaled bronchodilator therapy in mechanically ventilated patients. *American Journal of Respiratory and Critical Care Medicine*, **156**, 3–10.
7. Diot P, Morra L, and Smaldone GC. (1995). Albuterol delivery in a model of mechanical ventilation. Comparison of metered-dose inhaler and nebulizer efficiency. *American Journal of Respiratory and Critical Care Medicine*, **152**, 1391–4.
8. O'Riordan TG, Greco MJ, Perry RJ, and Smaldone GC. (1992). Nebulizer function during mechanical ventilation. *American Review of Respiratory Diseases*, **145**, 1117–22.
9. Ari A, Atalay OT, Harwood R, Sheard MM, Aljamhan EA, and Fink JB. (2010). Influence of nebulizer type, position, and bias flow on aerosol drug delivery in simulated pediatric and adult lung models during mechanical ventilation. *Respiratory Care*, **55**(7), 845–51.
10. Miller DD, Amin MM, Palmer LB, Shah AR, and Smaldone GC. (2003). Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. *American Journal of Respiratory and Critical Care Medicine*, **168**, 1205–9.
11. Fink JB, Dhand R, Duarte AG, Jenne JW, and Tobin MJ. (1996). Aerosol delivery from a metered-dose inhaler during mechanical ventilation. An in vitro model. *American Journal of Respiratory and Critical Care Medicine*, 154:382–87.
12. Fink JB, Dhand R, Grychowski J, Fahey PJ, and Tobin MJ. (1999). Reconciling in vitro and in vivo measurements of aerosol delivery from a metered-dose inhaler during mechanical ventilation and defining efficiency-enhancing factors. *American Journal of Respiratory and Critical Care Medicine*, **159**, 63–8.
13. Hess DR, Dillman C, and Kacmarek RM. (2003). In vitro evaluation of aerosol bronchodilator delivery during mechanical ventilation: pressure-control vs. volume control ventilation. *Intensive Care Medicine*, **29**, 1145–50.
14. Lin HL, Fink JB, Zhou Y, and Cheng YS. (2009). Influence of moisture accumulation in in-line spacer on delivery of aerosol using metered-dose inhaler during mechanical ventilation. *Respiratory Care*, **54**, 1336–41.
15. Goode ML, Fink JB, Dhand R, and Tobin MJ. (2001). Improvement in aerosol delivery with helium-oxygen mixtures during mechanical ventilation. *American Journal of Respiratory and Critical Care Medicine*, **163**, 109–14.
16. Duarte AG, Momii K, and Bidani A. (2000). Bronchodilator therapy with metered-dose inhaler and spacer versus nebulizer in mechanically ventilated patients: comparison of magnitude and duration of response. *Respiratory Care*, **45**, 817–23.
17. Ely EW, Baker AM, Evans GW, and Haponik EF. (2000). The distribution of costs of care in mechanically ventilated patients with chronic obstructive pulmonary disease. *Critical Care Medicine*, **28**, 408–13.
18. Chang LH, Honiden S, Haithcock JA, et al. (2007). Utilization of bronchodilators in ventilated patients without obstructive airways disease. *Respiratory Care*, **52**, 154–8.
19. Dhand R. (2012). Aerosol therapy in patients receiving noninvasive positive pressure ventilation. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, **25**, 63–78.
20. Fink J. (2003). *Egan's Fundamentals of Respiratory Care*. Wilkins RL, Stoller JK, Scanlan CL (eds), 8th edn, pp. 761–800. St. Louis, MO: Mosby.

PART 2.2

Cardiovascular drugs

CHAPTER 34

Vasopressors in critical illness

Daniel De Backer and Patrick Biston

Key points

- Norepinephrine is the agent of choice, especially in cardiogenic shock.
- Epinephrine is associated with more arrhythmias and metabolic undesired events, especially at high doses.
- Vasopressin, at low doses, seems to be a promising alternative to adrenergic agents.
- Nitric oxide inhibition should not be considered.
- Excessive vasoconstriction can compromise tissue perfusion.

Introduction

Vasopressor agents are used to increase arterial pressure in order to improve tissue perfusion. In most cases, these are used in patients with shock of various origins. Less frequently, they can be used to improve cerebral perfusion pressure.

Haemodynamic consequences of vasopressor agents

Vasopressor agents induce arterial vasoconstriction, resulting in an increase in blood pressure; the desired effect may also be accompanied by less desired effects. First, the increase in arterial pressure induces an increase in left ventricular afterload, which may impair cardiac output. Secondly, they may preferentially vasoconstrict some vascular beds, in particular, the skin and splanchnic area.

The haemodynamic consequences of vasopressor therapy vary according to the type of vasopressor agent and the indication for their use. In distributive shock, vasopressor agents help to counteract a markedly decreased vascular tone. Hence, the increase in left ventricular afterload is usually well tolerated. In addition, venous constriction of large capacitance veins decreases unstressed volume and increases ventricular preload [1] so that cardiac output is maintained in most cases. Skin and splanchnic vasoconstriction are usually limited [2]. In haemorrhagic and cardiogenic shock, the situation differs markedly. Regional vasoconstriction will already have occurred to preserve cerebral and myocardial perfusion. Administration of vasopressors further constricts these areas, potentially leading to local ischaemia. Left ventricular afterload increases and may impair cardiac output. The effects on myocardial oxygen balance are difficult to predict. The increase in diastolic pressure improves myocardial perfusion, but on the other hand, myocardial work also increases. Myocardial ischaemia may occur in some patients, especially when heart rate (HR) increases. In haemorrhagic shock, venous vasoconstriction has minimal effect, as capacitance veins are already empty. In cardiogenic shock, venous constriction of congested capacitance veins markedly increases ventricular preload that, combined with the increase in left ventricular afterload, may result in pulmonary congestion in patients with poor ventricular function.

When vasopressors are used to increase cerebral perfusion pressure, the increase in left ventricular afterload and increase in myocardial work are not compensated for by an increase in myocardial perfusion. It may result in myocardial ischaemia or even the Tako–Tsubo syndrome.

The impact on regional perfusion, in particular splanchnic and renal perfusion, also varies according to the indication. In vasodilatory shock, vasopressors usually preserve or even improve regional perfusion, while they further impair regional perfusion in other types of shock or when used to increased cerebral perfusion pressure.

Adrenergic vasopressor agents

Adrenergic agents exert their vasopressor effect through stimulation of alpha-adrenergic receptors. However, the different adrenergic vasopressor agents also variably stimulate beta and sometimes dopaminergic-adrenergic receptors. Stimulation of these receptors results in various haemodynamic and metabolic effects (Table 34.1).

Differences in receptor binding explain the different profiles of the various adrenergic vasopressor agents. Stimulation of beta-receptors is associated with an increase in contractility, HR, and regional perfusion [2], and is also associated with many potential untoward effects. Beta stimulation is responsible for the development of arrhythmias and metabolic effects, such as an increase in temperature, accelerated glycolysis, and hyperlactataemia. Beta stimulation also induces immunodepression [3]. Even though these effects are less pronounced in stress conditions than in healthy conditions [4], they may endanger haemodynamically-unstable critical patients.

Dopaminergic stimulation is associated with an increase in splanchnic and renal blood flow. However, this effect is almost non-existent in critically-ill patients. It also induces depression of the hypothalamo-pituitary axis [5], with suppression of prolactin release that may induce immunosuppression.

Most of the differences in haemodynamic effects between vasopressor adrenergic agents depend on the strength of stimulation of alpha- and beta-adrenergic receptors.

Norepinephrine

Norepinephrine is a powerful alpha-adrenergic agent with minimal beta-adrenergic effect, which results in a large increase in blood

Table 34.1 Main effects of adrenergic vasopressor agents

Receptor stimulation	Effects	Consequences
Alpha-adrenergic	Arterial constriction	Increase in arterial pressure
		Increased in cardiac afterload (= > decrease in cardiac output)
	Splanchnic constriction	Impaired splanchnic perfusion
	Venous constriction	Increase in cardiac preload (= > increase in cardiac output in preload dependent patients)
Beta-adrenergic	Cardiac (inotropic)	Increase in cardiac output
	Cardiac (chronotropic)	Tachycardia/arrhythmias
	Peripheral vasodilation	Hypotension
	Splanchnic vasodilation	Increase splanchnic perfusion
	Metabolic	Hyperthermia, accelerated glycolysis, hyperlactataemia, increased VO_2
	Immunological	Immunosuppression
Dopaminergic	Splanchnic dilation	Increase splanchnic and renal perfusion (questioned)
	Endocrine	Pituitary dysfunction

pressure, while cardiac output is preserved or even increased. It has minimal impact on HR [6].

Phenylephrine

Phenylephrine is a pure alpha-adrenergic agent that markedly increases blood pressure and may decrease cardiac output. The impact on cardiac output depends on relative changes in afterload and preload, and to the position on Starling curve. In preload dependent patients, cardiac output is usually preserved while it decreases in preload independent patients [7]. At a given volaemic state, phenylephrine, compared with norepinephrine, is associated with a decrease in cardiac output and splanchnic perfusion [8]. There are not enough data to evaluate the impact of this agent on outcome.

Epinephrine

Epinephrine results in a marked and proportional stimulation of alpha- and beta-adrenergic receptors, resulting in a combined increase in arterial pressure and cardiac output. As doses of this agent are titrated to its effect on blood pressure, beta-adrenergic stimulation may become excessive at high doses. As a result of this metabolic stimulation, an imbalance between oxygen demand and oxygen delivery may be observed, and this effect is even more pronounced in the splanchnic area [9]. When patients are randomized to receive norepinephrine or epinephrine, similar doses are required to reach the same blood pressure level [10–12]. Usual doses of epinephrine and norepinephrine are between 0.1 and 1.0 mcg/kg/min, but there is no upper dose recommended for either agent (very high doses may be futile, but survival has sometimes been observed in patients treated with doses of 5–10 mcg/kg/min for a few hours). Interestingly, HR, temperature, blood glucose, and blood lactate levels increase in patients receiving epinephrine, but not norepinephrine [10–12]. On the other hand, pH is usually lower in epinephrine than in norepinephrine patients. These differences decrease with time of exposure, but may last up to 2 days. Arrhythmias are more frequent in epinephrine-treated patients. Only one trial compared the effects of epinephrine with a combination of norepinephrine and dobutamine on outcome in patients with septic shock [10]. Mortality at 28 days did not differ significantly between the groups (epinephrine 40% versus norepinephrine 34%, $p = 0.31$), but the trial was not powered to evaluate the 6% difference in mortality rate. In addition, 5 mcg/kg/min of dobutamine was used in all patients in norepinephrine arm, and this dose was tapered down only when mean arterial pressure was at least 70 mmHg, which may have resulted in unnecessary beta-stimulation in many patients. A trial comparing epinephrine and norepinephrine in patients with cardiogenic shock is currently under way in France.

Dopamine

Dopamine has a relatively similar profile to epinephrine, but results in less potent stimulation on both alpha- and beta-receptors. Accordingly, around one-third of shock patients fail to respond to maximal doses of dopamine (20 mcg/kg/min), while most respond to norepinephrine or epinephrine. Compared with norepinephrine, dopamine is associated with a higher HR, while other haemodynamic variables are similar. In addition, there is an increase in arrhythmias, while the other side effects did not differ between the two drugs.

In a large-scale randomized trial comparing dopamine and norepinephrine as the first vasopressor agent, we failed to observe significant differences in day 28 risk of death between dopamine and norepinephrine (relative risk 1.17 [0.97–1.42], $p = 0.10$) [6]. Importantly, in the predefined subgroup of patients with cardiogenic shock ($n = 280$), there was a significant increase in mortality with dopamine (relative risk 1.38 [1.03–1.85], $p = 0.03$). In a meta-analysis focusing on patients with septic shock ($n = 1408$), there was also a significant increase in mortality with dopamine (relative risk 1.10[1.01–1.20], $P = 0.035$) [13].

Vasopressinergic agents

Arginine vasopressin is the most commonly used agent, characterized by a short half-life. Lysine vasopressin can also be used and

seems equally effective as vasopressin [14], but is characterized by a longer half-life and has been studied less. Selective V1 receptor agonists are currently in development. Only arginine vasopressin will be covered here. Vasopressin exerts its vasopressor properties through stimulations of V1 receptors, but also facilitates the response to adrenergic vasopressors. Vasopressin has weak vasopressor effects in normal conditions, but can markedly increase vascular tone in shock states, and especially in septic shock. This accentuated response to vasopressin in shock may be related to decreased endogenous levels of vasopressin, which usually occur after a few days, especially in septic shock, even though endogenous vasopressin levels are usually elevated during the initial phase. Vasopressin receptor stimulation also decreases vascular leakage. Of note, stimulation of V2 receptors favours platelet aggregation. Distribution of vasopressin receptors in the vascular tree is heterogeneous. Accordingly, vasopressin markedly decreases splanchnic perfusion (and portal vein pressure), especially at high doses. In the kidney, it also constricts efferent more than afferent arterioles, leading to an increase in glomerular filtration pressure.

Vasopressin use is mostly proposed in distributive and especially in septic shock. Arginine vasopressin at doses of 0.02–0.04 U/min increases blood pressure and spares adrenergic vasopressor use. Cardiac output is usually preserved, even though HR decreases slightly. Interestingly, urine output and creatinine clearance may increase during vasopressin administration, even though vasopressin is also named antidiuretic hormone [15]. The safety profile of this agent has been reported in several observational trials, but there is only one large-scale randomized trial that compared vasopressin with norepinephrine in the treatment of 778 patients with septic shock [16]. The haemodynamic profile of patients treated by these agents was similar with the exception that HR that was significantly lower in patients treated with vasopressin [17]. Of note, inotropic agents were more frequently used in vasopressin-treated patients. This trial did not demonstrate any difference in outcome in the entire population (28 days mortality: 35% in vasopressin group versus 39%, in norepinephrine group; $P = 0.26$) [16]. There were no differences in the incidence of side effects. In a predefined subgroup analysis, a decrease in mortality reaching borderline statistical significance was observed in the subgroup of patients treated with low doses of norepinephrine (less than 15 mcg/min) at the time of randomization (27 versus 36%, respectively, $p = 0.05$ for unadjusted Chi-square and $p = 0.03$ with log rank statistics), but not in the other patients (44 versus 43%, respectively, $p = 0.76$). These results, although promising, require confirmation. Of note, the criteria defining low severity at baseline is difficult to use at the bedside. It can change over time and, more importantly, patients of different weight receiving the same dose of norepinephrine (expressed in mcg/kg/min) may be classified differently.

Other vasopressor agents

Nitric oxide (NO) inhibition can be considered as NO may be implicated in excessive vasodilation in sepsis and in resuscitated cardiogenic shock. Disappointing results have been reported with non-selective NO synthase inhibitors. In a randomized trial including 797 patients with septic shock, 28 days mortality was higher in the NO inhibitor group compared with the placebo group (59 versus 49%; $P < 0.001$) [18]. A trial in patients with cardiogenic shock was stopped for futility after inclusion of 398 patients [19].

Selective inducible nitric oxide synthase (iNOS) inhibition may be more effective, but no compound has reached the clinical arena.

Methylene blue, as an inhibitor of guanylate cyclase, can blunt the effects of NO and thus improve vascular tone. This compound has only been tested in small trials, but improves arterial pressure and myocardial contractility with a short-lasting effect [20]. The impact on outcome has not been evaluated.

References

1. Monnet X, Jabot J, Maizel J, Richard C, and Teboul JL. (2011). Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients (R3). *Critical Care Medicine*, **39**, 689–94.
2. Zhang H, De Jongh R, De Backer D, Cherkaoui S, Vray B, and Vincent JL. (2001). Effects of alpha- and beta-adrenergic stimulation on hepatosplanchnic perfusion and oxygen extraction in endotoxic shock. *Critical Care Medicine*, **29**, 581–8.
3. van der Poll T, Coyle SM, Barbosa K, Braxton CC, and Lowry SF. (1996). Epinephrine inhibits tumor necrosis factor-alpha and potentiates interleukin 10 production during human endotoxemia. *Journal of Clinical Investigation*, **97**, 713–19.
4. Uusaro A, Hartikainen J, Parviainen M, and Takala J. (1995). Metabolic stress modifies the thermogenic effect of dobutamine in man. Critical Care Medicine, **23**, 674–80.
5. van den Berghe G and de Zegher F. (1996). Anterior pituitary function during critical illness and dopamine treatment. *Critical Care Medicine*, **24**, 1580–90.
6. De Backer D, Biston P, Devriendt J, et al. (2010). Comparison of dopamine and norepinephrine in the treatment of shock. *New England Journal of Medicine*, **362**, 779–89.
7. Cannesson M, Jian Z, Chen G, Vu TQ, and Hatib F. (2012). Effects of phenylephrine on cardiac output and venous return depend on the position of the heart on the Frank–Starling relationship. *Journal of Applied Physiology*, **113**, 281–9.
8. Reinelt H, Radermacher P, Kiefer P, et al. (1999). Impact of exogenous beta-adrenergic receptor stimulation on hepatosplanchnic oxygen kinetics and metabolic activity in septic shock. *Critical Care Medicine*, **27**, 325–31.
9. De Backer D, Creteur J, Silva E, and Vincent JL. (2003). Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? *Critical Care Medicine*, **31**, 1659–67.
10. Annane D, Vignon P, Renault A, et al. (2007). Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet*, **370**, 676–84.
11. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, and Santamaria J. (2008). A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Medicine*, **34**, 2226–34.
12. Levy B, Perez P, Perny J, Thivilier C, and Gerard A. (2011). Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. *Critical Care Medicine*, **39**, 450–5.
13. De Backer D, Aldecoa C, Njimi H, and Vincent J-L. (2012). Dopamine versus norepinephrine in the treatment of septic shock: a metaanalysis. *Critical Care Medicine*, **40**, 725–30.
14. Morelli A, Ertmer C, Rehberg S, et al. (2009). Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. *Critical Care Medicine*, **13**, R130.
15. Patel BM, Chittock DR, Russell JA, and Walley KR. (2002). Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology*, **96**, 576–82.
16. Russell JA, Walley KR, Singer J, et al. (2008). Vasopressin versus norepinephrine infusion in patients with septic shock. *New England Journal of Medicine*, **358**, 877–87.
17. Gordon AC, Wang N, Walley KR, Ashby D, and Russell JA. (2012). The cardio-pulmonary effects of vasopressin compared to norepinephrine in septic shock. *Chest* **142**(3), 593–605.

18. Lopez A, Lorente JA, Steingrub J, et al. (2004). Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Critical Care Medicine*, **32**, 21–30.
19. Alexander JH, Reynolds HR, Stebbins AL, et al. (2007). Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. *Journal of the American Medical Association*, **297**, 1657–66.
20. Preiser JC, Lejeune P, Roman A, et al. (1995). Methylene blue administration in septic shock: a clinical study. *Critical Care Medicine*, **23**, 259–64.

CHAPTER 35

Vasodilators in critical illness

A. B. J. Groeneveld and Alexandre Lima

Key points

- Administration of vasodilators is the treatment of choice for hypertensive emergencies and cardiogenic pulmonary oedema.
- Vasodilating therapy may alleviate pulmonary hypertension, but often at the expense of an increased venous admixture of oxygen in the lungs.
- Vasodilators can be used as potential adjunctive therapy to recruit microvascular perfusion in circulatory shock.
- Vasodilators may precipitate harmful hypotension and tachycardia, and should be carefully dosed.
- Invasive monitoring may be indicated for proper institution and guidance of vasodilator therapy.

Introduction

Vasodilator drugs play a major therapeutic role in hypertensive emergencies, primary and secondary pulmonary hypertension, and acute left heart and circulatory shock. Intravenous administration and titration guided by the haemodynamic response is preferred in the intensive care unit (ICU). There are large differences between individuals and drugs in dose–response relationships. As a rule, the vasodilating effect is greatest in patients with severe vasoconstriction.

Classes and types of vasodilators

The term vasodilator refers to drugs acting directly on the smooth muscles of peripheral vessel walls, and drugs are usually classified based on their mechanism or site of action. Some drugs have a predominant effect on resistance vessels (arterial dilators), while others primarily affect venous capacitance vessels (venous dilators). Although drugs may be classified as 'arterial' or 'venous' vasodilators, most have mixed properties. If the goal of vasodilation is preload reduction, one should target capacitance vessels. This will decrease venous return, and could lead to a fall in cardiac output and blood pressure. If the aim of vasodilation is an afterload reduction, one should target peripheral resistance vessels, which will improve forward stroke volume. Drugs can be divided in two types of pharmacological effects—vasodilator drugs with direct action on smooth muscle and drugs acting indirectly as vasodilators. Drugs with direct action target to relax vascular smooth muscle by interfering with calcium movements across cell membrane inhibiting the smooth muscle contracting process, such as calcium entry blockers. Drugs that interfere with sympathetic nervous system, block renin-angiotensin system, phosphodiesterase inhibitors and alpha-adrenoreceptor antagonists are some examples of drugs with indirect effect. Table 35.1 summarizes the main types of vasodilators drugs commonly used in the ICU.

Vasodilator therapy to control arterial blood pressure and to unload the left heart

Hypertensive emergencies

Drugs used for the treatment of hypertensive emergencies in the ICU include intravenously administered calcium channel inhibitors, sodium nitroprusside, nitroglycerin, phentolamine, and other alpha-adrenergic blockers, diazoxide, hydralazine, and angiotensin-converting enzyme inhibitors. These drugs reduce arterial blood pressure in a relatively short period of time, but effects may be erratic with dangerous episodes of hypotension threatening vital organ perfusion. Intravenous administration of alpha- and beta-adrenergic-inhibiting labetalol has gained popularity. The sublingual administration of both nifedipine and captopril is slightly more rapidly effective than the oral route, and has been shown to be effective initial treatment.

Dissecting aneurysm

Treatment should diminish wall stress by reducing arterial blood pressure and pulse pressure. Vasodilators are often associated with reflex tachycardia and a rise in pulse pressure so should be combined with beta-blocking agents to prevent a rise in wall stress. The short-acting vasodilating beta-receptor blocker esmolol may be an option as is the combined alpha- and beta-receptor blocker labetalol. Trimetaphan, a sympatholytic agent, has been the drug of choice for the acute management of aortic dissection because of a lack of reflex tachycardia and rise in pulse pressure.

Accelerated hypertension in pregnancy

Angiotensin-converting enzyme inhibitors are relatively contraindicated because of the risk of fetal death, while nitroprusside and nifedipine are contraindicated because of fear of toxicity. Preferred drugs are labetalol, hydralazine, ketanserin, and calcium channel blockers.

Post-operative hypertension

The drugs used for post-operative hypertension in the recovery room or the ICU include calcium antagonists, labetalol, nitroglycerin (glyceryl trinitrate), nitroprusside, ketanserin, and beta-blocking esmolol.

Table 35.1 Vasodilators in use in the ICU

	Route	Dose	Onset	Duration	Side-effects
Nitrates					
Nitroglycerin	IV	0.07–5 μg/kg/min	Minutes	5–10 minutes	Tachyphylaxis, flush, headache, collapse, confusion
	Sublingual	0.4–1 mg	20–30 seconds	1 hours	
Isosorbide dinitrate	IV	0.5–3.5 μg/kg/min	Minutes	Minutes	Tachyphylaxis, flush, headache, collapse, confusion
	Oral	5–40 mg four times daily	15–40 minutes	4–6 hours	
Sodium nitroprusside	IV	0.5–50 μg/kg/min	30 seconds	2–3 minutes	Must be shielded from light, thiocyanate, and cyanide toxicity, methaemoglobinaemia, lactic acidosis, vitamin B12 deficiency
Alpha/beta-blockers					
Phentolamine	IV	0.5–15 μg/kg/min	1–2 minutes	1 hours	Flush, vertigo, angina
	IV	1–10 mg bolus			
Labetalol	IV	3–35 μg/kg/min	5–10 minutes	3–6 hours	Bronchoconstriction, heart block
	Oral	100–1000 mg bd	1 hour	6–12 hours	
Calcium antagonists					
Nifedipine	IV	0.1–0.3 μg/kg/min	Minutes	Minutes	Headache, ankle oedema, hyperglycaemia
	IV	5–10 mg bolus	Minutes	Minutes	
	Oral/sublingual	10–20 mg at 1 h or 10–40 mg three times daily	2–5 minutes	3–6 hours	
Isradipine	IV	0.15–0.6 μg/kg/min	Minutes	Minutes	Headache, ankle oedema, hyperglycaemia
	IV	0.5 mg bolus	8 minutes	1–2 hours	
	Oral	5 mg bd	2 hours	5–7 hours	
Nicardipine	IV	1–5 μg/kg/min	5–15 minutes	30 minutes	Headache, ankle oedema, hyperglycaemia
	Oral	20–40 mg tds	1–20 minutes	3 hours	
Nimodipine	IV	0.2–0.5 μg/kg/min	Minutes	Hours	Headache, ankle oedema, hyperglycaemia
	Oral	30–90 mg qds			
Clevidipine	IV	1 mg/h until a maximum of 21 mg/h	2–4 minutes	5–15 minutes	Arrhythmias, fever, gastrointestinal complaints
Angiotensin-converting enzyme inhibitors					
Captopril	Oral/sublingual	12.5–50 mg qds	10–15 minutes	6–12 hours	Renal failure, cough
Enalapril(at)	IV	0.2–0.4 μg/kg/min	15 minutes	6 hours	Headache, ankle oedema, hyperglycaemia
	Oral	5–40 mg/day	1 hours	4–6 hours	
Prostaglandins					
Epoprostenol	IV	5–35 ng/kg/min	Minutes	Minutes	Flush, hypoxaemia
Prostaglandin E_1	IV	20–100 ng/kg/min	Minutes	Minutes	Hypotension, diarrhoea, flush, headache

(*continued*)

Table 35.1 Continued

	Route	Dose	Onset	Duration	Side-effects
Phosphodiesterase inhibitors					
Enoximone	IV	Loading 0.1–2 mg/kg	10–30 minutes	3–6 hours	Arrhythmias, headache, gastrointestinal complaints
		Maintenance 5–20 μg/kg/min			
Amrinone	IV	Loading 0.75 μg/kg	10 minutes	3–6 hours	Arrhythmias, headache, gastrointestinal, thrombocytopenia
		Maintenance 5–10 μg/kg/min			
Milrinone	IV	Loading 50 μg/kg	5 minutes	6–8 hours	Arrhythmias, headache, gastrointestinal complaints
		Maintenance 0.5–0.75 μg/kg/min			
Miscellaneous					
Hydralazine	IV	0.2–5 μg/kg/min	15 minutes	3 hours	Tachycardia, lupus
	IV	5–10 mg bolus			
	Oral	25–100 mg bd	45 minutes	4–24 hours	
Ketanserin	IV	0.7–1.5 μg/kg/min	Minutes	1 hour	Arrhythmias, headache
	Oral	20–40 mg bd			
Trimetaphan	IV	5–50 μg/kg/min	1–5 minutes	10–15 min	Blurred vision, dry mouth, bladder, and gut paresis
Diazoxide	IV	0.7 μg/kg/min	5 minutes	6 hours	Hyperglycaemia
	IV	1–3 mg/kg bolus			
Levosimendan	IV	0.05–0.2 μg/kg/min	10–30 minutes	7 days (due to active metabolite)	Headache, arrhythmias

Acute congestive heart failure

Control of arterial blood pressure may help unload the heart and ameliorate pulmonary congestion. Nitroglycerin lowers the left heart filling pressure more than nitroprusside because of its greater venodilating effect. Unloading can also be performed by intravenous (iv) bolus doses of alpha-receptor blocking agents (such as phentolamine and urapidil) or enalaprilat, and by sublingual or iv doses of nifedipine and other first-generation calcium antagonists, although the latter have negative inotropic properties.

Vasodilator therapy to control pulmonary artery pressure and to unload the right heart

No systemically administered vasodilator has a completely selective pulmonary effect. In cases of shock complicated by pulmonary hypertension, systemic arterial hypotension aggravated by vasodilators may lead to (right) coronary hypoperfusion, further diminishing the right ventricular oxygen supply–demand balance and preventing a rise in cardiac output. Hence, it is better to treat pulmonary hypertension complicated by shock with vasoconstrictors rather than vasodilators [1].

Primary pulmonary hypertension

The treatment of primary pulmonary hypertension is often a matter of trial and error since sensitivity to one vasodilator does not imply sensitivity to another. Sensitivity can be tested in the ICU and this may help in the subsequent choice of vasodilators that can be administered orally on a long-term basis [2]. Acute responsiveness of the pulmonary circulation and long-term lowering of pulmonary artery pressure may improve right ventricular function and thereby ultimate survival [2].

Secondary pulmonary arterial hypertension

Vasodilators have been used to attenuate pulmonary hypertension selectively and unload the right heart. Epoprostenol appears to be a non-selective vasodilator that may lower pulmonary artery pressure and arterial oxygenation, and may not increase tissue oxygen delivery. In contrast, prostaglandin E_1 may have greater pulmonary vascular selectivity and less inhibitory effect on hypoxic vasoconstriction. Its administration in decompensated chronic obstructive lung disease may result in amelioration of pulmonary hypertension, and increased cardiac output and tissue oxygen delivery.

Pulmonary embolism

Some clinical studies have shown the potential haemodynamic and gas exchange benefit of nitric oxide (NO) inhalation in patients with pulmonary embolism [3]. Phosphodiesterase inhibitors and levosimendan have been used to restore right ventricular function in acute pulmonary embolism as a result of a combined pulmonary vasodilation and increased right ventricular contractility effect [3].

Septic shock and acute respiratory distress syndrome

During sepsis and acute respiratory distress syndrome, pulmonary vascular changes are thought to contribute to the diminished ability of the right heart to generate a sufficiently high cardiac output to meet increased tissue oxygen requirements [4]. Pulmonary hypertension can be ameliorated with the serotonin antagonist ketanserin without a rise in venous admixture. The use of (non-selective) nitrovasodilators and phosphodiesterase inhibitors may not increase tissue oxygen delivery due to a limited rise in cardiac output.

Vasodilating prostaglandins have been used as selective pulmonary vasodilators [5]. Prostaglandins may increase cardiac output, dilate pulmonary blood vessels, and maintain or increase PaO_2. Vasodilating prostaglandins have immunomodulating properties that may limit the inflammatory response in the lungs and thereby increase pulmonary gas exchange and patient survival [5]. NO inhalation dilates both airways and vessels locally, thereby improving ventilation-to-perfusion matching in during mechanical ventilation of severe cases of acute respiratory distress syndrome. Although effective on gas exchange and unloading the right ventricle, outcome benefit has not been proved.

Vasodilator therapy to improve the blood pressure–flow relationship

Vasodilator therapy has been used as an adjunct to recruit microvascular perfusion in circulatory shock. A rise in oxygen delivery and uptake may sometimes be accompanied by a rise in oxygen extraction, suggesting improved microcirculatory blood flow with this type of drug [6].

During reperfusion following ischaemia, cells are overloaded with calcium and this is believed to contribute to reperfusion injury. Hence, calcium antagonists have been studied in various models of shock and resuscitation for potentially protective effects on organ function. There is no place for the routine use of calcium antagonists in situations associated with ischaemia and reperfusion, even though the (cerebral) outcome of cardiac arrest was shown to be improved by the administration of the calcium antagonist nimodipine during prolonged cardiopulmonary resuscitation [7].

In subarachnoid haemorrhage nimodipine reduces cerebral vasospasm and subsequent ischaemic necrosis by dilating cerebral vessels and inhibiting cellular calcium overload thereby protect neurones. Adjunctive treatment with such drugs has been shown to improve neurological status and survival following subarachnoid haemorrhage [7].

Specific drugs

Nitrovasodilators

These drugs are the most frequently used vasodilators in the ICU [8]. Although sodium nitroprusside has mainly arterial vasodilating properties, nitroglycerin compounds are predominantly venodilators. At higher doses, they also have an arterial dilating effect and lower arterial blood pressure. The compounds release NO stimulating production of cyclic guanosine monophosphate in the vessel wall, leading to relaxation [8]. When administered intravenously, they have a rapid onset of action that is of short duration. The major limitation is the development of nitrate tolerance, most often seen after long-term continuous administration that can be circumvented by nitrate-free intervals (asymmetric dosing).

The drugs are occasionally used as adjunctive therapy in the treatment of shock, particularly if caused by a low cardiac output (e.g. in cardiogenic shock, after cardiopulmonary surgery, etc.). Nitroglycerin has been the vasodilator of choice to recruit the microcirculation in critically-ill patients. Apart from its quick onset of action (2–5 minutes) with half-life elimination of 1–3 minutes, the specific effect on smooth muscle mainly on the venous side of the vasculature leads to an increase in intravascular pressure gradient and in microvascular blood flow.

The major side-effect of nitroprusside is thiocyanate and cyanide toxicity, a complication that is usually avoided if treatment is limited to 3 days at maximum doses below 3 micrograms/kg/min with normal renal function. Signs of toxicity include central nervous system symptoms. Monitoring of thiocyanate levels in blood is mandatory during prolonged treatment with nitroprusside. The treatment of choice for toxicity is iv hydroxocobalamin (5 mg). Another potential specific side-effect of nitrovasodilators is methaemoglobinaemia.

Alpha-blockers

Some alpha-receptor blockers, such as phentolamine ($alpha_{1-2}$ blockade) are non-selective, and others, such as labetalol ($alpha_1$- and beta-blocker), are selective. Stimulation of the $alpha_1$ receptor causes arteriolar and venous constriction, and stimulation of the $alpha_2$-receptor causes decreased central sympathetic outflow. This type of drug is particularly useful in the treatment of pheochromocytoma crises, hypertension following intracranial hypertension, and pregnancy-induced hypertension [7].

Calcium antagonists

The first-generation calcium antagonists nifedipine, verapamil, and diltiazem have negative inotropic properties rendering these drugs less suitable for patients with (borderline) heart failure or for combination therapy with beta-blockers. The second-generation drugs, which include isradipine, nicardipine, and nimodipine, have fewer side-effects. These drugs have powerful vasodilating properties, and lack significant effects on cardiac conduction and contractility.

Clevidipine, a third-generation dihydropyridine calcium-channel blocker with unique pharmacodynamic and pharmacokinetic properties, is an ultra-short-acting selective arteriolar vasodilator that reduces blood pressure by a direct and selective effect on arterioles. This drug has been shown beneficial in the treatment of hypertensive emergencies and post-operative hypertension [9].

The compounds are commonly used in the ICU for control of arterial blood pressure and vasospasm. Intravenous forms can be used to control arterial blood pressure, and to unload the left heart during accelerated arterial hypertension. Oral and iv nimodipine can be used to prevent and treat cerebral vasospasm during subarachnoid haemorrhage.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors can be used both intravenously and orally. They unload the heart by lowering systemic vascular resistance, and can be useful in the acute (and chronic) treatment of arterial hypertension and cardiac pump failure. They can be administered intravenously or sublingually/orally for the rapid lowering of arterial blood pressure. The relatively slow onset and long duration of action make angiotensin-converting enzyme inhibitor a poor choice for use in a hypertensive crisis. Contraindications for their use include serious disturbance of renal function and the presence of a renal artery stenosis, since administration of these drugs in these situations can lead to severe renal dysfunction.

Phosphodiesterase inhibitors

The mechanism of action of these drugs is inhibition of phosphodiesterase in the heart and vascular wall with accumulation of cAMP. These 'inodilators' increase myocardial contractility without a major rise in heart rate or myocardial oxygen demand, and produce a fall in peripheral vascular resistance without a major blood pressure lowering effect. They may specifically unload the right heart. They increase cardiac compliance and have a prolonged duration of action. They can be used judiciously, mainly as an adjunct to standard therapy in patients in whom cardiac output is (relatively) low, for instance during post-myocardial infarction shock and after cardiopulmonary bypass surgery. Severe hypotension does not usually occur, but can be a major limitation in some patients. The drugs are also used when acute pulmonary hypertension contributes to predominant right heart failure (cor pulmonale).

Miscellaneous drugs

Hydralazine, diazoxide, and phentolamine can be administered continuously and, since the blood-pressure-lowering effect may be relatively prolonged, as a bolus. The ganglion blocker trimetaphan has been used in the past for the treatment of aortic dissection and for controlled hypotension during surgery. This drug, which is continuously infused, acts rapidly and has a short duration of action. It inhibits the action of acetylcholine at autonomic ganglia competitively, thereby blocking sympathetic and parasympathetic pathways. Thus, the hypotensive effect is not accompanied by a baroreceptor-mediated reflex tachycardia.

Levosimendan is indicated to conditions where vasodilation together with enhanced myocardial contractility is needed. Therefore, it is mainly used for haemodynamic support in acute pulmonary embolism or as short-term treatment of acutely decompensated severe chronic heart failure or cardiogenic shock. Its slower elimination and the active circulating metabolites are the main drawbacks of levosimendan [2].

References

1. Price LC, McAuley DF, Marino PS, Finney SJ, Griffiths MJ, and Wort SJ. (2012). Pathophysiology of pulmonary hypertension in acute lung injury. *American Journal of Physiology—Lung Cellular and Molecular Physiology*, **302**(9), L803–15.
2. Douwes JM, van Loon RL, Hoendermis ES, et al. (2011). Acute pulmonary vasodilator response in paediatric and adult pulmonary arterial hypertension: occurrence and prognostic value when comparing three response criteria. *European Heart Journal*, **32**(24), 3137–46.
3. Torbicki A, Perrier A, Konstantinides S, et al. (2008). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *European Heart Journal*, **29**(18), 2276–315.
4. Simonneau G, Robbins IM, Beghetti M, et al. (2009). Updated clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology*, **54**(1 Suppl.), S43–54.
5. Prewitt RM. (1987). Pathophysiology and treatment of pulmonary hypertension in acute respiratory failure. *Journal of Critical Care*, **2**, 206–18.
6. Boerma EC and Ince C. (2010). The role of vasoactive agents in the resuscitation of microvascular perfusion and tissue oxygenation in critically ill patients. *Intensive Care Medicine*, **36**(12), 2004–18.
7. Vaughan CJ and Delanty N. (2000). Hypertensive emergencies. *Lancet*, **356**(9227), 411–17.
8. Munzel T, Daiber A, and Gori T. (2011). Nitrate therapy: new aspects concerning molecular action and tolerance. *Circulation*, **123**(19), 2132–44.
9. Varon J. (2008). Treatment of acute severe hypertension: current and newer agents. *Drugs*, **68**(3), 283–97.

CHAPTER 36

Inotropic agents in critical illness

Abdallah Fayssoil and Djillali Annane

Key points

- Inotropes are pharmacological agents used to improve cardiac contractility.
- Dobutamine is a cardiac beta-receptor agonist and is used as a first line inotrope in patients with severe heart failure and a systolic blood pressure of less than 85 mmHg or sepsis with myocardial dysfunction.
- Levosimendan is a calcium sensitizer agent that has positive inotropic action and vasodilator effect.
- Phosphodiesterase (PDE) inhibitors are inotropic agents that increase intracellular cyclic adenosine monophosphate (cAMP) and are no more used routinely.
- Epinephrine is a non-selective alpha- and beta-agonist agent.

Introduction

In the ICU, inotropes are pharmacological agents that are used for haemodynamic support in patients with shock. Inotropes act on cardiac contractility and improve cardiac output. This phenomenon relies on mobilization of intracellular calcium. Inotropes are mainly indicated in patients with hypoperfusion and low cardiac output. In the Acute Decompensated Heart Failure Registry (ADHERE), an inotrope was administrated in 19% of patients with reduced left ventricular ejection fraction (LVEF) [1]. In the Euro-Heart Failure Survey II (EHFS II), 25% of patients with acute heart failure (AHF) were treated with inotropes [2].

Classification of inotropes according to their mechanism of action

Different inotropes have been described according to their mechanism of action. Inotropes improve cardiac output by an increase in stroke volume and heart rate [3]. Stimulation of beta-adrenergic receptors leads to an increase in myocardial contractility, heart rate (HR), hepatosplanchnic blood flow and results in vasodilation (via beta 2-receptors). Inotropic agents are classified as:

- **Agents increasing intracellular cyclic adenosine monophosphate (cAMP)**: beta-adrenergic receptor (beta-AR) agonists and phosphodiesterase (PDE) inhibitors. These agents increase intracellular concentration of cAMP. The protein kinase A (PKA) is activated and followed by phosphorylation of other proteins involved in myocardial contraction (phospholamban, sarcolemmal calcium channels, troponin I). PDE inhibitors increase cAMP concentration by inhibiting cAMP degradation.
- **Agents increasing sensitivity to intracellular calcium**: e.g. levosimendan.
- **Agents inhibiting Na+/K+ ATPase pump**: e.g. digoxin.

Classification according pharmacological properties

Digoxin

Digoxin is an old drug used in heart failure. Digoxin has positive inotrope effects by inhibiting the Na-K-ATPase pump and increasing intracellular calcium. Inhibition of Na-K-ATPase pump diminishes outward sodium pumping and increases intracellular calcium. According to the European Society of Cardiology (ESC), digoxin is recommended in patients with symptomatic heart failure who are unable to tolerate a beta-blocker (GRADE 1B). Also, digoxin is recommended as a second drug, in addition to beta-blocker, in order to control ventricular rate in patients with inadequate response to beta-blocker (GRADE 1B). Digoxin should be using with caution in patients with renal failure. Furthermore, toxicity is increased in patients with hypokalaemia, hypomagnesaemia and ischaemic disease.

Catecholamines

Dobutamine

Dobutamine acts on **beta 1**- and **beta 2**-receptors with variable action on alpha-receptor. Dobutamine is the most commonly used inotropic agent worldwide. Dobutamine stimulates cardiac beta 1-receptors, thereby increasing stroke volume, HR, and cardiac output. Tachyphylaxis may occur after 72 hours of continuous dobutamine infusion, as a result of down-regulation and desensitization of beta 1-myocardial receptors [4]. On vascular smooth muscle, dobutamine stimulates **alpha 1**-adrenergic receptors and **beta 2**-receptors resulting in vasodilation, particularly at lower doses (≤5 micrograms/kg/min). Dobutamine is recommended in patients with severe heart failure and a systolic blood pressure of less than 85 mmHg[5]. The European Society of Cardiology guidelines recommend initiation of Dobutamine at low dose (2 micrograms /kg/min) and to not exceed 20 micrograms /kg/min in acute heart failure [5]. According to the

Surviving Sepsis Campaign (SSC) [6], dobutamine is the preferred inotropic agent in patients with low cardiac output. The SSC recommend a dobutamine infusion up to 20 micrograms/kg/min or in addition to a vasopressor (if in use) in the presence of myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or ongoing signs of hypoperfusion despite achieving adequate intravascular volume and adequate mean arterial pressure (GRADE 1C). Dobutamine increases myocardial oxygen consumption and can cause arrhythmias and myocardial ischaemia.

Dopamine

Dopamine is a precursor of norepinephrine. Dopamine acts on dopaminergic receptors located in mesenteric, renal, and coronary vessels. Dopamine stimulates cardiac **beta 1**- and **beta 2**-receptors. In peripheral vasculature, dopamine stimulates **alpha**-receptors. It is important to note that pharmacological effects of dopamine are dose-dependent. At a dose of <3 micrograms/kg/min, dopamine vasodilates by stimulating dopaminergic receptors (D1) in the kidneys and splanchnic vessels. At doses between 3 and 5 μg/kg/min, dopamine increases myocardial contractility and heart rate by stimulating cardiac beta 1-receptors. At higher dose, i.e. >5 micrograms/kg/min, dopamine vasoconstricts and thereby increases afterload. In theory, dopamine may increase renal blood flow and may improve renal function [7]. In practice, in critically-ill patients, low-dose dopamine showed no evidence for any potential benefits [6]. Dopamine is usually used as a vasopressor agent. In critically-ill patients with shock, a randomized controlled trial showed dopamine was associated with a risk of arrhythmias (24.1 versus 12.4%, $p < 0.001$) when compared with norepinephrine [8]. In a recent meta-analysis, in patients with septic shock, dopamine was associated with higher mortality and a risk of life threatening arrhythmias, compared with norepinephrine [9].

Norepinephrine

Norepinephrine stimulates mainly **alpha**-adrenergic receptors and has modest **beta**-agonist activity. Thus, this drug induces vasoconstriction with less inotropic function. In septic shock, norepinephrine increases venous return and venoconstriction [10]. In post-operative cardiac surgery, norepinephrine may increase cardiac function by veno-constriction [11].

Epinephrine

Epinephrine is a non-selective **alpha**-agonist and **beta**-agonist agent. At a low dose <0.05 micrograms/kg/min, epinephrine stimulates mainly beta-receptors leading to an increase in HR and contractility. At a higher dose, epinephrine stimulates vascular alpha 1-receptors and myocardial beta 1-receptors leading to an increase in systolic and diastolic pressures. In patients not responding to norepinephrine, the SSC [6] recommend the introduction of epinephrine in patients with septic shock to maintain adequate blood pressure (GRADE 2B). Epinephrine may induce arrhythmia and ischemic events. In the CATS trial [12] epinephrine infusion was associated with 12% supraventricular arrhythmias, 7% ventricular arrhythmias, 3% acute coronary events, 1% stroke, and 1% limb ischaemia.

Non-catecholergic agents

Levosimendan

Levosimendan is a calcium sensitizer agent that has a positive inotropic action and vasodilator effects. Levosimendan acts on myocardial contraction via calcium sensitization effects on the contractile apparatus, with a resulting increase in myocardial contraction, and by acting on ATP-dependent potassium channels on vessels with resulting vasodilation. Levosimendan increases cardiac contraction, decreases pulmonary artery wedge pressure, pulmonary artery pressure and systemic vascular resistance. The LIDO trial compared short-term haemodynamic effects of 24-hour intravenous (iv) infusion of levosimendan to dobutamine in patients with severe low-output heart failure [13]. In this trial, the haemodynamic end-point (an increase of 30% or more in cardiac output and a decrease of 25% or more in pulmonary artery wedge pressure at 24 hours) was achieved in significantly more levosimendan-treated than dobutamine-treated patients (28 versus 15%, $p= 0.022$). The SURVIVE (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotrope Support) study compared levosimendan to dobutamine in patients with acute heart failure [14]. At 6 months, there was no significant difference in mortality between groups (26 versus 28%, p 0.40). The ESC guidelines recommend infusion of levosimendan (or a phosphodiesterase inhibitor) to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to heart failure [5] .

Phosphodiesterase inhibitors

Phosphodiesterase inhibitors increase intracellular cAMP by decreasing its degradation. In vascular smooth muscle cells, PDE inhibitors induce relaxation of smooth muscle and lead to vasodilation. Milrinone is a phosphodiesterase 3 inhibitor that blocks the breakdown of cAMP in cardiac cells and vascular smooth muscle leading to inotropic action and pulmonary vasodilation. Milrinone is usually used at doses ranging from 0.375 to 0.75 micrograms/kg/min in acute heart failure. Compared with dobutamine, milrinone causes a greater decrease in systemic vascular resistance, pulmonary artery wedge pressure, and mean pulmonary artery pressure. The effects of iv milrinone for exacerbations of chronic heart failure were investigated in a randomized controlled study that included 949 patients with acute exacerbation of chronic heart failure and low left ventricle (LV) ejection fraction [15]. In this trial, milrinone administration was associated with a significant increase in the rate of hypotension (10.7 versus 3.2%, $p < 0.001$) and of atrial arrhythmias (4.6 versus 1.5%, $p < 0.004$) without survival benefit. Enoximone is another phosphodiesterase inhibitor that can be used in acute heart failure. Enoximone is usually used at dose ranging from 5 to 20 micrograms/kg/min [5].

Potential future inotropes

Cardiac myosin activators

These drugs target myocardial myosin adenosine triphosphate. The result is an increase in the efficiency of actin–myosin cross-bridge formation. This phenomenon induces contractility without affecting intracellular calcium levels.

Istaroxime

Istaroxime is an agent with inotropic and lusitropic effects. This drug induces an inhibition of Na-K-ATPase, leading to an increase in cytosolic calcium and an activation of sarcoplasmic reticulum calcium ATPase isoform-2(SERCA 2). Subsequently, calcium reuptake is enhanced and improves myocardial relaxation (lusitropy). Istaroxime improves left ventricular diastolic function.

SERCA 2A activators

In heart failure, SERCA 2A favours the reuptake of calcium into the sarcoplasmic reticulum. In heart failure, down-regulation of SERCA 2A leads to an increase in calcium in the cytoplasm with subsequently arrhythmia and cardiac dysfunction.

References

1. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC, and ADHERE Scientific Advisory Committee and Investigators. (2006). Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *Journal of the American College of Cardiology*, **47**(1), 76–84.
2. Nieminen MS, Brutsaert D, Dickstein K, et al. (2006). EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *European Heart Journal*, **27**(22), 2725–36.
3. Hasenfuss G and Teerlink JR. (2011). Cardiac inotropes: current agents and future directions. *European Heart Journal*, **32**(15), 1838–45.
4. Fowler MB, Laser JA, Hopkins GL, Minobe W, and Bristow MR. (1986). Assessment of the beta-adrenergic receptor pathway in the intact failing human heart: progressive receptor down-regulation and subsensitivity to agonist response. *Circulation*, **74**(6), 1290–302.
5. McMurray JJ, Adamopoulos S, Anker SD et al. (2012). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *European Heart Journal*, **33**, 1787–847.
6. Dellinger RP, Levy MM, Rhodes A, et al. (2013). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine*, **41**(2), 580–637.
7. Debaveye YA and Van den Berghe GH. (2004). Is there still a place for dopamine in the modern intensive care unit? *Anesthesia & Analgesia*, **98**(2), 461–8.
8. De Backer D, Biston P, Devriendt J, et al. (2010). Comparison of dopamine and norepinephrine in the treatment of shock. *New England Journal of Medicine*, **362**(9), 779–89.
9. De Backer D, Aldecoa C, Njimi H, and Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis. *Critical Care Medicine*, **40**(3), 725–30.
10. Persichini R, Silva S, Teboul JL, et al. (2012). Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. *Critical Care Medicine*, **40**(12), 3146–53.
11. Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, and Jansen JR. (2013). Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. *Critical Care Medicine*, **41**(1), 143–50.
12. Annane D, Vignon P, Renault A, et al. (2007). Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet*, **370**(9588), 676–84.
13. Follath F, Cleland JG, Just H, et al. (2002). Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet*, **360**(9328), 196–202.
14. Mebazaa A, Nieminen MS, Packer M, et al. (2007). Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. *Journal of the American Medical Association*, **297**(17), 1883–91.
15. Cuffe MS, Califf RM, Adams KF Jr, et al. (2002). Outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure (OPTIME-CHF) investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *Journal of the American Medical Association*, **287**(12), 1541–7.

CHAPTER 37

Anti-anginal agents in critical illness

Ajay Suri and Jean R. McEwan

Key points

- A full understanding of anti-anginals and their mechanism of action, possible side effects, contraindications and interactions, and effects of withdrawal is of paramount importance in the critically-ill patient.
- Beta-blockers and calcium (Ca) channel blockers are the usual first-line treatments for angina, but may not be ideal in the critically-ill patient because of their negative inotropic and chronotropic effects.
- Nitrates reduce blood pressure without typically affecting heart rate. Their most common side effect is profound hypotension. Nicorandil has a similar mechanism of action and tends to be given orally.
- Ivabradine, an I_f channel blocker, is a newer anti-anginal. Its primary mechanism of action is to reduce heart rate, while not affecting blood pressure.
- Ranolazine is the one of the newest anti-anginal agents. Its effects are independent of heart rate and blood pressure.

Introduction

Angina is chest pain resulting from the lack of blood supply to the heart muscle. This is usually caused by insufficient blood flow through coronary arteries, most commonly due to obstructive atherosclerotic plaque, although rarely may be due to coronary artery spasm [1]. Other causes of angina include hypertrophic cardiomyopathy, where a combination of increased demand by the hypertrophied muscle and poor tissue perfusion, due to poor flow down small vessels is thought to be the cause of the ischaemic pain. Patients on intensive care units (ICUs) who experience chest pain will usually be bedbound and at physical rest. However, surgical wounding and sepsis increase metabolic demand, and there may be other stresses such as anaemia, so sympathetic drive with increased heart rate will increase the demand on the heart. In addition, the patient with sepsis or who is post-surgery will be pro-thrombotic and at increased risk of thrombus formation on an unstable plaque.

Patients in the intensive treatment unit (ITU) may be sedated, fully anaesthetized or receiving analgesia for other reasons and, in these circumstances, may not complain of pain. Electrocardiogram (ECG) and haemodynamic monitoring, including echocardiographic imaging of function may detect cardiac ischaemia. The angina experienced by ICU patients is correctly considered as unstable, requiring urgent medical treatment to help alleviate distressing symptoms for the patient, and because the chest pain or ECG changes indicates critical coronary perfusion and may herald a myocardial infarction.

Anti-anginals are drugs that are used in the treatment of stable angina and they may also help alleviate ECG, and haemodynamic or echocardiographic signs of cardiac ischaemia. These drugs can be used alone or in conjunction with each other, but are most effective if used with a full understanding of their mechanism of action, possible side effects, contraindications, and interactions. While they may be prescribed in an effort to control new symptoms and signs of myocardial ischaemia in ICU patients, another consideration is that patients who become acutely unwell may experience the effects of sudden withdrawal of long-term medications, such as beta-blockers, prescribed previously for stable angina.

Beta-blockers

Beta-adrenoceptor blockers work as competitive inhibitors of the endogenous catecholamines, adrenaline, and noradrenaline at the β-adrenergic receptors of the sympathetic nervous system. This system mediates the fight-or-flight response and beta-blockers blunt metabolic and cardiovascular pathways that are stimulated in sick patients. There is some evidence that beta-blockade may reduce peri-operative mortality in patients undergoing major non-cardiac surgery, who are also at high coronary vascular risk [2,3]. However, some trials have shown the opposite with increased death and adverse outcomes [4], and currently the best treatment strategy is still debated.

Beta-blockers work on beta 1-, beta 2-, and beta 3-receptors. The anti-anginal effects are mainly through beta 1-blockade. This reduces heart rate and myocardial contractility, while reducing blood pressure and cardiac after-load. As a result, myocardial oxygen consumption and the potential for ischaemia under conditions of sympathetic drive, such as exercise or pain are reduced [5]. Beta 2-adrenergic receptor blockade inhibits smooth muscle relaxation in blood vessels, bronchi, gastrointestinal, and the genito-urinary tract and beta 3-adrenoceptors are known as metabolic receptors, where they mediate lipolysis in adipose tissue. However, evidence is emerging that these receptors are also expressed in human cardiomyocytes and endothelial cells [6], where they are thought to mediate coronary dilatation through the production

of endothelium-derived relaxing factor and endothelium-derived hyperpolarization factors [7].

Beta-blockers can be given orally or intravenously. Metoprolol is the most commonly used short-acting agent, and has readily available oral and intravenous (iv) preparations. Bisoprolol is a beta-1 receptor cardioselective agent and has the advantage of once daily (od) only administration. An additional benefit from beta-blockers comes from their potential anti-arrhythmic effects. The most important side effects of beta-blockers in ICU patients are the ones that may affect haemodynamics, ventilation, or metabolic homeostasis.

Haemodynamic side effects

Beta-blockers may cause hypotension, heart failure, bradycardia, and heart block. Unusually, beta-blocker-induced diarrhoea can cause volume loss and exacerbate hypotension. Bronchoconstriction is a beta 2-related side effect and may be problematic in asthmatics and patients with chronic obstructive pulmonary disease. Other beta 2 side effects include peripheral vasoconstriction. Metabolic side effects include beta-blocker-induced inhibition of both glycogenolysis and gluconeogenesis, resulting in hypoglycaemia [8]. Therefore, beta-blockers should be used in caution in diabetics, as the opening warning sign of tachycardia may be masked. Non-selective and beta 1-selective beta-blockers also affect lipid metabolism by reducing high-density lipoprotein (HDL) possibly through intrinsic sympathomimetic activity. Low-density lipoproteins (LDL) are felt to increase slightly with these agents, as well as triglycerides through unopposed alpha-adrenergic receptor blockade, inhibiting the lipase that acts on triglycerides [9]. Notably, all these side effects are less common in beta 1-selective beta-blockers, but at higher doses, receptor selectivity diminishes.

Of particular relevance to intensive care patients are the more lipophilic beta-blockers, such as propranolol and metoprolol, are much more likely to cross the blood–brain barrier, and could potentiate insomnia, hallucinations, and nightmares [10]. Abrupt withdrawal of beta-blockers may cause rebound hypertension, arrhythmias, and angina.

Ca channel blockers

Ca channel blockers work by inhibiting calcium movement through voltage-gated Ca channels in myocardium and blood vessels [11]. There are two classes of Ca channel blockers. The dihydropyridine Ca channel blockers work primarily by causing dilatation and relaxation of arterial vascular smooth muscle, reducing systemic resistance and blood pressure [12]. Dihydropyridine Ca channel blockers are more commonly used to treat hypertension, rather than angina. They may cause a reflex tachycardia, so this class may be theoretically less useful as an anti-anginal. However, with lower blood pressure the afterload decreases and there is less work for the heart. The stress developed in the left ventricle during ejection is therefore considerably less and myocardial oxygen consumption is decreased. Only dihydropyridines amlodipine, nifedipine, and nicardipine are licensed to treat chronic stable angina.

The non-dihydropyridine Ca channel blockers are further sub-divided into phenylalkylamine (verapamil) and benzothiazepine (diltiazem) groups [12]. Both verapamil and diltiazem treat angina by reducing heart rate and force of contraction, thereby reducing myocardial oxygen demand. Verapamil is more negatively inotropic than diltiazem and, although both have minimal vasodilatory effects, they also slow down the conduction of electrical activity within the heart by blocking the Ca channel during the plateau phase of the action potential of the heart. These Ca channel blockers may be used alone or in combination with other drugs for rate or rhythm control in atrial arrhythmias, such as atrial fibrillation, which may induce angina through tachycardia. Side effects tend to be minor and can be due to its vasodilatory effects, such as flushing and headache. Others include nausea, rashes, tiredness, leg oedema, and dizziness. Sudden withdrawal of Ca channel blockers may worsen angina and also promote tachycardia.

Nitrates

Nitrates have not influenced outcomes (death or cardiovascular events) in clinical trials of myocardial infarction [13], but can be used treat anginal chest pain and manipulate haemodynamics. Nitroglycerin is usually given as a sublingual spray or, less commonly, as a buccal tablet. There is a rapid onset of action as this mode of delivery avoids first-pass metabolism. The effects are short-lived, lasting around 30 minutes. The effects of transdermal patches can last for up to 24 hours. Oral nitrate preparations with a longer onset of action and duration of treatment are isosorbide mononitrate and isosorbide dinitrate. Oral preparations usually require higher doses as they do not bypass first pass metabolism in the liver, but isosorbide mononitrate is not metabolized in the liver and so has almost 100% bioavailability.

In intensive care patients, the most commonly used preparations are iv formulations. These can be titrated to symptoms and also have the added benefit of being able to also treat hypertension and acute heart failure. Intracellular enzymes and sulphydryl groups reduce the drug's nitrate groups to s-nitrosithiol and then to nitric oxide (NO) or directly to NO. Through multiple mechanisms NO cause the relaxation of vascular smooth muscle, which is its primary effect while endogenous. NO also inhibits platelet aggregation, which is the interaction between leukocytes and endothelium, and is anti-inflammatory. Nitrates dilate veins more effectively than arteries and this reduces ventricular preload. In addition, the reduction in diastolic ventricular wall stress helps improve subendocardial blood flow and improves oxygen supply/demand ratio.

The most common side effects of nitrates are headache and skin flushing. More serious side effects are hypotension and reflex tachycardia that may exacerbate angina. Another important consideration is patients with pulmonary hypertension and right-sided heart failure on cyclic guanosine monophosphate (cGMP)-dependent phosphodiesterase inhibitors (e.g. sildenafil, tadalafil) used for the management of pulmonary hypertension and acute respiratory distress syndrome (ARDS), may experience further worsening of angina if nitrate is prescribed concomitantly. The reason for this adverse reaction is that nitrates stimulate cGMP production and cGMP-dependent phosphodiesterase inhibitors inhibit cGMP degradation so when combined, these two drug classes greatly potentiate cGMP levels, leading to impaired coronary perfusion through profound hypotension. Withdrawal from nitrates should always be gradual as sudden cessation may cause angina, myocardial infarction, or even sudden death.

Nicorandil

Nicorandil belongs to a class of drugs known as the K^+_{ATP} channel agonists. It mainly functions as an arterial vasodilator, but has the added property of further arteriolar and venodilatation attributable to a nitrate group of its structure. There is some evidence to suggest that potassium (K) channel activation may also exert a direct cytoprotective effect against ischaemia through pharmacological preconditioning and the activation of K^+_{ATP} channels within myocardial mitochondria, although the exact mechanism remains unclear. Nicorandil is given orally, although there is some experimental evidence for its benefits intravenously. Outcome evidence for this drug is exhibited in the Impact of Nicorandil on Angina (IONA) trial, which showed benefit in stable non-ITU patients with a dose of 20 mg bd [14]. The most common cause for discontinuation of this drug is headache in around 5% of patients, but starting patients at the initial lower dose of 5 mg bd may overcome this. Other side effects include flushing, nausea, mouth ulcers, and palpitations. There is no evidence of an abrupt withdrawal syndrome with sudden cessation of nicorandil.

Ivabradine

This novel agent was first approved in Europe in 2005 and works by selectively inhibiting the I_f channel within the sino-atrial node. In contrast to the other anti-anginals that slow heart rate, this drug is not negatively inotropic and could be useful in sick patients who already have poor cardiac function. The I_f channel is highly expressed in the sino-atrial node and is a mixed Na^+–K^+ inward current channel activated by hyperpolarization and modulated by the autonomic nervous system. Ivabradine blocks this channel in a dose-dependent manner, thereby reducing the cardiac pacemaker activity of the node. The BEAUTIFUL study looked at nearly 11,000 patients across 33 countries and showed that ivabradine significantly reduced the rates of coronary events, myocardial infarction, and coronary revascularization in angina patients with a heart rate above 70 bpm [15]. Ivabradine is therefore used in patients who cannot or should not be on beta-blockers and can be used in combination with beta-blockers in patients with inadequately-controlled chronic stable angina, whose heart rate exceeds 60 bpm on a beta-blocker alone. The SHIFT study also showed that adding ivabradine to optimal heart failure medication decreases both cardiovascular death rate and risk of hospitalization for heart failure [16].

The most common side-effect of ivabradine is a luminous phenomenon described by patients as sensations of enhanced brightness in a fully-maintained visual field, which are often mild, short-lived, and fully reversible. This is probably due to blockage of the I_h ion channels in the retina, which are very similar to cardiac I_f channels. In clinical studies, about 1% of all patients had to discontinue the drug because of these sensations that occurred, on average, 40 days after starting the drug. The next most common problem is bradycardia in 5% of patients on the maximum 10 mg dose. Up to 4.8% of patients report headaches. Other common drug reactions are ventricular extrasystoles, dizziness, blurred vision, and first-degree atrioventricular block. Ivabradine is contraindicated in patients with sick sinus syndrome with both bradycardia and tachycardia, and should not be used concomitantly with inhibitors of cytochrome p450 34A as azole antifungals (ketoconazole and itraconazole), macrolide antibiotics (clarithromycin), chemotherapeutics, and the anti-HIV protease inhibitor drugs, nelfinavir and ritonavir. Importantly, abrupt withdrawal of this drug has not resulted in an exacerbation of angina.

Ranolazine

Ranolazine is thought to have its effects through altering the transcellular late Na current, thereby decreasing Na entry into ischaemic myocardial cells [17]. It is proposed that ranolazine reduces calcium uptake via the Na/Ca exchanger and preserves ionic haemostasis, thereby reducing diastolic wall tension and ischaemia-induced contractile dysfunction [17]. Ranolazine is a partial fatty acid oxidation inhibitor and also shifts ATP production from fatty acid to more oxygen-efficient carbohydrate oxidation [18]. Ranolazine does not affect the heart rate or blood pressure, and so in the sick patient in intensive care this drug may be of benefit where these indices should not be lowered further. Ranolazine is known to prolong the QT interval and, therefore, there is a risk of inducing serious ventricular arrhythmias. It should be used in caution in patients already on drugs that prolong the QT interval. Ranolazine is also contraindicated in patients with any degree of hepatic dysfunction as this drug is metabolized by the liver. Ranolazine is metabolized by the cytochrome CYP3A enzyme, a member of the cytochrome P450 system, and is also partially metabolized by cytochrome CYP2D6. Therefore, drugs that may interact and should have their doses reduced include digoxin, simvastatin, verapamil, diltiazem, azole antifungals, and macrolide antibiotics. Abrupt withdrawal of ranolazine does not worsen angina.

Acknowledgements

The authors would like to acknowledge the significant contribution made to the writing of this chapter by Dr Abdul Malik.

References

1. Warren J. (1962). Remarks on angina pectoris. *New England Journal of Medicine*, **266**, 3–7.
2. Mangano DT, Layug EL, Wallace A, and Tateo I. (1996). Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter study of perioperative ischemia research group. *New England Journal of Medicine*, **335**, 1713–20.
3. London MJ, Hur K, Schwartz GG, and Henderson WG. (2013). Association of perioperative beta-blockade with mortality and cardiovascular morbidity following major noncardiac surgery. *Journal of the American Medical Association*, **309**, 1704–13.
4. Bouri S, Shun-Shin MJ, Cole GD, Mayet J, and Francis DP. (2013). Meta-analysis of secure randomised controlled trials of beta-blockade to prevent perioperative death in non-cardiac surgery. *Heart*, **100**(6), 456–64.
5. Frishman WH. (1983). Multifactorial actions of beta-adrenergic blocking drugs in ischemic heart disease: current concepts. *Circulation*, **67**, I11–18.
6. Dessy C and Balligand JL. (2010). Beta3-adrenergic receptors in cardiac and vascular tissues emerging concepts and therapeutic perspectives. *Advances in Pharmacology*, **59**, 135–63.
7. Balligand JL. (2013). Beta3-adrenoreceptors in cardiovascular diseases: new roles for an 'old' receptor. *Current Drug Delivery*, **10**, 64–6.
8. Lager I. (1983). Adrenergic blockade and hypoglycaemia. *Acta Medica Scandinavica. Supplementum*, **672**, 63–7.
9. Fonseca VA. (2010). Effects of beta-blockers on glucose and lipid metabolism. *Current Medical Research and Opinion*, **26**, 615–29.

10. Cruickshank JM. (2010). Beta-blockers and heart failure. *Indian Heart Journal*, **62**, 101–10.
11. Cauvin C, Loutzenhiser R, and Van Breemen C. (1983). Mechanisms of calcium antagonist-induced vasodilation. *Annual Review of Pharmacology and Toxicology*, **23**, 373–96.
12. National Clinical Guidelines Centre (UK). (2011). Stable Angina: Methods, Evidence & Guidance. NICE Clinical Guidelines, No. 126. HYPERLINK "http://www.rcplondon.ac.uk/Pages/index.aspx" Royal College of Physicians (UK), London. Available at http://www.ncbi.nlm.nih.gov/books/NBK83597/ (Accessed 28 October 2015).
13. Gruppo Italiano per lo Studio della Soprawivenza nell'Infarto Miocardico. (1994). Gissi-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet*, **343**, 1115–22.
14. IONA Study Group (2002). Effect of nicorandil on coronary events in patients with stable angina: the Impact of Nicorandil in Angina (IONA) randomised trial. *Lancet*, **359**, 1269–75.
15. Ferrari R, Ford I, Fox K, Steg PG, and Tendera M. (2008). The beautiful study: randomized trial of ivabradine in patients with stable coronary artery disease and left ventricular systolic dysfunction—baseline characteristics of the study population. *Cardiology*, **110**, 271–82.
16. Swedberg K, Komajda M, Bohm M, et al. (2010). Ivabradine and outcomes in chronic heart failure (shift): a randomised placebo-controlled study. *Lancet*, **376**, 875–85.
17. Chaitman BR, Skettino SL, Parker JO, et al. (2004). Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *Journal of the American College of Cardiology*, **43**, 1375–82.
18. Chaitman BR, Pepine CJ, Parker JO, et al. (2004). Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *Journal of the American Medical Association*, **291**, 309–16.

CHAPTER 38

Anti-arrhythmics in critical illness

John LeMaitre and Jan Kornder

Key points

- Cardiac arrhythmias are often the consequence of conditions such as sepsis, electrolyte imbalance, and hypoxia. Correcting the underlying problem should be the first principle.
- No anti-arrhythmic medication has shown mortality benefit. Amiodarone is the most useful acute agent for both ventricular and supraventricular arrhythmias.
- Anti-arrhythmic drugs are still the therapeutic modality of choice in the treatment of cardiac arrhythmias, despite advances in non-pharmacological approaches, such as catheter ablation and the implantable cardioverter defibrillator (ICD).
- Magnesium is useful in torsades de pointes. It may also be useful for refractory ventricular tachycardia (VT) post-myocardial infarction (MI), and VT associated with digoxin toxicity.
- Routine treatment of premature ventricular contractions (PVCs), premature atrial contractions (PACs), and non-sustained ventricular runs is not indicated.

Introduction

Although anti-arryhthmic drugs (AADs) are commonly effective, they are now understood to be pro-arrhythmic and can result in excess mortality. The therapeutic range is frequently narrow, and they often have toxic side effects and deleterious effects on myocardial contractility, conduction, and therefore cardiac output. AADs remain the first-line treatment for situations where haemodynamic instability is dependent on abnormalities of cardiac rhythm and where treatment of the underlying illness is not effective in controlling heart rhythm.

Attention should be first paid to the correction of non-cardiac disease states, such as sepsis, hypoxia, and metabolic derangement, all of which are associated with cardiac rhythm abnormalities. The correction of these may render management of the arrhythmia easier or even unnecessary. Despite correction of any underlying illness, there will remain situations where correction of cardiac rhythm abnormalities using AADs will be necessary.

AADs are traditionally classified using the Vaughan-Williams system, which groups drugs based on similar mechanisms of action at a cellular level (Table 38.1).

Class 1 anti-arrhythmic agents

Class 1 agents block the rapid Na^+ channel slowing conduction velocity. They have varying effects upon the K^+ current and, as such, differing effects upon action potential (AP) duration.

Class 1a drugs

Quinidine affects both atrial and ventricular tissue. It is an effective agent for supraventricular and ventricular arrhythmias, but has fallen out of favour due to risk of pro-arrhythmia. It is increasingly difficult to obtain. A large meta-analysis suggested excess mortality due to drug-induced torsade de pointes (Tdp) [1]. It directly suppresses sinoatrial (SA) and atrioventricular (AV) node conduction, and increases the refractory period of atrial, ventricular, and His-Purkinje tissue. It has a vagolytic effect and may paradoxically increase AV nodal conduction. The most important side effect is Tdp due to early after-depolarizations associated with prolonged AP duration (and hence QT prolongation). Other side effects include diarrhoea, tinnitus, thrombocytopenia, and hypotension due to vasodilatation. The drug may precipitate or worsen digoxin toxicity. It is metabolized in the liver and dose reduction is necessary in patients with hepatic disease.

Procainamide has a similar mode of action to quinidine, but has a very rapid onset. It is generally safe and well tolerated. Long-term administration may result in a lupus syndrome, particularly in slow acetylators. Agranulocytosis is a rare, but serious complication. Tdp is less common. The usual dose is 15 mg/kg body weight at a rate of 50 mg/min. A maintenance infusion of 2–6 mg/min may be required. The plasma half-life is short, requiring multiple daily doses.

Disopyramide is profoundly negatively inotropic, which makes it unsuitable for use in critically-ill patients with impaired myocardial function. Gastrointestinal side effects are generally fewer, but anticholinergic side effects are more prominent. This may cause acceleration of AV nodal conduction and may require co-administration of AV nodal blocking drugs when used for the treatment of supraventricular arrhythmias. It is only available orally and has a rapid onset of action.

Class Ib drugs

The class 1b drugs all share properties of rapid binding/unbinding kinetics, minimal pro-arrhythmic effects and shortening of the AP duration.

Table 38.1 The Vaughan-Williams classification: the major electrophysiological actions of commonly used anti-arrhythmic drugs

Class	Mode of action	Site of action	Examples
I	Membrane-stabilizing agents (fast sodium-channel inhibition)		
	(Ia) Delayed repolarization. Broadened action potential	Atrium ventricle Accessory pathway	Quinidine Procainamide Disopyramide
	(Ib) Decreased action potential duration. Accelerated repolarization	Ventricle	Lidocaine Mexiletine
	(Ic) QRS prolongation. No change in action potential	Atrium ventricle His–Purkinje tissue Accessory pathway	Flecainide propafenone Encainide
II	Beta-blocking agents	Sinus node. AV node	Carvedilol Atenolol Bisoprolol Esmolol
III	Prolongation of repolarization	Atrium AV node. Accessory pathway Ventricle His–Purkinje tissue	Amiodarone Dronedarone Sotalol Ibutilide Bretylium
IV	Ca-channel antagonists	AV node	Diltiazem Verapamil

AV, atrioventricular.

Data from Vaughan-Williams EM, 'Classification of antiarrhythmic drugs'. In: *Symposium on Cardiac Arrhythmias*. Sandoe E., et al. (eds). Sodertalje: AB Astra, 1970, pp. 449–72.

Lidocaine remains the first-line treatment for ventricular arrhythmias, despite the lack of clinical evidence for its efficacy. Like other class 1b drugs, it has no effect on the onset of the AP in normal circumstances and does not slow conduction velocity, but during acidosis, substantial conduction slowing can occur. It suppresses early and delayed after-depolarizations and automaticity. There is little vasodilatory effect. Lidocaine is most appropriately used to treat significant ventricular arrhythmias in the post-myocardial infarction setting, where acute ischaemia is suspected in the pathogenesis of ventricular arrhythmias. It is no longer advocated for the primary prophylaxis of ventricular tachycardia or fibrillation. It is usually administered as a bolus injection (100 mg over 1–2 min) followed by a maintenance infusion of 1–4 mg/min if required, as plasma levels fall rapidly after a single bolus. If a bolus is ineffective, it is unlikely that an infusion will succeed. Toxicity manifests with confusion, twitching, paresthesiae, and epileptiform fits.

Mexiletine is an oral agent with the same electrophysiological actions as lidocaine. It has little haemodynamic consequence with very little myocardial contractility suppression or vasodilatory effect. Unfortunately, it has a narrow therapeutic window and titration of oral dose can take days. Toxic side effects are similar to those encountered with lidocaine.

Class Ic drugs

The 1c drugs have the slowest binding kinetics of the class 1 anti-arrhythmics and slow conduction velocity in both atrial and ventricular tissue. They have little effect upon AP duration.

Flecainide is negatively inotropic and, although very effective at suppressing PVCs, data from the CAST trial demonstrated excess mortality in those treated with flecainide or encainide compared with placebo in the post-MI setting [2]. There is no prolongation of QT interval. Flecainide is useful for cardioversion of atrial fibrillation (AF) and flutter, and maintenance of sinus rhythm, and for treatment of AV re-entrant arrhythmias utilizing an accessory pathway. It should be avoided in patients at risk of developing re-entrant ventricular arrhythmias (e.g. the presence of ischaemic heart disease or other cardiomyopathy) or any situation where the negative inotropic effects are undesirable (e.g. heart failure). For conversion of AF, bolus administration of 1–2 mg/kg (maximum 150 mg) over 30 min is usual, watching for hypotension as a consequence of myocardial depression. Class 1c drugs increase pacing thresholds by up to 200%.

Propafenone prolongs refractoriness and slows heart rate due to mild beta-blocking and Ca^{2+}-channel blocking action. It is less negatively inotropic, but can still precipitate heart failure and should be avoided in those patients at risk of ventricular re-entrant arrhythmias due to its pro-arrhythmic effect. It is effective for the pharmacological conversion of AF.

Class 2 anti-arrhythmic agents: beta-blockers

Beta-blocking agents act by attenuating the effects of catecholamines on the heart and, therefore, exert their maximal effect on areas where the sympathetic innervation is rich. Beta-blockers

suppress automaticity at the SA and AV nodes, slow conduction, and increase refractoriness. Their direct effect on SA and AV nodal tissue also explains their usefulness for re-entrant arrhythmias utilizing these tissues, e.g. AV nodal re-entrant tachycardia (AVNRT) or AV re-entrant tachycardias. They are also useful for catecholamine-dependent VTs and for idiopathic VT arising from the outflow tracts.

In critically-ill patients, catecholamine excess (either endogenously or as a consequence of inotropic support) may be an appropriate and physiological response. Therefore, beta-blockers should be used cautiously in this group.

Carvedilol, atenolol, and bisoprolol have long half-lives, and adverse haemodynamic effects may persist. Carvedilol increases vasodilation through alpha-receptor blockade. In contrast, esmolol, is an ultra-short-acting beta-blocker with a half-life of 9 minutes, enabling transient use of beta-blockade in situations such as post-operative hypertension and where haemodynamic effect is uncertain. The usual dosage range is 50–200 mcg/kg/min.

Class 3 anti-arrhythmic drugs

The class 3 drugs prolong AP duration through the blockade of the potassium (K^+) channels responsible for repolarization.

Amiodarone is an extremely attractive AAD in the setting of the critically-ill patient. It is effective in a wide spectrum of atrial and ventricular arrhythmias, including the post-surgical junctional ectopic tachycardia seen in paediatric patients. The negative inotropic effect is significantly less than that of the majority of AADs. There is less concern in the acutely ill about the extensive long-term toxicity that is seen with chronic oral usage, although acute respiratory distress syndrome due to pneumonitis can be seen at any time during therapy. Amiodarone has a complex mode of action with activity in all Vaughan-Williams classes. It has a delayed prolongation of AP duration, which necessitates aggressive intravenous (iv) loading (usually 300 mg over 30 min followed by a maintenance infusion of 900–1200 mg/24 hours) preferably via central venous access to avoid phlebitis. Acute infusion at high rates may lead to significant hypotension due to an alpha-receptor blocking effect. Even with such loading, effective class 3 anti-arrhythmic action will not be seen acutely and the principle acute efficacy of amiodarone is through beta-blockade. Metabolism is mainly hepatic to desethylamiodarone, which also has anti-arrhythmic action. Amiodarone potentiates oral anticoagulation and increases blood levels of digoxin, quinidine, and flecainide. Although the drug prolongs the QT interval, drug-induced Tdp is less common than with other class 3 AADs. Amiodarone is more effective than sotalol at preventing sudden cardiac death, but less effective than the implantable defibrillator [3].

Dronedarone is an analogue of amiodarone without an iodine moiety. Although beneficial for control of paroxysmal AF, with approximately half the efficacy of amiodarone and no toxic side effects, dronedarone is not recommended for patients with persistent AF or reduced left ventricle (LV) function due to excess mortality [4,5].

Sotalol is a weak non-cardioselective beta-blocker with class 3 action, and is effective for ventricular and atrial arrhythmias, including VT and AF. It is less effective than amiodarone overall, with a higher risk of Tdp. The risk can be reduced by ensuring the QTc does not exceed 500 ms. Sotalol should be avoided in the presence of LV dysfunction in the absence of an implantable defibrillator due to the risk of Tdp [6].

Ibutilide is useful for the conversion of AF or flutter to sinus rhythm, but the same cautions exist regarding the risk of Tdp and the need to avoid the agent in individuals pre-disposed (e.g. hypokalaemia, heart failure). Dofetilide has only class 3 action with close monitoring of QTc required, but is effective for conversion of AF.

Bretylium tosylate is rarely used now. It has a unique mode of action—it concentrates in the terminal sympathetic neurons, causing transient release of stored norepinephrine before blocking further release. The effect is of a chemical sympathectomy, which also gives rise to its major side effect of hypotension. It can be used in patients with ventricular tachycardia refractory to other anti-arrhythmic drugs, although has been superseded by amiodarone, which causes significantly less hypotension. It may cause chemical cardioversion of ventricular fibrillation or facilitate cardioversion of ventricular fibrillation refractory to electrical cardioversion.

Class 4 anti-arrhythmic agents: Ca^{2+}-channel antagonists

The non-dihydropyridine Ca^{2+}-channel antagonists—verapamil and diltiazem—have important anti-arrhythmic action via the modification of the slow Ca^{2+} current responsible for depolarization in the SA and AV nodes. By slowing conduction, these agents may terminate junctional re-entrant arrhythmias and slow the ventricular rate in AF, flutter, or atrial tachycardia. They can be administered by iv bolus—verapamil 5–10 mg over 30–60 seconds, diltiazem 10–20 mg over 30–60 seconds, for acute rate control. Although these drugs have little effect on other atrial or ventricular tissues, certain idiopathic VTs are now recognized to be exquisitely sensitive to Ca^{2+}-channel blockade and verapamil is an effective therapy. For other scar-related VT, however, where significant LV dysfunction exists, these agents should be avoided due to their negative inotropy and vasodilating action. Additionally, SA node dysfunction, either pre-existing or acquired may be exacerbated by co-administration of these agents.

Other drugs

Digoxin

Digoxin is frequently used to control ventricular rate in patients with rapidly conducted atrial arrhythmias, particularly AF. It may be ineffective alone and often requires the addition of other agents, such as beta-blockers or Ca^{2+}-channel antagonists, to gain adequate rate control. In this setting, iv loading with 0.5–1 mg over 24 hours followed by maintenance doses of 125–250 micrograms/day is usual. The therapeutic range is narrow. Arrhythmias seen with toxicity include atrial tachycardia with block, junctional tachycardia, ventricular premature beats, ventricular tachycardia, including bi-directional VT, sinus bradycardia, and varying degrees of AV block. Toxicity may be exacerbated by renal impairment, dehydration, hypokalaemia, many drugs (including amiodarone, verapamil, and quinidine) and old age. In cases of severe overdose, ventricular arrhythmias may require lidocaine or phenytoin, and bradycardia may require temporary pacing. Digoxin-specific antibodies can be administered in extreme cases.

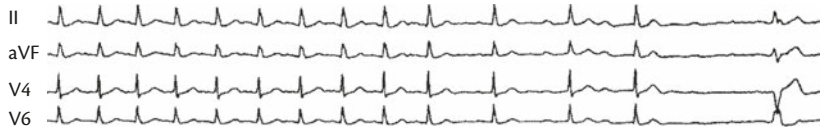


Fig. 38.1 Termination of AVNRT with 12 mg of iv adenosine. Note impaired atrioventricular conduction in beats after successful termination.
Data from Camm AJ and Garratt CJ, 1991, 'Adenosine and supraventricular tachycardia', *New England Journal of Medicine*, 325, pp. 1621–1629.

Although digoxin is by far the most widely used cardiac glycoside, its prolonged onset of action (1–5 hours) may make it unsuitable in the setting of the critically-ill patient. Rarely used, ouabain and deslanoside are only available as iv preparations, but both have a rapid onset of action within 10–30 min.

Magnesium

Intravenous magnesium is a safe and effective therapy in Tdp. Withdrawal of offending drugs, correction of metabolic abnormalities, and pacing, together with iv administration of magnesium sulfate (2–4 g), form the cornerstone of therapy. It may also be of use following cardiac surgery, where significant magnesium depletion can occur in the immediate post-operative period.

Adenosine

Adenosine is an endogenous nucleoside that is capable of causing pharmacological AV block. It has the advantage of having a plasma half-life of only a few seconds. Side effects are usually transient, and include flushing, chest tightness, and bronchospasm, and sustained acceleration of atrial flutter from 2:1 to 1:1 AV conduction has been reported. AV block may persist for several seconds. It has superseded verapamil as the agent of choice for the acute termination of AVNRT and junctional re-entrant arrhythmias. It is administered as a rapid iv bolus of between 3 and 20 mg in an escalating regime (Fig. 38.1) [7].

Adenosine also has a role in the diagnosis of arrhythmias, particularly broad complex arrhythmia, where it may not be easy to distinguish between VT and supraventricular arrhythmias conducted with aberration.

Pro-arrhythmia

Arrhythmia may be worsened in 5–10% of patients taking AADs, sometimes with lethal consequences [8]. Such pro-arrhythmic events are more likely with combinations of anti-arrhythmic drugs and in the presence of metabolic abnormalities, particularly hypokalaemia. Two major patterns of ventricular pro-arrhythmia are seen with anti-arrhythmic drugs. Class 1a and class 3 agents cause QT prolongation and may precipitate Tdp (Fig. 38.2), whereas class 1c agents may give rise to a sinusoidal VT refractory to both pharmacological and electrical therapy.

Conclusion

There is no ideal anti-arrhythmic drug. Considering the diverse mechanisms underlying cardiac arrhythmias, this is not surprising. AADs almost always have adverse effects on haemodynamics and their use in patients who are critically ill must be carefully considered, with correction of underlying disease states likely to be at least as important as the use of AADs.

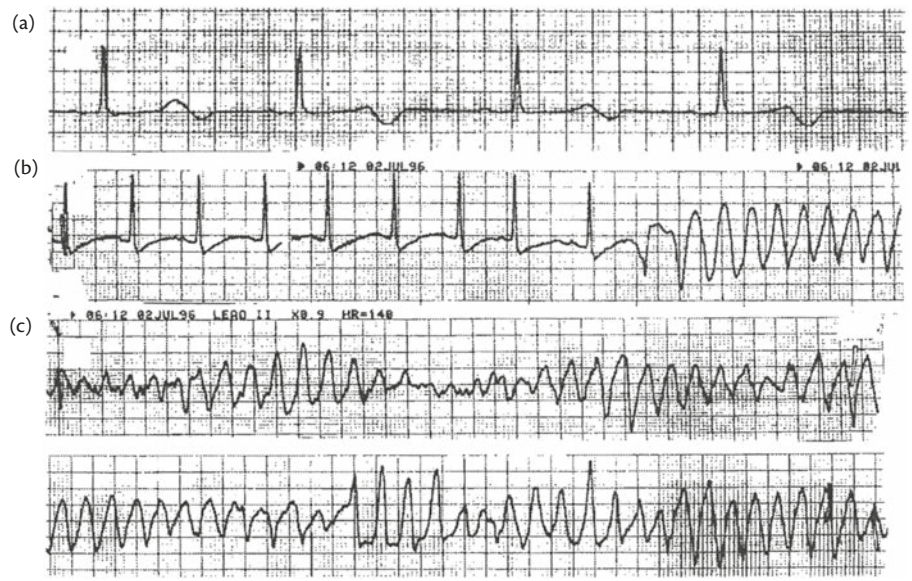


Fig. 38.2 Ventricular pro-arrhythmia from class 3 anti-arrhythmic drugs. (a) Sinus bradycardia with a QT interval of 650 ms in an elderly patient taking amiodarone 400 mg od and atenolol 50 mg od for rate control of atrial fibrillation. (b) Initiation of Tdp with a single ventricular premature beat. (c) Rhythm strip from the same episode showing characteristic twisting of the electrical axis about the baseline. This episode stopped spontaneously and the pro-arrhythmia was treated by drug withdrawal and temporary pacing.

Acknowledgements

The editors were saddened to hear of the death of Dr Jan Kornder since writing this chapter of the book.

References

1. Coplen SE, Antman EM, Berlin JA, Hewitt P, and Chalmers TC. (1990). Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation*, **82**(4), 1106–16.
2. Akiyama T, Pawitan Y, Greenberg H, Kuo CS, and Reynolds-Haertle RA. (1991). Increased risk of death and cardiac arrest from encainide and flecainide in patients after non-Q-wave acute myocardial infarction in the Cardiac Arrhythmia Suppression Trial. CAST Investigators. *American Journal of Cardiology*, **68**(17), 1551–5.
3. Bardy GH, Lee KL, Mark DB, et al. (2005). Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *New England Journal of Medicine*, **352**(3), 225–37.
4. Køber L, Torp-Pedersen C, McMurray JJ, et al. (2008). Increased mortality after dronedarone therapy for severe heart failure. *New England Journal of Medicine*, **358**(25), 2678–87.
5. Connolly SJ, Camm AJ, Halperin JL, et al. (2011). Dronedarone in high-risk permanent atrial fibrillation. *New England Journal of Medicine*, **365**(24), 2268–76.
6. Waldo AL, Camm AJ, deRuyter H, et al. (1996). Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival with oral d-sotalol. *Lancet*, **348**(9019), 7–12.
7. Camm AJ and Garratt CJ. (1991). Adenosine and supraventricular tachycardia. *New England Journal of Medicine*, **325**(23), 1621–9.
8. Roden DM. (1994). Risks and benefits of antiarrhythmic therapy. *New England Journal of Medicine*, **331**(12), 785–91.

CHAPTER 39

Pulmonary vasodilators in critical illness

Benjamin Chousterman and Didier Payen

Key points

- Pulmonary vasodilators (PV) are used to treat pulmonary hypertension and/or hypoxaemia.
- Inhalation of PV is the most suitable way of administration to treat hypoxaemia.
- The use of systemic PV may lead to a decrease in mean arterial pressure and worsening of hypoxaemia.
- Despite their effectiveness, PV have not shown any benefits in mortality in acute respiratory distress syndrome.
- Rebound of hypoxaemia and/or pulmonary arterial hypertension should be prevented during PV treatment discontinuation with a slow de-escalation protocol.

Introduction

Pulmonary vasodilators (PV) are commonly used in the intensive care unit (ICU). These drugs are prescribed to treat pulmonary hypertension (PH) associated right ventricular overload or failure (RVF) and/or hypoxaemia. PH during critical illness may be new or an exacerbation of a chronic pulmonary hypertension and can be classified according to the 2008 Dana Point conference [1] as PH associated with lung diseases and/or hypoxaemia, PH with left heart disease or PH due to embolic disease. PH is hallmark of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) in combination with hypoxaemia. Both pressure and hypoxaemia can be an indication to use PV, taking into account the presence or absence of intrapulmonary shunt. Treatment of PH is necessary when it contributes to RVF, especially in ARDS, being a poor prognostic factor. The ideal PV has to:

- Be selective for pulmonary vasculature.
- Maintain hypoxic pulmonary vasoconstriction (HPV), avoiding deterioration of intrapulmonary shunt.
- Be a safe product with pharmacokinetic and pharmacodynamics properties appropriate for acute situations.

Use of PVs

PVs are first considered when there is venous congestion associated with cardiac output limitation due to right ventricular afterload, usually secondary to elevated pulmonary artery pressure (PAP). In addition, due to pericardial constraint the enlarged diastolic right ventricle may impair the filling of the left ventricle, reducing stroke volume and cardiac output. The second reason to use PV is to improve the ventilation perfusion ratio. Dilation of vessels in aerated zones may divert flow from shunt zones, improving ventilation/perfusion matching and PaO_2. Finally, PV-induced reduction in PAP reduces lung microvascular filtration pressure and alveolo-interstitial oedema [2].

Systemic versus inhaled treatment

Pulmonary vasodilating drugs can be used via a systemic route (oral or intravenous) or via inhalation. The decision depends on therapeutic goals, pharmacological properties, and side effects. The systemic route is easier to titrate knowing pharmacokinetics and the dose–response curve. The limitation comes from the systemic effects with a risk of arterial hypotension and/or worsening hypoxaemia when ventilated and non-ventilated area vessels are both dilated. Inhaled treatments increase the flow to well-aerated alveoli selectively (see Fig. 39.1)?

Systemic PV

Phosphodiesterase inhibitors

Cyclic monophosphate nucleotides (cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP)) are responsible for smooth muscle cell (SMC) relaxation and are hydrolysed by phosphodiesterases (PDEs) 3 and 5. The inhibition of PDEs by PDE inhibitors (PDEI) leads to an elevation of these molecules' concentrations that results in continued SMC relaxation and, therefore, pulmonary vessel vasodilation. Milrinone is a selective inhibitor of the PDE 3 with inotropic and vasodilatory effects. Milrinone reduces pulmonary vascular resistance (PVR) and RVF. In non-hypoxaemic patients, milrinone increases the cardiac output and DO_2, but could lower the PaO_2 [3]. Inhibition of PDE 5 seems to be more selective for the pulmonary vessels causing less systemic hypotension. Although extensively studied in chronic PH, the data on milrinone use in critically-ill patients are limited.

Sildenafil is a specific PDE 5 inhibitor. It increases cardiac output and reduces PVR. The experience is limited in critically-ill patients. Retrospective studies show a good effect on reducing PAP with a limited fall of MAP after cardiac surgery, but show a decrease in PaO_2 with shunt augmentation in ARDS patients [4].

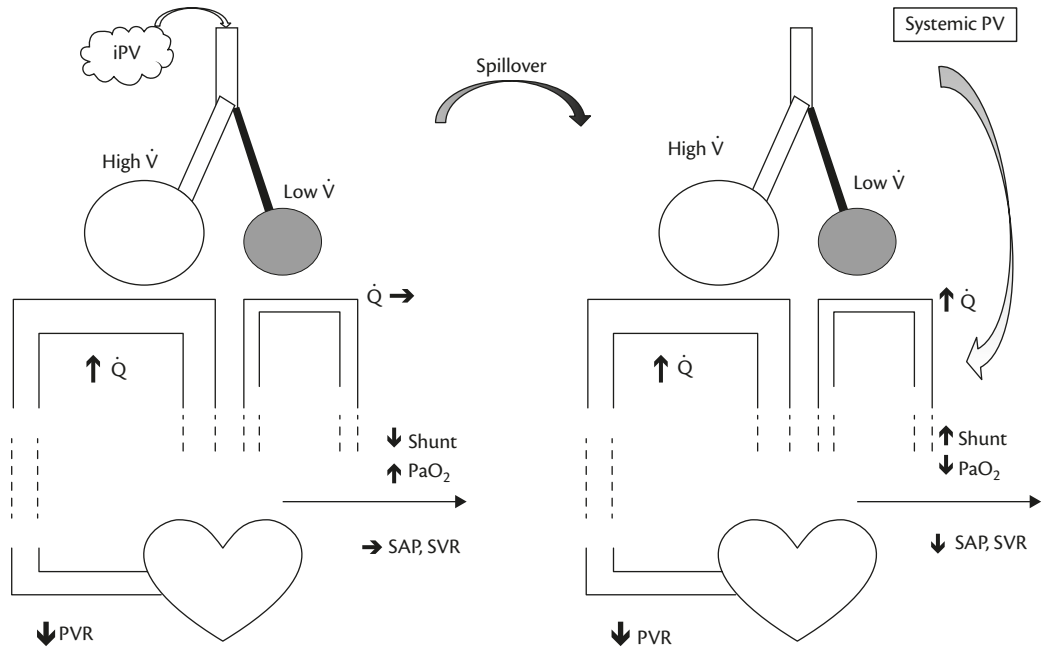


Fig. 39.1 Effects of systemic PVs versus iPV. Systemic vasodilation affects all vascular beds, thereby decreasing MAP and worsening oxygenation by increasing blood flow to poorly-ventilated alveoli, secondary to reversal of hypoxic pulmonary vasoconstriction. iPVs selectively dilate pulmonary arterioles in alveoli that are well ventilated, thus reducing PAP while improving ventilation/perfusion matching and oxygenation. However, 'spillover' of inhaled drugs in pulmonary circulation may lead to systemic effects of iPV.

Q, perfusion; V, ventilation; SAP, systemic arterial pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

Data from Siobal MS, 'Pulmonary vasodilators', *Respiratory Care*, 2007, **52**, 7, pp. 885–99 [13] with permission.

PDEIs can be used alone or in combination with inhaled pulmonary vasodilators (iPVs). The haemodynamic effects of sildenafil are observed after 15 minutes of administration, peak at 30–60 minutes, and last several hours. Sildenafil use may prevent the rebound effect associated with inhaled nitric oxide gas (iNO) weaning.

Drug use in clinical practice

Milrinone is usually used as a continuous infusion at doses ranging from 0.25 to 0.75 micrograms/kg/min, with or without a loading dose of 25–75 micrograms/kg. Its half-life is 1.5–2 hours and the optimal blood concentration seems to be around 100 ng/mL. Sildenafil can be administered to patients via a nasogastric tube at doses ranging from 12.5 to 100 mg, bd.

Side effects and pitfalls

Milrinone has been associated with atrial fibrillation and supraventricular arrhythmias. Episodes of thrombocytopenia have also been observed. Sildenafil's side effects are essentially headaches and flushes.

Intravenous prostacyclins

Intravenous prostacyclins (IVPCs) have the same pharmacodynamic properties as inhaled prostacyclins (iPCs) except their pulmonary selectivity is lost causing systemic hypotension and they may worsen hypoxaemia. IVPCs are an essential treatment of chronic PH, but are, nowadays, less frequently used in ICUs. IVPCs are indicated for the treatment of severe PH and/or RVF after cardiothoracic surgery or for patients with pre-existing chronic PH [5]. The observed reduction of PVR is nearly 40% and the cardiac output is 35% improved. Trepostinil, a long-acting prostacyclin analogue, is an effective treatment of PH, but its pharmacodynamic properties make it less suitable for ICU, especially where there is haemodynamic unstability.

Drug use in clinical practice

Epoprostenol should be started at a dose of 1–2 ng/kg/min and titrated, until the desired effect is reached, by steps of 0.5–1 ng/kg/min every 15–30 minutes. Target dose can vary between 5 and 35 ng/kg/min. Alprostenol can be started with a dose of 5 ng/kg/min and titrated by steps of 5 ng/kg/min. Target doses for this molecule range between 20 and 100 ng/kg/min.

Side effects and pitfalls

The side effects of IVPCs are more pronounced than in inhaled prostacyclins (iPCs). The main complication is dose-dependent systemic arterial hypotension. Conscious patients may complain of headaches, nausea, vomiting, and diarrhoea. Extremely severe rebound effects have been observed with the sudden cessation of IVPCs treatment.

Others

Many of the following PVs are indicated for the treatment of chronic PH. Most of them are not selective for pulmonary vessels and should, therefore, be used with caution in ICU patients.

Isoproterenol

Isoproterenol is a beta-adrenergic agonist acting on both beta 1 and beta 2 adrenergic receptors. This molecule has been used to treat PH during cardiac surgery, as well as for its chronotropic effects to increase the heart rate. Isoproterenol increases cardiac output

and, thus, diminishes PVR. The direct effects on PVR are low. Isoproterenol must be used as a continuous IV infusion. The main side effect is arrhythmias and, therefore, this molecule is not suitable as a first-line treatment in ICU.

Nesiritide

Nesiritide is a recombinant form of the brain natriuretic peptide. The main pharmacodynamic effect is to increase the cGMP in SMCs and then induce relaxation with vasodilation. It is mainly used for the treatment of acute heart failure in USA. The effects of neseritide on PH are controversial, but benefits could be observed in case of left ventricular overload or failure (LVF) associated with RVF.

Sodium nitroprusside

Sodium nitroprusside is a member of the nitric oxide (NO) donors family. This short-acting drug is licenced by the US Food and Drug Administration (FDA) as a treatment of acute hypertensive crisis. It has been shown to reduce pulmonary arterial pressure. Some studies have focused on its inhaled administration, which could be effective [6]. The side effects of this molecule are similar to those of NO-like Met-Hb and mitochondrial respiratory chain blockade.

Calcium channel blockers

The most studied molecules are nifedipine, diltiazem, and amlodipine. They are usually used in ICU as antihypertensive treatment. They diminish hypoxic pulmonary vasoconstriction and are associated with worsening hypoxaemia in ARDS patients.

Endothelin-1 receptor antagonists

Endothelin-1 (ET-1) Receptor Antagonists ETA is the only class of molecules acting on the ET-1 pathway. Bosentan is the main molecule studied. It is an antagonist of both endothelin receptors A and B, and is available only for oral use. A new antagonist, tezosentan, available as an IV solution, is under investigation and may reduce PH without a significant effect on MAP.

Inhaled PV

Nitric oxide

The molecule known as the endothelial-derived relaxing factor was found to be NO in 1987 and this discovery opened the field of investigation of the nitrovasodilators. In physiology, NO is synthetized by NO synthase in the endothelium. NO stimulates adjacent SMCs' soluble guanylate cyclase to produce cGMP, which will induce a calcium influx leading to SMC relaxation. It's a major component of vascular tone equilibrium. NO can only be used as iNO. It is delivered to the best-ventilated alveoli with little getting to the poorly-ventilated areas of the lung. NO diffuses through the alveolo-capillary membrane and cause vasodilation of the pulmonary vessels. The duration of effect is only a few minutes. Once NO enters the blood vessel, it is inactivated within seconds by several mechanisms, including the molecule binding to haemoglobin or plasma proteins. This rapid inactivation confers on NO its particular selectivity for the pulmonary vessels without systemic effects. The consequence of iNO administration is a reduction of the PAP and improvement of the PaO_2 via a better ventilation:perfusion ratio in 60% of patients. NO has been used in ICUs since the early 1990s. Despite all its beneficial effects, the use of NO has not shown a benefit in outcome. Five randomized controlled trials (RCT) in ARDS compared the use of NO with placebo and a meta-analysis did not find any benefit in mortality [7]. No RCT have been performed to evaluate the effects of NO in cardiothoracic surgery or RVF. Despite common belief, there is no (or little) alteration of the NO pathway after prolonged use (up to 6.5 days) [8]. However, at the end of NO inhalation, a rebound can be observed with an increase of the PH or hypoxaemia. This rebound can be prevented with the use of a slow NO dose de-escalation protocol. Experts still recommend the use of iNO as rescue treatment in patients with severe refractory hypoxaemia [9].

Drug use in clinical practice

In ICU, NO is usually administered to ventilated patients. It can be added to the air/oxygen mixture before or after the ventilator. NO administration just before the tracheal tube can be done in line with a gas tank containing a known concentration of NO (usually 225 or 450 parts per million (ppm), 1 ppm = 40 nM), in a NO-N_2 mixture. It delivers a precise amount of NO to the inspiratory limb. The amount of NO delivered can be calculated following this formula:

$$CBF = CPP/CVR$$

NO can also be administered to non-intubated patients through a face mask connected to a non-rebreathing circuit. The usual doses used range from 5 to 20 ppm. The peak effect on PaO_2 is observed below 20 ppm (it could be effective at 1 ppm) with the dose–response effect of NO on pulmonary arterial pressure steadily diminishing in a non-linear fashion. To treat severe PH, short course use of higher doses (up to 40 ppm) could be of help.

Side effects and pitfalls

NO is unstable in the presence of oxygen (O_2) with oxidation leading to the generation of nitrogen dioxide (NO_2), which is a toxic gas. Exposure to high levels of NO_2 can cause pulmonary oedema. The final concentration of NO_2 must be less than 1 ppm. Usually, at the doses used in ICU this limit is rarely reached. When NO enters the vessel lumen, it interacts with haemoglobin and forms methaemoglobin (Met-Hb). When high dose NO is used, the level of Met-Hb should be monitored at the 4th hour and daily thereafter; a level of Met-Hb below 4% is acceptable. NO can also cause toxicity by its interaction with reactive oxygen species (ROS), especially the anion superoxide, that will result in peroxynitrite synthesis. Finally, NO causes inhibition of platelet aggregation, and should be carefully used in presence of thrombocytopenia or coagulation disorder.

Prostacyclins

Prostacyclins (PCs; prostaglandin I-2 (PGI2), and prostaglandin E-1, (PGE1)) are naturally occurring prostanoids that are endogenously produced as metabolites of arachidonic acid in the vascular endothelium. While NO stimulates the guanylate cyclase of SMCs, PCs enhance the adenylate cyclase, converting adenosine triphosphate (ATP) to cAMP. Like cGMP, cAMP leads to calcium influx in the SMC producing cell relaxation. By the same mechanism as NO, inhaled PCs (iPCs) reduce PAP and improve arterial oxygenation. iPCs were mainly studied for the treatment of PH and/or RVF, but some studies exist in the ARDS setting [10]. iPCs have also been shown to be anti-inflammatory mediators, PGE1 impairs neutrophil chemotaxis and decreases macrophage

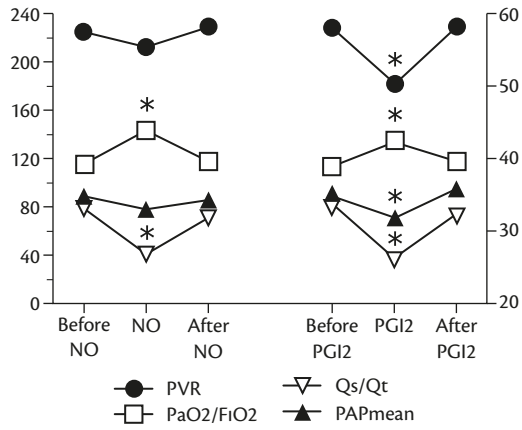


Fig. 39.2 Effects of aerosolized prostacyclin (PGI2) (mean dose = 7.5 ng/kg/min) and inhaled NO (mean dose = 18 ppm) in 16 acute respiratory distress syndrome patients.
PVR = pulmonary vascular resistance, dynes s^{-1} cm^{-5}. PaO_2/FiO_2 = ratio of PaO_2 to fraction of inspired oxygen ratio. PAPmean = mean pulmonary artery pressure, mmHg. Qs/Qt = shunt fraction. *$p < 0.05$.
Data adapted from Siobal M, 'Aerosolized prostacyclins', *Respiratory Care*, 2004, **49**(6), pp. 640–52; and Walmrath D, et al., 'Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome', *American Journal of Respiratory and Critical Care Medicine*, 1996, **153**(3), pp. 991–6 [11].

activation, PGI2 reduces neutrophil adhesion. The main advantage of iPCs is that they are a low-cost alternative to NO. The vasodilator effects of iPCs epoprostenol (PGI2) and alprostadil (PGE1) are similar or better than iNO in ARDS patients [11]. The half-life of these drugs is around 5 minutes. Epoprostenolappears to be more effective than alprostadil in reducing PAP and improving oxygenation. PCs have an antithrombotic effect on platelets and this effect could explain, in part, the effect of these drugs in ARDS patients. Used as aerosolized drugs, iPCs are up to 10 times less potent than their intravenous administration to correct PH. Iloprost is a long-acting PGI2 and is currently the sole PC approved for inhalation by the FDA, although its use in ventilated patients has not been validated. Its effects can last up to 2 hours and it is, therefore, possible to use this drug in intermittent dosing regimens. However, a decrease of the mean systolic arterial pressure was observed with inhaled iloprost, probably due to a spillover of the drug to the systemic circulation. Although good results were obtained in studies focusing on iPCs in clinical practice, the level of evidence is still low and no benefits on mortality have been shown yet (see Fig. 39.2) [12].

Drug use in clinical practice

PCs must be aerosolized. The administration of aerosolized PCs is very inefficient, with only 3% of the nominal dose deposited in the lung. Nebulizers that produce droplets of a few micrometres diameter are optimal; ultrasonic nebulization is also possible. Although usually used in ventilated patients, iPCs can also be considered for non-intubated patients. iPCs, except iloprost, are used in a continuous regimen.

The dose range for inhaled epoprostenol was determined using experimental trials and comparison with iNO and ranges from 10 to 50 ng/kg/min. The starting dose is 50 ng/kg/min (peak benefits) with a slow reduction to the appropriate dose. Experience with inhaled alprostadil is limited in ICU settings; the dose used is 10 ng/kg/min.

Side effects and pitfalls

Systemic hypotension and bleeding disorders are the main side effects of iPCs. Systemic arterial vasodilation can occur for PGI2 doses higher than 200 ng/kg/min. High doses of long-acting PC like iloprost could result in a spillover of the molecule and cause hypotension. While no bleeding events have been attributed to iPCs, their use should be cautious in patients with coagulation disorders. A rebound effect can also be observed and can be prevented by slow weaning. iPCs can cause bronchospasm, especially in patients with bronchial hyper-reactivity.

References

1. Simonneau G, Robbins IM, Beghetti M, et al. (2009). Updated clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology*, **54**(1 Suppl.), S43–54.
2. Radermacher P, Santak B, Wüst HJ, Tarnow J, and Falke KJ. (1990). Prostacyclin for the treatment of pulmonary hypertension in the adult respiratory distress syndrome: effects on pulmonary capillary pressure and ventilation-perfusion distributions. *Anesthesiology*, **72**(2), 238–44.
3. Prielipp RC, MacGregor DA, Butterworth JF, 4th, et al. (1996). Pharmacodynamics and pharmacokinetics of milrinone administration to increase oxygen delivery in critically ill patients. *Chest*, **109**(5), 1291–301.
4. Cornet AD, et al. (2010). Sildenafil attenuates pulmonary arterial pressure but does not improve oxygenation during ARDS. *Intensive Care Medicine*, **36**(5), 758–64.
5. Hoeper MM, et al. (2011). Pulmonary hypertension due to chronic lung disease: updated recommendations of the Cologne Consensus Conference 2011. *International Journal of Cardiology*, **154**(Suppl. 1), S45–53.
6. Mestan KK, Carlson AD, White M, et al. (2003). Cardiopulmonary effects of nebulized sodium nitroprusside in term infants with hypoxic respiratory failure. *Journal of Pediatrics*, **143**(5), 640–3.
7. Afshari A, Brok J, Møller AM, and Wetterslev J. (2010). Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. *Cochrane Database Systems Review*, 2010 Jul 7(7), CD002787.
8. Lukaszewicz AC, et al. (2005). Lack of alteration of endogenous nitric oxide pathway during prolonged nitric oxide inhalation in intensive care unit patients. *Critical Care Medicine*, **33**(5), 1008–14.
9. Germann P, Braschi A, Della Rocca G, et al. (2005). Inhaled nitric oxide therapy in adults: European expert recommendations. *Intensive Care Medicine*, **31**(8), 1029–41.
10. Siobal M. (2004). Aerosolized prostacyclins. *Respiratory Care*, **49**(6), 640–52.
11. Walmrath D, Schneider T, Schermuly R, Olschewski H, Grimminger F, and Seeger W. (1996). Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **153**(3), 991–6.
12. Afshari A, et al. (2010). Aerosolized prostacyclin for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). *Cochrane Database Systems Review*, 2010 (8), CD007733.
13. Siobal MS. (2007). Pulmonary vasodilators. *Respiratory* Care, **52**(7), 885–99.

PART 2.3

Gastrointestinal drugs

CHAPTER 40

Gastrointestinal motility drugs in critical illness

Sonja Fruhwald and Peter Holzer

Key points

- The gastrokinetic domperidone (off-label) has an arrhythmogenic effect related to dose and treatment duration.
- Metoclopramide (off-label) plus erythromycin is a rescue combination therapy in severe gastroparesis.
- Neostigmine is indicated for the management of paralysis and Ogilvie syndrome, but its dosage must be carefully selected.
- Osmotic and stimulant laxatives (polyethylene glycol, bisacodyl) are important options to manage constipation in critically-ill patients.
- Alvimopan (short-term use), methylnaltrexone and naloxegol (off-label) are options to manage constipation associated with opioid analgesic therapy.

Dopamine receptor antagonists

Domperidone

An antagonist of peripheral dopamine D_2-receptors with anti-emetic and prokinetic effects on oesophagus and stomach [1]. The drug can be used in children and patients with Parkinson's disease because it lacks an effect on the brain.

Dosage and pharmacokinetics

Domperidone is only available as an oral preparation and is rapidly absorbed reaching peak plasma levels within 30 minutes. Because of first pass metabolism in the intestine and liver, the bioavailability (13–17%) is low [2]. The recommended dose is as low as possible, not exceeding 30 mg/day.

Adverse effects and drug interactions

- Gynecomastia and galactorrhoea.
- Noteworthy is an arrhythmogenic effect (torsades des pointes) via QT prolongation, guiding the current recommendation of dosage and co-medication with other CYP3A4-metabolized drugs (e.g. ketoconazole, erythromycin, amiodarone, warfarin, and others).

Use in critical care

This is not licensed in the USA and in the EU is restricted to short-term use in nausea and vomiting. Its off-label use in intensive care is limited because of oral administration. It is useful in extubated patients, when longer treatment is necessary, or for prophylactic use in patients with high risk of gastroparesis (Table 40.1).

Metoclopramide

This is a drug with multiple actions—an antagonist of peripheral and central dopamine D_2-receptors, an antagonist of serotonin (5-hydroxytryptamine, 5-HT) 5-HT_3-receptors, and an agonist of 5-HT_4-receptors [1]. It increases lower oesophageal sphincter pressure and stimulates gastroduodenal motility.

Dosage and pharmacokinetics

For use as a gastrokinetic, parenteral administration is preferred. The maximum dose of 10 mg three times daily (tds) needs to be reduced in renal failure; in patients on dialysis 10 mg once daily (od) is recommended [3]. Efficacy declines rapidly over time—in patients with high gastric residual volumes enteral feeding is established in <20% after 3 days of treatment [4].

Adverse effects and drug interactions

- Gynecomastia, secondary to enhanced prolactin release, arrhythmia via QT prolongation. Extrapyramidal motor reactions, such as drowsiness, agitation, irritability, fatigue, and in less than 1% tardive dyskinesia (Table 40.1).
- Extrapyramidal effects appear to be more common in children, young adults, and at high doses.

Use in critical care

In the EU it is restricted to short-term use in nausea and vomiting. The risk for extrapyramidal motor effects increases with treatment duration. Efficacy after traumatic brain injury is doubtful, in patients with post-operative ileus metoclopramide is ineffective.

Macrolides

Erythromycin

Erythromycin binds to motilin receptors and stimulates migrating motor complex and upper gut motility. For efficacy, endogenous motilin levels need to be low.

Dosage and pharmacokinetics

The effective dose is 1 mg/kg intravenously; for practical reasons 100 mg tds is given. Since efficacy is reduced after 3–4 days of therapy, treatment should be limited to 3 days [3,5]. The combination of erythromycin and metoclopramide restores the efficacy of both drugs [4].

Table 40.1 GI motility drugs used in critical care

Substance	Indication	Recommended dose	Side effects	Attention
Domperidone	Gastroparesis	≤30 mg/day orally	Gynecomastia, galactorrhoea, arrhythmia	Off-label use, dose limitation 30mg/day
Metoclopramide	Gastroparesis	10 mg tds iv 10 mg od in renal failure	Galactorrhoea, arrhythmia, extrapyramidal side effects	Off-label use, contraindicated in Parkinson's disease, tachyphylaxis
Erythromycin	Gastroparesis	100 mg tds iv	Diarrhoea, tachyphylaxis, QT prolongation	Tachyphylaxis
Neostigmine	Paralysis, Ogilvie syndrome	0.5–1.5–(2.5) mg short infusion	Bronchospasm, bradycardia	Up to 2.5 mg in Ogilvie syndrome, higher doses inhibit motility
PEG	Constipation	<25–30 mg orally	Flatulence, abdominal pain, diarrhoea	Contraindicated in Ogilvie syndrome
Bisacodyl	Constipation	10–(20) mg/d rectally	Flatulence, abdominal pain, diarrhoea	Contraindicated in Ogilvie syndrome
Naloxone	Constipation, paralysis	3–12 mg tds orally	Symptoms of withdrawal	Inhomogeneous data, not recommended
Alvimopan	Constipation	12 mg BD orally	Flatulence, abdominal pain, diarrhoea	Limited to 15 doses because of cardiovascular side effects
Methylnaltrexone	Constipation, paralysis	8–12 mg sc	Flatulence, diarrhoea, abdominal perforation	Off-label use
Naloxegol	Constipation	25 mg od orally	Abdominal pain, diarrhoea, nausea, headache, flatulence	Off-label use

Data from Fruhwald S and Kainz J, 'Effect of ICU interventions on gastrointestinal motility', *Current Opinion in Critical Care*, 2010, **16**, pp. 159–64.

Adverse effects and drug interactions

Antibiotic resistance is unlikely, but conclusive data are not available. Diarrhoea is common, but unrelated to *Clostridium difficile*. QT prolongation and risk of arrhythmia are characteristic for macrolides.

Use in critical care

In severe gastroparesis, a combination of erythromycin and metoclopramide (Table 40.1) is used as rescue therapy [4]. Since, in the intensive care unit (ICU), a combination of several drugs prolonging the QT interval is common, adequate monitoring is mandatory.

Azithromycin

This macrolide, a relative to erythromycin, has a longer duration of action, comparable prokinetic efficacy, and a more favourable adverse effect profile [6]. Despite a lack of drug interactions via cytochrome P450 enzymes, there is a significantly increased risk of cardiovascular death (hazard ratio 2.88) in patients treated with azithromycin in antibiotic doses [7].

5-HT_4-receptor agonists

5-HT is involved in the regulation of gastrointestinal (GI) motility, secretion, and sensation. Activation of 5-HT_4-receptors, expressed by enteric neurons and smooth muscle cells, leads to the release of acetylcholine from excitatory motor neurons and nitric oxide from inhibitory motor neurons, stimulating GI motility.

Cisapride and tegaserod

Both moderately selective 5-HT_4-receptor agonists were taken off the market. Cisapride was removed because of arrhythmias via hERG-channel stimulation, and tegaserod is now limited to emergency use in the USA, because of an increased risk of cardiovascular adverse events. The mechanism of this adverse effect (calculated as 0.1% risk) is unknown.

Prucalopride

A highly selective 5-HT_4-receptor agonist that stimulates colonic motility, but seems to have limited efficacy in the upper gut [8].

Dosage and pharmacokinetics

Prucalopride (1–2 mg) was approved for women with chronic constipation in whom laxatives are ineffective (Table 40.1). Since 85% of the patients studied were women, prucalopride's efficacy in men awaits to be proven.

Adverse effects and drug interactions

Headache, nausea, and diarrhoea; because of its high selectivity, cardiovascular adverse effects appear negligible. Dose reduction (1 mg) in patients with a glomerular filtration rate < 30 mL/min, severe liver failure, and elderly patients.

Use in critical care

Data on prucalopride's usefulness in the ICU are not available, while beneficial effects on opioid-induced constipation have been reported.

Velusetrag

A highly selective 5-HT_4-receptor agonist with prokinetic effects on the entire GI tract demonstrated in large Phase IIb trials. Of three doses tested, 15 mg has the most favourable therapeutic index and adverse effect profile (diarrhoea, nausea, vomiting, and headache). A metabolite (THRX-830449) is almost as potent as the

parent compound; its elimination half-life is 16 hours after single dosing and 35 hours after multiple dosing [8].

Somatostatin analogs

Octreotide

A synthetic octapeptide, sharing a 4-amino acid sequence with somatostatin. Because of poor bioavailability, it is administered parenterally. As it is excreted renally, dose adjustment is required in renal failure. Octreotide's value as a prokinetic is marginal because low doses stimulate, whereas high doses inhibit motility.

Cholecystokinin agonists and antagonists

Cholecystokinin agonist: ceruletide

A cholecystokinin (CCK) analog with potent prokinetic effects on gallbladder, bile duct, small bowel, and colon, and a stimulant effect on digestive secretion. It also has a beneficial effect in post-operative ileus. Delayed gastric emptying, requiring treatment, is a potential side effect. Ceruletide is currently not available.

CCK antagonists: loxiglumide and dexloxiglumide

These CCK_1-receptor antagonists are of potential value in critically-ill patients with increased CCK levels and gastroparesis, but their efficacy for this indication awaits investigation.

Cholinergic drugs

Neostigmine

This acetylcholine esterase inhibitor increases the concentration of acetylcholine at the receptor and, thus, facilitates parasympathetic and enteric stimulation of GI contractility.

Dosage and pharmacokinetics

Neostigmine has a quick onset (5 minutes) and short duration of action (elimination half-life of 25 minutes). Dose recommendations for short infusions are between 0.5 and 1.5 mg for GI paralysis in the ICU and up to 2.5 mg for Ogilvie syndrome. Care needs to be taken in dosing, because higher neostigmine doses inhibit motility [3].

Adverse effects and drug interactions

Bradycardia, hypotension, and bronchospasm (Table 40.1). In renal failure the elimination half-life is more than doubled. Neostigmine is contraindicated in patients with clinical signs of intestinal perforation.

Use in critical care

Neostigmine is beneficial in post-operative ileus and acute colonic pseudo-obstruction, although its efficacy in critically-ill patients is less pronounced [3], given that the motility disturbances are complex, and involve electrolyte imbalances, hypervolaemia, reduced intestinal secretion, and adverse drug effects (opioids, analgesics, catecholamines).

Acotiamide

Acotiamide is an acetylcholine esterase inhibitor under clinical evaluation. It does not affect gastric emptying in healthy volunteers, but enhances gastric contractility and accelerates delayed gastric emptying in patients with functional dyspepsia [9].

Laxative drugs

Laxatives used in the ICU (bulk-forming, osmotic, or stimulant) either

- Enhance retention of intraluminal fluid by hydrophilic or osmotic mechanisms.
- Decrease GI absorption of fluid due to effects on fluid and electrolyte transport.
- Enhance GI ion/fluid secretion and, thus, stimulate GI motility.

Methylcellulose, psyllium, and polycarbophil

Bulk-forming laxatives are frequently used to relieve constipation, especially if patients are unable to ingest sufficient amounts of dietary fibre. Because of their slow onset of action (up to 72 hours) and the need of adequate fluid intake, bulk-forming laxatives are not recommended in critically-ill patients.

Sorbitol, lactulose, magnesium salts, and polyethylene glycol

Osmotic laxatives draw water into the intestinal lumen and thereby stimulate motility. Of all compounds in this group, polyethylene glycol (PEG) seems to be most efficacious and cost-effective [10].

Dosage and pharmacokinetics

While PEG is inert, lactulose and sorbitol are degraded by colonic bacteria to low molecular weight acids. They increase stool acidity and osmolarity, and cause the accumulation of fluid in the colonic lumen. Recommended doses of lactulose and sorbitol are about 20 mg/day, of magnesium salts between 0.1 mg/kg and 15 g/day, and of PEG between 13 and 30 g.

Adverse effects and drug interactions

Flatulence, nausea, abdominal pain, and diarrhoea. Being renally excreted, magnesium salts should be used with care in patients with renal failure. Contraindications include lactose and sorbitol intolerance (lactulose and sorbitol), renal insufficiency and electrolyte imbalances (electrolyte-enriched PEG), and patients suffering from or being at risk of Ogilvie syndrome (osmotic laxatives in general). On the other hand, PEG is effective in reducing the recurrence rate after Ogilvie syndrome.

Use in critical care

Few studies report on the use of osmotic laxatives in the ICU, with PEG being the most efficacious drug (Table 40.1). PEG is also used prophylactically in opioid-treated patients to avoid constipation and normalize defaecation. One study reports PEG to slightly lower the incidence of Ogilvie syndrome.

Bisacodyl

Bisacodyl is a drug that actively increases the luminal fluid and electrolyte content, and stimulates colonic motility.

Dosage and pharmacokinetics

Taken orally, bisacodyl undergoes enterohepatic circulation before it is activated by esterases in the bowel, which delays the onset of action by up to 12 hours. Doses higher than 10 mg may lead to sudden and powerful bowel movements. Intrarectal administration circumvents enterohepatic circulation and causes laxation within 60 minutes. The maximum dose is 20 mg/day.

Adverse effects and drug interactions

- Bloating
- Light-headedness.
- Nausea.
- Abdominal cramps.
- Discomfort (Table 40.1).

Use in critical care

Although evidence-based data are sparse, bisacodyl (and osmotic laxatives) are recommended for critically-ill patients to improve intestinal motility [3,5].

Lubiprostone

A derivative of prostaglandin E_1, which stimulates fluid secretion by activating CIC-2 chloride channels in colonocytes. Approved for the management of chronic idiopathic constipation (USA, Switzerland, UK), irritable bowel syndrome with constipation and opioid-induced constipation (USA, Switzerland). Studies are ongoing evaluating the effect of lubiprostone on post-operative bowel dysfunction.

Dosage and pharmacokinetics

Lubiprostone accelerates colonic transit and increases the number of spontaneous bowel movements [11]. The recommended dose is 24 micrograms twice daily (bd) for chronic constipation and 8 micrograms BD for irritable bowel syndrome.

Adverse effects and drug interactions

Nausea (20–30%), diarrhoea (13%), abdominal distention, flatulence, and vomiting. The incidence of nausea is reduced when lubiprostone is taken with a meal.

Linaclotide

A peptide analog of guanylin, which activates guanylate cyclase-C, opens cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels, and thus stimulates colonic chloride and bicarbonate secretion and motility. Doses of 145 and 290 μg improve stool consistency and frequency, and reduce abdominal pain. Nausea is a side effect. Linaclotide is currently approved for irritable bowel syndrome with constipation (USA, EU) and chronic idiopathic constipation (USA), the recommended dose is 290 micrograms od. Its usefulness in opioid-induced constipation is under investigation.

Opioid-receptor antagonists

Opioids used in the management of moderate to severe pain frequently cause constipation. Apart from laxatives, peripheral opioid-receptor antagonists can be used to restore GI motility, while analgesia is preserved.

Naloxone

A high-affinity opioid-receptor antagonist. Taken orally, naloxone has low systemic bioavailability due to extensive hepatic first pass metabolism. Doses of 3–12 mg tds are sufficient to antagonize opioid-induced constipation, but too low to have systemic effects. Naloxone is not recommended in critically-ill patients because of insufficient and inhomogeneous evidence.

Alvimopan

A peripheral opioid-receptor antagonist, which inhibits opioid-induced constipation, but does not compromise opioid-induced analgesia. Alvimopan accelerates the time to recovery of bowel function and hospital discharge after abdominal surgery and opioid treatment of post-operative pain (Table 40.1). Because of an increased risk of myocardial infarction associated with long-term use, alvimopan is approved in the USA for the short-term (7 days, 12 mg BD) prevention of post-operative ileus following bowel resection.

Methylnaltrexone

Methylnaltrexone (MNTX) is a peripheral opioid-receptor antagonist approved for the treatment of opioid-induced constipation in patients with advanced illness who do not respond to laxatives.

Dosage and pharmacokinetics

The recommended dose of MNTX is 8 mg for patients weighing 38–61 kg, and 12 mg for patients weighing 62–114 kg. The dose should be reduced in patients with renal failure (creatinine clearance <30 mL/min). No dose adjustment is required in mild to moderate hepatic impairment.

Adverse effects and drug interactions

Flatulence, abdominal pain, nausea, and mild diarrhoea (Table 40.1). Since few cases of intestinal perforation have been reported, MNTX is contraindicated in patients in whom the structural integrity of the gut is compromised.

Use in critical care

There is limited, but promising evidence for a beneficial effect of MNTX in critically-ill patients. Therefore, MNTX is used off-label in the ICU.

Naloxegol

Naloxegol is a PEGylated derivative of naloxone, the PEG moiety making the compound a substrate for P-glycoprotein transporters which limit its entry into the central nervous system. It is thus a peripherally acting μ-opioid receptor antagonist that has been approved in the USA and UK for the treatment of opioid-induced constipation in patients who do not appropriately respond to laxatives [12].

Dosage and pharmacokinetics

Naloxegol is available as tablets, and the recommended dose is 25 mg od. Although the drug is primarily cleared by a hepatic route, no dose adjustment is required in mild renal and mild to moderate hepatic impairment.

Adverse effects and drug interactions

The most commonly reported adverse reactions of naloxegol are abdominal pain, diarrhoea, nausea, headache and flatulence, usually graded as mild to moderate (Table 40.1).

Use in critical care

The use of naloxegol in critically-ill patients has not yet been evaluated.

References

1. Thompson JS and Quigley EM. (1999). Prokinetic agents in the surgical patient. *American Journal of Surgery*, **177**, 508–14.
2. Boyce MJ, Baisley KJ, and Warrington SJ. (2012). Pharmacokinetic interaction between domperidone and ketoconazole leads to QT prolongation in healthy volunteers: a randomized, placebo-controlled, double-blind, crossover study. *British Journal of Clinical Pharmacology*, **73**, 411–21.
3. Fruhwald S, Holzer P, and Metzler H. (2008). Gastrointestinal motility in acute illness. *Wiener klinische Wochenschrift*, **120**, 6–17.
4. Nguyen NQ, Chapman MJ, Fraser RJ, Bryant LK, and Holloway RH. Erythromycin is more effective than metoclopramide in the treatment of feed intolerance in critical illness. *Critical Care Medicine*, **35**, 483–9.
5. Herbert MK and Holzer P. (2008). Standardized concept for the treatment of gastrointestinal dysmotility in critically ill patients—current status and future options. *Clinical Nutrition*, **27**, 25–41.
6. Larson JM, Tavakkoli A, Drane WE, Toskes PP, and Moshiree B. (2010). Advantages of azithromycin over erythromycin in improving the gastric emptying half-time in adult patients with gastroparesis. *Journal of Neurogastroenterology Motility*, **16**, 407–13.
7. Ray WA, Murray KT, Hall K, Arbogast PG, and Stein CM. (2012). Azithromycin and the risk of cardiovascular death. *New England Journal of Medicine*, **366**, 1881–90.
8. Tack J, Camilleri M, Chang L, et al. (2012). Systematic review: cardiovascular safety profile of 5-HT_4 agonists developed for gastrointestinal disorders. *Alimentary Pharmacology & Therapeutics*, **35**, 745–67.
9. Tack J and Janssen P. (2011). Acotiamide (Z-338, YM443), a new drug for the treatment of functional dyspepsia. *Expert Opinion on Investigational Drugs*, **20**, 701–12.
10. Wald A. (2007). Appropriate use of laxatives in the management of constipation. *Current Gastroenterology Reports*, **9**, 410–14.
11. Camilleri M. (2012). Pharmacology of the new treatments for lower gastrointestinal motility disorders and irritable bowel syndrome. *Clinical Pharmacology and Therapeutics*, **91**: 44–59.
12. Garnock-Jones KP. (2015). Naloxegol: a review of its use in patients with opioid-induced constipation. *Drugs*, **75**, 419–25.

CHAPTER 41

Stress ulcer prophylaxis and treatment drugs in critical illness

Waleed Alhazzani and Deborah J. Cook

Key points

- Stress-ulcer gastrointestinal (GI) bleeding is less common in critically-ill patients today than years ago.
- Histamine-2-receptor antagonists prevent GI bleeding more effectively than no prophylaxis and proton pump inhibitors prevent GI bleeding more effectively than histamine-2-receptor antagonists (H2RAs).
- The associations of acid suppression with pneumonia are less concerning today than potential associations with *Clostridium difficile*.
- Randomized trials to date in this field, with some exceptions, are of moderate quality.
- The use of stress ulcer prophylaxis should be tailored according to the patient's risk of bleeding and local epidemiological data.

The past, present, and future

Stress ulcer-related gastrointestinal (GI) bleeding was first described in 1969. In 1971, a large case series describing this condition in more detail was published, labelling 'stress-related erosive syndrome' in 300 patients [1]. Many concepts have evolved over the last four decades, practice has changed considerably, and a profusion of studies have been published since the original research.

The story of upper GI bleeding during critical illness is interesting. Table 41.1, outlines past, present, and future trends regarding upper GI bleeding and its prevention. First, the burden of illness has decreased, in that upper GI bleeding acquired in the intensive care unit (ICU) used to be a common problem, but today, the incidence is much lower. Secondly, the mortality associated with upper GI bleeding from stress ulceration used to be high, but the severity of this problem appears to have attenuated. Prevention of GI bleeding was previously universal in the ICU. Eventually, a more targeted approach was adopted, based on risk factors that identified vulnerable subgroups, and the recognition that some patients are at such low risk of bleeding that prophylaxis may not be warranted. While dual drug prevention was previously used, at most, one agent is prescribed today.

Stress ulcer prophylaxis (SUP) has been part of 'standard critical care practice' in many jurisdictions.

Bleeding definitions

Several definitions have been used to describe different manifestations of stress ulcer bleeding. The definition is central to the discussion of this topic because most early literature conflates occult bleeding, trivial bleeding, minor, and more serious bleeding. Across this spectrum, many issues differ:

- Baseline bleeding rates.
- Risk factors.
- Consequences such as transfusions.
- Attributable morbidity and mortality.
- Health care costs.
- The propensity to prophylax.

Definitions used in the literature

Occult bleeding is usually defined as a positive guiac test on a faecal sample without overt GI bleeding. Overt bleeding is macroscopic, usually defined as haematemesis, coffee ground emesis, melena, or bloody nasogastric aspirate. Clinically important bleeding (CIB) is usually defined as overt bleeding plus one of the following four features, in the absence of other causes:

- A spontaneous fall in systolic or diastolic blood pressure of >20 mmHg within 24 hours of upper gastrointestinal bleeding, an orthostatic increase in pulse rate of 20 beats per minute and decrease in systolic blood pressure of 10 mmHg.
- A decrease in haemoglobin of >2 g/dL (20 g/L) in 24 hours.
- Transfusion of >2 units of packed red blood cells within 24 hours of bleeding [2].

Incidence and implications of GI bleeding

There are variable estimates of the incidence of upper GI bleeding due to no standard definition and the heterogeneity of bleeding risk among patients. The incidence of 'mucosal injury' based on endoscopy was reportedly as high as 75–100%, observed within 24 hours of ICU admission [1,3]. The incidence of occult bleeding ranges from 15–50% [4]. The incidence of overt bleeding is 5–25% in

Table 41.1 Stress ulcer bleeding: past, present, and future

	Past	Present	Future
Clinically important bleeding	Common	Uncommon	Rare?
Prophylaxis	Universal	Targeted	Highly selected?
# Prophylactic drugs	2	1	1 or none?
Main drugs	Prostaglandins, anticholinergics, antacids, sucralfate	H2RAs, PPIs	PPIs versus Nil?

ICU patients not receiving prophylaxis [5]. However, overt bleeding does not usually progress to CIB [6]. In two large prospective cohort studies, the incidence of CIB was 1.5 and 3.5%, respectively [2,7]. The mortality of bleeding patients was significantly higher compared with patients who did not bleed (48.5 versus 9.1%) [7].

The incidence of bleeding was also recorded in other populations. In a retrospective review of 526 non-trauma neurosurgery patients in Hong Kong, the prevalence of overt GI bleed and CIB was 6.8 and 2.8%, respectively. Most of the patients with overt GI bleed received a histamine-2-receptor antagonist (H2RA) for prophylaxis [8]. Two prospective cohort studies in cardiac surgery patients included 11,508 and 6186 patients, and found the incidence of CIB to be 0.3 and 0.8%, respectively [9,10]. Temporal examination of the literature suggests the incidence of stress ulcer GI bleed has decreased. In studies published before 1999, the incidence of CIB was between 2 and 6% in patients not receiving prophylaxis; however, in studies published since 2001, the incidence of CIB has reportedly ranged from 0.1 to 4% with or without prophylaxis [11]. This may relate to the overall improvement in critical care, particularly resuscitation, mitigating gastric mucosal hypoperfusion. Trends could also reflect more widespread SUP, since this is now encoded into many ICU admission order sets and practice guidelines. Increasing and earlier enteral nutrition may also play a role.

Bleeding risk factors

A large prospective ICU cohort study showed that need for mechanical ventilation for >48 hours and coagulopathy (platelet count< 50,000/mm^3, INR > 1.5, or APTT > twice the upper limit of normal) were the only independent factors associated with increased risk of CIB in multivariable regression analysis. Of 847 patients who had one or both risk factors, 3.7% developed CIB, while only 0.1% of 1405 patients without either of those risk factors developed CIB [7]. In a subsequent prospective multicentre cohort study of 874 ICU patients, 79 patients (9%) developed overt GI bleeding; however, the incidence of CIB was not reported [12]. In the second study, several factors were associated with increased risk of overt bleeding in multivariable analysis:

- Acute hepatic failure.
- Nasogastric tube placement for over 5 days.
- History of alcohol abuse.
- Chronic renal failure.
- A positive *Helicobacter pylori* serology [12].

In mechanically-ventilated patients acute renal failure was associated with increased risk of bleeding in multivariable analysis performed in another study [13]. The growing prevalence of *Helicobacter pylori* may tend to increase the risk of CIB, although causation has not been determined in critical illness.

Other factors associated with increased risk of GI bleeding include severe head or spinal cord injury, thermal injury involving > 35% of the body surface area, major surgery (> 4 hours duration), high-dose corticosteroids, and acute lung injury.

Prophylaxis options

Antacids, sucralfate, anticholineric agents, and prostaglandin analogues have been studied and used in the past for SUP, but they are rarely used today. The mainstay of SUP is acid suppression in the form of 2 drug classes: H2RAs and proton pump inhibitors (PPIs).

H2RAs versus placebo

A recent systematic review comparing H2RAs to placebo that included 1836 patients from 17 RCTs reported a significant reduction in CIB (OR 0.47; 95% CI, 0.29–0.76; $p < 0.002$) [14]. Neither of the prior meta-analyses nor this one showed a significant increase in the risk of nosocomial pneumonia associated with H2RAs compared with placebo (OR 1.53; 95% CI 0.89–2.61).

H2RAs versus sucralfate

A recent meta-analysis included 10 RCTs with a total of 2092 patients, although there were only three RCTs with CIB as an outcome. Pooled results for CIB were not reported due to significant heterogeneity among trials. For overt bleeding, the six RCTs indicated no difference in bleeding (OR 0.87, 95% CI 0.49–1.53) [15]. The risk of nosocomial pneumonia was not significantly higher in patients treated with H2RA (OR 1.32; 95% CI 1.07–1.64).

PPIs versus H2RAs

A recent meta-analysis included 1720 patients from 14 RCTs, and found that PPIs were more effective than H2RAs in preventing CIB (RR 0.36; 95% CI 0.19, 0.68) [16]. Pre-determined subgroup analyses suggested that choice of delivery (oral versus parenteral) and dosing (od versus bd) did not influence the results. No significant impact on nosocomial pneumonia was demonstrated [16]. Based on the most recent evidence synthesis, PPIs seem to be more effective than H2RAs in preventing CIB and overt upper GI bleeding. The robustness of this conclusion is limited by the trial methodology, few events, and subgroup differences (the biggest effect is in the trials at highest risk of bias). No differences were found between drugs in the risk of pneumonia, death, or ICU length of stay.

Enteral feeding

In animal models, enteral alimentation may protect the gastric mucosa from stress-related gastric mucosal damage. However, no

RCTs compare enteral feeding to H2RA or other drugs. A recent meta-analysis comparing H2RA with placebo examined studies in which most patients (>50%) received enteral feeding; in this subgroup, H2RA did not change the risk of bleeding (OR 1.26; 95% CI, 0.43–3.7). The mortality was higher in patients receiving H2RAs in those studies (OR 1.89; 95% CI, 1.04–3.44; $p = 0.04$) [14]. The findings, however, were derived from only three3 RCTs, two of which were unblinded, and inferences are limited. Whether enteral nutrition represents effective SUP is based on scant quantity and quality of evidence.

To summarize, no prior meta-analyses demonstrated an effect of SUP on mortality or ICU length of stay. Cautious interpretation of all of these results is warranted. The risk of bias was variable across trial quality domains and across trials. Specifically, subgroup analysis suggested that the treatment effect favouring PPIs over H2RAs was higher in trials of lower quality. It is thus possible that suboptimal trial design, especially the lack of blinding, has inflated the observed benefits of PPIs.

Nosocomial pneumonia

Studies suggest that PPI therapy may be associated with increased risk of hospital-acquired pneumonia. The proposed mechanism includes rising of gastric pH, promoting the growth of bacteria in the stomach (particularly duodenal Gram-negative bacilli) with oesophageal reflux and aspiration of gastric contents leading to airway colonization or pneumonia.

The meta-analysis reported earlier [16] showed no difference in the risk of nosocomial pneumonia between H2RAs and PPIs. Also, there was no increased risk of nosocomial pneumonia in the meta-analysis of H2RA versus placebo [15]. Since these trials were not powered to detect a small risk increase in these events, we cannot be certain of the effect. Furthermore, most of these trials were conducted prior to the era of wide spread ventilator-associated pneumonia (VAP) prevention resulting in lower VAP rates than in years past.

Cardiovascular events

The efficacy of platelet inhibition may be reduced by PPIs, causing an increased risk of cardiovascular events [17]. Indeed the, Food and Drug Administration has warned that omeprazole, esomeprazole, and cimetidine should not be prescribed concomitantly with clopidogrel. Other joint guidelines from the American College of Cardiology, the American Heart Association and the American College of Gastroenterology recommend PPI therapy for those on clopidogrel with high risk of bleeding. Most observational studies have shown that PPI therapy is preferentially prescribed to those that have multiple comorbidities and observational data on the harms of PPI therapy may relate to this confounding factor.

Clostridium difficile infection

More recently, questions have arisen about the influence of H2RA and PPI on the incidence of *Clostridium difficile* [18,19]. Gastric acid helps to eliminate ingested bacteria from the digestive tract, and it is biologically plausible that raising the pH of the stomach may result in an increased load of pathogenic microbes and consequently increased infectious risk. Indirect evidence derived from observational studies, both in-patient and out-patient studies, suggest increased risk of *Clostridium difficile* infections in those receiving acid-suppression (OR associated with PPIs was 1.96, 95% CI 1.28–3.00 compared with OR associated with H2RA of 1.40, 95% CI 0.85–2.29) [20]. However, no RCT data are available in critically-ill population about the effect of acid suppression on *Clostridium difficile* infections. Specifically, none of the RCTs comparing PPIs and H2RAs for SUP in ICU patients have reported this outcome.

When deciding to provide SUP, it is often difficult to determine risk:benefit ratios when the quality of evidence is different for the risks versus the benefits. In this case, there is RCT evidence that PPIs are beneficial with respect to lower GI bleeding risk, and observational evidence suggesting an association with *Clostridium difficile*. The association with PPI use and *Clostridium difficile* could be real, or due to residual confounding or other methodological issues affecting observational studies. Large rigorous RCT evidence examining all-cause mortality would help to address these concerns.

Surviving sepsis campaign recommendations

The Surviving Sepsis Campaign underscores how the balance of benefits and risks for SUP depend on the individual patient's characteristics, as well as on the local epidemiology of VAP and *Clostridium difficile* infections. Indiscriminate use of SUP in all ICU patients is not warranted and may be harmful. The guidelines recommend that patients should be periodically evaluated for the need for SUP. It must be acknowledged that many of the smaller RCTs in this field informing the choice of SUP agent are at moderate to high risk of bias.

Guidelines suggest that SUP using H2RAs or PPIs be given to patients with severe sepsis/septic shock who have bleeding risk factors (grade 1B). Secondly, when SUP is used, guidelines suggest the use of PPIs, rather than H2RAs (grade 2C). Thirdly, guidelines suggest a targeted, rather than universal approach to SUP, not prescribing it to patients without risk factors (grade 2B).

On the need for future research

It may be hard to believe after four decades of studies, but more rigorous research is needed on GI bleeding rates, hypothesized to be low in today's practice, potentially reduced recently by optimal resuscitation and/or early enteral nutrition. If true, this would increase the number needed to treat with prophylaxis to prevent a bleed, and correspondingly, increase the cost per event averted. Furthermore, adverse event rates might be changing, as well as GI bleeding rates. For example, VAP rates appear to be decreasing, perhaps due to more effective prevention strategies. This apparent trend could be factitious due to reduced VAP reporting; alternatively, prior VAP rates may have been factitiously high due to non-specific VAP definitions used in the past. By contrast, the risk of *C. difficile* appears to be increasing; this may have as much to do with the bacteria or the community of bacteria comprising the gut microbiome as physician drug prescribing. The role of acid suppression predisposing to *C. difficile* infection in critically-ill patients warrants careful investigation as no trials to date have examined this relationship, and the relationship is heavily confounded by antibiotics in the ICU setting.

Augmenting today's clinical observations with summaries of yesterday's research helps to inform new investigations that may impact on future practice. As critical care evolves, epidemiology appears to change, and the standards for research improve, the international ICU community needs to re-examine practice in the context of the evidence upon which it is founded. Interventions introduced many years ago, which are in widespread use today might not have the same uptake if they were to be introduced anew today.

Large modern observational studies and RCTs would help to re-evaluate baseline risks, and test prevailing approaches to SUP versus no prophylaxis on the full spectrum of clinically relevant outcomes, to determine the risk:benefit and cost:benefit of this aspect of critical care practice today.

References

1. Lucas CE, Sugawa C, Riddle J, Rector F, Rosenberg B, and Walt AJ. (1971). Natural history and surgical dilemma of 'stress' gastric bleeding. *Archives of Surgery*, **102**, 266–73.
2. Cook DJ, Griffith LE, Walter SD, et al. (2001). The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Critical Care*, **5**, 368–75.
3. Czaja AJ, McAlhany JC, and Pruitt BA, Jr. (1974). Acute gastroduodenal disease after thermal injury. An endoscopic evaluation of incidence and natural history. *New England Journal of Medicine*, **291**, 925–9.
4. Duerksen DR. (2003). Stress-related mucosal disease in critically ill patients. *Best Practice & Research Clinical Gastroenterology*, **17**, 327–44.
5. Shuman RB, Schuster DP, and Zuckerman GR. (1987). Prophylactic therapy for stress ulcer bleeding: a reappraisal. *Annals of Internal Medicine*, **106**, 562–7.
6. Cook DJ, Reeve BK, Guyatt GH, et al. (1996). Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses. *Journal of the American Medical Association*, **275**, 308–14.
7. Cook DJ, Fuller HD, Guyatt GH, et al. (1994). Risk factors for gastrointestinal bleeding in critically ill patients. *New England Journal of Medicine*, **330**, 377–81.
8. Chan KH, Mann KS, Lai EC, Ngan J, Tuen H, and Yue CP. (1989). Factors influencing the development of gastrointestinal complications after neurosurgery: results of multivariate analysis. *Neurosurgery*, **25**, 378–82.
9. D'Ancona G, Baillot R, Poirier B, et al. (2003). Determinants of gastrointestinal complications in cardiac surgery. *Texas Heart Institute Journal from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital*, **30**, 280–5.
10. Andersson B, Nilsson J, Brandt J, Hoglund P, and Andersson R. (2005). Gastrointestinal complications after cardiac surgery. *British Journal of Surgery*, **92**, 326–33.
11. Alhazzani W, Alshahrani M, Moayyedi P, and Jaeschke R. (2012). Stress ulcer prophylaxis in critically ill patients: review of the evidence. *Polskie Archiwum Medycyny Wewnętrznej*, **122**(3), 107–14.
12. Ellison RT, Perez-Perez G, Welsh CH, et al. (1996). Risk factors for upper gastrointestinal bleeding in intensive care unit patients: role of *Helicobacter pylori*. Federal Hyperimmune Immunoglobulin Therapy Study Group. *Critical Care Medicine*, **24**, 1974–81.
13. Cook D, Heyland D, Griffith L, et al. (1999). Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. *Critical Care Medicine*, **27**, 2812–17.
14. Marik PE, Vasu T, Hirani A, and Pachinburavan M. (2010). Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. *Critical Care Medicine*, **38**, 2222–8.
15. Huang J, Cao Y, Liao C, et al. (2010). Effect of histamine-2-receptor antagonists versus sucralfate on stress ulcer prophylaxis in mechanically ventilated patients: a meta-analysis of 10 randomized controlled trials. *Critical Care*, **14**, 1–10.
16. Alhazzani W, Alanezi F, Moayyedi P, Jaeschke R, and Cook D. (2013). Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis. *Critical Care Medicine*, **41**, 693–705.
17. Van-Boxel OS, Van-Oijen MG, Hagenaars MP, and Siersema PD. (2010). Cardiovascular and gastrointestinal outcomes in clopidogrel users on proton pump inhibitors: results of a Large Dutch Cohort Study. *American Journal of Gastroenterology*, **105**, 2430–6.
18. Janarthanan S, Ditah I, Adler DG, and Ehrinpreis MN. (2012). *Clostridium difficile*-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. *American Journal of Gastroenterology*, **107**, 1001–10.
19. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, and Loke YK. (2012). Risk of *Clostridium difficile* infection with acid suppressing drugs and antibiotics: A meta-analysis. *American Journal of Gastroenterology*, **107**(7), 1011–19.
20. Leonard J, Marshall JK, and Moayyedi P. (2007). Systematic review of the risk of enteric infection in patients taking acid suppression. *American Journal of Gastroenterology*, **102**, 2047–56; quiz 2057.

PART 2.4

Nervous system drugs

CHAPTER 42

Sedatives and anti-anxiety agents in critical illness

Curtis N. Sessler and Katie M. Muzevich

Key points

- Use a structured multidisciplinary approach to managing sedation in critically-ill patients.
- Routinely evaluate level of consciousness using a validated sedation-agitation scale.
- Select sedative and anti-anxiety medications based upon patient characteristics and published literature.
- Routinely apply a protocol to sedation management that targets the lightest effective level of sedation.
- Link arousal from sedation to spontaneous breathing trials and early mobilization.

Introduction

The majority of mechanically-ventilated ICU patients are given sedative medications to promote comfort and improve tolerance of the ICU environment [1,2]. These medications are often combined with opioid analgesic agents since pain, dyspnoea, and other forms of discomfort are common. Additionally, an acute confusional state—or delirium—is frequently recognized as a facet of 'brain dysfunction', and contributes to clouded thinking and anxiety. The ICU environment is poorly conducive to restful sleep because of excessive light, noise, and patient arousal for interventions. Sleep deprivation contributes to heightened perception of pain and anxiety, and is considered a major stressor by ICU patients.

As a result of inadequately managed pain, anxiety, and confusion, some patients develop overt agitation, which is characterized by excessive motor activity associated with internal tension. Agitated behaviour can be dangerous to the patient—with self-removal of critical tubes and vascular catheters—or to care-providers from assault. Agitation is often accompanied by poor coordination between the patient's respiratory efforts and the mechanical ventilator, i.e. patient–ventilator asynchrony. Agitation is typically accompanied by a stress–response characterized by high levels of circulating catecholamines, tachycardia, tachypnoea, and hypertension, and can provoke myocardial ischaemia or increased intracranial pressure. Finally, there is evidence that pain and the stress response can contribute to hypercoagulability, hyperglycaemia, increased catabolism, depressed immune response, and other physiological derangements that can have downstream consequences.

It is clear that effective management of anxiety, pain, confusion, and other forms of distress and discomfort is important for the well-being of critically-ill patients. However, prolonged or deep sedation can have negative consequences, including delayed recovery from respiratory failure. Furthermore, administration of benzodiazepines has been linked to the development of delirium, which in turn, is associated with impaired long-term cognitive function. Accordingly, evidence supports and experts recommend targeting a light level of sedation and minimizing sedation whenever possible [1].

Approach to sedation management

Administering sedative and anti-anxiety drugs to a critically-ill patient begins with an assessment of the goals of therapy and the patient specific characteristics that might influence the approach to therapy [1,2]. A useful starting place is the consideration of the patient's underlying medical issues and home medications. Recognition of home use of benzodiazepine, psychotropic agents, or opioid analgesics is crucial, as is identifying underlying alcohol or substance abuse, which might lead to withdrawal symptoms. Organ dysfunction and medication allergies can impact drug selection. The clinician should also consider other predisposing and causative factors that can influence the presence and severity of anxiety, pain, and delirium [2]. In some cases, non-pharmacological interventions, such as minimizing disturbances during sleep, optimizing ventilator settings, and providing verbal reassurance, can improve patients' comfort.

While providing patient comfort and freedom from distress are universal goals, the patient's condition and interventions influence more specific goals of therapy. For example, development of patient–ventilator asynchrony that results in severe hypoxaemia may prompt targeting sufficiently deep sedation to improve patient–ventilator interactions. The presence of overt agitation requires pharmacological control of these behaviours, and administration of neuromuscular blocking agents (NMBA) mandates concomitant administration of sedative and analgesic agents to prevent unrecognized awareness and/or pain. The specific indications for sedative, and analgesic medications and goals of therapy should be periodically re-evaluated.

Titration of sedative medications should be governed by concerns for safety and effectiveness. Effectiveness is primarily evaluated as successfully achieving the goals of therapy such as adequate control of pain, anxiety, dyspnoea, and tolerance of ICU interventions. Safety includes prevention, recognition, and management of adverse effects of medications together with avoidance of

unnecessarily deep or prolonged sedation. Accurately gauging the level of consciousness is guided by routinely assessing arousal using a sedation scale. A variety of scales have been developed and validated, and useful features of effective scales include:

- Multidisciplinary development.
- Ease of administration, recall, and interpretation.
- Well-defined discrete criteria.
- Sufficient sedation levels for drug titration.
- Assessment of agitation.
- Demonstration of validity and inter-rater reliability [3].

Many scales assign progressive hierarchical numbers corresponding to deeper levels of sedation that are defined by responses (including arousal and cognition) to stimuli escalating from auditory to tactile stimuli. Additionally, some scales address grades of agitation. Among published scales, the Richmond Agitation–Sedation Scale (RASS) [4] and Sedation Agitation Scale (SAS) [5] had superior psychometric properties in comprehensive testing and are recommended in the 2013 guidelines [1].

Sedative and anti-anxiety medication administration

Sedative medications are administered intravenously to most ICU patients, particularly in the setting of mechanical ventilation (MV). The primary agents include the benzodiazepines midazolam and lorazepam, as well as propofol and dexmedetomidine (Table 42.1) [1,2]. Propofol was the most commonly administered agent in a survey of USA ICU patients [6]. A single sedative medication is typically administered in combination with an opioid analgesic, although combinations of multiple sedative agents can have synergistic effects.

Pharmacology of sedative agents

Benzodiazepines are GABA receptor agonists that provide sedation via both anxiolysis and amnestic effects [1,2]. Lorazepam and midazolam are used most frequently, but both agents have the potential for drug accumulation and toxicity. Midazolam is a short-acting agent when bolus doses are given to patients with preserved organ function. However, because it is metabolized via the cytochrome P450 enzyme system, which produces active metabolites that undergo renal elimination, it often has prolonged effects when administered to patients with organ dysfunction. Lorazepam is a longer-acting agent that is metabolized via glucuronidation without production of active metabolites. While the metabolic profile makes it advantageous for patients with organ dysfunction, the parent drug is poorly water soluble requiring the addition of propylene glycol to the intravenous formulation. Propylene glycol accumulates in patients with renal dysfunction and can cause metabolic acidosis. Diazepam is used infrequently for ICU sedation, as it has multiple long-acting active metabolites.

Propofol is a lipophillic sedative drug, which exhibits both GABA-agonism and NBDA-antagonism [1,2]. Like benzodiazepine drugs, it provides sedative effect with both anxiolysis and amnestic effects; however, it is extremely short-acting and does not accumulate in patients with organ dysfunction. Propofol is formulated in a soybean oil lipid emulsion, a significant source of calories

Table 42.1 Pharmacological properties of sedative drugs

	Lorazepam	Midazolam	Propofol	Dexmedetomidine
Usual maintenance dose	0.01–0.1 mg/kg/hour	0.02–0.1 mg/kg/hour	5–50 micrograms/kg/min	0.2–0.7 micrograms/kg/hour
Anxiolysis	X	X	X	X
Amnesia	X	X	X	
Analgesia				X
GABA-agonist	X	X	X	
NMDA-antagonist			X	
Central alpha-2 agonist				X
Fast onset (<2 minutes)		X	X	
Short duration (with preserved organ function)		X	X	
Respiratory depression	X	X	X	
Accumulation with organ dysfunction		X		
Delirium	X	X		
Hypotension and/or bradycardia			X	X
Hypertriglyceridaemia			X	

GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate.

Data from Barr J et al., 'Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit', *Critical Care Medicine*, 2013, **41**(1), pp. 263–306; and Sessler CN and Varney K, 'Patient-focused sedation and analgesia in the ICU', *Chest*, 2008, **133**, 2, pp. 552–65.

(i.e. 1.1 kcal/mL), and can also cause hypertriglyceridaemia and pancreatitis, especially with high doses and prolonged therapy. Propofol can cause hypotension, and should be used with caution in the haemodynamically unstable patient. Propofol-related infusion syndrome (PRIS) is the most significant potential adverse effect and is thought to be secondary to drug-induced mitochondrial toxicity. PRIS is characterized by metabolic acidosis, rhabdomyolysis, arrhythmias, renal failure, and death. Risk of PRIS increases with higher doses and longer duration of therapy.

Dexmedetomidine is a central alpha 2 receptor agonist, which exhibits sedative and analgesic properties [1,2]. Unlike benzodiazepines and propofol, dexmedetomidine does not cause respiratory depression and can be used as a bridge to liberation from MV. Although an initial bolus dose is recommended, it is associated with hypotension and bradycardia and is frequently omitted. Even without bolus dosing, dexmedetomidine should be used with caution in patients with haemodynamic instability, as it can cause bradycardia and hypotension. Dexmedetomidine is US Food and Drug Administration-approved for durations of up to 24 hours. However, longer durations of therapy have been studied in clinical trials. While dexmedetomidine is generally short-acting (terminal half-life = 2 hours), the potential for accumulation and drug withdrawal exists, especially with prolonged administration.

The choice of the best sedative medication should be individualized, based upon the medication properties, the sedative indication, and patient characteristics. Additionally, general recommendations can be guided by the results of randomized controlled trials (RCTs). In a meta-analysis of 16 RCTs published in 2008 in which propofol was compared with benzodiazepines for moderate-to-long duration sedation, propofol was associated with shorter duration of MV and shorter ICU length of stay (LOS) [7]. Similarly, a 2010 meta-analysis of 24 RCTs demonstrated shorter ICU LOS with dexmedetomidine compared with other agents, although no difference in duration of MV was found [8]. Recent RCTs, performed in the current era, in which a more alert patient state is emphasized are revealing. In an international multicentre RCT, dexmedetomidine was associated with shorter duration of MV and lower prevalence of delirium, but was less potent in comparison to midazolam [9]. A recent multicentre RCT also showed shorter duration of MV, as well as better patient interaction (communication, arousability, cooperation) with dexmedetomidine compared with midazolam [10]. In the same study, dexmedetomidine and propofol had similar outcomes except patients who received dexmedetomidine had better patient interaction as judged by ICU nurses [10]. Patient who received dexmedetomidine had more bradycardia and hypotension in these RCTs. Recent guidelines suggest using non-benzodiazepine agents, such as propofol or dexmedetomidine in preference to benzodiazepines for mechanically-ventilated adult ICU patients (+2B recommendation) [1].

Protocol-based management of sedation

Numerous studies demonstrate that using a structured approach to manage sedation—and analgesia—in the ICU is associated with improved outcomes [11–18]. Most strategies focus on reducing the amount of sedative medication to the lowest effective dose and achieving the lightest level of sedation compatible with effectiveness and safety. Use of a sedation scale to guide therapy has become routine. Specific strategies include:

- Close monitoring of level of consciousness using validated tools and titrating sedative medications to a specific sedation target that is as light as is feasible.
- Administering sedative drugs intermittently.
- Interrupting sedative infusions on a daily basis until the patient is alert or agitated.
- Administering analgesic medications before sedative drugs.

Based upon the recognition that continuous infusion sedation is associated with delayed recovery [19], an early single-centre RCT demonstrated the benefit of a nurse-implemented protocol that focused on administering sedative and analgesic medications intermittently, rather than by continuous infusion [12]. Another early landmark single-centre RCT demonstrated that daily interruption of continuously infused sedative and analgesic medications (DIS) until the patient was sufficiently awake to perform simple tasks or became agitated, was associated with shorter duration of MV, shorter ICU LOS, and other favourable outcomes [13]. These approaches hasten recovery by reducing drug accumulation, plus promoting earlier identification of the ability to breathe independently. In fact, the combination of DIS plus performance of the pivotal component of ventilator weaning protocols—the spontaneous breathing trial (SBT)—was superior to SBT alone in a multicentre RCT [14]. In a recent multicentre RCT, patients randomized to an intermittent therapy-based protocol or to DIS had nearly identical outcomes, although DIS required greater nursing work [15].

It is important to consider that the abrupt cessation of sedative drugs is associated with a surge in circulating catecholamines, tachycardia, and hypertension, and a higher likelihood of agitated behaviour. Accordingly, it is appropriate to avoid or modify the approach in patients with active seizures, active alcohol withdrawal, worsening agitation, recent myocardial ischaemia, elevated intracranial pressure, or receiving NMBA, and to take precautions to avoid self-extubation [14]. Concerns about the potentially negative impact of abrupt awakening on long-term mental health were alleviated by follow-up studies that demonstrated trends for better neuropsychological status several months after DIS [16].

Another approach to reduce sedative drug administration is to focus first on pain control and analgesia, so called 'analgesia-first'. Several clinical trials have demonstrated shorter duration of MV with analgesia-based strategies compared with hypnotic-based sedation [11]. In a single-centre RCT, patients randomized to receive only morphine boluses (no routine sedation) had shorter duration of MV and ICU LOS compared with patients who received morphine plus sedation (propofol × 48 hours, then midazolam), but also had three-fold higher rates of agitation [17]. These results may not be generalizable to all hospitals, since their ICU had a high nurse-to-patient ratio and liberal availability of 'sitters' to prevent patients from injuring themselves. Nevertheless, focusing first on analgesia, then on sedation, received an endorsement (+2B recommendation) in 2013 guidelines [1].

Modern ICU sedation management is clearly enhanced by implementing a protocol that targets light sedation and/or incorporates daily awakening, as recommended in 2013 guidelines [1]. Furthermore, enhanced patient arousal can facilitate ventilator liberation, as well as earlier mobilization and rehabilitation [18]. While many clinical trials that tested various sedation management strategies did not implement them until after 48 hours of MV, a recent

cohort study demonstrated worse outcomes among patients who had deep sedation in the first 48 hours of MV [20]. Accordingly, we encourage clinicians to initiate protocolized patient-focused sedation from the onset of MV. Practical issues for sustained successful protocol implementation includes multidisciplinary development and implementation, incorporation of the protocol into standard practice, provision of care-provider education, and use of pre-printed protocols, order sets, and checklists, as recommended in recent guidelines [1,2,11].

To summarize, the administration of sedative and anti-anxiety medications to critically-ill patients can improve patient comfort, but has the potential to worsen important outcomes. Structured management should be multidisciplinary in design and implementation, and focus on the patient as an individual with unique challenges. Key components of sedation management include:

- Patient assessment, including pre-existing conditions and medications.
- Monitoring sedation using a validated sedation scale.
- Selection of appropriate medications based upon patient characteristics and published research.
- Implementation of a protocol that focuses on maintaining the lightest effective level of sedation.

References

1. Barr J, Fraser GL, Puntillo K, et al. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical Care Medicine*, **41**(1), 263–306.
2. Sessler CN and Varney K. (2008). Patient-focused sedation and analgesia in the ICU. *Chest*, **133**(2), 552–65.
3. Sessler CN. (2004). Sedation scales in the ICU. *Chest*, **126**, 1727–30.
4. Sessler CN, Gosnell MS, Grap MJ, et al. (2002). The Richmond Agitation–Sedation Scale: validity and reliability in adult intensive care unit patients. *American Journal of Respiratory and Critical Care Medicine*, **166**(10), 1338–44.
5. Riker RR, Picard JT, and Fraser GL. (1999). Prospective evaluation of the Sedation–Agitation Scale for adult critically ill patients. *Critical Care Medicine*, **27**(7), 1325–9.
6. Wunsch H, Kahn JM, Kramer AA, and Rubenfeld GD. (2009). Use of intravenous infusion sedation among mechanically ventilated patients in the United States. *Critical Care Medicine*, **37**(12), 3031–9.
7. Ho KM and Ng JY. (2008). The use of propofol for medium and long-term sedation in critically ill adult patients: a meta-analysis. *Intensive Care Medicine*, **34**(11), 1969–79.
8. Tan JA and Ho KM. (2010). Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: a meta-analysis. *Intensive Care Medicine*, **36**(6), 926–39.
9. Riker RR, Shehabi Y, Bokesch PM, et al. (2009). Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *Journal of the American Medical Association*, **301**(5), 489–99.
10. Jakob SM, Ruokonen E, Grounds RM, et al. (2012). Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *Journal of the American Medical Association,* **307**(11), 1151–60.
11. Sessler CN and Pedram S. (2009). Protocolized and target-based sedation and analgesia in the ICU. *Critical Care Clinics*, **25**(3), 489–513.
12. Brook AD, Ahrens TS, Schaiff R, et al. (1999). Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Critical Care Medicine*, **27**(12), 2609–15.
13. Kress JP, Pohlman AS, O'Connor MF, and Hall JB. (2000). Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New England Journal of Medicine*, **342**(20), 1471–7.
14. Girard TD, Kress JP, Fuchs BD, et al. (2008). Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): a randomised controlled trial. *Lancet*, **371**(9607), 126–34.
15. Mehta S, Burry L, Cook D, et al. (2012). Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. *Journal of the American Medical Association*, **308**(10), 1985–92.
16. Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, and Hall JB. (2003). The long term psychological effects of daily sedative interruption on critically ill patients. *American Journal of Respiratory and Critical Care Medicine*, **168**(12), 1457–61.
17. Strom T, Martinussen T, and Toft P. (2010). A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet*, **375**(9713), 475–80.
18. Schweickert WD, Pohlman MC, Pohlman AS, et al. (2009). Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomized controlled trial. *Lancet*, **373**(9678), 1874–82.
19. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, and Sherman G. (1998). The use of continuous IV sedation is associated with prolongation of mechanical ventilation. *Chest*, **114**(2), 541–8.
20. Shehabi Y, Bellomo R, Reade MC, et al. (2012). Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *American Journal of Respiratory and Critical Care Medicine*, **186**(8), 724–31.

CHAPTER 43

Analgesics in critical illness

Mayur B. Patel and Pratik P. Pandharipande

Key points

- Pain is common in the critically ill. When it is recognized and treated appropriately the risk of multisystem complications can be diminished.
- Regional analgesia can improve respiratory function, bowel function, mental status, and comfort, but it is limited by local anaesthetic toxicity and invasiveness.
- Non-opioid analgesic classes include non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, ketamine, and α2 agonists. They are used as adjuncts to opioid-based or regional analgesia.
- Opioid analgesia in the intensive care unit (ICU) is commonly infusion-based using fentanyl, hydromorphone, morphine, or recently, remifentanil.
- Naloxone can protect against opioid-related respiratory depression using a low-dose infusion, but in an opioid-tolerant patient it can result in a dramatic and acute withdrawal.

Introduction

Critically-ill patients experience pain from obvious sources like invasive procedures, operations, and trauma. Other under-appreciated sources include routine nursing care, endotracheal tube suctioning, prolonged immobility, and pre-existing chronic pain states.

Irrespective of aetiology, uncontrolled pain can have adverse effects on an already critically-ill patient by increasing sympathetic activity, stressing the cardiovascular system, creating a hypermetabolic state and raising oxygen demand [1]. If left untreated, this may progress to excessive catabolism, decreased immune function, delayed wound healing, impaired physical mobility, increased thromboembolic complications, and increased risk of delirium [2]. Thus, analgesia is a critical component of ICU care.

Mechanism of pain

The word analgesic derives from the Greek word *an*—('without') and *algos* ('pain'). Damaged peripheral tissue is usually the source of pain is related to increased levels of histamine, serotonin, and prostaglandins that activate nerve terminals of C and A delta fibres. This afferent pathway synapses in the spinal cord and activates neurons that originate in the diencephalic portion of the reticular activating system. Available analgesics act at these pre- and post-synaptic sites, and can be targeted individually or as part of a comprehensive strategy aimed at multiple sites for additive or synergistic effects.

Assessment of pain

Pain is sometimes undertreated because of concerns about the adverse respiratory and haemodynamic effects of medications, addiction potential of opioids, and lack of proper knowledge in pain assessment and treatment.

Only 25% of surgical patients in the USA received adequate pain relief. Pain assessments using a self-reporting scale, such as a Visual Analog Scale or Numeric Rating Scale [3], are not always possible in those with delirium or coma, although can be used in patients that are communicative. Routine pain assessment that includes intensity, quality, and location has been associated with lower analgesic and sedative utilization, and decreased time on mechanical ventilation and in the ICU [4].

Analgesia

In managing pain in the ICU, non-pharmacological methods are often ignored despite being effective and safe. These methods include patient repositioning, injury stabilization, removal of noxious or irritating stimuli, and use of heat or cold [5,6]. Repositioning and additional support, especially for the lumbar region, are increasingly important in obese patients. Acupuncture, neurolytic agents, cognitive-behavioural interventions, and transcutaneous electrical nerve stimulation all have roles in pain management, but are beyond the scope of this chapter [5,7].

Non-pharmacological approaches should be attempted before supplementing analgesia with regional or systemic therapy. Analgesics commonly used for the treatment of acute pain are listed in Table 43.1.

Regional analgesia

Regional analgesic therapies target specific areas of the body, while limiting the systemic effects of intravenous analgesics. While these procedures are useful adjuncts to decrease exposure to side effects of potent analgesics, they are not without risk and should only be performed by specially-trained clinicians.

Blockade of an individual nerve or nerve plexus may provide relief of pain localized to one extremity. Continuous peripheral nerve blockade via catheter is associated with lower pain scores [8], facilitating earlier rehabilitation. Post-traumatic or surgical pain in the thoracic or upper abdominal areas can be managed by intercostal nerve blocks, paravertebral blocks, or epidural catheters that can improve respiratory mechanics to reduce the risk of pulmonary compromise or pneumonia [9]. Epidural analgesia is used for the management of pain from thoracic, abdominal, or lower extremity

Table 43.1 Opioid and non-opioid analgesics

Class (prototypical agents)	Routes of administration	Mechanism of action	Side-effects
Local anaesthetics (lidocaine, bupivacaine)	EA/SA, PNB/C, sc, TR	Inhibition of Na channels	Hypotension, motor block, myotoxicity, systemic toxicity (seizure, cardiac dysrhythmias, cardiac arrest)
Opioids (fentanyl, morphine)	EA/SA, iv, sc, TR	μ-receptor agonist	Sedation, nausea, vomiting, pruritis, respiratory depression, immunosuppression
Acetaminophen	po, iv	Uncertain	Hepatic toxicity and liver failure, hypersensitivity
NSAIDs (ibuprofen, ketorolac)	po, iv	Inhibition of cyclo-oxygenase	Gastrointestinal bleeding, platelet inhibition, renal failure, hypersensitivity
Gabapentinoids (gabapentin, pregabalin)	po	Inhibition of voltage-gated Ca channels	Sedation, peripheral oedema, gastrointestinal
α_2 agonists (clonidine, dexmedetomidine)	po, iv	α_2-receptor agonist	Sedation, hypotension, bradycardia
Ketamine	iv, im	NMDA-receptor antagonist	Tachycardia, hypertension, increased secretions, hallucinations

EA/SA, epidural/spinal; PNB/C, peripheral nerve block/catheter; sc, subcutaneous; TR, transdermal; iv, intravenous; po, oral.

operative procedures, and it can provide bilateral analgesia in specific dermatomes. Extrapulmonary advantages include lower pain scores, reduced risk of myocardial infarction and dysrhythmias in high risk patients, and earlier return of bowel function [10]. The most easily blocked nerves are sympathetic, sensory, and motor nerves, in that order. Simple neurological testing of motor function or of sensory deficits shows the extent of the block. Bupivacaine and ropivacaine are the local anaesthetics most commonly used for regional analgesia. However, opioids, clonidine, dexamethasone, and other pharmaceutical adjuncts are often used.

The disadvantages of regional anaesthesia are procedure invasiveness, technical complexity, risks of local anaesthetic toxicity, and infection of in-dwelling catheters. The most common adverse effect, especially for epidural catheters, is hypotension due to the blockage of paravertebral sympathetic nerves. This can be reduced by decreasing the rate of the local anaesthetic infusion by administering fluids and initiating a low-dose phenylephrine infusion [9,10]. General contraindications for regional analgesia include coagulopathy, sepsis, and for epidural placement, alterations in spinal anatomy (injury, instrumentation, or congenital).

Systemic analgesia: opioid analgesics

Opioids are the most commonly used ICU analgesics. Their central nervous system pain inhibition is via μ_1 opioid receptor stimulation. Hepatic metabolism and renal clearance is the basis of opioid metabolism. All opioids have the potential to induce tolerance over time, resulting in the need for escalating doses to achieve the same analgesic effect. The selection of an opioid for systemic analgesia has traditionally depended on the pharmacology of the specific opioid and the probable required duration.

Respiratory depression and sedation is commonly seen with opioid use and co-administration of additional sedative agents. Respiratory rate is typically reduced with the preservation of tidal volume ('slow and deep' breathing). Other side effects include decreased gastrointestinal motility, pruritus, flushing, urinary retention, and delirium. Opioid-induced hyperalgesia, distinct from analgesia tolerance, is a paradoxical response to opioids resulting in increased sensitivity to painful stimuli and possibly related to *N*-methyl-D-aspartate (NMDA) glutamate receptor activation. This difficult-to-diagnose entity can occur with either chronic or acute pain, and may be attenuated by NMDA antagonists [9].

Naloxone, a pure competitive antagonist at μ, δ, and κ receptors, can be used to protect against opioid related respiratory depression at infusion rates of 0.25 micrograms/kg/h [11]. Using naloxone in an opioid-tolerant patient can result in a dramatic and acute withdrawal associated with vomiting, aspiration, and severe agitation, as these patients are not fully awake. The doses used for respiratory depression reversal range from 0.4 to 2 mg intravenously (iv).

Other than central pain inhibition, opioids may alter acute brain dysfunction outcomes. Studies in trauma and burn critically-ill patients have also reported on the beneficial effects of morphine and methadone in reducing the development of delirium [12]. However, meperidine and morphine have been positively associated with increased risk for delirium [13], although meperidine use has declined due to increased seizure potential.

Morphine

Morphine has become second-line opioid treatment in many ICUs due to its histamine release causing more hypotension, tachycardia, and bronchospasm than other newer opioids. Additionally, it has an active, sedative metabolite, morphine-6-glucuronide that requires renal elimination and accumulates during renal failure. In rare pain emergencies in those without iv access, it is the only intramuscularly (im) or subcutaneously (sc) deliverable opioid. Morphine infusions are often started at 1 mg/hour and titrated upwards. Intermittent doses of 1–4 mg iv are administered every 5–15 minutes until the pain is controlled, followed by similar doses on a scheduled basis every 2–4 hours. Longer-acting oral formulations are available for basal and chronic pain control.

Hydromorphone

Hydromorphone is a synthetic, hydrogenated ketone of morphine that is at least five times more potent, has higher lipid solubility and blood–brain barrier penetrance, but similar onset, duration, and glucuronide metabolism as morphine. Hydromorphone is broken

down to two active metabolites that have insignificant analgesic activity, but may have some neuro-excitatory properties. Plasma concentrations are increased in patients with renal failure, thus lower starting doses or longer dosing intervals are recommended. In addition to treatment of acute breakthrough pain, it is an alternative for chronic pain and also severe, painful dry coughing. Both iv and oral (po) formulations are available. Its lack of histamine release and decreased incidence of side effects make it a useful alternative to morphine, with typical dosing ranges of 0.2–1 mg iv every 10–15 minutes until pain is controlled followed by similar doses every 2–4 hours; infusions start at 0.2 mg/hour and are titrated upwards.

Methadone

Methadone is a μ receptor agonist and an NMDA receptor antagonist. It has a slow metabolism and very high fat solubility, making it last much longer than morphine-based drugs, but is less useful in acute pain scenarios. Methadone metabolism ranges widely between individuals. Because of its availability orally in solution form and its long half-life, it is ideal for the ICU patient who is expected to need a long recovery period and helps the shift away from moderate- to high-dose analgesia infusions. Recent data suggest that it may result in a decrease in weaning time from mechanical ventilation, compared with IV fentanyl [14]. Electrocardiogram monitoring of QTc interval is recommended. Starting doses range from 2 to 5 mg staggered every 8–12 hours.

Fentanyl

Fentanyl is a synthetic opioid 100 times more potent than morphine. It has a rapid onset and short duration of action, is not renally eliminated, and releases minimal histamine. It is the preferred opioid analgesic in haemodynamically-unstable patients or those with renal insufficiency. It has a large volume of distribution secondary to its lipophilicity, while its clearance correlates most closely with pharmacokinetic mass (similar to lean body mass). Therefore, significant drug accumulation and a prolonged context sensitive half-life can occur with prolonged infusions. It is vagotonic and, in large bolus doses >400 micrograms, can cause severe bradycardia and chest wall rigidity. It is easily titratable as a continuous infusion, secondary to its short half-life. In general, loading doses of 25–100 micrograms of fentanyl are given every 5–10 minutes until pain is controlled, followed by infusion rates of 25–250 micrograms/hr [15]. Transdermal fentanyl is not recommended for routine treatment of acute pain in opioid naïve patients; iontophoretic delivery of fentanyl, effectively transdermal patient controlled analgesia, is under development [9].

Remifentanil

Remifentanil, a derivative of fentanyl, is a selective μ opioid receptor agonist. Its ester linkage undergoes rapid hydrolysis by non-specific blood and tissue esterases with a terminal half-life of 10–20 minutes, regardless of infusion duration. It is used in peri-operative anaesthesia and non-surgical mechanically-ventilated patients. Hypotension and bradycardia are the most common side effects. As a result of its ultra-short half-life, supplemental analgesic medication is required at the conclusion of a remifentanil infusion. It is utilized primarily as an infusion (0.05–2 micrograms/kg/min) based on ideal body weight or lean body mass.

Remifentanil provided better time at optimal arousal level, necessity of supplemental sedation, duration of mechanical ventilation, and extubation time than morphine in one randomized double-blind study [16]. Remifentanil and fentanyl have displayed equal efficacy in achieving sedation goals with no difference in extubation times. Patients receiving fentanyl required more breakthrough sedatives, but experienced less pain after extubation compared with patients receiving remifentanil [17]. Higher cost and reports of withdrawal and hyperalgesia have limited the widespread utilization of remifentanil in the ICU.

Systemic analgesia: non-opioid analgesics

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit inducible and constitutive cyclo-oxygenase enzymes (COX) that are involved in the inflammatory response to injury (COX-2) and protective prostaglandin synthesis (COX-1), respectively. Non-selective NSAIDs, such as ibuprofen and ketorolac), have side-effect profiles that include nausea, gastrointestinal bleeding, inhibition of platelet function, and renal insufficiency, especially in the elderly. Ketorolac is administered at 15 mg iv every 6 hours for a maximum of 5 days. Selective COX-2 inhibitors, such as celecoxib, rofecoxib, or valdecoxib, may be associated with decreased gastrointestinal side effects, but due to imbalance in prostaglandin production, may be associated with cardiovascular morbidity.

Gabapentinoids

Gabapentin and pregabalin were primarily used for anti-seizure activity, but are increasingly used for neuropathic and post-operative pain. They bind to a subunit of the voltage-gated Ca channel, inhibit Ca influx and release of excitatory neurotransmitters. Randomized clinical trial data suggests gabapentin will decrease post-operative pain and opioid consumption, but may increase sedation. There are less data for pregabalin [9]. Gabapentin is generally used as a pain adjunct with opioids at a dose of 100 mg tds, titrated upwards to effect.

Ketamine

Ketamine is a derivative of the hallucinogen phencyclidine (PCP). Its mechanism of analgesic action appears to involve NMDA receptor blockade. The dose for analgesia without loss of consciousness is 0.2–0.3 mg/kg iv, but ketamine can be administered po, rectally, or im. There is increased interest in ketamine's role as an adjunct to opioid administration, as low-dose infusions decrease pain scores and opioid consumption [9]. Ketamine does have sympathomimetic properties, so care must be taken where tachycardia and hypertension would be deleterious.

α_2 Agonists

Clonidine and dexmedetomidine are α_2 agonists that have analgesic and sympatholytic properties, the latter more selective than the former. Clonidine is an anti-hypertensive agent that is associated with rebound hypertension after it is discontinued. Dexmedetomidine is a superior iv short-acting sedative that has brain-protective effects against delirium and coma. It may improve outcome in sepsis [18] and has also been used to control post-operative pain in patients taking the opioid buprenorphine

[19]. Its major side effects are hypotension and bradycardia. Dexmedetomidine infusions start at 0.2 micrograms/kg/min and have been used up to 2.0 μg/kg/min. Clonidine dosing starts at 0.1 mg enterally bd and is longer acting.

References

1. Berns GS, Chappelow J, Cekic M, Zink CF, Pagnoni G, and Martin-Skurski ME. (2006). Neurobiological substrates of dread. *Science*, **312**(5774), 754–8.
2. Molina PE. (2006). Opioids and opiates: analgesia with cardiovascular, haemodynamic and immune implications in critical illness. *Journal of Internal Medicine*, **259**(2), 138–54.
3. Chanques G, Payen J-F, Mercier G, et al. (2009). Assessing pain in non-intubated critically ill patients unable to self report: an adaptation of the Behavioral Pain Scale. *Intensive Care Medicine*, **35**(12), 2060–7.
4. Payen J-F, Bosson J-L, Chanques G, Mantz J, Labarere J, and DOLOREA Investigators (2009). Pain assessment is associated with decreased duration of mechanical ventilation in the intensive care unit: a post hoc analysis of the DOLOREA study. *Anesthesiology*, **111**(6), 1308–16.
5. Erstad BL, Puntillo K, Gilbert HC, et al. (2009). Pain management principles in the critically ill. *Chest*, **135**(4), 1075–86.
6. Brush DR and Kress JP. (2009). Sedation and analgesia for the mechanically ventilated patient. *Clinics in Chest Medicine*, **30**(1), 131–41, ix.
7. Dhanani NM, Caruso TJ, and Carinci AJ. (2011). Complementary and alternative medicine for pain: an evidence-based review. *Current Pain and Headache Reports*, **15**(1), 39–46.
8. Richman JM, Liu SS, Courpas G, et al. (2006). Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. *Anesthesia & Analgesia*, **102**(1), 248–57.
9. Wu CL and Raja SN. (2011). Treatment of acute postoperative pain. *Lancet*, **377**(9784), 2215–25.
10. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, and Wu CL. (2003). Efficacy of postoperative epidural analgesia: a meta-analysis. *Journal of the American Medical Association*, **290**(18), 2455–63.
11. Patel SB and Kress JP. (2012). Sedation and analgesia in the mechanically ventilated patient. *American Journal of Respiratory and Critical Care Medicine*, **185**(5), 486–97.
12. Agarwal V, O'Neill PJ, Cotton BA, et al. (2010). Prevalence and risk factors for development of delirium in burn intensive care unit patients. *Journal of Burn Care & Research*, **31**(5), 706–15.
13. Dubois MJ, Bergeron N, Dumont M, Dial S, and Skrobik Y. (2001). Delirium in an intensive care unit: a study of risk factors. *Intensive Care Medicine*, **27**(8), 1297–304.
14. Wanzuita R, Poli-de-Figueiredo LF, Pfuetzenreiter F, Cavalcanti AB, and Westphal GA. (2012). Replacement of fentanyl infusion by enteral methadone decreases the weaning time from mechanical ventilation: a randomized controlled trial. *Critical Care*, **16**(2), R49.
15. Jacobi J, Fraser GL, Coursin DB, et al. (2002). Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Critical Care Medicine*, **30**(1), 119–41.
16. Dahaba AA, Grabner T, Rehak PH, List WF, and Metzler H. (2004). Remifentanil versus morphine analgesia and sedation for mechanically ventilated critically ill patients: a randomized double blind study. *Anesthesiology*, **101**(3), 640–6.
17. Spies C, Macguill M, Heymann A, et al. (2011). A prospective, randomized, double-blind, multicenter study comparing remifentanil with fentanyl in mechanically ventilated patients. *Intensive Care Medicine*, **37**(3), 469–76.
18. Pandharipande PP, Pun BT, Herr DL, et al. (2007). Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *Journal of the American Medical Association*, **298**(22), 2644–53.
19. Mantz J, Josserand J, and Hamada S. (2011). Dexmedetomidine: new insights. *European Journal of Anaesthesiology*, **28**(1), 3–6.
20. Jodka P and Heard SO. (2005). Management of acute pain in the intensive care unit. In: Abraham E, Fink MP, Vincent J-L, Kochanek P (eds). *Textbook of Critical Care*, pp. 13–16. Philadelphia, PA: WB Saunders Company.

CHAPTER 44

Antidepressants in critical illness

Scott R. Beach and Theodore A. Stern

Key points

- Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, and mirtazapine are typically the first-line agents for the treatment of depression in the intensive care unit (ICU) setting given their safety and tolerability.
- Serotonin syndrome is a significant risk in overdose of most antidepressants and can also be seen in the setting of combining more than one antidepressant.
- Stimulants can be used safely and effectively to treat apathy, loss of appetite, and low energy in ICU patients.
- Antidepressants should typically be continued during ICU stays (except in the presence of delirium), as abrupt cessation may produce a withdrawal phenomenon.
- Current evidence does not recommend prophylactic initiation of antidepressants following trauma.

Introduction

Pharmacological treatment of depression began in the late 1950s with the introduction of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitor (MAOIs). Following the introduction of fluoxetine in 1988, the selective serotonin reuptake inhibitors (SSRIs) became the third class of drugs with a proven effect in the treatment of depression, and quickly became first-line agents due to their more benign side-effect profiles and safety in overdose. The past two decades have seen the addition of serotonin norepinephrine reuptake inhibitors (SNRIs) and several atypical compounds that share some, but not all of the pharmacological features of TCAs or SSRIs.

SSRIs

All six SSRIs currently available worldwide (Table 44.1) inhibit the presynaptic reuptake of serotonin. Sertraline, fluoxetine, citalopram escitalopram, and fluvoxamine demonstrate a relative specificity for the serotonin uptake transporter, whereas paroxetine also has anticholinergic and antihistaminergic effects. SSRIs, like other antidepressants, probably exert their effects via downstream consequences on secondary messenger systems, including increased production of proteins such as brain-derived neurotrophic factor (BDNF).

All SSRIs effectively treat depression. They are also commonly used to treat anxiety disorders, including generalized anxiety disorder (GAD) and obsessive-compulsive disorder (OCD) [1]. Occasionally, these agents are utilized in patients with eating disorders or to treat specific symptoms of personality disorders, such as impulsivity.

SSRIs are associated with fewer anticholinergic side effects and less weight gain than TCAs, although all cause some weight gain [2]. Orthostatic hypotension (OH) is not a common side effect of treatment. SSRIs are safe in patients with coronary artery disease (CAD) and may be effective at treating depression in this population. The major side effects are insomnia, gastrointestinal (GI) discomfort, sexual dysfunction, and headache.

In general, SSRIs typically reduce the heart rate by 7–8 beats/minute. Though previously thought to be free of cardiac conduction abnormalities, all except paroxetine have been associated with prolongation of the QT interval at therapeutic doses and in overdose. Citalopram is thought to be the most highly associated with QT prolongation and malignant ventricular arrhythmias like torsades de pointes (TdP), and in 2011 the Food and Drug Administration (FDA) issued a warning that doses of citalopram higher than 40 mg daily should be avoided if possible due to an association with QT prolongation [3].

SSRIs are far safer than TCAs when taken in overdose. Nonetheless, deaths have been reported from overdoses of all agents. Cardiac conduction abnormalities can be seen in overdose.. Serotonin syndrome (with a triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities) is also a risk in overdose. Symptoms of serotonin syndrome include tremor, confusion, incoordination, hyperreflexia, diaphoresis, mydriasis, and clonus; it progresses to agitated delirium, muscle rigidity, hypertension, hyperthermia, and shock if left untreated (2). Treatment is largely supportive, including intravenous (IV) fluids, cooling blankets, and benzodiazepines for muscle rigidity, though serotonin antagonists are sometimes also used.

SSRIs and SNRIs

The SNRIs, venlafaxine and duloxetine, are similar in most respects to SSRIs (see Table 44.1). They are used primarily to treat depression, although they may have additional benefits in treating neuropathic pain [1]. Due to their additional action on norepinephrine, these agents are more commonly associated with hypertension, and routine monitoring of blood pressure (BP) is recommended. Headaches may also be a more common side effect than with SSRIs. Duloxetine has been associated with drug-induced liver injury, including cholestatic jaundice and hepatitis in patients with chronic liver disease or cirrhosis [4]. Its use is therefore contraindicated in patients with chronic alcohol use or chronic liver disease. It is important to note that venlafaxine is excreted renally,

Table 44.1 Side effect profiles and available formulations of antidepressants

Medication	Therapeutic dose range (mg/day)	Sedative potency	Anticholinergic effects	Blood pressure effects	Other side effects	Alternate formulations
SSRIs					Insomnia, GI discomfort, sexual dysfunction, akathisia, headache	
Citalopram	20–40	Low	Absent	Minimal		Liquid; dissolvable tablet
Escitalopram	10–30	Low	Absent	Minimal		Liquid
Fluoxetine	10–60	Low	Absent	Minimal		Liquid; enteric-coated weekly fluoxetine
Fluvoxamine	50–300	Low	Absent	Minimal		Extended-release capsule
Paroxetine	10–40	Low	Low	Minimal		Liquid; extended-release capsule
Sertraline	50–200	Low	Absent	Minimal		Liquid
SNRIs					Insomnia, GI discomfort, sexual dysfunction, akathisia, headache	
Duloxetine	20–120	Low	Absent	Minimal		
Venlafaxine	75–375	Low	Absent	Moderate		Extended-release capsule
Desvenlafaxine	50	Low	Absent	Moderate		Extended-release tablet
Milnacipran (not approved for depression in USA)	100–200	Low	Absent	Minimal		
Atypical antidepressants						
Bupropion	100–450	Low	Absent	Minimal	Agitation, headache, nausea, tremor, seizure	Extended-release capsule
Mirtazapine	15–45	High	Absent	Minimal	Weight gain	Dissolvable wafer
Vilazodone	10–40	High	Absent	Minimal	GI discomfort	
Tianeptine (not available in the USA)	37.5	Low	Low	Minimal	Insomnia, vivid dreams	
Reboxetine (not available in the USA)	8–10	Low	Moderate	Minimal	Headache, sweating, insomnia, sexual dysfunction	
Agomelatine (not available in the USA)	25–50	High	Absent	Minimal		
TCAs						
Amitriptyline	50–300	High	High	Considerable	Weight gain, tachycardia	
Amoxapine	50–300	Low	Low	Moderate	Stimulation, EPS	
Clomipramine	50–250	High	High	Considerable	Tremor, GI discomfort, sexual dysfunction	
Desipramine	50–300	Low	Low	Considerable	Palpitations, tachycardia	
Doxepin	25–300	High	High	Moderate	Tachycardia	Liquid
Imipramine	50–300	Moderate	Moderate	Considerable	Tachycardia	
Maprotiline	50–200	Moderate	Low	Moderate	Tremor, seizure	
Nortriptyline	25–150	Low	Low	Minimal	Tremor, headache	Liquid

(*continued*)

Table 44.1 Continued

Medication	Therapeutic dose range (mg/day)	Sedative potency	Anticholinergic effects	Blood pressure effects	Other side effects	Alternate formulations
MAOIs						
Phenelzine	15–90	Low	Very low	Considerable	Insomnia, sexual dysfunction	
Selegiline	6–12	Low	Very Low	Moderate		Transdermal patch
Tranylcypromine	10–90	Low	Very Low	Considerable	Insomnia, tremor	
Stimulants					Insomnia, tremor, decreased appetite	
Dextroamphetamine	2.5–30	Absent	Very Low	Minimal		Liquid
Methylphenidate	5–40	Absent	Very Low	Minimal		Liquid, transdermal patch

GI, gastrointestinal; EPS, extrapyramidal symptoms; SSRIs, selective serotonin reuptake inhibitor; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; MAOIs, monoamine oxidase inhibitors.

and its levels therefore increase significantly in patients with renal dysfunction.

Venlafaxine is typically dosed two or three times daily, due to its short half-life, although an extended-release formulation allows for once daily dosing. Duloxetine is generally dosed once or twice daily.

In overdose, SNRIs typically have sympathomimetic effects, including hypertension and tachycardia. Prolongation of the QT interval has been described in case reports with venlafaxine, but not with duloxetine [5,6]. Serotonin syndrome may occur with these agents when used in combination with other serotonergic agents.

Atypical antidepressants

Bupropion is a relatively selective dopamine-uptake blocker that is effective in treating depression (Table 44.1). Its efficacy and side effect profile are similar to those of SSRIs, but bupropion does not cause sexual dysfunction. High doses are associated with an increased risk of seizures [2]. Two distinct extended-release formulations are available.

Mirtazapine is an α_2 antagonist that effectively increases the levels of serotonin and norepinephrine in the synaptic cleft (Table 44.1). It is highly antihistaminergic, leading to prominent side effects of sedation and weight gain. These effects are frequently capitalized upon in medically-ill patients who have poor sleep patterns and low appetite. Mirtazapine has the unusual distinction of causing more antihistaminergic effects at lower doses. Its incidence of sexual side effects is lower than that with SSRIs or SNRIs. Mirtazapine has been associated with prolongation of the QT interval in overdose [7].

Stimulants

Some evidence suggests that dextroamphetamine and methylphenidate may effectively treat depression in elderly and medically-ill patients. Stimulants can also be used safely and effectively to treat apathy and loss of appetite. Although stimulants suppress appetite at higher doses, they tend to improve appetite at low doses. Their onset of effect is much faster than that of SSRIs and TCAs. Caution is warranted with the use of stimulants in patients with untreated hypertension, arrhythmias, or known structural heart defects [8]. Stimulants have the potential to induce or worsen delirium, and should be used cautiously in high-risk patients.

TCAs

TCAs (Table 44.1) effectively treat the neurovegetative signs of depression. Clomipramine is also used to treat OCD. Amitriptyline, clomipramine, and doxepin have a high affinity for muscarinic cholinergic receptors and cause more anticholinergic side effects (e.g., dry mouth, blurred vision, constipation, urinary retention) than the other cyclic compounds. All the TCAs may cause OH, although nortriptyline carries the lowest risk [2]. OH occurs before the therapeutic effect of TCAs.

TCAs cause a predictable increase in heart rate, and all cause prolongation of the QT interval through Na^+ channel blockade, but generally only pose a significant risk of ventricular arrhythmia to patients with pre-existing cardiac disease. Amoxapine has been associated with atrial flutter and fibrillation in case reports. TCAs are not recommended in patients with CAD because of an increased risk of ventricular arrhythmias and myocardial infarction (MI).

MAOIs

Phenelzine and tranylcypromine have traditionally been the two most frequently used MAOIs (Table 44.1). These drugs inhibit both monoamine oxidase isozymes (A and B), which raise the level of norepinephrine, serotonin, and dopamine in the synaptic cleft, as well as the level of exogenous monoamines taken up by the GI tract. The recent development of a transdermal form of selegiline, an irreversible inhibitor of MAO-B, has resulted in resurgence of its use. All MAOIs are primarily used to treat depression, although they are also employed for refractory anxiety and for treatment of specific symptoms, such as impulsivity in patients with personality disorders.

The sympathomimetic pressor amine tyramine, delivered by food to the GI tract, can rise to high levels during MAOI therapy and lead to potentially lethal hypertensive crises, characterized by an elevation of BP, severe headache, nausea, vomiting, and diaphoresis. A tyramine-low diet is recommended in patients taking oral MAOIs, although patients on low-dose selegiline patch do not have

dietary restrictions. MAOIs used in conjunction with other serotonergic agents also carry a risk of serotonin syndrome.

MAOIs have a very low affinity for post-synaptic receptors and, therefore, many of the side effects seen with TCAs are absent. However, insomnia is seen frequently and often requires treatment.

Treatment strategies

The selection of an antidepressant should be based on the side effect profile of the drug and the type of depressive disorder. The SSRIs, SNRIs, mirtazapine, and bupropion are recommended as first-line drugs. Nortriptyline and desipramine are preferred over the other TCAs because of their favourable side effect profile. Amitriptyline and amoxapine are considered third-line drugs because of their propensity to induce significant side effects. The MAOIs are also third-line drugs in the treatment of depression. Stimulants have a rapid onset of effect and can be used effectively in medically-ill patients with prominent apathy and lack of appetite.

Monotherapy is typically the initial treatment strategy. Initiating treatment at low doses and increasing the dose to usual therapeutic drug levels reduces the risk of adverse effects. Monitoring of blood levels is recommended for some TCAs.

If the first antidepressant has not shown a therapeutic effect within 8 weeks, alternative strategies should be considered. Switching to another antidepressant (even of the same class) is reasonable. Augmentation of an insufficient treatment response with a second antidepressant, lithium, a stimulant, or thyroid hormone may also be helpful. Combining pharmacological treatment with psychotherapy is another strategy. Patients who do not respond to adequate trials of antidepressants should be considered for electroconvulsive therapy (ECT).

If the patient recovers from a depressive episode, maintenance treatment should be considered to reduce the significant risk of relapse associated with major depression.

Special issues regarding antidepressant use in the ICU

Use of linezolid with antidepressants

Most antidepressants have the potential to induce serotonin syndrome when used in combination with other agents. One commonly encountered scenario in the ICU involves the use of linezolid in patients maintained on antidepressants. Linezolid is a mild, reversible, non-selective MAOI, and at least 20 case reports have highlighted the potential for serotonin syndrome when used in combination with a serotonergic agent (e.g. an SSRI) [9]. Current recommendations include a washout period of at least 2 weeks for most antidepressants (and 5 weeks for fluoxetine) prior to the initiation of linezolid. This is rarely feasible in the setting of acute infection, however, and a more reasonable guideline may include initiation of linezolid with careful monitoring for signs and symptoms of serotonin syndrome. The decision about stopping the antidepressant should be made after a careful risk–benefit analysis. In the case of a lethal depressive disorder with multiple past suicide attempts, the benefit of continuing the antidepressant may outweigh the relatively low risk of serotonin syndrome. Ideally, an additional washout period of 2 weeks is recommended, following the cessation of linezolid prior to restarting other serotonergic agents.

Special formulations

Many patients in the ICU are unable for a variety of reasons to take pills by mouth, and it is therefore important for critical care physicians to be aware of alternative preparations of these agents (see Table 44.1) [10].

Withdrawal from antidepressants

Another common decision in the ICU involves the continuation of antidepressants. Many critical care physicians favour discontinuation of any non-essential medications. Furthermore, a majority of patients in the ICU will develop delirium at some point during their stay. While most SSRIs, with the exception of paroxetine, are not thought to be highly deliriogenic, all may increase the risk for, or prolong, the course of delirium. The issue is complicated, however, by the fact that an SSRI-discontinuation syndrome has been described in the setting of acute cessation of these agents and is considered to be most significant with paroxetine due to its short half-life [11]. The syndrome is marked by the rapid onset of symptoms that may include anxiety, crying, dizziness, headache, insomnia, irritability, myoclonus, nausea, parasthesias, and tremor. There are currently no guidelines for the maintenance of antidepressants in the ICU setting. In the absence of side effects, it is reasonable to continue these agents, although many would advocate for discontinuing any psychoactive substances should delirium develop. Patients in whom SSRIs are stopped abruptly should be monitored closely for signs of withdrawal.

Starting SSRIs immediately after trauma

Psychiatric consultants are often asked to opine on the utility of starting antidepressant therapy as prophylaxis for depression following a significant trauma. Commonly-encountered situations include a patient who has suffered traumatic para- or quadriplegia or one with a new diagnosis of terminal illness. Although many clinicians assume that anyone in such a situation would become depressed, evidence suggests that in fact, only a minority of such patients develop an episode of major depression. The issue is complicated by the fact that many patients become demoralized, which can mimic depression, but has not been found to be responsive to medication. Given the risks associated with antidepressant medications, there is currently no evidence to recommend empiric initiation of antidepressants patients with catastrophic illness. Instead, patients should be carefully monitored over a period of several weeks for mood changes, with psychiatric involvement as needed.

References

1. Stevens JR, Fava M, Rosenbaum JF, and Alpert JE. (2010). Psychopharmacology in the medical setting. In: Stern TA, Fricchione GL, Cassem NH, Jellinek MS, and Rosenbaum JF (eds). *Massachusetts General Hospital Handbook of General Hospital Psychiatry*, 6th edn, pp. 441–66. Philadelphia: Saunders Elsevier.
2. Huffman JC and Stern TA. (2008). Side effects of psychotropic medications. In: Stern TA, Rosenbaum JF, Fava M, Biederman J, and Rauch SL (eds). *Massachusetts General Hospital Comprehensive Clinical Psychiatry*, 1st edn, pp. 705–20. Philadelphia: Mosby Elsevier.
3. FDA (2012). FDA Drug Safety Communication: abnormal heart rhythms associated with high doses of celexa (citalopram hydrobromide). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm269086.htm

4. Vuppalanchi R, Hayashi PH, Chalasani N, et al. (2010). Duloxetine hepatotoxicity: a case-series from the drug-induced liver injury network. *Alimentary Pharmacology & Therapeutics*, **32**(9), 1174–83.
5. Letsas K, Korantzopoulos P, Pappas L, Evangelou D, Efremidis M, and Kardaras F. (2006). QT interval prolongation associated with venlafaxine administration. *International Journal of Cardiology*, **109**(1), 116–17.
6. Nelson JC, Pritchett YL, Martynov O, Yu JY, Mallinckrodt CH, and Detke MJ. (2006). The safety and tolerability of duloxetine compared with paroxetine and placebo: a pooled analysis of 4 clinical trials. *Primary Care Companion Journal of Clinical Psychiatry*, **8**(4), 212–19.
7. Waring WS, Graham A, Gray J, Wilson AD, Howell C, and Bateman DN. (2010). Evaluation of a QT nomogram for risk assessment after antidepressant overdose. *British Journal of Clinical Pharmacology*, **70**(6), 881–5.
8. Lorberg B and Prince JB. (2010). Psychopharmacological management of children and adolescents. In: Stern TA, Fricchione GL, Cassem NH, Jellinek MS, and Rosenbaum JF (eds) *Massachusetts General Hospital Handbook of General Hospital Psychiatry*, 6th edn, pp. 497–98. Philadelphia: Saunders Elsevier.
9. Quinn DK and Stern TA. (2009). Linezolid and serotonin syndrome. *Primary Care Companion Journal of Clinical Psychiatry*, **11**(6), 353–6.
10. Muramatsu RS, Litzinger MHJ, Fisher E, and Takeshita J. (2010). Alternative formulations, delivery methods, and administration options for psychotropic medications in elderly patients with behavioral and psychological symptoms of dementia. *American Journal of Geriatric Pharmacotherapy*, **8**(2), 98–114.
11. Schatzberg AF, Blier P, Delgado PL, Fava M, Haddad PM, and Shelton RC. (2006). Antidepressant discontinuation syndrome: consensus panel recommendations for clinical management and additional research. *Journal of Clinical Psychiatry*, **67**(Suppl. 4), 27–30.

CHAPTER 45

Antiseizure agents in critical illness

Sebastian Pollandt and Lori Shutter

Key points

- Currently available antiseizure drugs do not affect the development of epilepsy.
- Benzodiazepines are the most effective agents for termination of acute seizures.
- After termination of acute seizures, several effective drugs are available for prevention of seizure recurrence.
- Intravenous (iv) formulations of antiseizure drugs are recommended for management of seizures in ICU populations.
- Drug levels can vary significantly due to drug–drug interactions and co-morbidities, thus frequent monitoring is recommended.

Introduction

Clinical and subclinical seizures are frequent in critically-ill patients, and are often due to intracranial structural lesions, central nervous system (CNS) infections, metabolic derangements, exogenous toxins, or medications [1] that lower the seizure threshold. A full discussion of these issues is beyond the scope of this chapter. The mechanisms of seizure generation and perpetuation are thought to be related to excitatory inputs that exceed inhibition and result in neuronal hypersynchrony. Thus, any disease process that alters the balance of excitation and inhibition has the potential to cause epileptic seizures. Accordingly, antiseizure drugs employ various strategies to either increase inhibition by augmenting GABAergic transmission or reduce excitation, most commonly via Na channel blockade. The most challenging clinical scenario encountered in the intensive care unit (ICU) is status epilepticus, defined as 5 minutes or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery (returning to baseline) between seizures [2]. Pharmacological treatment of status epilepticus involves emergent termination of acute seizures with primarily benzodiazepines, followed by rapidly achieving therapeutic concentrations of an antiseizure drug via intravenous (iv) infusion to prevent seizure recurrence.

Agents available for management and prevention of seizures do not prevent development of epilepsy, thus the term 'anti-epileptic' is not accurate. The term anticonvulsant is also imprecise in that it neglects the effects of these drugs on non-convulsive seizures. Agents used for management of seizures will be referred to as antiseizure agents. The choice of an antiseizure agent must be influenced by the clinical situation and potential for drug interactions. Highly protein-bound agents, such as phenytoin, carbamazepine, or valproate, often require monitoring of free plasma levels in the ICU setting.

Benzodiazepines

Benzodiazepines are widely regarded as the agent of choice for emergent treatment of clinical and subclinical seizures [2]. They enhance inhibitory GABAergic transmission via the $GABA_A$ receptor, resulting in hyperpolarization of the membrane. Treiman et al. performed a blinded, randomized, prospective study of four iv regimens, including lorazepam, phenytoin, phenobarbital, and diazepam for primary treatment of status epilepticus. Lorazepam was found to be significantly more successful than phenytoin alone in aborting overt status epilepticus within 20 minutes of therapy, although no treatment regimen was found to be superior in the intent-to-treat analysis [3]. Intravenous lorazepam and diazepam have been shown to be superior to placebo in termination of out-of-hospital status epilepticus, with a trend towards better efficacy for lorazepam [4]. A double-blind, randomized, non-inferiority trial of iv lorazepam versus intramuscular (im) midazolam in the out-of-hospital setting showed non-inferiority for midazolam and a trend towards better results with im midazolam, which may have been related to shorter time to administration [5]. All benzodiazepines are known to result in the development of tolerance, thus dose escalation may be necessary. Propylene glycol is commonly used as a solvent for diazepam and lorazepam, which can cause hypotension and peripheral venous irritation, and may be avoided by modifying the method of administration (slower rate, use of a central venous line). In some countries, diazepam in a lipid emulsion is available for iv and im injections, which has been shown to reduce pain and thrombophlebitis [6].

Lorazepam

Lorazepam is less lipophilic than diazepam and redistribution is slower, resulting in longer duration of action. Lorazepam is administered at an initial dose of 0.1 mg/kg iv up to 4 mg/dose, with a maximum administration rate of 2 mg/min [2]. This dose may be repeated every 5–10 minutes up to a maximum cumulative dose of 8–10 mg, but occasionally higher doses have been used. Common adverse effects include hypotension and respiratory depression, which may necessitate intubation and mechanical ventilation.

Midazolam

Midazolam is soluble in water and available for iv and im injection, as well as buccally or intranasally. It is rapidly redistributed, resulting in a short duration of action. Initial dosing in status epilepticus starts with boluses of 0.2 mg/kg iv, given at a maximum rate of 2 mg/min up to a total of 10 mg. The dosing range for a continuous infusion is typically 0.05–2 mg/kg/hour. For breakthrough status epilepticus, a bolus of 0.1–0.2 mg/kg, together with an increase of the infusion rate by 0.05–0.1 mg/kg/hour every 3–4 hours is recommended [2]. Prolongation of the half-life with sustained infusions has been reported, thus the infusion rate should be decreased if extended use is required [7]. Hypotension and respiratory distress occur, but less frequently than with diazepam or lorazepam. Tachyphylaxis is a known phenomenon and may require switching to an alternative antiseizure agent.

Diazepam

Diazepam is very lipophilic, penetrates quickly into the CNS, but then redistributes rapidly out into peripheral tissues, which can result in a precipitous decline in CNS concentrations and early seizure recurrence. The initial dose is 0.15 mg/kg iv up to 10 mg/dose, which may be repeated after 5 minutes. The administration rate should not exceed 5 mg/min. Diazepam is commonly used in paediatric populations via per rectum administration. The dosing in children aged 2–5 years is 0.5 mg/kg, ages 6–11 years is 0.3 mg/kg, and children older than 12 years should get 0.2 mg/kg [2]. Intravenous formulations of diazepam containing propylene glycol may result in hypotension and respiratory depression.

Clonazepam

Clonazepam is used outside North America in a similar fashion to lorazepam, but the iv formulation is not available in the USA. Multiple studies have found it to be effective in status epilepticus [8].

Barbiturates

Barbiturates exert antiseizure properties by enhancing inhibitory transmission via the $GABA_A$ receptor. Agents used in clinical practice include phenobarbital, pentobarbital, and thiopental. Although highly effective in treating refractory status epilepticus, they have considerable adverse effects, including cardiac toxicity, haemodynamic instability, respiratory depression, ileus, and nosocomial infections. Additionally, iv formulation of both phenobarbital and pentobarbital contain propylene glycol, which is associated with hypotension, renal dysfunction, and cardiac arrhythmias.

Phenobarbital

The initial dose is 20 mg/kg iv administered at 50–100 mg/min. An additional 5–10 mg/kg may be given 10 minutes after the loading infusion [2]. The most relevant adverse effects include hypotension, sedation, and respiratory depression. It has a long plasma half-life of 53–118 hours (mean 79 hours), making it an attractive agent for chronic maintenance therapy.

Pentobarbital

The loading dose is 5–15 mg/kg, with additional boluses of 5–10 mg/kg, typically with the goal of burst-suppression on EEG. This should be administered at 50 mg/min or less. The recommended dosing range for a continuous infusion is 0.5–5 mg/kg/hour. For breakthrough status epilepticus, the recommended treatment is a bolus of 5 mg/kg, followed by an increase in the infusion rate by 0.5–1 mg/kg/hour every 12 hours [2]. Common adverse effects are hypotension, respiratory depression requiring intubation and mechanical ventilation, cardiac depression, and paralytic ileus.

Thiopental

Thiopental is a short-acting barbiturate that is metabolized to pentobarbital. The loading dose is 2–7 mg/kg, administered at 50 mg/min or less. A maintenance infusion is typically dosed at 0.5–5 mg/kg/hour. For breakthrough status epilepticus, the suggested treatment is a bolus of 1–2 mg/kg, followed by an increase of the infusion rate by 0.5–1 mg/kg/h every 12 hours [2] Adverse effects are similar to pentobarbital.

Phenytoin

Phenytoin is a hydantoin and acts by blocking Na channels. It is available in various formulations—immediate and extended release capsules, chewable tablets, oral suspension, and as a solution for injection. Absorption and bioavailability is variable, with close monitoring recommended when switching between formulations. Patients receiving continuous enteral nutrition have lower than expected phenytoin concentrations, and dose adjustments together with more frequent phenytoin concentration monitoring are recommended. The initial dose in status epilepticus is 20 mg/kg iv, given at a maximum rate of 50 mg/min. An additional 5–10 mg/kg may be given 10 minutes after the loading infusion [2]. Phenytoin is indicated for all seizure types, and requires propylene glycol as a solvent. Phenytoin is highly protein-bound (>90%); thus free serum concentrations can vary significantly depending on the patient's nutritional status. Unbound phenytoin is metabolized via a saturable hepatic metabolism, resulting in non-linear kinetics and toxic levels with small increases in dosing. Hypotension is common and often related to rapid infusion rates. Phenytoin is known to exert cardiotoxic effects, and thus requires cardiac monitoring and sometimes external pacing. It is contraindicated in sinus bradycardia, sino-atrial block, second—and third-degree atrioventricular block, and patients with Adams–Stokes syndrome. The most common additional side effects are dizziness, drowsiness, and lethargy. At toxic doses, seizures, coma, and death are possible. Serious skin reactions include Stevens Johnson syndrome, purple-glove syndrome, and toxic epidermal necrolysis.

Fosphenytoin

Fosphenytoin is metabolized to phenytoin and the differences between the two are related to their pharmacokinetic profiles. Fosphenytoin is soluble in water and is dosed in milligrams of phenytoin equivalents (PE). Fosphenytoin may be administered at a maximum rate of 150 PE mg/min.

Levetiracetam

The precise mechanism of action is unknown, but it has been shown to bind to the synaptic vesicle protein 2A (SV2A), which plays a role in release of neurotransmitter. The loading dose is generally 1000–3000 mg iv in adults, while higher doses are used

in paediatric populations (20–60 mg/kg). It is most commonly administered as bd intermittent bolus doses of 500–3000 mg, but has been used as a continuous infusion at 2–5 mg/kg/min [9]. It has minimal drug–drug interactions and is not hepatically metabolized. The dose must be reduced for patients with renal dysfunction, and supplemental doses after intermittent haemodialysis are necessary. In patients on continuous renal replacement therapy dosing is very challenging and thus other agents are more appropriate. Side effects are typically minimal, but psychosis, somnolence, dizziness, agitation, or other behavioural disturbances have been reported. In 2008, Rüegg et al. [10] retrospectively assessed the safety and efficacy of iv levetiracetam in 50 critically-ill patients. The authors reported cessation of seizure activity, or prevention of its recurrence in 41 of 50 patients (82%) without notable adverse effects [10]. Another study retrospectively assessed iv levetiracetam for treatment of refractory status epilepticus. A median daily dose of 3000 mg with a range of 1000–9000 mg was administered as an iv bolus or continuous pump infusion. Status epilepticus was terminated in 69%. Treatment failure was associated with age >80 years, non-convulsive status epilepticus, periodic lateralized epileptiform discharges (PLEDs) on electroencephalography (EEG) and acute lesions, such as stroke, intracranial haemorrhage, encephalitis, or brain trauma [9]. A trial comparing iv clonazepam alone to iv clonazepam plus iv levetiracetam administered by emergency medical services personnel in a pre-hospital setting in generalized convulsive status epilepticus is ongoing [11].

Propofol

Propofol is thought to act by blockade of Na channels and modulation of GABAergic neurotransmission. When treatment is escalated to a continuous propofol infusion, mechanical ventilation is usually necessary. The loading dose is 1–2 mg/kg, followed by a continuous infusion starting at 20 micrograms/kg/min. Maintenance dosing typically ranges from 30–200 micrograms/kg/min. For breakthrough seizures, it is recommended to increase the infusion rate by 5–10 micrograms/kg/min every 5 minutes, or to administer an iv bolus at 1 mg/kg bolus with subsequent titration of the continuous infusion. Caution is recommended for administration of doses in excess of 80 micrograms/kg/min for prolonged periods of time, i.e. greater than 48 hours, due to the risk of propofol infusion syndrome (PRIS), which is a rare, but potentially fatal adverse effect. PRIS is characterized by heart failure, rhabdomyolysis, metabolic acidosis, renal failure, hyperkalaemia, hypertriglyceridaemia, and hepatomegaly [12]. Children are at greater risk for PRIS; thus, propofol is contraindicated in this population. It is also associated with hypotension, particularly with higher loading doses. Due to the short-half-life, a rapid taper of propofol should be avoided to prevent withdrawal seizures. Of note, propofol provides a significant amount of lipid-based calories (1.1 kcal/mL), which should be considered when addressing nutritional needs.

Lacosamide

Lacosamide is a novel antiseizure agent that enhances slow inactivation of voltage-gated Na channels, which is thought to stabilize hyperexcitable neuronal membranes and inhibit repetitive neuronal firing. It also modulates collapsin response mediator protein 2 (CRMP2), a phosphoprotein that is involved in neuronal differentiation and control of axonal outgrowth. The role of CRMP2 in seizure control is unclear. There is some support in the literature for use of lacosamide in status epilepticus [13]. It is administered initially at 200–400 mg iv at a rate of 200 mg/15 min [2], and is subsequently dosed intermittently bd with a total daily dose of 200–400mg/day. Lacosamide and its major metabolite are eliminated from systemic circulation primarily by renal excretion, with approximately 40% excreted unchanged in urine. Hepatic metabolism does play a role in the biotransformation of lacosamide, thus lower doses are recommended in patients with moderate hepatic impairment. It has not been evaluated in patients with severe hepatic impairment. Protein binding is less than 15% and it is effectively removed from plasma by haemodialysis, so supplementation after intermittent haemodialysis is recommended. Lacosamide has no known relevant drug–drug interactions, but may prolong the PR interval and cause hypotension.

Topiramate

The mechanism of action of topiramate remains to be elucidated. It has been shown to block voltage-dependent Na channels, augment GABAergic transmission, exert antagonism at the AMPA/kainate subtype of the glutamate receptor, and inhibit carbonic anhydrase enzyme. It is available for PO administration only and has been used for add-on therapy in the setting of refractory status epilepticus [14]. The initial loading dose of topiramate is typically 200–400 mg po, with maintenance doses of 300–1600 mg/day, divided 2–4 times daily [2]. Common adverse effects include sedation and metabolic acidosis. Topiramate is not extensively metabolized, and about 70% of the administered dose is excreted unchanged in urine. It is also removed by haemodialysis, and a supplemental dose after intermittent haemodialysis is recommended.

Valproate

The mechanism of action of valproate remains unclear, but may be related to increased brain concentrations of GABA. The initial loading dose in status epilepticus is 20–40 mg/kg iv given at a rate of 3–6 mg/kg/min. An additional dose of 20 mg/kg may be given 10 minutes after the loading dose. In paediatric populations, the recommended dose is 1.5–3 mg/kg/min [2]. Valproate has numerous side effects, most notably hyperammonaemia, pancreatitis, thrombocytopenia, and hepatotoxicity, as well as drug–drug interactions. It may be the best choice for patients with primary generalized epilepsy. A randomized study comparing iv phenytoin with iv valproate in status epilepticus refractory to benzodiazepines found both drugs equally effective in termination of seizures without any differences in adverse events [15].

References

1. Abou Khaled KJ and Hirsch LJ. (2008). Updates in the management of seizures and status epilepticus in critically ill patients. *Neurologic Clinics*, **26**(2), 385–408, viii.
2. Brophy GM, Bell R, Claassen J, et al. (2012). Guidelines for the Evaluation and Management of Status Epilepticus. *Neurocritical Care*, **17**(1), 3–23.
3. Treiman DM, Meyers PD, Walton NY, et al. (1998). A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *New England Journal of Medicine*, **339**(12), 792–8.

4. Alldredge BK, Gelb AM, Isaacs SM, et al. (2001). A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *New England Journal of Medicine*, **345**(9), 631–7.
5. Silbergleit R, Durkalski V, Lowenstein D, et al. (2012). Intramuscular versus intravenous therapy for prehospital status epilepticus. *New England Journal of Medicine*, **366**(7), 591–600.
6. von Dardel O, Mebius C, Mossberg T, and Svensson B. (1983). Fat emulsion as a vehicle for diazepam. A study of 9492 patients. *British Journal of Anaesthesia*, **55**(1), 41–7.
7. Naritoku DK and Sinha S. (2000). Prolongation of midazolam half-life after sustained infusion for status epilepticus. *Neurology*, **54**(6), 1366–8.
8. Pinder RM, Brogden RN, Speight TM, and Avery GS. (1976). Clonazepam: a review of its pharmacological properties and therapeutic efficacy in epilepsy. *Drugs*, **12**(5), 321–61.
9. Möddel G, Bunten S, Dobis C, et al. (2009). Intravenous levetiracetam: a new treatment alternative for refractory status epilepticus. *Journal of Neurology, Neurosurgery & Psychiatry*, **80**(6), 689–92.
10. Rüegg S, Naegelin Y, Hardmeier M, Winkler DT, Marsch S, and Fuhr P. (2008). Intravenous levetiracetam: treatment experience with the first 50 critically ill patients. *Epilepsy & Behavior*, **12**(3), 477–80.
11. Navarro V, Dagron C, Demeret S, et al. (2011). A prehospital randomized trial in convulsive status epilepticus. *Epilepsia*, **52**(Suppl. 8), 48–9.
12. Diedrich DA and Brown DR. (2011). Analytic reviews: propofol infusion syndrome in the ICU. *Journal of Intensive Care Medicine*, **26**(2), 59–72.
13. Höfler J, Unterberger I, Dobesberger J, Kuchukhidze G, Walser G, and Trinka E. (2011). Intravenous lacosamide in status epilepticus and seizure clusters. *Epilepsia*, **52**(10), e148–52.
14. Towne AR, Garnett LK, Waterhouse EJ, Morton LD, and DeLorenzo RJ. (2003). The use of topiramate in refractory status epilepticus. *Neurology*, **60**(2), 332–4.
15. Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, and Garg N. (2007). Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure*, **16**(6), 527–32.

CHAPTER 46

Inhalational anaesthetic agents in critical illness

Laurent Beydon and Flavie Duc

Key points

- Sevoflurane and isoflurane are inhaled agents with interesting pharmacological properties and may be used for sedation in the intensive care unit.
- Sevoflurane and isoflurane require specific administration devices not routinely available.
- Renal toxicity is unlikely despite a sizeable increase in inorganic fluoride level.
- Sevoflurane and isoflurane have been shown to improve patients suffering life-threatening asthma.
- The usefulness of halogenates in status epilepticus is not sufficiently supported to be considered in practice.

Introduction

Inhalational agents are widely used in the operating theatre for general anaesthesia. Their use in the intensive care unit (ICU) is limited as administration requires specific equipment not routinely available. Clinical indications are limited since the use and versatility of relatively cheap competing intravenous drugs only requires conventional peristaltic or syringe pumps. Nevertheless, inhalational agents have also been proposed for short sedation by some authors. Halogenates provide a more predictable dose–response effect, and allow faster awakening than midazolam or propofol. Moreover, they may have therapeutic effects in refractory status asthmaticus or epilepticus.

Administration of inhaled agents in ICU

Three halogenated agents are available currently—isoflurane, sevoflurane, and desflurane. They are all suitable to provide sedation/anaesthesia in the ICU, but require special equipment for their delivery.

Nitrous oxide, a less potent anaesthetic gas shall be considered as an adjunctive agent, which potentiates general anaesthesia. Used alone with oxygen, it allows light sedation and analgesia required for technical and moderately painful procedures (catheter insertion, superficial biopsies . . .). It is available in cylinders mixed to 50% oxygen, ready to be dispensed by a face mask and a demand valve in any place without requiring further equipment.

Xenon, an inert gas with anaesthetic properties cannot yet be considered as a clinically useful means to deliver sedation due to its price and the need for anaesthesia machines specifically compatible with this gas.

Delivery of inhaled anaesthetic agents presents a practical difficulty, which may explain the limited use of inhaled anaesthesia/sedation in ICU practice.

The conventional anaesthesia machine

These large and somewhat cumbersome machines with closed circuit architecture have long been judged as unsuitable for use in ICU. Rarely available outside the operating theatre, it is problematic to remove them from the operating theatre even for short use in ICU. The poor pneumatic performance of anaesthesia machines has traditionally been another limitation for ICU use, but modern devices comprise all the main ventilatory modes, including pressure-controlled ventilation and inspiratory pressure support. All halogenates can be delivered via the integrated evaporators, in the same way as in the operating theatre. Moreover, these machines comprise a sampling gas monitor, which allows closed loop ventilation with CO_2 scavenging via the in-line soda lime canister. This close loop architecture is of major interest as it limits halogenate consumption and costs, and room air pollution. A charcoal scavenging canister fitted to the machine gas exhaust port is recommended when used in ICU to suppress air pollution fully. Using an anaesthesia machine to administer halogenate-inhaled sedation is a straight forward solution. However, one should consider the size of these machines (Fig. 46.1), which, in addition to limited availability, impedes the generalization of their use. The three halogenates routinely used in anaesthesia (isoflurane, sevoflurane, desflurane) can be dispensed by this method.

Reflection HME filter (AnaConDa®)

This reflection HME filter (AnaConDa®, Sedana Medical™, Sundbyberg, Sweden) has been developed to administrate halogenates without the use of an anaesthesia machine (Fig. 46.2). In addition to the 'conventional' HME filter the device includes a carbon layer capturing halogenates from exhaled gas and allowing them to be re-inhaled during inspiration. Halogenate is infused at the patient side of the filter, via an external conventional syringe pump, which controls the inspiratory fraction of the halogenate in use. The intended inspired halogenate fraction is linearly related to the infusion rate (Fig. 46.3). Gas partial pressure (CO_2 and halogenate) can be monitored by an external monitor via a sampling port on the device (Fig. 46.2). Isoflurane and sevoflurane are the two agents

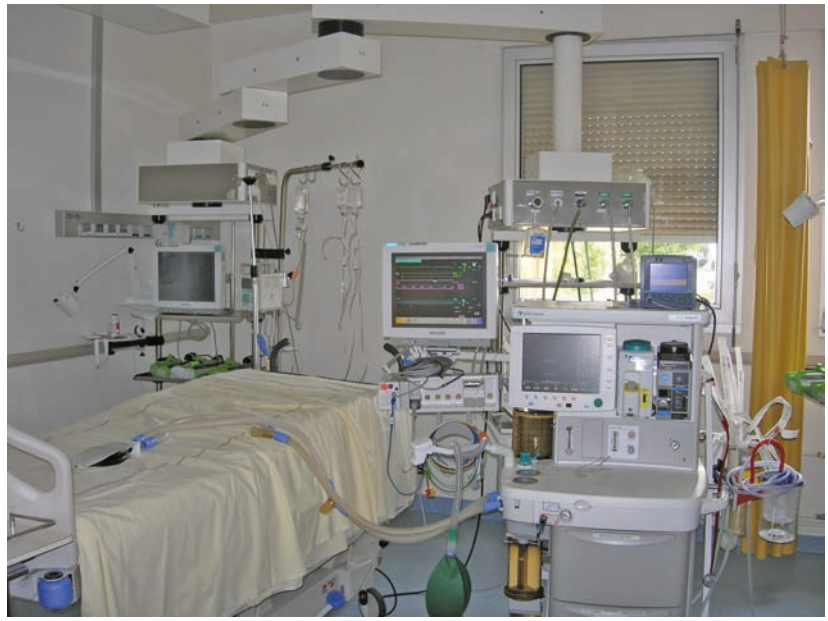


Fig. 46.1 An ICU bed equipped with an anaesthesia closed loop ventilator in order to deliver halogenates. Note the size and room occupancy of this setting.

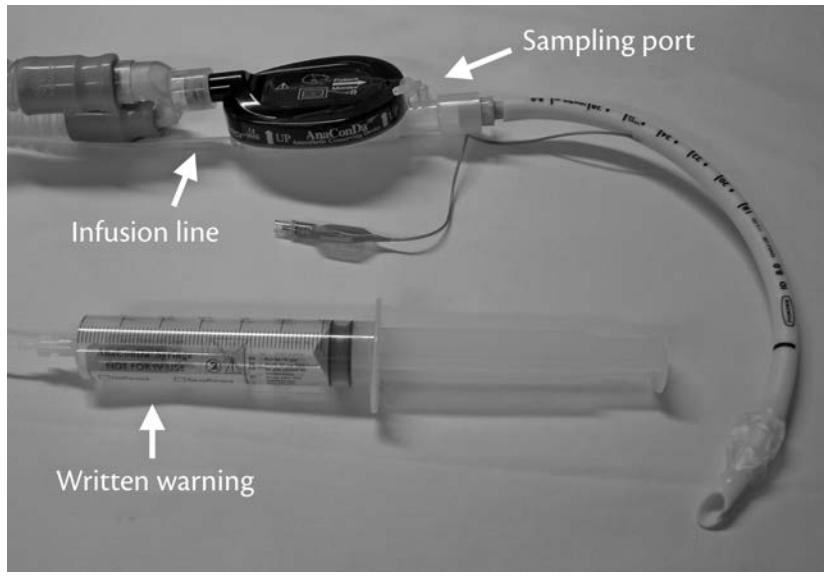


Fig. 46.2 Picture of the AnaConDa® filter showed in a clinical setting.
Reproduced from Berton J et al., 'AnaConDa reflection filter: bench and patient evaluation of safety and volatile anesthetic conservation', *Anesthesia and Analgesia*, **104**, 1, copyright 2007 permission from International Anesthesia Research Society.

that can be safely delivered with this system. The rate of halogenate reinhalation (≈90%) is comparable with that of a low flow anaesthesia machine [1]. Any ICU ventilator can be used in association with this dispensing HME filter. These devices have made it possible to reconsider the usage of inhaled halogenate agents in ICU.

Inhalational anaesthetic agents

Sevoflurane, isoflurane, and desflurane

These three halogenated anaesthetic gases are used in anaesthesia worldwide. The vaporization temperature of the desflurane is 23°C, thus requiring a heated evaporator that is only available on anaesthesia machines. Therefore, unlike isoflurane and sevoflurane, desflurane cannot be dispensed with the AnaConDa® HME filter.

Their potency can be summarized by the minimum alveolar concentration (MAC) principle, which is the percentage exhaled fraction at steady state providing immobility on surgical stimulation in 50% of patients (desflurane, 6.0%; sevoflurane, 2.0%; isoflurane, 1.1%). Opiates and nitrous oxide have an additive effect when co-administered with halogenates, and permit reduced concentration and, consequently, side effects.

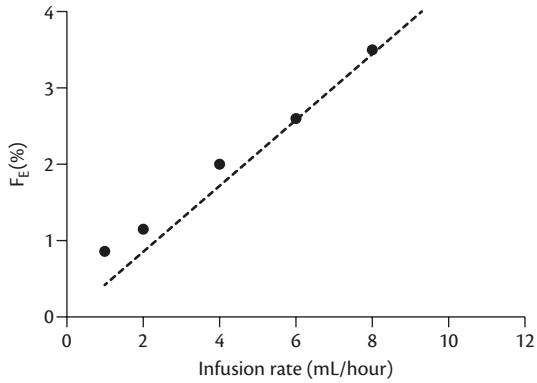


Fig. 46.3 Plot of infusion rate versus expired fraction of isoflurane (F_E%) in the bench study.
Tidal volume, VT = 500 mL; respiratory rate, RR = 12 breaths/minute; respiratory 'duty cycle', Ti/Ttot = 33%; no positive end-expiratory pressure; and constant flow during inspiration. Reproduced from Berton J et al., 'AnaConDa reflection filter: bench and patient evaluation of safety and volatile anesthetic conservation', *Anesthesia and Analgesia*, **104**, 1, copyright 2007 permission from International Anesthesia Research Society.

Isoflurane, sevoflurane, and desflurane are well tolerated with minimal side effects [2]. In short, they moderately depress cardiac output, which is partly compensated by a rise in cardiac frequency. They depress arterial pressure in response to a dose-dependent decrease in systemic vascular resistance [3]. These effects are dose dependent. In addition, sevoflurane may prolong the QT interval [4]. Interestingly, halogenates are cadioprotective when used in cardiac surgery [5]. Isoflurane and sevoflurane decrease airway resistance in cases of bronchospasm, whereas desflurane is irritant to the respiratory tree. Halogenates are also known to potentiate the effects of muscle relaxants and can generate malignant hyperthermia in genetically susceptible patients. When used above 1 MAC, halogenates raise the cerebral blood flow and cerebral blood volume. This contributes to a rise in intracranial pressure in cases of brain damage as the vasodilatatory effect of halogenates is greater than the decrease in cerebral metabolic rate caused. Therefore, halogenates should be used below 1 MAC under moderate hypocapnia, in acute cerebral disease to avoid the deleterious effects of a pharmacologically-induced luxury perfusion. Sevoflurane is known to favour seizure-like EEG activity, especially in children, with possible clonic movements. At the same time, sevoflurane is known to exert neuroprotective effects. Halothane has been shown to be hepatotoxic in rare cases, but this risk in virtually absent in modern halogenates.

Isoflurane and desflurane are not significantly metabolized unlike sevoflurane of which 5% is metabolized via the cytochrome pathway to inorganic fluoride, and hexafluoroisopropanol. These metabolites react with carbon dioxide absorbents (soda lime) in anaesthesia ventilators to form potentially nephrotoxic products where low fresh gas flow is used. No clinically significant renal injury has been documented despite some authors reporting an increase in sensitive markers of renal integrity after sevoflurane anaesthesia [6]. Consequently, sevoflurane should not be used with a fresh gas flow <2 L/min in closed circuit with soda lime, especially for prolonged exposures. This issue has raised concerns about using sevoflurane for sedation in ICU. Insufficient experience has been gained to rule out any renal safety issue when sevoflurane is used for prolonged sedation in ICU. Carbon monoxide is also produced by the interaction between soda lime and desflurane, and to a lesser extent, isoflurane. There are conflicting data on the reproductive hazards related to the exposure of health care workers to halogenates (and nitrous oxide) [7]. When halogenates are used in ICU, charcoal cylinders should be used to suppress air pollution.

Nitrous oxide

Nitrous oxide is not usually available in the ICU, except in the form of 50% N_2O/O_2 cylinders. Accordingly, N_2O may be used to induce light analgesia/sedation for short procedures; in the same way as in office-based surgery. It is an agent of limited potency, but may provide marginal interest in limited cases.

Xenon

For more than 50 years xenon, has been known for its anaesthetic properties at inhaled concentrations around 30% in O_2. Moreover, xenon tends to induce minimal cardiovascular or respiratory depression compared with halogenates. It also allows extremely fast induction and awakening, whatever the duration of anaesthesia, as it is not metabolized and is highly insoluble in blood (blood/gas partition coefficient, 0.115). It has been shown to provide neurological and cardio-protective effects in vivo, which seem promising [8]. It does not induce intracranial hypertension in experimental brain injury, in contrast to halogenates [9]. As a natural compound obtained as a by-product of industrial extraction of oxygen, it does not contribute to atmospheric pollution unlike halogenates and nitrous oxide. However, its price and rarity limits the generalization of its use which is only possible with specific anaesthesia ventilators. Monitoring inspired/expired concentration requires specific technologies (heat conductivity or radiofrequency-based measurement). EEG based monitoring of the depth of anaesthesia can be used in Xenon anaesthesia [10].

At present, its routine use in ICU is out of reach, although some authors foresee applications in cardiac vulnerable patients or after neonatal brain injury.

Inhaled anaesthetics in ICU: a limited experience

Inhaled anaesthetics used for sedation from a few hours to several days has been reported in a limited number of studies. One can summarize these reports by citing the results of several typical studies in order to understand what can be expected from this mode of sedation. Mesnil et al. [11] compared sedation with midazolam (0.1 mg/kg/hour), propofol (2 mg/kg/hour) or sevoflurane (expired fraction: 0.5% with AnaConDa®), in association with remifentanil in 47 ICU patients, for 50 hours, on average. Doses were adjusted to reach the same sedation level according to a sedation scale. Average doses delivered at steady state were: remifentanil: 9–12 micrograms/kg/hour. Awakening duration was shorter with sevoflurane (18 minutes) compared with propofol (91 minutes) and midazolam (260 minutes). Sedation level was more stable with sevoflurane with less hallucinations and a striking reduction in consumption of morphine after extubation. The mean fluoride concentration was 82 μmol/L (range 12–220) with no rise in serum creatinine, aspartate transaminase (AST) or alanine transaminase (cystic fibrosis transmembrane conductance regulator ALT). Sackey et al. [12], comparing isoflurane and midazolam sedation for 96 hours, report a similar shorter time to extubation with isoflurane compared with

midazolam (10 versus 110 minutes). Series of published literature using inhaled halogenates compared with propofol or midazolam has been reviewed with similar findings and no consequence on renal function [13]. Others confirmed the absence of renal consequence after a short sevoflurane sedation (≈ 9 hours) despite a rise in inorganic fluoride levels (average 39 μmol/L) compared with the propofol group [14]. Fluoride level has been shown to return to normal levels by the fifth day after discontinuation of halogenates (isoflurane) [15].

Inhaled sevoflurane [16] and isoflurane [17] have been shown to improve blood gases (decreased pH and $PaCO_2$) and clinical outcome in children ventilated in a state of life-threatening asthma. Refractory status epilepticus has been treated with isoflurane and desflurane, but data are insufficient to recommend their use at present [18].

Xenon (inhaled fraction: 28%) has been used for 8 hours post-operative sedation in comparison with propofol/alfentanil infusion. Haemodynamics were more stable and recovery faster with xenon [19].

Conclusion

Limited experience has been achieved with halogenates and xenon to produce short sedation in ICU. Results seem promising especially because the stability of sedation was achieved with virtually no side effects. However, development of this mode of sedation is limited by the specific devices required to administer these agents. Isoflurane and sevoflurane may be useful to treat life-threatening asthma. Their usefulness in the refractory status epilepticus remains to be confirmed. Xenon, is a difficult to recommend solution as long as its price remains high.

References

1. Berton J, Sargentini C, Nguyen JL, Belii A, and Beydon L. (2007). AnaConDa reflection filter: bench and patient evaluation of safety and volatile anesthetic conservation. *Anesthesia and Analgesia*, **104**, 130–4.
2. Torri G. (2010). Inhalation anesthetics: a review. *Minerva anestesiologica*, **76**, 215–28.
3. Malan TP, Jr, DiNardo JA, Isner RJ, et al. (1995). Cardiovascular effects of sevoflurane compared with those of isoflurane in volunteers. *Anesthesiology*, **83**, 918–28.
4. Han DW, Park K, Jang SB, and Kern SE. (2010). Modeling the effect of sevoflurane on corrected QT prolongation: a pharmacodynamic analysis. *Anesthesiology*, **113**, 806–11.
5. Landoni G, Fochi O, and Torri G. (2008). Cardiac protection by volatile anaesthetics: a review. *Current Vascular Pharmacology*, **6**, 108–11.
6. Ebert TJ, Frink EJ, Jr, and Kharasch ED. (1998). Absence of biochemical evidence for renal and hepatic dysfunction after 8 hours of 1.25 minimum alveolar concentration sevoflurane anesthesia in volunteers. *Anesthesiology*, **88**, 601–10.
7. Martin JL and Njoku DB. (2005). Metabolism and toxicity of modern inhaled anesthetics. In: Miller RD (ed.) *Miller's Anesthesia*, 6th edn, pp. 231–72. London: Elsevier/Churchill Livingstone.
8. Preckel B, Weber NC, Sanders RD, Maze M, and Schlack W. (2006). Molecular mechanisms transducing the anesthetic, analgesic, and organ-protective actions of xenon. *Anesthesiology*, **105**, 187–97.
9. Darby JM, Nemoto EM, Yonas H, and Melick J. (1991). Stable xenon does not increase intracranial pressure in primates with freeze-injury-induced intracranial hypertension. *Journal of Cerebral Blood Flow Metabolism*, **11**, 522–6.
10. Stoppe C, Peters D, Fahlenkamp AV, et al. (2012). aepEX monitor for the measurement of hypnotic depth in patients undergoing balanced xenon anaesthesia. *British Journal of Anaesthesia*, **108**, 80–8.
11. Mesnil M, Capdevila X, Bringuier S, et al. (2011). Long-term sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. *Intensive Care Medicine*, **37**, 933–41.
12. Sackey PV, Martling CR, Granath F, and Radell PJ. (2004). Prolonged isoflurane sedation of intensive care unit patients with the anesthetic conserving device. *Critical Care Medicine*, **32**, 2241–6.
13. Soukup J, Scharff K, Kubosch K, Pohl C, Bomplitz M, and Kompardt J. (2009). State of the art: sedation concepts with volatile anesthetics in critically ill patients. *Journal of Critical Care*, **24**, 535–44.
14. Rohm KD, Mengistu A, Boldt J, Mayer J, Beck G, and Piper SN. (2009). Renal integrity in sevoflurane sedation in the intensive care unit with the anesthetic-conserving device: a comparison with intravenous propofol sedation. *Anesthesia and Analgesia*, **108**, 1848–54.
15. Spencer EM, Willatts SM, and Prys-Roberts C. (1991). Plasma inorganic fluoride concentrations during and after prolonged (greater than 24 h) isoflurane sedation: effect on renal function. *Anesthesia and Analgesia*, **73**, 731–7.
16. Watanabe K, Mizutani T, Yamashita S, Tatekawa Y, Jinbo T, and Tanaka M. (2008). Prolonged sevoflurane inhalation therapy for status asthmaticus in an infant. *Paediatric Anaesthesia*, **18**, 543–5.
17. Shankar V, Churchwell KB, Deshpande JK. (2006). Isoflurane therapy for severe refractory status asthmaticus in children. *Intensive Care Medicine*, **32**, 927–33.
18. Mirsattari SM, Sharpe MD, and Young GB. (2004). Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. *Archives of Neurology*, **61**, 1254–9.
19. Bedi A, Murray JM, Dingley J, Stevenson MA, and Fee JP. (2003). Use of xenon as a sedative for patients receiving critical care. *Critical Care Medicine,* **31**, 2470–7.

CHAPTER 47

Muscle relaxants in critical illness

Brian J. Pollard

Key points

- Relaxants antagonize the action of acetylcholine. Important factors that may modify the action include acid-base disturbances, electrolyte changes, muscle diseases, and drug interactions.
- The principal differences are in onset, duration, and side-effects.
- Succinylcholine is normally used for rapid tracheal intubation. Rocuronium in a higher dose is also effective.
- Train of four is the most convenient method for monitoring muscle relaxation.
- Indications include tracheal intubation, facilitation of procedures, to assist ventilation, critical gas exchange, tetanus, and transfers.

Physiology

The neuromuscular junction lies between motor nerve and striated muscle. The transmitter is acetylcholine, which synthesized in the cytoplasm of the pre-junctional nerve ending. It is stored in vesicles and released into the junctional cleft in response to a nerve impulse. The released transmitter crosses the space to react with receptors, which lie on the shoulders of the folds of the post-junctional membrane. Each receptor unit is integral with its ion channel and the simultaneous binding of two acetylcholine molecules (to the alpha subunits of the chain) causes the channel to open. Occupation of either or both receptor sites by an antagonist molecule will result in the channel being inactivated, unable to open and thus unable to conduct the impulse onwards. The channels on the post-junctional membrane are selective for small cations; it is the sudden transmembrane flux of Na ions through a large number of channels activated simultaneously that is responsible for the generation of an endplate potential. This is followed by the onward propagation of the impulse across the membrane of the muscle cell.

Receptors also exist in other locations, in particular on the pre-junctional nerve endings and these are involved in modulation of impulse transmission via changes in transmitter mobilization and release particularly at higher frequencies of stimulation.

Pharmacology

The clinical use of the muscle relaxants is regarded as having begun in 1942, although early formulations had been tried out over the previous approximately 40 years. Many different agents have been introduced into clinical practice, some naturally occurring (e.g. tubocurarine) and some totally synthetic (e.g. pancuronium). Only a small number have become established in modern clinical practice, the main reason being issues with undesirable side effects and differences in elimination characteristics.

The principal differences between the available drugs are in their onset of action, duration of action, route of elimination, and side effects.

- Rapidity of onset is important when tracheal intubation must be secured urgently.
- An intermediate duration of action is convenient because it offers better control than a long-acting drug. A short-acting drug might be regarded as better still, although the rate of consumption of a short-acting drug would be excessive if its use is prolonged. A long-acting drug may accumulate.
- Elimination of muscle relaxants is principally through the kidneys and liver. Since impairment of renal and hepatic function are common in the critically ill, any drug used in the ICU should rely as little as possible on either of these organs for its elimination.
- Since many critically-ill patients have significant cardiovascular instability any drug should have minimal effects on the cardiovascular system.

There are a number of medical conditions and pathophysiological changes (acid base, electrolyte) that are common in the ICU patient and which may interfere with the action of muscle relaxants. Acidosis, hypothermia, hypokalaemia, hypocalcaemia, hypernatraemia, and hypomagnesaemia may all potentiate neuromuscular block. Muscular, neurological, and neuromuscular disorders (e.g. myasthenia gravis, myotonias, muscular dystrophies) may also prolong neuromuscular block. In addition, the ICU patient will receive many concomitant drugs and some may interfere with the action of the relaxants, e.g. antagonism by neostigmine, ecothiopate, alkylating agents, trimetaphan, or potentiation by calcium channel blockers, aminoglycoside antibiotics, immunosuppressants, furosemide, and lithium.

Choice of muscle relaxant

Summary information concerning the five non-depolarizing relaxants is given in Tables 47.1 and 47.2.

Table 47.1 Basic pharmacodynamics data for five non-depolarizing relaxants

	ED95 (mg/kg)	Approximate infusion rate to maintain steady state (mg/kg/h)	Approximate duration of one ED95 dose (minutes)
Atracurium	0.23	0.25	20–30
Vecuronium	0.04	0.08	20–30
Pancuronium	0.06	0.03	40–60
Cisatracurium	0.05	0.1	25–35
Rocuronium	0.3	0.5	20–30

Succinylcholine

Succinylcholine remains the only depolarizing agent in current clinical use. Its speed of onset has not so far been surpassed, although there have been many attempts, and its short duration of action has not hitherto been bettered. Its principal use is to secure the airway rapidly. This is of particular advantage when the time of last food intake is unknown, or gastric stasis and a full stomach are suspected. It is often used for this purpose in new admissions to the ICU. It would be unusual to continue to use succinylcholine to continue a block in an ICU patient.

Succinylcholine has a number of unwanted side effects, most of which (e.g. fasciculations, myalgia, masseter spasm) are not of importance in the ICU patient. A dose of succinylcholine may, however, cause a significant increase in the serum potassium concentration and this may be particularly hazardous in the ICU patient. Although this increase is normally of the order of 0.5–1.0 mmol/L in normal patients it may be accentuated in patients with burns, muscle trauma, immobility, and spinal cord injuries. The use of succinylcholine in these patients, or in those with an already raised potassium, may precipitate a cardiac arrest and should only be considered with great caution.

Non-depolarizing relaxants

Pancuronium

This agent is a synthetic steroid based substance [1]. It was first introduced into clinical use in the 1960s and still remains on the formulary in many hospitals. It used to be used as the mainstay of muscle relaxation in the ICU, but has been largely superseded by modern agents. It is a potent relaxant with a relatively slow onset and long duration of action. It is devoid of ganglion blocking activity and histamine release. There is a small rise in the heart rate (by a combination of mild vagal inhibition and sympathetic stimulation) and the blood pressure is well maintained. It is metabolized in the liver and excreted by the kidneys so its action may be prolonged in patients with impairment of one or both of these systems. If pancuronium is used, it is recommended that it should be administered by intermittent bolus doses, not by infusion and to measure the degree of relaxation regularly in order to guard against accumulation.

Table 47.2 Elimination characteristics of five non-depolarizing relaxants. Elimination (beta) half-lives in minutes

	Normal patients	Hepatic disease	Renal disease
Atracurium	20	25	22
Vecuronium	54	90	76
Pancuronium	123	200–270	240–1000
Cisatracurium	29	24	24
Rocuronium	87	97	97

Vecuronium

Also a steroid-based synthetic molecule, its potency is similar to that of pancuronium. It has a very clean cardiovascular profile and does not release histamine. It has an intermediate duration of action and has been a popular choice in many ICUs. It is well suited to administration by continuous infusion or intermittent bolus. It is metabolized in the liver, one of the metabolic products being 3-hydroxy vecuronium, which is also a muscle relaxant with a potency of about 70% of that of vecuronium. Both vecuronium and its metabolites are eliminated in the urine. Its action may therefore be prolonged in patients with renal insufficiency and there are reports of patients where recovery from a block has taken many hours (or days) following an infusion of vecuronium in the presence of renal failure.

Evidence exists for a possible deleterious effect of vecuronium when given by prolonged infusion in the critically-ill patient. Critically-ill patients may develop a myopathy as a part of the critical illness process and this seems to be more prevalent when a vecuronium prolonged infusion has been used. This so-called 'steroid myopathy' is poorly understood, and doubt has been cast on its existence and incidence. Some ICUs do not favour the use of vecuronium for these various reasons.

Atracurium

Atracurium is a racemic mixture and not all isomers have relaxant activity. Another intermediate duration relaxant, it is suitable for administration by continuous infusion. It is virtually devoid of side effects, but histamine release at higher doses has been reported. This does not seem to be a problem in the ICU patient. It has a novel method of metabolism where approximately 60% is broken down by esterases in the liver, while the remainder undergoes spontaneous degradation in the plasma by the Hofmann elimination reaction. This latter reaction is independent of all organ systems and takes place spontaneously at body temperature and pH. Because of this, there is negligible prolongation of its action in the presence of liver or renal disease. Recovery is predictable and it can be reliably expected that the effect of a bolus dose or a continuous infusion will have worn off after about 1 hour.

The metabolites of atracurium have no muscular relaxant action, although they include other substances that may have potentially toxic effects, namely laudanosine and acrylates. Acrylates are potentially hepatotoxic, but are produced in such extremely small amounts so as to be insignificant. Interest has centred around laudanosine, a substance that can cause cerebral excitation in some laboratory animals, although there is no evidence of any toxic effects in humans. Laudanosine is renally excreted and so may accumulate if atracurium is given by a prolonged infusion in the presence of

impaired renal function. It appears unlikely on present evidence that laudanosine is of clinical relevance.

The use of atracurium by prolonged infusion may be associated with a phenomenon of resistance. After a delay of about 2–4 days, it is found that an increase in the infusion rate is needed in order to maintain the same degree of paralysis. As time then progresses, the infusion rate needs to be steadily increased, occasionally to quite remarkable levels. This is not observed in every patient and the mechanism is unclear.

Cisatracurium

Cisatracurium is the component isomer of atracurium with the greatest intrinsic relaxant activity. It is approximately four times more potent than atracurium and so less is required to produce the same degree of block. Otherwise, the side effect profile, suitability for infusion use, etc., are all as for atracurium. As less is required to produce a neuromuscular block then lower concentrations of all metabolites will be produced.

Rocuronium

This is another steroid-based molecule and is an analogue of vecuronium. It is stable in solution and so does not need to be reconstituted just before use. It has a potency of about one-eighth that of vecuronium. The normal intubating dose is 0.6mg/kg, but if given in a dose of 1.0 mg/kg, it produces an onset close to that of suxamethonium at 60–90 seconds. The duration of a normal intubating dose is about 30–40 minutes and higher doses last longer. It can readily be reversed with neostigmine, but also by the specific antagonist sugammadex. Rocuronium has a very clean side effect profile with very little change in cardiovascular parameters and negligible histamine release in clinical doses.

Monitoring neuromuscular blockade in the ICU

It is a general maxim of medicine that whenever a drug is administered to a patient then its effect should be monitored in order to prevent inadequate or excessive effect. In the case of the muscle relaxants, this is relatively straightforward. There are many commercially-available monitoring systems on the market that make use of force displacement or acceleration transducers. These are not necessary for routine clinical use. The use of a simple train of four supramaximal stimuli from a portable hand-held nerve stimulator is recommended. This pattern of stimulation consists of four stimuli each separated by 0.5 seconds from that preceding or following. Two self-adhesive surface (ECG-type) electrodes are placed over the ulnar nerve at the wrist and a stimulus applied. The current needed should be commenced at 20 mA and increased stepwise to a maximum of 70 mA. The movements of the thumb are then detected either visually or by palpation. The number of twitches of the thumb present correlates well with the degree of neuromuscular block ranging from no block with four strong equal twitches to 100% block with no twitches. A useful general rule is to maintain the level of block where the first twitch of the train of four is present and there is a very weak second response with no third or fourth responses. Some hand-held stimulators are also capable of providing a double-burst pattern. Two very short pulses at a base frequency of 50 Hz are given, separated by 0.75 seconds. When there is no neuromuscular block, two strong movements of the thumb can be felt. With increasing neuromuscular block the second movement fades to zero followed by the first. A neuromuscular block with a weak first response only would be a suitable level for most situations on the ICU. If the ulnar nerves are not available then the facial nerve just in front of the ear is commonly used.

It must be remembered the response may vary from day-to-day due to a variety of factors, including changes in skin impedance and the presence of tissue oedema. The electrodes should be changed at least daily, the skin cleaned carefully and the position of the electrodes kept constant. If tissue oedema is present, it is usually possible to reduce the problem by exerting a firm pressure over the electrodes for 1–2 minutes before stimulating.

Indications for the use of a muscle relaxant

At the start of the 1980s, almost every patient on the ICU received a muscle relaxant as a routine part of their sedation regimen, despite these drugs having no sedative action [2]. Use fell markedly over the ensuing 5–10 years. The current situation is that a muscle relaxant is only used where there is a specific indication. Many intensivists nowadays only resort to the use of a muscle relaxant, when all other techniques have been exhausted. Nevertheless, they remain a valuable part of our management strategy when used appropriately. When used by continuous infusion, tachyphylaxis occasionally develops, which may be managed by temporarily changing to a different relaxant.

Tracheal intubation

Tracheal intubation is possible without the use of a relaxant when the patient is weak, has depressed airway reflexes or has received a generous dose of an anaesthetic agent. A bolus dose of remifentanil may also assist in tracheal intubation. The use of local analgesia in the pharynx and larynx may also aid tracheal intubation, and this is usually needed if fibre optic intubation is to be performed. A muscle relaxant is often used to facilitate intubation because it provides completely relaxed muscles of the airway, reduces the potential for trauma, and facilitates a rapid intubation. If speed of intubation is required then the usual drug of choice is succinylcholine. If succinylcholine is contraindicated then a dose of rocuronium at 1.0 mg/kg will produce neuromuscular blockade almost as rapidly as succinylcholine.

Assisting ventilation

It is occasionally not possible for a patient to tolerate intermittent positive pressure ventilation or certain other modes of ventilation when using sedatives alone. The result may be marked swings in intrathoracic, intracranial, and intra-abdominal pressure as the patient attempts to breathe out of phase with the ventilator. This may have significant adverse effects on cardiovascular and other responses. It is often the case that a short period of muscular relaxation will help to establish smooth controlled ventilation after which it can be weaned off. Many consider the use of a muscle relaxant in patients with a raised intracranial pressure to be mandatory.

In patients with a poor lung compliance there may be difficulty in achieving satisfactory gas exchange with sedative agents alone. The addition of a muscle relaxant, possibly for only a short period, often improves oxygenation.

Tetanus

A muscle relaxant will reduce muscle spasms and facilitate positive pressure ventilation. It must be remembered, however, that the relaxant, by masking the spasms, may hinder the overall management and measurements of progress of the patient.

Disadvantages of using a muscle relaxant

Neurological assessment

When a patient has received a muscle relaxant it is difficult or even impossible to perform a meaningful neurological assessment [3]. Focal or localizing neurological signs may be missed leading to delay in treatment, which itself may have potentially serious consequences. Epileptiform seizures may also be masked. If it is decided to use a relaxant then it must be discontinued at regular intervals to allow accurate neurological assessments to be made. Inadequate sedation may be masked by the presence of a relaxant. It is essential to be certain that the patient is adequately sedated when using a relaxant.

Disuse atrophy

Muscle weakness is present in many critically-ill patients as a consequence of their disease process. It is possible that long-term use of a muscle relaxant (particularly a steroid-based one) may exacerbate this phenomenon.

Increased risk of venous thromboembolism

The incidence of deep venous thrombosis and pulmonary embolism has been reported to be more common in the paralysed patient. The evidence is conflicting, however, and with modern prophylactic techniques this is likely not to be a significant issue.

Reversal of neuromuscular block

In the ICU patient, this is normally achieved by stopping the infusion (or intermittent administration) and awaiting metabolism. In some reported cases, recovery has been reported to be prolonged. These include renal failure when pancuronium or vecuronium are used in higher doses. The breakdown of atracurium and cisatracurium is independent of renal or hepatic function, and so either of these drugs may be a better choice in these patients. The use of an anticholinesterase to secure reversal is rarely required.

A new agent, sugammadex, has recently become available as a selective antagonist for rocuronium and vecuronium. It works by chelating and inactivating the molecules in the plasma. Reversal is thus rapid and complete, although such a rapid reversal is unlikely to be required in an ICU. The dose is 2–4 mg/kg up to 16 mg/kg maximum. It can be safely used in patients with some renal or hepatic disease with no dose adjustment. Safety data on its use in patients with severe renal impairment is currently not available.

References

1. Fink H, Blobner M, and Martyn JAJ. (2004). Neuromuscular blocking drugs and reversal drugs. In: Evers AS and Maze M (eds), *Anaesthetic Pharmacology*, pp. 573–97. London: Churchill Livingstone.
2. Hunter JM (1994). Neuromuscular blocking agents in intensive therapy. In: Pollard BJ (ed.), *Applied Neuromuscular Pharmacology*. Oxford University Press, 188–201.
3. Johnson KL. (2007). Neuromuscular complications in the intensive care unit. *AACN Advanced Critical Care*, **18**, 167–82.

CHAPTER 48

Neuroprotective agents in critical illness

Jerrold L. Perrott and Steven C. Reynolds

Key points

- For patients with aneurysmal subarachnoid haemorrhage (SAH) pravastatin or simvastatin may be considered to possibly reduce rates of vasospasm, vasospasm-associated delayed ischaemic deficits, and mortality.
- Nimodipine is recommended to reduce the risk of poor neurological outcome and delayed ischaemia in patients with aneurysmal subarachnoid haemorrhage.
- In traumatic brain injury (TBI), and especially for those patients at high risk, phenytoin is recommended to reduce the risk of early seizures, although this intervention does not reduce the risk of seizures beyond 7 days.
- Patients with TBI should not be resuscitated with albumin-based colloids, as these products are associated with increased mortality.
- Corticosteroids should not be given to patients with TBI as they increase the risk of death.

Introduction

Pharmacological neuroprotection following insult to the central nervous system (CNS) has been and remains an enticing goal in the field of critical care medicine. With the exception of certain planned situations, such as neurosurgery or induced cardiac arrest for cardiothoracic surgery, prophylaxis against the primary brain injury is not possible, leaving the target of most interventions as the reduction of secondary injury, and subsequent neuronal dysfunction and death. It is also being increasingly recognized that the neuronal support network, including endothelial, astroglial, microglial, and oligodendroglial cells, play an important role in potentiating and/or mitigating secondary injury [1].

Despite the diversity of mechanisms of primary injury, including traumatic, ischaemic, and haemorrhagic events, it is thought that a number of common pathways converge to result in secondary and ongoing injury [2], many of which offer potential therapeutic targets for intervention (Table 48.1).

Numerous preclinical studies have examined a multitude of agents to address these common pathways of secondary injury with varying degrees of success. More than 30 clinical trials have been conducted with agents targeting single specific pathways, but few have shown positive outcomes. The lack of success with agents targeting single pathways has contributed to a shift in focus, with an emphasis on investigating agents that likely have an effect on multiple pathways. Examples include [2]:

- **Hydroxymethylglutaryl-coenzyme A inhibitors** (statins): may target excitotoxicity, apoptosis, and blood–brain barrier disruption.
- **Cyclosporin:** may target mitochondrial dysfunction, calpain activation, apoptosis, and oxidative stress.
- **Progesterone:** may target inflammation, oedema, oxidative stress, apoptosis, and excitotoxicity.

A representative list of therapeutic classes that have failed to translate preclinical success to positive clinical trials are presented in Table 48.2.

This disappointing lack of success in translating preclinical findings to positive clinical trials of potential medical interventions is common in research in the critically ill. There are multiple reasons, but the most prominent are biological difference between humans and animal models, inadequate animal models, clinical study design, end-point definitions, and recruitment issues [1]. For further discussion of these interventions and challenges, the reader is directed to a number of review articles on the challenges of translating positive preclinical studies to clinical trials on this topic for further information [1,2].

Specific neuroprotective pharmacotherapeutic

Aneurysmal subarachnoid haemorrhage

As opposed to other causes of subarachnoid haemorrhage, specifically trauma and other types of stroke, cerebral vasospasm is the primary driver of secondary neural injury in aneurysmal subarachnoid haemorrhage (aSAH), once the aneurysm has been surgically or interventionally controlled [3]. While arterial vasospasm is arguably beneficial in situations of injury to peripheral vessels to limit catastrophic blood loss, when it occurs in the brain secondary to aSAH, it can induce significant downstream ischaemia and infarct or **delayed ischaemic deficits**.

Two classes of medication have been successfully shown to reduce the adverse sequelae of vasospasm in randomized controlled trials (RCTs)–statins and dihydropyridine Ca channel blockers.

Statins

The mechanism of benefit of statins on vasospasm and outcomes in this population is not well elucidated, but is generally described in terms of their pleotropic effects.

Table 48.1 Potential mechanisms of secondary neuronal injury [2]

Category	Mechanisms and targets
Inflammation	◆ Cytokines ◆ Nitric oxide ◆ Prostaglandins
Blood–brain barrier disruption	◆ Cerebral oedema ◆ Hypoxia ◆ Ischaemia
Cell death	◆ Apoptosis/necrosis ◆ Caspases
Mitochondrial dysfunction	◆ PARP-1 activation ◆ Depletion of ATP and NAD^+ ◆ Calpain activation ◆ Altered membrane permeability
Excitotoxicity	◆ Glutamate → NMDA receptor activation ◆ Ca^{2+} influx
Oxidative stress	◆ Free radicals ◆ Lipid peroxidation

Data from Loane DJ, Faden AI, 'Neuroprotection for traumatic brain injury: translational challenges and emerging therapeutic strategies', *Trends in Pharmacological Sciences*, 2010, **31**(12), pp. 596–604.

To date, four small and one large RCTs have been published on the effect of statin therapy in aSAH. A meta-analysis of the results of the first three of these trials showed a relative risk (with 95% confidence intervals) for statin versus control of incident vasospasm of 0.73 (0.54–0.99), vasospasm-related delayed ischaemic deficits 0.38 (0.17–0.38), and mortality 0.22 (0.06–0.82) [4]. These results translate into a number need to treat (NNT) to prevent incident vasospasm of 6, for delayed ischaemic deficits 5, and for mortality 7. The fourth small pilot study (n = 39) showed non-significant reductions in mortality [5] and the most recent study, the STASH Trial (n = 803), failed to demonstrate any improvements in clinically meaningful outcomes [6]. This most recent trial has introduced significant controversy into the use of statins for aSAH. Statins are generally well tolerated and the regimens used in the published studies, common side effects, and contraindications are presented in Table 48.3.

Table 48.2 Example agents with positive preclinical, but negative clinical trials [1]

Primary injury mechanism	Pharmacological intervention
Stroke	◆ Anti-inflammatory agents ◆ *N*-methyl-D-aspartate (NMDA) antagonists ◆ Dexanabinol ◆ Na channel blockers ◆ Growth factors ◆ Free radical scavengers
Traumatic brain injury	◆ NMDA antagonists ◆ Dexanabinol ◆ Glucocorticoids ◆ Erythropoetin ◆ Ca channel blockers

Data from Faden AI and Stoica B, 'Neuroprotection – challenges and opportunities', *Archives of Neurology*, 2007, **64**, pp. 794–800.

Table 48.3 Statin therapy for the prevention of vasospasm and sequelae [4–7]

Regimen [4–6]	Contraindications Common for all statins	Adverse effects* Common for all statins
◆ Pravastatin 40 mg po daily for 14 days ◆ Pravastatin 40 mg po daily for 14 days or until hospital discharge ◆ Simvastatin 80 mg po daily until ICU discharge ◆ Simvastatin 80 mg po daily for 21 days or until ICU discharge ◆ Simvastatin 40 mg po daily for 21 days or until neurosurgical discharge	◆ Hypersensitivity to drug or component ◆ Acute liver disease ◆ Pregnancy ◆ Breastfeeding ◆ Concurrent use of strong CYP3A4 inhibitors or cyclosporin (with simvastatin)	◆ Hepatotoxicity (including asymptomatic elevations in transaminases through acute liver failure) ◆ Myopathy/rhabdomyolysis ◆ Myalgia ◆ Gastrointestinal (GI) upset or abdominal pain ◆ Headache

*Only ICU relevant, serious, and/or common adverse effects are listed here, see reference for comprehensive list.

Data from Sillberg VAH, et al., 'Do statins improve outcomes and reduce the incidence of vasospasm after aneurysmal subarachnoid hemorrhage: a meta-analysis', *Stroke*, 2008, **39**, pp. 2622–6; Chou SHY, et al., 'A randomized, double-blind, placebo-controlled pilot study of simvastatin in aneurysmal subarachnoid hemorrhage', *Stroke*, 2008, **39**, pp. 2891–3; Kirkpatrick PJ, et al., 'Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial', *Lancet Neurology*, 2014, **13**, pp. 666–75; and Lexi-Comp Online, Lexi-Drugs Online, Hudson, OH: Lexi-Comp, Inc., October 31, 2013.

Calcium channel blockers

Ca channel blockers have been extensively investigated for their potential role in directly mitigating cerebral vasospasm, through their vasodilatory effect, and for preventing secondary injury, through modulation of cellular Ca permeability within the CNS. Nimodipine has the most conclusive supporting evidence, with a Cochrane meta-analysis of RCTs comparing oral nimodipine versus placebo demonstrating a relative risk (with 95% CI) of poor neurological outcome of 0.67 (0.55–0.81) with an associated NNT of 19. It also demonstrated reductions in incident secondary ischaemia and a trend toward reduced mortality. Studies of other Ca channel blockers, including intravenous (iv) nimodipine and magnesium sulfate have failed to demonstrate statistically significant effects on outcomes. The nimodipine regimen used in the published studies, common side effects, and contraindications are presented in Table 48.4 [8].

Traumatic brain injury

The discovery of neuroprotective agents in traumatic brain injury (TBI) remains an ongoing challenge, with very few successful and a number of harmful interventions found to date.

Perhaps the only pharmacological intervention post-TBI that has any proven benefit is the use of prophylactic phenytoin to reduce early post-traumatic seizures (PTS). In the hallmark

Table 48.4 Nimodipine therapy for the prevention of vasospasm and sequelae [7,8]

Regimen	Contraindications	Adverse effects*
Nimodipine 60 mg po every 4 hours for 21 days	Severe hypotension†	◆ Hypotension† ◆ Headache ◆ Rash ◆ GI upset

*Only ICU relevant, serious, and/or common adverse effects are listed here, see reference for comprehensive list.

†Some clinicians will divide the regimen to 30 mg po Q2H to mitigate some of the hypotension, although this regimen has not been evaluated in clinical trials.

Data from Lexi-Comp Online, Lexi-Drugs Online, Hudson, OH: Lexi-Comp, Inc., October 31, 2013; and Dourhout Mees S, et al., 'Calcium antagonists for aneurysmal subarachnoid haemorrhage (review)', *Cochrane Database of Systemic Reviews*, 2007, **3**, CD000277.

Table 48.5 Phenytoin prophylaxis for early seizures post-TBI [7,9]

Regimen	Contraindications	Adverse effects*
Phenytoin 20 mg/kg iv load, then maintenance dose adjusted to maintain serum trough concentration of 40–80 µmol/L	◆ Hypersensitivity to phenytoin or other hydantoins ◆ Concurrent use of delaviridine or other non-nucleoside reverse transcriptase inhibitors	◆ Hypotension ◆ Sinus bradycardia ◆ Heart block ◆ Cardiovascular collapse (especially with rapid iv administration) ◆ Thrombophlebitis ◆ Nystagmus (with supratherapeutic concentrations) ◆ Drug rash with eosinophilia and systemic symptoms

*Only ICU relevant, serious, and/or common adverse effects are listed here, see reference for comprehensive list.

Data from Lexi-Comp Online, Lexi-Drugs Online, Hudson, OH: Lexi-Comp, Inc.; October 31, 2013; and Temkin NR, et al., 'A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures', *New England Journal of Medicine*, 1990, **323**, pp. 497–502.

paper published in 1990 [9], phenytoin administered within 24 hours of injury and continued for 1 year led to a reduction in early seizures (days 0–7 from randomization) from 14.2% in the placebo arm to 3.6% in the phenytoin arm ($p < 0.001$). However, this did not translate into any statistically significant reductions in seizure risk beyond 7 days. Additionally, the study found no differences in mortality. The regimen used in the study, common side effects, and contraindications are presented in Table 48.5. The Brain Trauma Foundation, in its guidelines, also reports that valproic acid has been shown to offer equivalent efficacy to phenytoin to reduce early PTS, but with a trend towards increased mortality [10]. Certain risk factors are associated with increased risk of PTS, and are often used by clinicians to select patients for prophylaxis. These risks include decreased level of consciousness (GCS<10), cortical contusion, depressed skull fracture, subdural haematoma, epidural haematoma, intracerebral haematoma, penetrating head wound, and seizure within 24 hours of the primary injury [10].

The challenges in identifying effective neuroprotective agents in the TBI population have led to many failed studies, due to lack of effect and at least two interventions that have demonstrated harm. Specifically, these are the use of corticosteroids for the prevention of secondary injury and iv albumin for resuscitation.

The CRASH trial collaborators conducted an RCT examining the effects of iv corticosteroids on mortality in ~10,000 TBI patients [11]. After enrolling approximately half of their target number of subjects, the data safety and monitoring board was forced to recommend discontinuation of the study due to a significant increase in the risk of 2-week mortality with steroids versus placebo of 21 versus 18% ($p = 0.0001$), respectively. As such, it is recommended that steroids be avoided in the TBI population.

Intravenous human albumin has been used as a resuscitation fluid in a number of patient populations. A subgroup analysis of the 460 patients enrolled with TBI into the SAFE trial [12] was published as a separate paper [13]. In this post hoc analysis of critically-ill patients with TBI, the use of albumin versus saline as a resuscitation fluid was associated with an increased risk of mortality of 33.2 versus 20.4% (relative risk 1.63; 95% CI 1.17–2.26; $p = 0.003$). While recognizing the data were from a post hoc analysis of a large RCT, it does still support the practice of using crystalloid and avoiding albumin resuscitation in the TBI population.

Conclusion

Despite significant amounts of preclinical and clinical research, there remain few evidence-based neuroprotective pharmacological interventions available. Ongoing and future research on this topic is eagerly awaited as our understanding of the underlying mechanisms of secondary neuronal injury evolves.

At present, the best therapies we can offer our patients remain nimodipine and possibly statins for aneurysmal subarachnoid haemorrhage, phenytoin for TBI, and avoidance of harmful interventions such as corticosteroids and albumin in TBI.

References

1. Faden AI and Stoica B. (2007). Neuroprotection—challenges and opportunities. *Archives of Neurology*, **64**, 794–800.
2. Loane DJ and Faden AI. (2010). Neuroprotection for traumatic brain injury: translational challenges and emerging therapeutic strategies. *Trends in Pharmacological Sciences*, **31**(12), 596–604.
3. Liu-DeRyke X and Rhoney DH. (2006). Cerebral vasospasm after aneurysmal subarachnoid hemorrhage: an overview of pharmacological management. *Pharmacotherapy*, **26**(2), 182–203.
4. Sillberg VAH, Wells GA, and Perry JJ. (2008). Do statins improve outcomes and reduce the incidence of vasospasm after aneurysmal subarachnoid hemorrhage: a meta-analysis. *Stroke*, **39**, 2622–6.
5. Chou SHY, Smith EE, Badjatia N, et al. (2008). A randomized, double-blind, placebo-controlled pilot study of simvastatin in aneurysmal subarachnoid hemorrhage. *Stroke*, **39**, 2891–3.
6. Kirkpatrick PJ, Turner CL, Smith C, et al. (2014). Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. *Lancet Neurology*, **13**, 666–75.
7. Lexi-Comp Online (2013). Lexi-Drugs Online. Hudson, OH: Lexi-Comp, Inc. http://online.lexi.com/
8. Dourhout Mees S, Rinkel FJE, Feigin VL, et al. (2007). Calcium antagonists for aneurysmal subarachnoid haemorrhage (review). *Cochrane Database of Systemic Review*, **3**, CD000277.
9. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, and Winn R. (1990). A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *New England Journal of Medicine*, **323**, 497–502.

10. Brain Trauma Foundation (2007). Guidelines for the management of severe traumatic brain injury 3rd edition. *Journal of Neurotrauma*, **24**(S1), S1–106.
11. CRASH trial collaborators, Roberts I, Yates D, et al. (2004). Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet*, **364**, 1321–8.
12. SAFE study investigators, Finfer S, Bellomo R, et al. (2004). A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *New England Journal of Medicine*, **350**, 2247–56.
13. SAFE study investigators, Myburgh J, Cooper DJ, et al. (2007). Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *New England Journal of Medicine*, **357**, 874–84.

PART 2.5

Hormonal drugs

CHAPTER 49

Hormone therapies in critical illness

Mark S. Cooper

Key points

- Thyroid function tests are commonly abnormal during critical illness and are part of 'non-thyroidal illness syndrome'. This does not usually indicate a need for treatment with thyroid hormones.
- Specific situations where thyroid hormone therapy has been used include during and after cardiac surgery, and in the preservation of the brain stem dead organ donor. The evidence in support in these situations is weak.
- 'Anabolic' hormones, such as growth hormone have been shown to be detrimental in general critical care patients. However, in the specific situation of burns the use of growth hormone and anabolic steroids has shown a potential benefit.
- Vitamin D deficiency is common in critically-ill patients and is associated with a poor outcome. It is not yet clear whether outcomes can be improved by the administration of vitamin D.
- With acute intracranial injury adrenocorticotropic hormone (ACTH) deficiency is difficult to diagnose and easily missed. In this setting, a low random cortisol should prompt the use of hydrocortisone replacement therapy.

Introduction

A range of hormonal manipulations have been proposed as adjunctive therapies during critical care. Some of these are dealt with elsewhere in chapters of their own ('Insulin and Oral Anti-hyperglycaemic Agents in Critical Illness', 'Steroids in Critical Illness'). This chapter reviews the other hormonal therapies that have been proposed.

Changes in hormonal systems during critical illness

Critical illness is associated with a range of hormonal changes. Many of the early changes are likely to have evolved to be adaptive and protective, but the usefulness of longer-term changes is much less clear. An endocrine disorder could be the primary problem underlying the development of critical illness, or it could develop during critical illness due to the underlying disease or as a side effect of treatment. Since the changes in the endocrine system during critical illness are often profound, it is more difficult to produce reliable 'normal' ranges or to determine with certainty when a test is abnormal. The first part of this chapter considers hormone therapies that might be of use in patients without previously recognized endocrine disorders. The second part will consider hormone therapies in specific disorders that are common or important in the critical care setting.

Hormonal therapy in the absence of a specific endocrine disorder

Thyroid hormones

All types of severe illness are associated with dramatic changes in the hypothalamo-pituitary thyroid axis. These changes are collectively referred to as 'non-thyroidal illness' [1]. Circulating levels of tri-iodothyronine (FT3) levels fall dramatically and remain low until recovery. The levels of thyroxine (FT4) and thyroid-stimulating hormone (TSH) are normal or elevated in the acute phase of illness, but tend to decline with prolonged illness. These changes in circulating levels are due to a combination of altered expression and activity of tissue deiodinase enzymes (which leads to a switch towards inactivation of thyroid hormones), and a reduced central drive towards thyrotropin-releasing hormone (TRH) and TSH secretion. Even though these changes could lead to reduced cardiac contractility and other features considered to be detrimental in critical illness, these changes are thought to be adaptive in the early phase of illness. The use of thyroid hormone treatment in the setting of non-thyroidal illness has been explored in a limited number of studies, primarily focusing on patients post-cardiac surgery. The use of liothyronine (tri-iodothyronine) in adult patients post-cardiac surgery has been explored in several studies. These have demonstrated effectiveness in increasing indices of cardiac output post-operatively, but they have not shown a reduction in mortality or length of stay [2]. Smaller trials in children using the same hormone have also generally demonstrated improved cardiac contractility with no adverse outcomes, but these trials are more heterogeneous in their inclusion criteria and design. In contrast, a trial of levothyroxine therapy in patients with acute renal failure failed to show any benefit in terms of recovery from renal failure and was associated with a three-fold increased risk of mortality [3].

The other critical care setting where thyroid hormone treatment is common is in the maintenance of the brain stem dead organ donor. The use of liothyronine or levothyroxine as part of 'hormone replacement therapy' (methyprednisolone, vasopressin, and

thyroid hormone) is widely recommended in this setting and the combination of all three treatments has been shown to improve the utilization of donor organs. However, the specific benefit of thyroid hormones has been questioned. A randomized trial of liothyronine treatment of cardiac donors failed to demonstrate any haemodynamic effect during the trial, but it is still possible that this therapy has a useful role in maintaining cardiac function once the organ has been grafted [4].

GH/IGF1

Growth hormone (GH) and insulin-like growth factor-1 (IGF1) are important anabolic hormones. GH is released from the anterior pituitary and IGF1 is generated primarily in the liver in response to GH. During critical illness there is a decrease in the level of IGF1. The level of GH increases in the acute phase of illness, but there appears to be a degree of resistance to GH action, possibly due to a down-regulation of GH receptor expression. In prolonged illness, the level of GH also falls. It was previously hypothesized that the changes in the GH/IGF1 axis could be detrimental, since a decrease in their levels could contribute to the catabolic state, thus prolonging recovery from severe illness. Several small randomized trials also supported this concept, demonstrating that GH could reduce the negative nitrogen balance seen in critical illness. However, in a publication that combined two related randomized placebo controlled trials of GH treatment of critically-ill patients a clear, detrimental effect with increased mortality (by approximately 40%) and morbidity in those treated with GH was seen [5]. This was despite an improved nitrogen balance with GH treatment. As such, GH treatment is contraindicated in most critically-ill patients.

A clinical situation where GH could be of benefit is the care of patients with burns. GH supplementation appears to aid skin healing and these benefits might outweigh the possible negatives. A randomized trial of recombinant GH therapy in severely-burned children has demonstrated an improvement in burn healing without an increase in adverse outcomes [6].

Oestrogens, androgens, and anabolic steroids

The normal response of the reproductive system to severe illness is a central decrease in the production of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle stimulating hormone (FSH). In the female, this leads to amenorrhoea and in the male, hypogonadism. Interestingly, however, in the acute phase of critical illness, the levels of oestrogen do not decline, but frequently increase. This is probably due to an increase in the peripheral generation of oestrogen via the aromatase enzyme. Aromatase activity can be stimulated by pro-inflammatory cytokines. Increased levels of oestradiol are associated with an adverse outcome in both women and men in several studies, although it is not clear whether the association is causal [7]. In addition to the possible negative role for oestrogens in critical illness, supplementation with oestrogen in females has generally also been avoided in this setting, given the well-established pro-thrombotic actions of oestrogen.

Due to the negative nitrogen balance and the marked loss of muscle mass seen in critical illness, the use of anabolic steroids might be of use in aiding recovery. However, androgens have also been associated with pro-inflammatory effects in preclinical models. A situation where anabolic steroid therapy might be of benefit is the treatment of patients with burns. Severe burns are associated with a particularly catabolic state. Clinical trials of oxandrolone (an anabolic steroid that has minimal virilizing effects and cannot be aromatized to oestrogen) have demonstrated beneficial effects of therapy, such as reduced hospital stay and improved muscle mass, in adults and children with burns, without any apparent changes in markers of inflammation [8,9]. There were, however, elevations of hepatic transaminases. Although promising, the effectiveness of oxandrolone and related anabolic steroids have not been confirmed in large multicentre randomized controlled trials.

Vitamin D

Recent studies have highlighted a potential link between low levels of vitamin D and adverse outcome in critically-ill patients [10]. Vitamin D deficiency (low levels of 25-hydroxyvitamin D) is particular prevalent in the intensive care unit (and in patients with illness in general). However, randomized trial data are lacking regarding the usefulness of supplementing patients with vitamin D. Clearly, in patients with a level of vitamin D sufficient to interfere with calcium homeostasis, e.g. leading to hypocalcaemia, which in turn leads to bone fragility or muscle weakness, then replacement is required. There has also been recent interest in the role that vitamin D might play in immune responses and, in particular, the role of vitamin D in the response to mycobacterial infection [11]. There is an indication that extra-renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D occurs in immune cells and thus in this setting 25-hydroxyvitamin D is likely to be more effective than 1,25-dihydroxyvitamin D. Currently, it would make sense to give vitamin D to patients who have any features of vitamin D deficiency. In the absence of marked hypocalcaemia, this can be with ergocalciferol or colecalciferol. A regimen of 50,000 units orally once per week or 300,000 units im should be sufficient to raise vitamin D levels to an acceptable level over a few days to weeks [12]. For a more rapid onset of action in patients with hypocalcaemia activated metabolites of vitamin D such as alphacalcidol or calcitriol at doses of 0.5–2 micrograms/day can be used.

Hormonal therapy for specific disorders

Patients with known hypopituitarism

Patients with pre-existing or acquired structural abnormalities of endocrine systems will generally need replacement therapy. Patients with Addison's disease during critical illness need replacement hydrocortisone in stress doses, e.g. 50 mg qds or the equivalent dose as a continuous infusion [13]. Patients with known hypopituitarism will also require an increase in their glucocorticoid replacement in a similar fashion to patients with Addison's disease. Although less important, replacement with levothyroxine can continue at the same dose.

Traumatic brain injury

Hypothalamic and pituitary dysfunction is being increasingly recognized in the acute and chronic phases of traumatic brain injury [14]. Although all pituitary hormonal axes could be affected, the major difficulty in this situation is recognizing hypoadrenalism secondary to ACTH deficiency. This is because the short ACTH (synacthen) test, a common measure of adrenal function, is unreliable in this setting. ACTH acts on the adrenal gland to stimulate acute release of cortisol, but also acts to maintain the integrity of the cortex. With acute ACTH deficiency the adrenal gland is still responsive to exogenous ACTH for 2–3 weeks. As such the

diagnosis of ACTH deficiency can only be made on the basis of a low basal cortisol in these patients. A level of <400 nmol/L is suggestive of deficiency and should prompt replacement hydrocortisone therapy until an ACTH stimulation test can be performed weeks to months later.

Abnormal posterior pituitary responses are also common after brain injury with diabetes insipidus (DI) occurring in up to 50% of patients. Hypernatraemia related to diabetes insipidus is associated with increased mortality emphasizing the importance of appropriate treatment. Treatment is with desmopressin given im. A well-recognized phenomenon in this setting is the triple phase response in which acute DI is followed by hyponatraemia before the patient develops permanent DI. The hyponatraemic phase is thought to be due to the (transient) release of preformed vasopressin from damaged neurones supplying the posterior pituitary. In view of the possibility that hyponatraemia could develop after early DI, desmopressin treatment should be administered by stat doses in this situation to avoid the development of severe hyponatraemia. Similar considerations regarding anterior and posterior pituitary dysfunction apply to patients undergoing pituitary surgery, a situation in which post-operative pituitary dysfunction is highly likely.

Thyroid storm and myxoedema coma

Abnormalities of thyroid function severe enough to cause critical illness are rare. Thyroid storm refers to severe thyrotoxicosis sufficient to cause circulatory collapse. It is usually caused by surgery, infection, or inappropriate use of iodine-containing medications in patients with uncontrolled thyrotoxicosis. Features include tachycardia/arrhythmias, hypotension, and hyperpyrexia. Treatment is with supportive care (hydration and cooling), drugs that block thyroid hormone synthesis (propylthiouracil or carbimazole/methimazole) and cautious use of beta blockers. Propylthiouracil is generally preferred as the thyroid hormone synthesis blocking drug of choice in this setting, since it has an additional action to inhibit the peripheral conversion of FT4 to FT3. Additional therapies, such as lithium and potassium iodide might also be considered after discussion with endocrine specialists. Iodine-containing medications should only be given 2–3 hours after thyroid blocking medications.

Myxoedema coma arises from severe prolonged deficiency of thyroid hormones. This is usually associated with primary hypothyroidism. The common features are hypothermia, respiratory depression, and coma. Since thyroid hormones have a long biological half-life, the response to treatment normally takes days. It is unclear whether initial treatment should be with levothyroxine or liothyronine. Levothyroxine has to be converted to T3 (the active thyroid hormone) in the body and, thus, the response to this will be slow. Liothyronine has the advantage of more rapid action, but it has been suggested that this is associated with a greater risk of developing cardiac arrhythmias [15]. If levothyroxine therapy is used it is advised to give a single loading dose of 500 micrograms followed by a maintenance dose of 100 micrograms/day. Stress dose glucocorticoid replacement should also be given since the risk of adrenal insufficiency in this setting is high.

References

1. Mebis L and Van den Berghe G. (2011). Thyroid axis function and dysfunction in critical illness. *Best Practice & Research Clinical Endocrinology & Metabolism*, **25**(5), 745–57.
2. Ranasinghe AM and Bonser RS. (2010). Thyroid hormone in cardiac surgery. *Vascular Pharmacology*, **52**(3–4), 131–7.
3. Acker CG, Singh AR, Flick RP, Bernardini J, Greenberg A, and Johnson JP. (2000). A trial of thyroxine in acute renal failure. *Kidney International*, **57**(1), 293–8.
4. James SR, Ranasinghe AM, Venkateswaran R, McCabe CJ, Franklyn JA, and Bonser RS. (2010). The effects of acute triiodothyronine therapy on myocardial gene expression in brain stem dead cardiac donors. *Journal of Clinical Endocrinology & Metabolism*, **95**(3), 1338–43.
5. Takala J, Ruokonen E, Webster NR, et al. (1999). Increased mortality associated with growth hormone treatment in critically ill adults. *New England Journal of Medicine*, **341**(11), 785–92.
6. Branski LK, Herndon DN, Barrow RE, et al. (2009). Randomized controlled trial to determine the efficacy of long-term growth hormone treatment in severely burned children. *Annals of Surgery*, **250**(4), 514–23.
7. May AK, Dossett LA, Norris PR, et al. (2008). Estradiol is associated with mortality in critically ill trauma and surgical patients. *Critical Care Medicine*, **36**(1), 62–8.
8. Wolf SE, Edelman LS, Kemalyan N, et al. (2006). Effects of oxandrolone on outcome measures in the severely burned: a multicenter prospective randomized double-blind trial. *Journal of Burn Care and Research*, **27**(2), 131–9.
9. Jeschke MG, Finnerty CC, Suman OE, Kulp G, Mlcak RP, and Herndon DN. (2007). The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase postburn. *Annals of Surgery*, **246**(3), 351–60.
10. Lee P, Eisman JA, and Center JR. (2009). Vitamin D deficiency in critically ill patients. *New England Journal of Medicine*, **360**(18), 1912–14.
11. Liu PT, Stenger S, Li H, et al. (2006). Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science*, **311**(5768), 1770–3.
12. Cooper MS and Gittoes NJ. (2008). Diagnosis and management of hypocalcaemia. *British Medical Journal*, **336**(7656), 1298–302.
13. Cooper MS and Stewart PM. (2003). Corticosteroid insufficiency in acutely ill patients. *New England Journal of Medicine*, **348**(8), 727–34.
14. Hannon MJ, Sherlock M, and Thompson CJ. (2011). Pituitary dysfunction following traumatic brain injury or subarachnoid haemorrhage. *Best Practice & Research Clinical Endocrinology & Metabolism*, **25**(5), 783–98.
15. Wartofsky L. (2006). Myxedema coma. *Endocrinology and Metabolism Clinics of North America*, **35**(4), 687–95.

CHAPTER 50

Insulin and oral anti-hyperglycaemic agents in critical illness

Roosmarijn T. M. van Hooijdonk and Marcus J. Schultz

Key points

- Hyperglycaemia and hypoglycaemia are frequently seen in critically-ill patients.
- Insulin infusion is preferred over oral anti-hyperglycaemic agents for blood glucose control in the intensive care unit.
- Insulin infusion requires frequent blood glucose measurements, a dedicated lumen of a central venous catheter, and trained nurses for adjustment of the insulin infusion rate.
- Hyperglycaemia, hypoglycaemia, and glycaemic variability are all independently associated with mortality and morbidity.
- Whether glycaemic variability can be kept minimal in critically-ill patients is uncertain.

Introduction

Dysglycaemia is frequently seen in the intensive care unit (ICU). Hyperglycaemia may be associated with critical illness or, less frequently, due to diabetic keto-acidosis. Patients who are severely ill may initially present with hypoglycaemia or may develop hypoglycaemia as a result of insulin for glucose control.

Practical aspects of infusion of insulin and the role for oral anti-hyperglycaemic agents in critically-ill patients with critical illness-associated hyperglycaemia are discussed.

Hyperglycaemia in critically-ill patients

For a long time hyperglycaemia was thought to be an adaptive and beneficial response to critical illness. Numerous studies, however, clearly show hyperglycaemia to be associated with increased morbidity and mortality of ICU patients [1,2]. Nowadays, high blood glucose levels are considered acutely toxic for critically-ill patients because of the risk of accentuated cellular glucose overload [3]. Indeed, during critical illness, expression of glucose transporters on the membranes of several cell types is up-regulated, which during reperfusion after ischaemia allow high circulating glucose levels to overload and damage these cells.

Critical illness-associated hyperglycaemia and diabetic keto-acidosis should be seen as different entities. Diabetic keto-acidosis results from a shortage of insulin, in response to which the body switches to burning of fatty acids and producing acidic ketone bodies, which cause most of the symptoms and complications of diabetic keto-acidosis. Critical illness-associated hyperglycaemia is caused, at least in part, by critical illness-dependent insulin resistance. With the disappearance of the critical condition, the insulin sensitivity normalizes. Treatment of diabetic keto-acidosis primarily focuses on normalization of the blood glucose level with insulin, after which home medication is restarted. Treatment of critical illness-associated hyperglycaemia also focuses on normalization of the blood glucose level with insulin, but with disappearance of the critical condition, insulin should be tapered and eventually stopped.

Laboratory assessment

Normal blood glucose levels are from 4.4 to 6.1 mmol/L (80–110 mg/dL). Hyperglycaemia is typically defined as mild or severe, when blood glucose levels are 8.3–10 mmol/L (150–180 mg/dL) or >10 mmol/L (180 mg/dL). Hypoglycaemia typically is defined as mild or severe, when blood glucose levels are 2.2–4.4 mmol/L (40–80 mg/dL) or < 2.2 mmol/L (<40 mg/dL).

Insulin and oral anti-hyperglycaemic agents

Insulin

Insulin is a hormone that affects carbohydrate, fat, and protein metabolism in many ways. Insulin stimulates glucose uptake in liver-, muscle-, and fat tissue. Insulin inhibits glucose production by the liver by inhibiting gluconeogenesis and stimulating glycogen synthesis from glucose. Insulin stimulates lipogenesis, and inhibits lipolysis and release of free fatty acids from adipose tissue. Insulin promotes protein metabolism by stimulating cellular uptake of amino acids. Finally, insulin increases cell wall permeability for several ions, including potassium, magnesium, and phosphate. Insulin analogs are manufactured through the use of recombinant DNA technologies, yielding products that are almost similar to human insulin. The amino acid sequence of insulin can be changed to alter its absorption, distribution, metabolism, and excretion characteristics, thereby making them 'long-', 'medium-' or 'short-acting'.

Notably, while most insulin analogs are registered for sc use, in critically-ill patients insulin is given iv and, in the blood compartment, insulin is always 'short-acting', with a half-life time of minutes. Since effects of subcutaneous administered insulin on blood glucose levels can be slow and sometimes even unpredictable, iv administration is preferred in critically-ill patients. Subcutaneous administration is only preferred in stable ICU patients, who are orally fed and almost ready for discharge to the step-down unit or normal ward.

Oral anti-hyperglycaemic agents

A large variety of oral anti-hyperglycaemic agents are presently available (Table 50.1). Most of them are relatively contraindicated in critically-ill patients, e.g. because of the risk of lactate acidosis. There are several other arguments to favour insulin over oral anti-hyperglycaemic agents for the treatment of critical illness-associated hyperglycaemia. First, the effects of iv infusion of insulin are far more predictable than oral anti-hyperglycaemic agents. Secondly, the biological availability of anti-hyperglycaemic agents in critically-ill patients is uncertain and may change over time, thereby making the effect of these agents on the blood glucose level highly unpredictable. Finally, while insulin has a short half-life time, oral anti-hyperglycaemic agents have longer-lasting effect, which could be unattractive in the critically ill. Although one study of critically-ill patients showed improved glycaemic control with metformin, in addition to insulin infusion [4], further studies are needed before this can be considered standard care.

Infusion of insulin in critically-ill patients

Several trials show glycaemic control aiming for normoglycaemia (4.4–6.1 mmol/L (80–110 mg/dL)) or so-called intensive insulin therapy to benefit critically-ill adult and paediatric patients [5,6]. Subsequent trials testing the efficacy and safety of intensive insulin therapy could not confirm this [7]. While there are numerous alternative explanations about why these later trials did not show beneficial effects of intensive insulin therapy, apart from the possibility that intensive insulin therapy may not benefit ICU patients [7], it has been questioned whether a strategy aiming for normoglycaemia is safe in critically-ill patients. International guidelines, therefore, recommend only treating extreme hyperglycaemia with insulin, aiming at blood glucose levels <8.3 mmol/L (150 mg/dL) [8], or <10.0 mmol/L (180 mg/dL). Whether such an approach is truly safer than intensive insulin therapy (aiming for normoglycaemia) is uncertain, let alone whether this approach is as effective in reducing morbidity and mortality as intensive insulin therapy.

Practical aspects of insulin infusion

A large variety of factors may affect efficacy and safety of any strategy using infusion of insulin (Fig. 50.1). Indeed, insulin titration, independent of the targeted blood glucose level, is a complex intervention that involves several sequential steps that all contain potential sources of variability, including the way the blood glucose level is measured, and the way insulin is delivered and titrated [7].

Blood glucose measurement is one major aspect of glucose control. Blood glucose measurements should be accurate, as inaccurate measurements could lead to potentially life-threatening insulin dose errors. Blood glucose levels can be determined in capillary, arterial, and venous blood. Adequate measurement of the blood glucose level using capillary blood, however, is a challenge and should be avoided [9]. Venous sampling serves as a good alternative, especially when taken from a central venous catheter, but there is a risk of contamination by agents infused through that catheter [9,10]. Arterial sampling, via an intra-arterial catheter, therefore, seems the best option [9,11].

Currently, handheld blood glucose meters or department–based blood gas analysers are the preferred method to measure the blood glucose level in the ICU [9]. Handheld blood glucose meters, however, are far from accurate, especially in the lower ranges of the blood glucose level [11]. Notably, regardless of using handheld meters or blood gas analysers, significant amounts of blood are used and much nursing time is spent. Automatic continuous

Table 50.1 Overview of oral anti-hyperglycaemic agents and its contraindications in the intensive care unit

Class	Mechanism of action	Main side-effects and reasons for caution	Relevant contraindications
Biguanides (e.g. metformin)	Inhibits hepatic gluconeogenesis and glucogenolysis, and increases sensitivity of insulin receptors	Lactic acidosis (rare)	Renal insufficiency, and acute and chronic metabolic acidosis
Sulfonylureas (e.g. tolbutamide (1st generation), or glibenclamide) (2nd generation))	Stimulates the release of insulin from the pancreas	Severe and prolonged hypoglycaemia (particularly in the elderly or those with chronic kidney disease)	Severe renal insufficiency and severe liver failure
Meglitides or glinides (e.g. repaglinide)	Stimulates the release of insulin from the pancreas	Hypoglycaemia	Severe liver failure and diabetic ketoacidosis
Dipeptidylpeptidase iv inhibitors (e.g. sitagliptin, saxagliptin, vildagliptin, and linagliptin)	Increases insulin release and decreases the glucagon concentrations in a glucose-dependent manner	Hypoglycaemia, pancreatitis (for sitagliptin)	Diabetic ketoacidosis
Incretine-mimetics Glucagon-like peptide-1 agonist (GLP1) (e.g. exenatide)	Stimulates insulin release and decreases glucagon concentrations in a glucose-dependent manner, often used in addition with other oral anti-hyperglycaemic agents	Hypoglycaemia, long–acting agents	Renal insufficiency, diabetic ketoacidosis

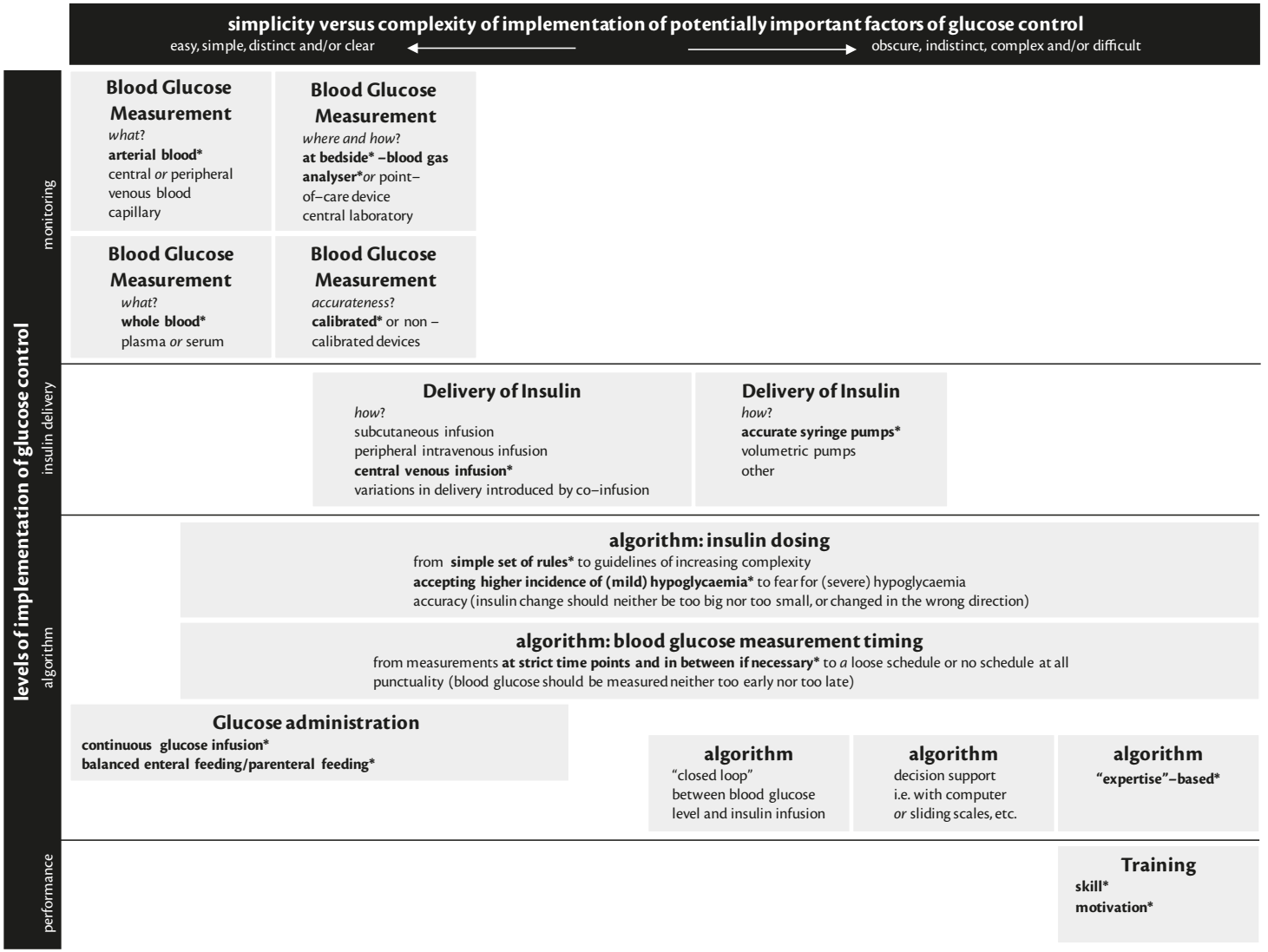


Fig. 50.1 Methodological aspects of intensive insulin therapy, which may contain potential sources of variability in the performance of this strategy. Items are categorized into the following subjects—'monitoring', 'insulin delivery', 'algorithm', and 'experience'. Items are also roughly positioned on a line from 'easy', 'simple', 'distinct', and/or 'clear' to implement towards 'obscure', 'indistinct', 'complex', and/or 'difficult' to translate from one centre to another. Specific elements per item indicated with * are as performed in the single-centre randomized controlled trials of intensive insulin therapy performed in Leuven, Belgium.

glucose measurement systems are being developed but not yet available. Such systems may reduce the amounts of blood used and lower the workload by nurses [12]. In addition, such systems could have the potential to improve safety and precision of insulin titration in the ICU [12].

Accurate insulin delivery is another important aspect of insulin therapy. For insulin therapy reliable, precise, and continuous infusion of insulin is needed [13]. This may include infusion via a dedicated lumen of a central venous catheter and an accurate syringe pump. Next, delicate insulin adjustments need to be performed by ICU nurses trained in using a local algorithm, possibly requiring a high level of intuitive decision-making [7].

Insulin therapy-associated hypoglycaemia and glycaemic variability

Hypoglycaemia is a real risk of insulin therapy in the ICU. Hypoglycaemia is independently associated with mortality and morbidity of critically-ill patients [14]. Whether the association is causal remains unclear. Neuroglycopenia may cause cerebral damage, epileptic insults, or even coma [15]. However, a causal link between hypoglycaemia and mortality has still not been demonstrated. More important, possibly, is that correction of hypoglycaemia with glucose, rather than hypoglycaemia itself may be detrimental [16]. Indeed, brain damage may correlate more to the concentration and amount of glucose used to correct hypoglycaemia [16]. Thus, precautions should be taken against overcorrection of hypoglycaemia, using only small amounts of glucose.

Rapid fluctuations of the blood glucose level, or increased glycaemic variability, is also independently associated with mortality and morbidity of critically-ill patients [17]. Increased glycaemic variability is thought to increase oxidative stress and may be more detrimental than sustained hyperglycaemia [18]. Prevention of glycaemic variability is suggested as a target of insulin therapy in critically-ill patients, in addition to the treatment of hyperglycaemia, and prevention and overcorrection of hypoglycaemia [19]. It is uncertain, however, whether glycaemic variability can be influenced [20]. Another risk of insulin therapy is a shift of potassium from the extracellular to the intracellular compartment, causing hypokalaemia [13]. Therefore, the potassium level should be monitored frequently during insulin infusion.

References

1. Bagshaw SM, Bellomo R, Jacka MJ, Egi M, Hart GK, and George C. (2009). The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. *Critical Care*, **13**(3), R91.
2. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, and Render ML. (2009). Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Critical Care Medicine*, **37**(12), 3001–9.
3. Van den Berghe G. (2004). How does blood glucose control with insulin save lives in intensive care? *Journal of Clinical Investigations*, **114**(9), 1187–95.
4. Ansari G, Mojtahedzadeh M, Kajbaf F, et al. (2008). How does blood glucose control with metformin influence intensive insulin protocols? Evidence for involvement of oxidative stress and inflammatory cytokines. *Advances in Therapy*, **25**(7), 681–702.
5. Van den Berghe G, Wouters P, Weekers F, et al. (2001). Intensive insulin therapy in the critically ill patients. *New England Journal of Medicine*, **345**(19), 1359–67.
6. Vlasselaers D, Milants I, Desmet L, et al. (2009). Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. *Lancet*, **373**(9663), 547–56.
7. Schultz MJ, Harmsen RE, and Spronk PE. (2010). Clinical review: strict or loose glycemic control in critically ill patients—implementing best available evidence from randomized controlled trials. *Critical Care*, **14**(3), 223.
8. Dellinger RP, Levy MM, Carlet JM, et al. (2008). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Critical Care Medicine*, **36**(1), 296–327.
9. Van Herpe T and Mesotten D. (2012). Blood glucose measurements in critically ill patients. *Journal of Diabetes Science and Technology*, **6**(1), 22–8.
10. Kavanagh BP and McCowen KC. (2010). Clinical practice. Glycemic control in the ICU. *New England Journal of Medicine*, **363**(26), 2540–6.
11. Kanji S, Buffie J, Hutton B, et al. (2005). Reliability of point-of-care testing for glucose measurement in critically ill adults. *Critical Care Medicine*, **33**(12), 2778–85.
12. Miller M, Skladany MJ, Ludwig CR, and Guthermann JS. (2007). Convergence of continuous glucose monitoring and in-hospital tight glycemic control: closing the gap between caregivers and industry. *Journal of Diabetes Science and Technology*, **1**(6), 903–6.
13. Van den Berghe G, Schetz M, Vlasselaers D, et al. (2009). Clinical review: Intensive insulin therapy in critically ill patients: NICE-SUGAR or Leuven blood glucose target? *Journal of Clinical Endocrinology and Metabolism*, **94**(9), 3163–70.
14. Krinsley JS and Grover A. (2007). Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Critical Care Medicine*, **35**(10), 2262–7.
15. Vriesendorp TM, DeVries JH, van Santen S, et al. (2006). Evaluation of short-term consequences of hypoglycemia in an intensive care unit. *Critical Care Medicine*, **34**(11), 2714–18.
16. Suh SW, Gum ET, Hamby AM, Chan PH, and Swanson RA. (2007). Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. *Journal of Clinical Investigations*, **117**(4), 910–18.
17. Krinsley JS. (2008). Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Critical Care Medicine*, **36**(11), 3008–13.
18. Monnier L, Mas E, Ginet C, et al. (2006). Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *Journal of the American Medical Association*, **295**(14), 1681–7.
19. Krinsley JS. (2011). Understanding glycemic control in the critically ill: three domains are better than one. *Intensive Care Medicine*, **37**(3), 382–4.
20. Meyfroidt G, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, and Van den Berghe G. (2010). Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. *Critical Care Medicine*, **38**(4), 1021–9.

PART 2.6

Haematological drugs

CHAPTER 51

Anticoagulants and antithrombotics in critical illness

Vickie McDonald and Marie Scully

Key points

- Coagulation is best thought of using the cell-based model of coagulation.
- Patients commenced on heparin therapy should have their platelet count monitored early because of the risk of heparin-induced thrombocytopenia (HIT), which can occur on any type or dose of heparin.
- Emergency reversal of warfarin should be with prothrombin complex concentrate (containing factors II, VII, IX and X) and not fresh frozen plasma.
- New oral anticoagulants have the advantage of predictable pharmacokinetics and do not require routine monitoring, but optimal reversal strategies for these agents are not clear.
- Thrombolytic agents lead to variable degrees of systemic lysis, which may cause haemorrhage including intracerebral haemorrhage.

Introduction

Thrombosis is the formation and propagation of a blood clot within a blood vessel that, under normal circumstances, is a protective mechanism against haemorrhage after injury. Anticoagulant and antithrombotic drugs are used to either treat patients who have developed pathological thrombosis or to prevent thrombosis in those felt to be at high risk. Historically, there have been a limited number available, for example, fibrinolytics for acute, usually arterial or large venous thrombosis, heparin, and warfarin. Recently, newer parenteral and oral anticoagulants targeting thrombin and Xa have been developed. Use of these newer agents present monitoring and reversal challenges, particularly around procedures.

Overview of haemostasis and the coagulation cascade

The coagulation cascade is a complex interaction between coagulation factors, coagulation factor inhibitors, the vessel wall, platelets, and fibrinolytic enzymes. The generation of thrombin is critical to successful haemostasis. Rather than the classical 'intrinsic' and 'extrinsic' pathways, coagulation is now better understood as a 'cell-based' model (Fig. 51.1), whereby coagulation occurs on phospholipid surfaces and is divided into three overlapping phases—initiation, amplification, and propagation [1]. Initiation involves the TF-VIIa complex activating factors IX (FIXa) and X (FXa), and trace amounts of thrombin being generated by FXa. During amplification and propagation, the small amounts of thrombin-generated activate factors leading to the explosive generation of thrombin and formation of a clot.

In-built inhibitory mechanisms to prevent excessive activation of the coagulation system include: Tissue factor pathway inhibitor, antithrombin (which inactivates FIXa, FXa, FXIa, and thrombin); Protein C and S pathways and thrombomodulin. During fibrinolysis, plasmin (derived from plasminogen) digests cross-linked fibrin to form D-dimers and other fibrinogen fragments.

Anticoagulants and antithrombotics

The main anticoagulants and the location of their effect on coagulation are summarized in Table 51.1 and Fig. 51.2.

Heparin

Unfractionated heparin (UFH) is a large glycosaminoglycan that potentiates the effect of antithrombin (AT) and requires adequate AT for therapeutic effect [2]. It predominantly inhibits thrombin and Xa. It is administered parenterally with a rapid anticoagulant effect. It has a short half-life and is fully neutralized by protamine sulfate, so can be used where the risk of bleeding is high. There is dose–response variability due to high non-specific protein binding necessitating frequent monitoring by (activated partial thromboplastin time (APTT)).

Low molecular weight heparins (LMWH) are prepared from UFH and have shorter chain lengths. They have predominantly anti-Xa activity with less anti-IIa activity [2] and adequate AT levels are required for therapeutic effect. They have a more predictable dose–response curve and are administered sc. Because of this, they are used in preference to UFH in most clinical cases. The half-life is roughly 4 hours and only approximately 50% of LMWH is neutralized by protamine. Monitoring via anti-Xa assays is recommended

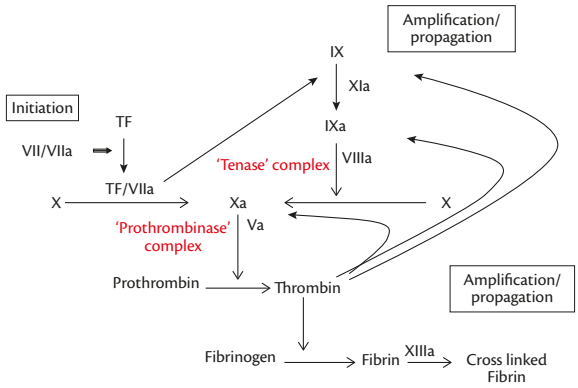


Fig. 51.1 The cell based model of coagulation.

in patients with renal impairment, pregnancy, children, and those with a large body habitus. Both heparin and LMWH are porcine in origin.

Use

- **UFH:** mechanical heart valves and extracorporeal circuits (such as cardiopulmonary bypass, haemodialysis haemofiltration); treatment and prevention of DVT/PE where LMWH are contraindicated; treatment of acute coronary syndromes (ACS) where LMWH are contraindicated
- **LMWH:** treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE); acute coronary syndromes; LMWH are not licensed for use with mechanical heart valves.

UFH and LMWH do not cross the placenta and are safe in pregnancy.

The APTT or activated clotting time ACT may be used to monitor UFH. In cases where the APTT may not be reliable, such as the presence of a lupus anticoagulant, anti-factor Xa assays should be performed. Specific anti-Xa assays also have to be performed to monitor LMWH. Peak levels should be taken 4 hours after the dose and samples need to analysed promptly (within 2 hours).

Complications

- **Bleeding:** risk factors include recent surgery or trauma, recent intracerebral haemorrhage or large stroke, active peptic ulcer disease, advanced age, or accumulation of the drug (e.g. with LMWH in renal failure). UFH has a short half-life and if severe bleeding occurs, it should be stopped immediately and reversed with protamine sulfate (1 mg protamine sulfate neutralizes 80–100 U heparin, but 10–20 mg is often sufficient) [3]. The response is assessed using the APTT and repeat doses may be needed. LWMH is only partially reversed by protamine. Therefore, in situations associated with a potential risk of bleeding, split dose injections should be considered.
- **Management around procedures:** UFH infusions should be stopped 4 hours prior to surgical procedures and should be started when haemostasis is achieved and maintained—usually 2–4 hours after procedures. Treatment dose LMWH should be stopped 12–24 hours before procedure and restarted 4–6 hours afterwards depending on procedures.
- **Heparin-induced thrombocytopenia (HIT) +/– thrombosis [HIT(T)]:** the immune form of HIT develops as a result of IgG antibody formation to heparin-PF 4 complexes, which activate platelets leading to a prothrombotic condition with a fall in platelet counts [4]. Patients commenced on heparin should have platelet counts monitored. The main features and risk factors are

Table 51.1 Anticoagulant drugs, mechanism of action, routes of administration and monitoring

Drug Class	Drug name	Mechanism of action	Mode of administration	Monitoring tests	Usual target range for therapeutic effect
Vitamin K antagonists	Warfarin Phenindione Acenocoumarol	Inhibits vitamin K-mediated gamma carboxylation of coagulation factors in the liver (II, VII, IX, X)	Oral	INR	2–3 3–4 in certain circumstances
Unfractionated heparin		Potentiate antithrombin leading to inhibition of IIa and Xa	iv or sc	APTT/APTT ratio	APTT ratio 1.5–2.5
LMWH	E.g. enoxaparin, dalteparin, tinzaparin	Potentiate antithrombin leading to inhibition of Xa and IIa	sc	Anti-Xa assay	0.5–1.0 IU/mL
Heparin pentasaccharide	Fondaparinux	Potentiate antithrombin leading to inhibition of Xa	sc	Anti-Xa assay	0.5–1.0 IU/mL
Heparinoid	Danaparoid	Potentiate antithrombin leading to inhibition of Xa	iv, sc	Anti-Xa activity	0.5–1.0 IU/mL
Direct thrombin inhibitor	Argatroban	Directly inhibit free and clot-bound thrombin	iv	APTT/APTT ratio	APTT ratio 1.5–3.0
Oral direct thrombin inhibitors	Dabigatran	Directly inhibits free and clot bound thrombin	Oral	Dilute thrombin time, ecarin clotting time	Not known
Direct Xa inhibitors	Rivaroxaban, apixaban, edoxaban	Directly inhibit Xa	Oral	Anti-Xa assay	0.5–1.0

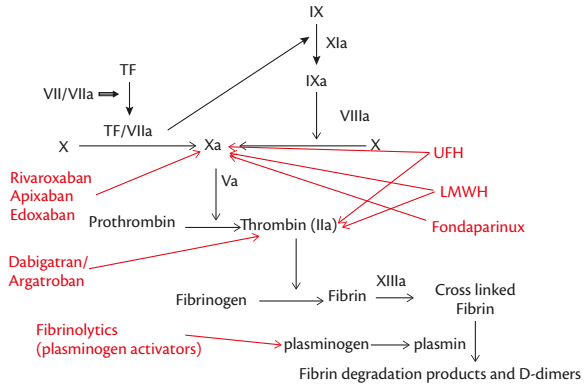


Fig. 51.2 Anticoagulants and antithrombotics. Sites of action of anticoagulants and antithrombotics. Unfractionated heparin potentiates the activity of antithrombin and leads to the inhibition of Xa and IIa. LMWH also act via antirhombin, but have relatively more anti-Xa activity than anti-IIa activity. Fondaparinux has anti-Xa activity only. Rivaroxaban is a direct inhibitor of Xa and dabigatran and argatroban are direct inhibitors of IIa. Fibrinolytic agents increase the conversion of plasminogen to plasmin which in turn degrades cross-linked fibrin leading to clot resolution.

shown in Box 51.1. It occurs after both therapeutic and prophylactic heparin (including heparin in catheter flushes).

The probability of HIT being the explanation for low platelets in ICU is approximately 1/100. If a diagnosis of HIT is suspected, heparin must be stopped and an alternative anticoagulant started [5]. Forty per cent of patients without thrombosis at the time of diagnosis of HIT develop thrombosis within 10 days of stopping heparin if no alternative anticoagulant is given. Patients who require longer-term anticoagulation should not have vitamin K antagonist therapy started until the platelet count has recovered. There is reportedly no amnestic response, therefore, patients with a history of HIT may be considered for heparin 90 days from the last heparin exposure. However, expert advice should be sought.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide subunit of heparin. It inhibits Xa activity and is, therefore, is not reversed by protamine. However, it has a similar efficacy profile to LMWH for treatment of thrombosis, with a slightly increased risk of bleeding. It can be used for thromboprophylaxis of DVT/PE in patients undergoing orthopaedic surgery where the dose is 2.5 mg daily. The dose for treatment of DVT/PE is typically 7.5 mg daily, adjusted for extremes of body weight and renal function [6]. It is as effective as LMWH in ACS [7] and it has been used in HIT but is not licensed for this indication.

Danaparoid

Danaparoid is a heparinoid indirect (i.e. antithrombin dependent) Xa inhibitor that is administered intravenously (loading dose followed by continuous infusion). It has a long half-life (25 hours). It is predominantly renally excreted and patients with renal impairment require dose modifications. Monitoring is with anti-Xa assay. Danaparoid is licensed for the treatment of HIT, but approximately 10% of HIT antibodies cross-react with danaparoid.

Argatroban

Argatroban is a direct thrombin inhibitor administered iv as a continuous infusion. It is predominantly excreted by the liver and requires dose modification in liver disease, but not in renal impairment. Plasma levels of the drug correlate well with the APTT. Initial dosing for HIT is 2 micrograms/kg/min, titrated to target APTT. In critical care, lower initial starting doses should be used because of the increased risk of bleeding. If haemorrhage occurs,

Box 51.1 Summary of risk factors, manifestations, diagnostic tools, and treatment modalities for HIT

Risk factors associated with development of HIT

- **Type of heparin**: UFH > LMWH (PROTECT study showed reduced HIT in ICU patients given dalteparin compared with unfractionated heparin [20]).
- **Duration of heparin**: >6 days increases risk.
- **Type of patient**: surgery > medical > obstetric.
- **Surgery type**: cardiac > other.
- **Age**: middle to old age > young.
- **Sex**: female > male.

Clinical manifestations of HITT

- Thrombocytopenia.
- Shortening of the APTT.
- **Venous thrombosis**: DVT, PE, other sites such as cerebral sinus are rare.
- Arterial thrombosis.
- **Skin lesions**: erythema or necrosis at injection site.

4T's scoring system

- **Thrombocytopenia**: >50% fall in platelet count.
- **Timing**: fall begins 5–14 days after exposure.
- **Thrombosis**: presence of thrombosis or other manifestations, such as skin erythema at injection site and allergic reactions to heparin.
- **Other**: other cause for low platelets more likely.

Assays

- **Immunological**: ELISA—detect antibodies by binding to plates coated with platelet factor 4.
- **Functional**: platelet aggregation, serotonin release, flow cytometry.

Treatment modalities

- **Danaparoid**: but contains heparin sulfate and 10% cross-reactivity with heparin-PF4 antibodies.
- Fondaparinux.

4 T's score: Adapted from Lo GK et al., 'Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings', *Journal of Thrombosis and Haemostasis*, 2006, **4**, 759–65. Wiley, copyright 2006 International Society on Thrombosis and Haemostasis, with permission.

the drug should be stopped. Due to a short half-life (<1 hour), the APTT usually comes down to normal within 2–4 hours. There is no specific reversal agent, but prothrombin complex concentrate may help in life-threatening bleeding. Argatroban may prolong the prothrombin time (PT) so caution is required with concurrent warfarin.

Warfarin

Vitamin K is essential for the γ-carboxylation of glutamic acid residues on clotting factors II, VII, IX, and X (and proteins C and S). Warfarin and other vitamin K antagonists block regeneration of vitamin K from its epoxide, thereby reducing γ-carboxylation and, in turn, function of the vitamin K-dependent factors.

Warfarin is rapidly absorbed from the gastrointestinal tract and has a half-life of approximately 40 hours in the circulation. The effect of warfarin is influenced by many factors, including compliance, vitamin K content of diet, liver function, concurrent illness, drugs, and genetics. The drugs that commonly influence the effect of warfarin are shown in Table 51.2.

Use

- Long-term anticoagulation.
- Warfarin is teratogenic in the first trimester of pregnancy and is difficult to manage around delivery, so is not recommended in pregnancy.

The (international normalized ratio (INR), based on the prothrombin time, monitors the effect of vitamin K antagonists on the haemostatic system. Despite regular monitoring, patients may be outside of therapeutic range for up to 40% of the time.

Table 51.2 Drugs that influence the effect of vitamin K antagonist (VKA) drugs (e.g. warfarin)

Effect of concurrent medication on warfarin and anticoagulant control	
Increased effect of warfarin (or other VKA)	*Reduced effects of warfarin (or other VKA)*
◆ Alcohol	◆ Alcohol
◆ Allopurinol	◆ St John's Wort
◆ Amiodarone	◆ Carbamazepine
◆ **Anti-platelet agents**: aspirin, clopidogrel, dipyridamole	◆ Primidone
◆ **Antibiotics**: ciprofloxacin, clarithromycin and erythromycin, metronidazole, sulphonamides, norfloxacin, cephalosporins, tetracyclines, trimethoprim, and penicillins*	◆ Griseofulvin
◆ **Anti-fungals**: fluconazole, itraconazole, ketoconazole, voriconazole	◆ Azathioprine
◆ Cranberry juice	◆ Mercaptopurine
◆ Entacapone	◆ Oestrogens and progestogens
◆ Esomeprazole and omeprazole	◆ Vitamin K
◆ Iloprost	
◆ Cimetidine	
◆ NSAIDs	
◆ Prolonged paracetamol use	
◆ Quinidine	
◆ SSRIs	
◆ Sodium valproate	
◆ Thyroid hormones	

*No laboratory effect, but clinical reports.

Complications

- **Bleeding:** the risk of major bleeding is around 2% per annum, with a case fatality of 20% and is increased when the INR is >5 [8]. Management is determined by the severity of the bleed and the INR. Vitamin K 5–10 mg iv has an initial onset of action after 4–6 hours, but is not maximal for at least 24 hours and, therefore, additional measures are required. Prothrombin complex concentrates that contain factors II, VII, IX, and X are now recommended as first-line for warfarin reversal [8], which is achieved within 30 minutes of infusion. Recommended dosing is 25–50 IU factor IX/kg body weight. These concentrates carry the potential risk of inducing thromboembolism; therefore, caution should be exercised when using these products in high-risk groups. In the absence of prothrombin complex concentrates, fresh frozen plasma FFP (12–15 mL/kg) can be used, but is not satisfactory as very large amounts of plasma (1–2 L) may need to be infused, and the concentration of factor IX is only minimally increased by treatment with FFP. In the absence of bleeding, over-anticoagulation with warfarin is managed by omitting the drug for a few doses and restarting when the INR is within the desired range. Administration of small doses of oral vitamin K (1–2.5 mg) may also be needed if the INR is >5.0.
- **Management around surgery:** warfarin therapy is suspended and substituted with LMWH therapy for most surgical procedures excepting minor dental surgery. For elective procedures, warfarin is stopped approximately 5 days prior to the procedure, LWMH started the day after stopping warfarin and the INR checked the day before the procedure. For emergency surgery vitamin K (5–10 mg) with/without prothrombin complex concentrate should be administered.

New oral anticoagulants

New oral anticoagulants targeting either Xa or IIa have been developed, which have fewer drug interactions, no dietary interactions, and more predictable pharmacokinetics negating the need for routine monitoring.

Rivaroxaban, apixaban, and edoxaban are Xa inhibitors. Rivaroxaban is renally excreted and has a half-life of 4–9 hours (13 hours in the elderly or when there is renal impairment). It is contraindicated if the creatinine clearance is <15 mL/min and with severe hepatic impairment. It has been shown to be non-inferior to standard anticoagulant therapy in the treatment of acute DVT and PE, in atrial fibrillation, and DVT/PE prevention after elective hip and knee replacements [9–12]. There are ongoing studies in acute coronary syndromes.

Apixaban has a half-life of 12 hours, with 25% renal elimination. Doses may need to be reduced in the elderly and those with low body weight. It is a licensed alternative to standard anticoagulant therapy in atrial fibrillation, and DVT/PE prevention after elective hip and knee replacements [13–15].

Dabigatran etexilate is a pro-drug metabolized to the active ingredient dabigatran, which binds free and clot-bound thrombin. It is predominantly renally excreted. The peak plasma concentration is achieved in 1.5 hours, with a half-life of 14–17 hours. Dabigatran has been shown to be equivalent to enoxaparin 40 mg od in elective

hip and knee surgery. It has also been shown to be effective in the prevention of stroke in AF [11,16].

The increased risk of bleeding with concurrent non-steroidal anti-inflammatory drug use still applies. There are no ideal monitoring assays for these drugs. For dabigatran, increased APTT and PT can be an indication of anticoagulation, but cannot be used for monitoring, so the dilute thrombin time (Hemoclot®) and ecarin clotting time should be used. For rivaroxaban an anti-Xa assay can be used to monitor therapeutic effect.

Complications

- **Bleeding:** at present, there are no specific reversal agents (although they are in development). Prothrombin complex concentrates and rVIIa have been suggested to treat bleeding with rivaroxaban, apixaban and dabigatran [3]. Charcoal administration reduces the absorption of dabigatran, and in cases of intractable haemorrhage, dialysis will reduce drug levels of dabigatran. Dialysis does not effectively remove rivaroxiban, which is 95% protein bound.
- **Management around surgery [17]:** in patients with normal renal function and a standard bleeding risk, discontinuation of dabigatran 24 hours before surgery will decrease plasma levels to approximately 25% of steady-state trough levels, reducing to approximately 12–15% of trough levels 36 hours before surgery and approximately 5–10% 2 days (48 hours) before surgery. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required dabigatran should be stopped 2–4 days before surgery and LMWH substituted where required. A similar regimen may be adopted for rivaroxiban.
- **Neuraxial anaesthesia [18]:** removal of the catheter must be delayed by an interval of at least two half-lives (i.e. <25% of the drug remains active) after the prophylactic anticoagulant has been administered. Therefore, it is suggested that with rivaroxaban, the catheter should not be removed for at least 20 hours after the previous dose and the next dose should be given no sooner than 6 hours after catheter removal. With dabigatran, recommendations are different. It has been proposed that the catheter should not be removed until 36 hours (two half-lives) have elapsed from the previous dose and the subsequent dose be given no sooner than 12 hours after catheter removal.

Thrombolytic agents

Thrombolytic agents are plasminogen activators that generally cause a state of systemic lysis by converting plasminogen to plasmin. This, in turn, leads to cleavage of cross-linked fibrin and the generation of fibrin degradation products that are cleared by the kidney and reticuloendothelial system. In excess, activators of the fibrinolytic system can lead to degradation of fibrinogen, as well as cross-linked fibrin. First generation thrombolytic agents, such as streptokinase, are more likely to induce systemic lysis than second (rtPA (alteplase)) and third generation (r-PA (reteplase), TNK-tPA (tenectaplase)) agents. These drugs are administered systemically and protocols for use in acute coronary thrombosis, stroke, peripheral arterial occlusion, and venous thrombosis and massive pulmonary embolism with haemodynamic compromise exist. Contraindications to thrombolysis are shown in Box 51.2.

Box 51.2 Contraindications to thrombolysis

Absolute contraindications

- Recent neurosurgery, head trauma or CNS haemorrhage.
- Intracranial/intraspinal neoplasm or aneurysm.
- Stroke within 6 months.
- Active or recent internal bleeding.
- Uncontrolled hypertension.
- Suspected aortic dissection.

Relative contraindications

- Surgery in last 2 weeks.
- Recent trauma (including CPR).
- Infective endocarditis, pericarditis.
- Pregnancy or recent delivery.
- Haemostatic defects.
- Active peptic ulcer disease.

Laboratory tests such as the thrombin time and fibrinogen levels will detect the presence of a systemic lytic state, but they do not predict the bleeding risk. Haemorrhage complicating these agents is most commonly local (e.g. at the site of catheterisation in the groin). However, intracranial (0.5–1.0%) or gastrointestinal bleeding may occur. Cryoprecipitate, fibrinogen concentrate or FFP can be given to treat the coagulopathy and red cells may be required. Antifibrinolytics may provide some benefit and patients who are also receiving heparin should receive protamine. Acylated plasminogen-streptokinase activator complex (APSAC), has a longer half-life of 90 minutes. A scoring system for predicting bleeding in patients receiving thrombolysis for stroke (haemorrhage after thrombolysis—HAT—score) can help to risk stratify patient bleeding risk before undertaking thrombolysis [19].

References

1. Hoffman M and Monroe DM, III. (2001). A cell-based model of hemostasis. *Thrombosis and Haemostasis*, **85**(6), 958–65.
2. Gray E, Mulloy B, and Barrowcliffe TW. (2008). Heparin and low-molecular-weight heparin. *Thrombosis and Haemostasis*, **99**(5), 807–18.
3. Makris M, Van Veen JJ, Tait CR, Mumford AD, and Laffan M. (2013). Guideline on the management of bleeding in patients on antithrombotic agents. *British Journal of Haematology*, **160**(1), 35–46.
4. Warkentin TE. (2011). How I diagnose and manage HIT. *Hematology. American Society of Hematology. Education Program*, **2011**, 143–9.
5. Warkentin TE, Greinacher A, Koster A, and Lincoff AM. (2008). Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, **133**(6 Suppl.), 340S–80S.
6. Buller HR, Davidson BL, Decousus H, et al. (2004). Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Annals of Internal Medicine*, **140**(11), 867–73.

7. Yusuf S, Mehta SR, Chrolavicius S, et al. (2006). Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *New England Journal of Medicine*, **354**(14), 1464–76.
8. Keeling D, Baglin T, Tait C, et al. (2011). Guidelines on oral anticoagulation with warfarin—fourth edition. *British Journal of Haematology*, **154**(3), 311–24.
9. Bauersachs R, Berkowitz SD, Brenner B, et al. (2010). Oral rivaroxaban for symptomatic venous thromboembolism. *New England Journal of Medicine*, **363**(26), 2499–510.
10. Buller HR, Prins MH, Lensin AW, et al. (2012). Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *New England Journal of Medicine*, **366**(14), 1287–97.
11. Gomez-Outes A, Terleira-Fernandez AI, Suarez-Gea ML, and Vargas-Castrillon E. (2012). Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *British Medical Journal*, **344**, e3675.
12. Patel MR, Mahaffey KW, Garg J, et al. (2011). Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *New England Journal of Medicine*, **365**(10), 883–91.
13. Granger CB, Alexander JH, McMurray JJ, et al. (2011). Apixaban versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine*, **365**(11), 981–92.
14. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, and Ramirez LM. (2010). Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *New England Journal of Medicine*, **363**(26), 2487–98.
15. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, and Hornick P. (2010). Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet*, **375**(9717), 807–15.
16. Connolly SJ, Ezekowitz MD, Yusuf S, et al. (2009). Dabigatran versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine*, **361**(12), 1139–51.
17. Spyropoulos AC, Douketis JD, Gerotziafas G, Kaatz S, Ortel TL, and Schulman S. (2012). Periprocedural antithrombotic and bridging therapy: recommendations for standardized reporting in patients with arterial indications for chronic oral anticoagulant therapy. *Journal of Thrombosis and Haemostasis*, **10**(4), 692–4.
18. Rosencher N, Bonnet MP, and Sessler DI. (2007). Selected new antithrombotic agents and neuraxial anaesthesia for major orthopaedic surgery: management strategies. *Anaesthesia*, **62**(11), 1154–60.
19. Lou M, Safdar A, Mehdiratta M, et al. (2008). The HAT score: a simple grading scale for predicting hemorrhage after thrombolysis. *Neurology*, **71**(18), 1417–23.
20. Cook D, Meade M, Guyatt G, et al. (2011). Dalteparin versus unfractionated heparin in critically ill patients. *New England Journal of Medicine*, **364**(14), 1305–14.

CHAPTER 52

Haemostatic agents in critical illness

Beverley J. Hunt

Key points

- Antifibrinolytics have been shown to reduce bleeding and blood transfusion during surgery.
- Tranexamic acid is recommended over aprotinin in view of concerns about the safety of the latter.
- In bleeding trauma, tranexamic acid reduces mortality by 9% and should be given as early as possible after injury.
- Desmopressin may have a place in reducing bleeding in those with uraemia.
- The efficacy of rFVIIa in off-licence 'rescue therapy' is uncertain and it is associated with an increased rate of arterial thrombosis especially in the elderly.

Introduction

Pharmacological agents are used in two ways, either to prevent excessive bleeding or to treat established bleeding. The agents used can be broadly classified into three groups—antifibrinolytics, desmopressin, and the recombinant prohaemostatic factors, such as recombinant activated factor VIIa (rFVIIa).

Antifibrinolytics

These include the lysine analogues, tranexamic acid (TA) and epsilon-amino caproic acid (EACA), which are competitive inhibitors of plasminogen binding to fibrin and plasminogen receptors; and aprotinin, a serine protease inhibitor, which has a powerful direct antiplasmin effect and inhibits a number of other haemostatic enzymes, including kallikrein. Although *in vitro* TA has approximately 10 times the antifibrinolytic activity of EACA, TA, and other lysine analogues have similar clinical efficacy in reducing bleeding and blood usage peri-operatively [1]. However, the withdrawal of aprotinin due to safety concerns, and demonstration that TA reduces mortality in patients with traumatic bleeding [2] has pushed TA to the fore, as an efficacious, safe, and cost effective agent.

Tranexamic acid in traumatic bleeding

The CRASH-2 study was a randomized controlled trial (RCT) of TA versus placebo in the management of bleeding after trauma and recruited 20,000 patients worldwide [2]. The primary outcome was death in hospital within 4 weeks of injury. All-cause mortality was significantly reduced with tranexamic acid: (1463 (14.5%) versus 1613 (16.0%) placebo; relative risk 0.91, 95% CI, 0.85–0.97; $p = 0.0035$). The risk of death due to bleeding was significantly reduced by 9% (489 (4.9%) versus 574 (5.7%); relative risk 0.85, 95% CI, 0.76–0.96; $p = 0.0077$). TA was also was shown to be safe, as there were no adverse events and, importantly for a drug that affects haemostasis, there were no increased thrombotic events. Indeed, there was a trend to a lower rate of arterial events in those receiving TA. Further analysis of the data showed benefit was greatest the earlier that TA was given after injury and that there was a possibility of negative benefit when given after 3–6 hours from injury [3].

The estimated incremental cost per life year gained of administering TA is $48, $66, and $64 in Tanzania, India, and the UK, respectively, making it highly cost effective [4]. The WHO has recently classed it as an essential drug.

CRASH-2 recruited patients who had or were at risk of significant bleeding, and included patients with massive bleed loss. The majority of lives saved were those who had significant bleeding, but did not have massive blood loss at presentation. A recent publication [5] confirmed the same reduction of mortality applied to this latter group, i.e. there was no evidence of heterogeneity in the effect of TA on different groups. Thus, TA should not be restricted to those with the most severe injuries or those with hyperfibrinolysis changes on their thromboelastography trace, for although this would save about 20,000 lives a year worldwide, this would deny benefit to the majority of patients who would benefit. Recent work has shown that activation of fibrinolysis is present in most trauma patients and thromboelastography only detects the most severe activation of fibrinolysis [6]. If tranexamic acid is given to all bleeding trauma patients worldwide there is a potential to save 120,000 lives a year.

Treatment of established bleeding and prevention of peri-operative bleeding with the lysine analogues

Since the withdrawal of aprotinin, TA has been widely used to reduce bleeding in cardiac surgery, but it is now also used in other types of surgery. A systematic review in 2012 [7], identified 129 trials that included 10,488 patients, carried out between 1972 and 2011. In this meta-analysis, TA reduced the probability of receiving a blood transfusion by a third (RR 0.62, 95% CI 0.58–0.65; $p < 0.001$). This effect remained when the analysis was restricted to trials using adequate allocation concealment (RR 0.68, CI 0.62–0.74; $p < 0.001$). Fewer deaths occurred in the tranexamic

acid group (RR 0.61, CI 0.38–0.98; $p = 0.04$), although when the analysis was restricted to trials using adequate concealment there was considerable uncertainty (RR 0.67, 0.33 to 1.34; $p = 0.25$). The authors concluded that cumulative meta-analysis showed reliable evidence that TA reduces the need for transfusion.

Another systematic review of 104 randomized trials examined whether the effect of TA on blood loss varies with the extent of surgical bleeding. The results suggest that, despite variation in the magnitude of blood loss between procedures and the heterogeneity of the studies included, the use of TA was associated with an overall reduction in surgical bleeding by about a third. This reduction in bleeding with TA is almost identical to the reduction in the risk of receiving a blood transfusion with TA suggesting, as expected in the closely monitored environment of an operating theatre, that unlike traumatic bleeding in CRASH-2, blood transfusion use was closely titrated to blood loss [8].

The dose of TA recommended by Kerr et all was 1–2 g in an adult patient, their analysis of all trials concluded there was no increased efficacy in using a higher dose. Indeed extremely high doses of TA (100 mg/kg or more) peri-operatively, have been associated with seizures, especially in patients with renal failure and older than 75 [9].

Aprotinin

Aprotinin has long been used in doses of 500,000 kallikrein inhibitory units (KIU) and greater as a treatment to reverse established fibrinolytic bleeding. In the 1980s, it gained a license for reducing bleeding high risk cardiac surgery by giving 2 million KIU to the patient, 2 million KIU to the cardiopulmonary (CPB) circuit and 50,000 KIU/hour during CPB. The original trial reduced post-operative drainage loss by 81%, and total haemoglobin loss by 89% [10]. Since aprotinin is a bovine protein that can provoke an immunological reaction, a test dose is required. By inhibiting kallikrein, aprotonin prolongs in vitro tests of the intrinsic system, including the activated clotting time (ACT), which is used to monitor heparin during cardiopulmonary bypass. In order to allow for adequate levels of heparin to run in patients receiving a high-dose aprotinin regimen, the ACT measured with a celite activator should be kept higher than the normal level of 500 seconds (ideally at 750 seconds) to compensate and allow for 'normal' heparin levels. Kaolin is used as an activator in some ACT tubes [11]. Since it is less affected by aprotinin kaolin ACTs can be monitored in the normal way.

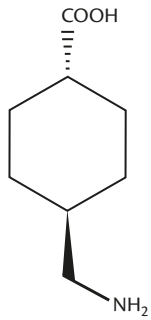


Fig. 52.1 The structure of tranexamic acid.

Aprotinin can also be used in established fibrinolytic bleeding. A good antiplasmin dose is 500,000 KIU iv.

The assumption that had been used for many years—that a reduction in blood loss is a surrogate marker of reduction in premature mortality has been shown to be false. A large open study of the use of antifibrinolytics in cardiac surgery suggested that although aprotinin reduced bleeding, it was associated with increased risk of death and renal dysfunction compared with other antifibrinolytics [12]. A prospective RCT comparing aprotinin versus EACA versus TA was halted by the data monitoring committee due to concerns about the death rate in patients receiving aprotinin [13]. A total of 74 patients (9.5%) in the aprotinin group had massive bleeding, compared with 93 (12.1%) in the TA group and 94 (12.1%) in the EACA group (relative risk in the aprotinin group for both comparisons, 0.79; 95% confidence interval (CI), 0.59–1.05). However, at 30 days the rate of death from any cause was 6.0% in the aprotinin group, as compared with 3.9% in the TA group (relative risk, 1.55; 95% CI, 0.99–2.42) and 4.0 in the EACA group (relative risk, 1.52; 95% CI, 0.98–2.36). The relative risk of death in the aprotinin group as compared with that in both groups receiving lysine analogues was 1.53 (95% CI, 1.06–2.22). There was voluntary suspension of marketing aprotinin. Subsequently, the use of aprotinin has declined and TA has replaced it's indications in most countries.

Mechanism of antifibrinolytics

TA and EACA are synthetic lysine analogues (see Fig. 52.1 for structure of TA), which bind to the lysine binding sites and thus prevent plasminogen from binding to fibrin, fibrinogen and plasminogen receptors as a competitive inhibitor. By preventing the generation of plasmin, and by blocking activation of plasminogen receptors on leucocytes and endothelial cells it probably has a weak anti-inflammatory effect and possibly minor antithrombotic effect. This area is the subject of current research.

In high doses (150–200 KIU), aprotinin inhibits kallikrein and the licensed regimen achieves blood levels of about 200 KIU/mL. However, even in lower concentrations, aprotinin is a plasmin inhibitor, which appears to be the main mechanism for its effect on bleeding; its molar potency in vitro is 100 and 1000 times that of TA and EACA [14].

Antifibrinolytics may also have a minor effect in preserving platelet membrane receptors by inhibiting plasmin-mediated degradation.

Desmopressin

Desmopressin acetate (DDAVP) is a synthetic vasopressin analogue. It increases the plasma concentrations and activity of von Willebrand Factor (vWF) 2–5-fold by inducing the release of vWF from Weibel Palade bodies in the endothelium. It also stimulates endothelial release of tissue plasminogen activator and promotes platelet activation.

Desmopressin shortens the bleeding time in patients with von Willebrand's disease, platelet function defects and uraemia and so is used for these indications, alongside tranexamic acid or EACA to prevent excess fibrinolytic activation.

Despite the success of early trials, a Cochrane systematic review of all 18 RCTs, where desmopressin was given to reduce perioperative bleeding concluded that there was no benefit [15], although it

may be helpful in the platelet defect in renal failure and in some types of platelet dysfunction. Side effects include flushing and an antidiuretic effect.

Recombinant activated factor VIIa

Recombinant activated factor VII (rFVIIa) is approved for the management of haemophilia A or B with inhibitors; acquired haemophilia; congenital FVII deficiency; and Glanzmann's thrombasthenia with refractoriness to platelet transfusion with antibodies to GPIIb/IIIa and/or HLA antigens.

However, rFVIIa has also been used widely as an 'off-label' treatment in patients with platelet dysfunction, thrombocytopenia, and massive transfusion after major surgery or trauma in patients without a pre-existing coagulopathy. Initially, the body of evidence for these indications was disappointingly mainly from case reports [16] and case series, but now data exists from 25 RCTs [17].

Mechanism of action of pharmacological doses of rFVIIa

About 1% of circulating factor VII is in the activated form, but the amount of circulating rFVIIa required to have an effect in haemophilia is much larger. There is disagreement whether rFVIIa has an effect independent of tissue factor. It has been demonstrated *in vitro* that rFVIIa is able to bind weakly to activated platelets and cause activation of FX. The need for binding of rFVIIa to activated platelets may explain why rFVIIa has an effect only at the site of bleeding. Others hold the view that VIIa binds to tissue factor in the normal way. Whatever the mechanism, coagulation activation with rVIIa only occurs locally at the site of bleeding without disseminated activation.

rFVIIa has a half-life of approximately 2.7 hours in adults. Even though the recommended dosage is 90 micrograms/kg in haemophiliac patients with inhibitors, it is clear the optimal dose and dosing intervals of rFVIIa in this group have not been established with certainty. Higher doses up to 300 micrograms/kg have proved to be more clinically efficacious in some patients.

Monitoring of rVIIa activity with routine assays is not possible. The prothrombin time (PT) and activated partial thromboplastin time (APTT) are shortened after pharmacological doses of rFVIIa, but they are only indirect correlates of its action. The measurement of FVII clotting activity (FVIIa:C) in the treatment of haemophilia-related bleeding has led to a recommendation of a minimum level of 6–10 IU/mL and peak levels of greater than 30–50 IU/mL when giving iv boluses. The use of thromboelastography and thrombin generation has also been explored, with limited success, in trying to find an *in vitro* measure that correlates with clinical response.

Platelet dysfunction occurs in uraemia and with aspirin, clopidogrel, and glycoprotein (GP) IIb/IIIa inhibitors in acute coronary syndromes. rFVIIa has been reported to control bleeding anecdotally in these situations.

Off-license use in patient groups other than haemophilia

Many bleeding patients without haemophilia have now been treated, off-license, with rFVIIa [17]. The patients' settings are very diverse, including surgery, gastointestinal bleeding, liver dysfunction, and intracranial and obstetric haemorrhage and trauma. Patients with liver dysfunction often have disproportionately low factor VII levels compared with the other vitamin K-dependent factors. rFVIIa normalizes the PT in liver disease with a single dose of 5–80 micrograms/kg.

Data from 25 RCTs enrolling around 3500 patients have now evaluated the use of rFVIIa as both prophylaxis to prevent bleeding (14 trials) or therapeutically to treat major bleeding (11 trials), in patients without haemophilia. When combined in meta-analysis [17], the trials showed modest reductions in total blood loss or red cell transfusion requirements (equivalent to less than one unit of red cell transfusion). For other endpoints, including clinically relevant outcomes, there were no consistent indications of benefit, and almost all of the findings in support of and against the effectiveness of rFVIIa could be due to chance (the exception was thromboembolic events). Other limitations applied in many trials, for example, uncertainty about the protocols for use of blood components.

Boffard et al. led the first randomized placebo-controlled trial of rFVIIa in blunt and penetrating trauma after patients had been transfused eight units of red cells suggested trends to requiring less red cells in those with penetrating injuries, without differences in thromboembolic but the findings were not replicated in a larger trial [18]. The trauma trials showed that rFVIIa is less effective in those who are acidotic or in severe shock. As for trauma, in the studies of patients with intracranial bleeding, although there were promising results in earlier therapeutic studies, the findings were not replicated in subsequent larger trials.

In both prophylactic and therapeutic groups of trials, there was a trend to increased thromboembolic events [19], with the increase in arterial thromboembolic events reaching statistical significance. Thromboembolic disease is multifactorial and for many of the patients in the clinical settings of the included studies, a higher risk of thrombosis might be expected. Underestimation of the rates of thromboembolic events from the RCTs compared with current hospital practice is also likely, as a history of thrombosis or vaso-occlusive disease was a common criterion for exclusion in most of the included studies. Levi et al. looked at published RCTs of rVIIa and company data [19]. There was no increased rate of venous thromboembolism, but significantly higher rates of arterial events, for example, 2.9% of those who had rVIIa had coronary thrombosis compare with 1.1% of controls. Rates of arterial events were particularly high in those over 65 years (9% versus 3.6%, $p = 0.003$), the rates were especially high in those over 75 years (10.8% versus 4.1%, $p = 0.02$). Concerns about the thrombotic risk, especially increased rate of arterial events associated with the off-license use of rVIIa led to a Black Box warning from the FDA in the USA early in 2010. Because of concerns about its benefit and safety, many guidelines are now recommending that rVII is only used as part of a clinical trial.

References

1. Henry DA, Carless PA, Moxley AJ, *et al.* (2007). Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews*, CD001886.
2. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. (2010). Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*, **376**(9734), 23–32.

3. CRASH-2 collaborators, Roberts I, Shakur H, et al. (2011). The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*, **377**(9771), 1096–101.
4. Guerriero C, Cairns J, Perel P, Shakur H, Roberts I, and CRASH 2 trial collaborators. (2011). Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS One*, **6**(5), e18987.
5. Roberts I, Perel P, Prieto-Merino D, et al. (2012). Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecific end analysis of data from randomized controlled trial. *British Medical Journal*, **345**, e5839.
6. Raza I, Davenport R, Rourke C, et al. (2013). The incidence and magnitude of fibrinolytic activation in trauma patients. *Journal of Thrombosis and Haemostasis*, **11**(2), 307–14.
7. Ker K, Edwards P, Perel P, Shakur H, and Roberts I. (2012). Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *British Medical Journal*, **344**, e3054.
8. Ker K, Prieto-Merino D, and Roberts I. (2013). Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. *British Journal of Surgery*, **100**, 1271–9.
9. Kalavrouziotis D, Voisine P, Mohammadi S, Dionne S, and Dagenais F. (2012). High-dose tranexamic acid is an independent predictor of early seizures after cardiopulmonary bypass. *Annals of Thoracic Surgery*, **93**, 148–54.
10. Royston D, Bidstrup BP, Taylor KM, and Sapsford RN. (1987). Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. *Lancet*, **2**, 1289–91.
11. Hunt BJ, Segal H, and Yacoub M. (1992). Aprotinin and heparin monitoring during cardiopulmonary bypass. *Circulation*, **86**, 410–12.
12. Mangano DT, Tudor IC, and Dietzel C, for Multicentre Study of Perioperative Ischemia Group and Ischemia Research & Education Foundation. (2006). The risk associated with aprotinin in cardiac surgery. *New England Journal of Medicine*, **354**, 353–65.
13. Fergusson DA, Hebert PC, Mazer CD, et al. (2008). A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *New England Journal of Medicine*, **358**, 2319–31.
14. Segal H and Hunt BJ. (2000). Aprotinin: pharmacological reduction of perioperative bleeding. *Lancet*, **355**, 1289–90.
15. Carless PA, Henry DA, Moxet AJ, et al. (2004). Desmopressin for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews*, CD001884.
16. Martinowirz U, Kenet G, Lubetski A, Luboshitz J, and Segal E. (2001). Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *Journal of Trauma*, **51**, 431–8.
17. Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, and Hyde C. (2012). Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database of Systematic Reviews*, **3**, CD005011.
18. Boffard KD, Bruno Riou B, Brian Warren B, et al. (2005). Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *Journal of Trauma*, **59**, 8–15.
19. Levi M, Levy JH, Andersen HF, and Truloff D. (2010). Safety of recombinant activated factor VII in randomized clinical trials. *New England Journal of Medicine*, 363(19), 1791–800. Erratum: **365**(20), 1944.

PART 2.7

Antimicrobial and immunological drugs

CHAPTER 53

Antimicrobial drugs in critical illness

A. P. R. Wilson and Preet Panesar

Key points

- Meningitis should be treated with cefotaxime or ceftriaxone +/– vancomycin.
- Piperacillin/tazobactam or ceftazidime are appropriate for treatment of ventilator-associated pneumonia more than 2 days after intubation.
- Meropenem or imipenem should be reserved for infections resistant to other agents and used first-line only when the risk of a multiresistant nosocomial infection is high.
- Teicoplanin is less likely to cause nephrotoxicity than vancomycin when used in combination with aminoglycoside.
- Some hospitals exclude cephalosporins and quinolones because of concern not to promote *C. difficile* infection, but a diversity of antibiotics is probably more effective.

Introduction

In critically-ill patients, the pharmacokinetic behaviour of many antibiotics is unpredictable, and clinical trials are difficult to perform and interpret. Antibiotic dose has to be modified repeatedly according to the observed renal or hepatic function. Pharmacodynamic factors are important, i.e. the rapidity of bactericidal effect, the post-antibiotic effect (the length of suppression of bacterial growth after antibiotic concentrations have fallen below inhibitory levels), and the serum half-life and tissue penetration of the antibiotic. The intravenous (iv) route is used because intramuscular administration is affected by changes in tissue perfusion. The penicillins, glycopeptides, and cephalosporins act against the cell wall of the organism and bacterial killing depends more on the time during which the minimum inhibitory concentration (MIC) is exceeded than the absolute tissue concentration, provided that the lowest concentration is at least four times the MIC. The aminoglycosides and quinolones require high peaks because bacterial killing depends on concentration rather than duration of exposure. The area under the curve of serum concentration (AUC) versus time and over the MIC (area under the inhibitory curve AUIC) can be used to predict efficacy: AUIC = (AUC0 – 24 hours)/MIC. The AUIC is predictive of bacterial eradication in vivo and hence pseudomonal pneumonia should be treated with a dose of 400 mg of ciprofloxacin every 8 hours and not 200 mg every 12 hours [1]. Vancomycin, teicoplanin, the aminoglycosides, the cephalosporins, and the penicillins are all excreted by the kidneys and will accumulate when creatinine clearance falls below 30 mL/min. Erythromycin, clindamycin, chloramphenicol, fusidic acid, and rifampin (rifampicin) are metabolized in the liver and, although safe in renal failure, should be avoided in liver failure. Clearance by haemodialysis or haemofiltration depends on the type of machine, the flow rates, and the duration [2]. Aminoglycoside and vancomycin dosage must be determined by serum assay. The cephalosporins are eliminated slowly, but dosage is usually reduced by at least half. The glycopeptides need only be given every 3–7 days after loading.

Empirical treatment

Antibiotic treatment should be started as soon as cultures have been taken, without waiting for the results to be reported. Treatment should be reviewed every 1–2 days and stopped at 5 days unless there is continuing sepsis. Maintaining a choice or diversity of empirical therapy or rotating antibiotic choice is used to delay the appearance of resistant strains [3].

Local susceptibility patterns should determine empirical antibiotic choice. For community-acquired infection, co-amoxiclav or a parenteral cephalosporin (cefuroxime, cefotaxime, ceftriaxone) are appropriate. For hospital-acquired infections, piperacillin/tazobactam, ciprofloxacin or ceftazidime can be used. For suspected vascular catheter infection or methicillin-resistant *Staphylococcus aureus* infection, teicoplanin or vancomycin should be used. Meropenem or imipenem should be reserved for second-line treatment if initial therapy fails. Table 53.1 shows the use and choice of antimicrobials in critical care [4–8].

Patients with febrile neutropenia will usually already be treated with antibiotics on arrival in ICU, usually piperacillin-tazobactam, meropenem, ceftazidime, or ciprofloxacin and, if catheter infection is suspected, a glycopeptide. Antifungals, usually caspofungin, fluconazole or liposomal amphotericin, are used if fungal infection is suspected, especially after 2–3 days antibacterial treatment.

Prophylaxis

For the prevention of surgical wound infection, sufficient antibiotic must be present in the tissue to kill the bacteria likely to contaminate the wound. Antibiotics given after surgery do not provide any additional benefit, and risk the emergence of resistance or acquisition of MRSA. For gut or respiratory tract procedures, a second generation cephalosporin and metronidazole is a common choice. Antibiotics for prophylaxis should be different from those used for treatment.

Table 53.1 Dosage, route of administration, adverse effects, contraindications [4–8]

Drug	Pathogen treated	Dose + route	Contraindications	Adverse effects
Benzylpenicillin (Penicillin G)	Streptococci, *N. meningitidis, C. perfringens, T. pallidum*	2.4–7.2g iv 4–6-hourly (up to 14.4g/day)	Penicillin allergy	Hypersensitivity, seizures with large doses in renal impairment
Flucloxacillin	*Staphylococcus aureus* (MSSA), *Streptococcus pyogenes*	1–2 g iv/po 4–6-hourly	Penicillin allergy Flucloxacillin-associated jaundice	Hypersensitivity, seizures, cholestatic jaundice with high dose and long course
Amoxicillin	Enterococci, *Listeria*, some Gram-negative species (mostly non-ICU)	1 g iv/po 6–8-hourly Meningitis/endocarditis: 2g IV 4–6-hourly	Penicillin allergy Glandular fever and lymphatic lymphoma	Hypersensitivity, maculopapular rash, seizures with large doses in renal impairment
Ampicillin	Enterococci, *Listeria*, some Gram-negative species (mostly non-ICU)	1–2 g iv 4–6-hourly	Penicillin allergy Glandular fever and lymphatic lymphoma	As for amoxicillin
Amoxicillin-clavulanate (co-amoxiclav)	*Escherichia coli*, *Klebsiella* spp., *Staph. aureus, Haemophilus influenzae, Neisseria gonorrheae*, and *Moraxella catarrhalis*	1.2 g iv 8-hourly	Penicillin allergy Penicillin-associated jaundice/hepatic dysfunction	As for other penicillins, cholestatic jaundice, maculopapular rash
Piperacillin-tazobactam	Gram-negative species including *Pseudomonas*, Enterococci	4.5 g iv 6–8-hourly	Penicillin allergy	As for other penicillins, risk of convulsions in renal impairment
Cefuroxime	*E. coli*, *Proteus* sp., *Klebsiella* sp., streptococci, and *Staph. aureus* (not MRSA)	750 mg–1.5g iv 6–8-hourly	Immediate and/or severe hypersensitivity reaction to β-lactam antibiotics	Risk of *C. difficile* infection, particularly in elderly
Cefotaxime	Gram-negative species, *Staph. aureus* streptococci, not enterococci	Up to 12 g daily in 3 or 4 divided doses	Immediate and/or severe hypersensitivity reaction to beta-lactam antibiotics	Risk of *C. difficile* infection, particularly in elderly
Ceftriaxone	Gram-negative species, *Staph. aureus*, streptococci, not enterococci	2–4 g iv 24-hourly	Immediate and/or severe hypersensitivity reaction to β-lactam antibiotics; Premature neonates with jaundice, hypoalbuminaemia	Risk of *C. difficile* infection, particularly in elderly, biliary obstruction, calcium ceftriaxone been mistaken for gallstones
Ceftazidime	Gram-negative species including *Pseudomonas*. Not enterococci	1–2 g iv 8-hourly	Immediate and/or severe hypersensitivity reaction to β-lactam antibiotics	Risk of *C. difficile* infection, particularly in elderly
Vancomycin	MRSA and other Gram-positive bacteria	Loading dose by weight: 1–2 g then 0.5–1.5 g iv 12–48-hourly by renal function Maintain trough level 10–15 mg/L (15–20 mg/L for less sensitive MRSA) *C. difficile*: 125 mg (up to 500mg) po qds 10–14 days	Care in renal insufficiency Avoid if previous hearing loss	Rapid infusion can cause flushing of the upper-body ('red-neck syndrome'), Nephrotoxicity, Ototoxicity
Teicoplanin	MRSA and other Gram-positive bacteria. VanB vancomycin-resistant enterococci	6 mg/kg iv 12-hourly for 3 doses, then 6 mg/kg 24-hourly 10–12 mg/kg for endocarditis/osteomyelitis	Caution in patients known to be hypersensitive to vancomycin	High doses can cause drug fevers and thrombocytopenia
Linezolid	MRSA, VRE, and other Gram positive bacteria	600 mg po/iv 12-hourly	Avoid concomitant use with MAOIs and SSRIs	Myelosuppression—monitor blood counts, serotonin syndrome, peripheral neuropathy, convulsions, optic neuritis

(*continued*)

Table 53.1 Continued

Drug	Pathogen treated	Dose + route	Contraindications	Adverse effects
Gentamicin	Gram-negative bacteria and staphylococci	Use ideal body weight for obese patients 1–1.5 mg/kg iv 8-hourly. Trough level <2 mg/L, peak level 5–10 mg/L or 7 mg/kg iv 24-hourly, but adjust by Hartford nomogram	Myasthenia gravis Keep duration as short as possible	Nephrotoxicity Ototoxicity
Amikacin	Gram-negative bacteria and staphylococci	15 mg/kg/day iv (max 1.5 g daily). Maintain trough <5 mg/L	Myasthenia gravis	Nephrotoxicity Ototoxicity
Imipenem/ cilastatin	Streptococci, staphylococci, *Pseudomonas* and other Gram-negative bacteria, and anaerobes; not MRSA or *Stenotrophomonas maltophilia*	500 mg–1 g iv 6–8-hourly	Hypersensitivity to any other β-lactam	Seizures with large doses in renal impairment
Meropenem	Streptococci, staphylococci, *Pseudomonas*, and other Gram-negative bacteria, and anaerobes; not MRSA or *Stenotrophomonas maltophilia*	500 mg–1 g iv 8-hourly Meningitis: 2 g iv 8-hourly	Hypersensitivity to any other β-lactam	Less potential to induce seizures than imipenem
Ciprofloxacin	*Pseudomonas* and other Gram-negative bacteria, limited staphylococci and streptococci	Oral: 500–750 mg 12-hourly iv: 200–400 mg 8–12-hourly	History of tendonitis Avoid in children, pregnant or breast-feeding women	Lowers seizure threshold, increases QT prolongation, hepatic failure reported, haemolysis in G6PD deficiency
Ofloxacin	*Pseudomonas* and other Gram-negative bacteria, limited staphylococci and streptococci	200 mg–400 mg IV / PO 12H	As for ciprofloxacin	As for ciprofloxacin
Erythromycin	Streptococci, *Corynebacterium diphtheriae, Staph aureus, Mycoplasma, Chlamydia, Legionella*	Oral or **Prokinetic**: 250–500 mg iv / PO 6H **iv**: 50 mg/kg/day (max 4g/day)	May aggravate myasthenia gravis Use with caution in patients with prolonged QT interval	Gastrointestinal upset, iv dosing can cause hearing disturbances
Clarithromycin	As erythromycin but better against *Haemophilus*	500 mg iv/po 12-hourly	As for erythromycin	As for erythromycin Less gastrointestinal adverse effects than erythromycin
Clindamycin	Anaerobes, staphylococci, streptococci. With primaquine, Pneumocystis	**po:** 300–450 mg 6-hourly **IV:** 600 mg–4.8 g/day in 2–4 divided doses		Risk of pseudomembraneous colitis
Co-trimoxazole (trimethoprim/ sulfamethoxazole)	Staphylococci, streptococci, Gram negative bacteria, *Pneumocystis*, not pseudomonas or anaerobes	**PCP**: 120 mg/kg daily in 3–4 divided doses for 3 days, then 90 mg/kg/day in 3–4 divided doses for 18 days	Avoid in liver parenchymal damage	Thrombocytopenia Skin rash Haemolysis in G6PD deficiency
Chloramphenicol	Gram positive and negative bacteria, anaerobes, Rickettsia, not Pseudomonas	12.5 mg/kg po/iv 6-hourly	Monitor levels in neonates, <4 years of age, elderly, and in renal and hepatic impairment	Bone marrow depression Optic and peripheral neuritis 'Grey syndrome' in infants and neonates
Sodium fusidate	*Staph aureus* (in combination)	500 mg iv/po 8-hourly	Regular monitoring of liver function	Pancytopenia Hepatotoxicity with iv

Doxycycline	Gram positive and negative bacteria, Lyme, Rickettsia	200 mg po on first day, then 100 mg po 12-hourly	Avoid in pregnancy, breast feeding and <12 years	Photo sensitivity
Metronidazole	Anaerobes, Giardia, Amoebae, parasites	**Oral**: 400 mg 8-hourly **iv**: 500 mg 8-hourly	Avoid in acute porphyria Disulfiram-like reaction with alcohol	Taste disturbances Peripheral neuropathy with prolonged therapy (>2 weeks)
Rifampicin	Staphylococci, corynebacteria, *Moraxella, Legionella*, M tuberculosis	**po**: 450–600 mg 24-hourly **iv**: 0.6–1.2 g iv daily in 2–4 divided doses	Jaundice Concurrently receiving saquinavir/ritonavir therapy	Hepatitis, flu-like syndrome, reddish colour of urine, sweat, sputum, and tears
Isoniazid	*M tuberculosis* and other mycobacteria	300 mg po 24-hourly	Drug-induced liver disease	Peripheral neuropathy Hepatitis
Pyrazinamide	*M. tuberculosis* and other mycobacteria	<50 kg–1.5 g po 24-hourly >50 kg–2 g po 24-hourly	Avoid in acute porphyria	Can precipitate gout, hepatotoxicity, rash, and photosensitivity
Ethambutol	*M tuberculosis* and other mycobacteria	15 mg/kg po/iv 24-hourly	Optic neuritis, poor vision	Optic neuritis and colour blindness, peripheral neuritis
Streptomycin	*M. tuberculosis* and other mycobacteria	15–20 mg/kg/day im (max 1 g per day)	Avoid in myasthenia gravis	Nephrotoxicity, ototoxicity, rash
Liposomal amphotericin	*Candida, Cryptococcus*, Histoplasma, *Aspergillus*, Leishmaniasis, not *C tropicalis*	Test dose 1 mg over 10 minutes, then 3 mg/kg iv 24-hourly (max 5 mg/kg—unlicensed)	Anaphylaxis reported so test dose recommended	Fever and chills/rigors, renal impairment, electrolyte disturbances
Caspofungin	*Candida; Aspergillus* (if not responded to other antifungals)	**<80 kg**: 70 mg iv on 1st day, then 50 mg iv 24-hourly **>80 kg**: 70 mg iv 24-hourly		Rash, pruritus, or bronchospasm Hepatitis
Fluconazole	*Candida, Cryptococcus*	400 mg iv on 1st day, then 200–400 mg iv 24-hourly (max 800 mg iv 24-hourly)	Acute porphyria	Hepatotoxicity Increased risk of QT prolongation
Voriconazole	*Aspergillus, Candida, Fusarium*	**po:** >40 kg—400 mg 12-hourly for 2 doses then 200 mg 12-hourly; <40kg—200 mg 12-hourly for 2 doses then 100 mg 12-hourly. **iv:** 6 mg/kg 12-hourly for 2 doses, then 4 mg/kg 12-hourly	Acute porphyria, avoid iv in renal impairment as increased risk of convulsions	Increased risk of QT prolongation, hepatotoxicity, blurred vision and optic neuritis, exfoliative cutaneous reactions, bone marrow depression
Aciclovir	*Herpes simplex, Varicella zoster*, not CMV	5 mg/kg iv 8-hourly (10 mg/kg in immunocompromised and encephalitis)		Adequate hydration of the patient should be maintained
Ganciclovir	CMV	5 mg/kg iv 12-hourly for 14–28 days	Potential carcinogen and teratogen—avoid in pregnancy and lactation	Bone marrow depression
Foscarnet	CMV, *Herpes simplex*	CMV disease 90 mg/kg iv 12-hourly 14–28 days	Pregnancy and lactation	Nephrotoxicity, electrolyte disturbances, rash
Oseltamivir	Influenza A and B	75 mg po 12-hourly for 5 days		Headaches and vomiting usually resolve after 1–2 days
Zanamivir	Influenza A and B	IV: 600 mg iv 12-hourly for 5 days (unlicenced) Inhaled: 10mg inh 12-hourly for 5 days	Risk of bronchospasm in asthma / COPD	Neuropsychiatric events especially in children and adolescents

iv, intravenous; po, oral; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor.

Data from Electronic Medicines Compendium. Available at: http://www.medicines.org.uk/EMC (accessed 15 May 2012); British National Formulary, Mar 2012; No. 63 Available at: http://www.medicinescomplete.com/mc/bnf/current/index.htm (accessed 15 May 2012); Shulman R et al., 'UKCPA Antiviral management of influenza A (H1N1) in critical care', UKCPA Critical Care Group, vers 5. Dec 2011; British HIV Association and British Infection Association, 'Guidelines for the treatment of Opportunistic Infection in HIV-seropositive individuals', *HIV Medicine*, 2011, **12**(Suppl. 2), pp. 1–5; and Thomson AH et al., 'Development and evaluation of vancomycin dosage guidelines designed to achieve new target concentrations', *Journal of Antimicrobial Chemotherapy*, 2009, **63**, pp. 1050–7.

Penicillins

The penicillins interrupt bacterial cell wall synthesis and are bactericidal. They penetrate well and reach high concentrations in the urine and the lung. Penicillin G (benzylpenicillin) is quickly excreted and another dose is needed after 4 hours. Allergic reactions develop in up to 10% of patients and can include drug-induced fever. Interstitial nephritis is suggested by a raised eosinophil count. High doses given to patients with meningitis and severe renal failure risk the development of seizures. Isoxazoyl penicillins (oxacillin, nafcillin, flucloxacillin, cloxacillin) have a synergistic interaction with aminoglycosides and are used to treat penicillin-resistant staphylococci. Methicillin-resistant *Staph. aureus* (MRSA) infections must be treated with glycopeptides. Hepatitis or cholestatic jaundice can occur during prolonged use of penicillins. Supplemental doses are required after haemodialysis. Amoxicillin has a longer half-life than ampicillin. Allergic reactions, particularly rash, are common. Co-amoxiclav is a combination of amoxicillin and clavulanic acid, which prevents the action of ß-lactamase. *Pseudomonas* species are resistant. It can be used as an alternative to cefuroxime in most infections and produces high urinary concentrations [9]. Ticarcillin–clavulanic acid is a similar combination agent with activity against some strains of *Pseudomonas* species.

Piperacillin is usually given in combination with a ß-lactamase inhibitor tazobactam. Piperacillin–tazobactam is a common choice in hospitals where cephalosporins and quinolones are discouraged, and is used in intra-abdominal (e.g. biliary) infections, respiratory or urinary infections, and septicaemia. Temocillin is increasingly used instead of carbapenem as it active against some beta-lactamase producing Gram-negative bacteria (except *Pseudomonas*).

Cephalosporins

The cephalosporins have relatively low toxicity and a broad spectrum. They inhibit bacterial cell wall synthesis. They are not effective against enterococci or methicillin-resistant staphylococci. Cephalosporins are frequently used in surgical prophylaxis and may be given in combination with gentamicin in bacteraemic shock. However, its popularity has declined as overuse in some hospitals has been linked to the emergence of MRSA and *Clostridium difficile* infections. Cefuroxime can be used in abdominal wound infections (with metronidazole) or orbital cellulitis. Pyelonephritis can be effectively treated by cefuroxime, cefotaxime, or ceftriaxone without an aminoglycoside. Vomiting and allergic reactions are the most common adverse effects. Oral (po) cephalosporins have poor activity against Gram-negative bacteria and are not po equivalents of cefuroxime. They should only be used for infections that do not respond to cheaper agents. Cefuroxime is used in a wide range of community-acquired or post-surgical infections. It is not recommended in meningitis. Thrombophlebitis and hypersensitivity are the only common adverse effects. Cefotaxime or ceftriaxone are given as empirical treatment of meningitis. Ceftriaxone is reduced in dosage only in severe renal failure or if there is liver and renal impairment. It is highly concentrated in bile and can produce biliary sludge, causing abdominal pain and vomiting. Ceftazidime penetrates the lung well and is commonly used in the treatment of ventilator-associated pneumonia, provided that staphylococcal pneumonia is excluded. It is used to treat febrile episodes in neutropenic patients and pseudomonal urinary infections.

Glycopeptides

Vancomycin and teicoplanin are the agents of first choice to treat infections caused by MRSA. Both are excreted by the kidneys and dosage reduction is necessary. Oral vancomycin (125 mg every 6 hours for 10 days) is used to treat antibiotic-associated colitis. Teicoplanin can be given iv as a bolus dose, but vancomycin requires a slow infusion over 1 hour to avoid flushing and hypotension. Teicoplanin has a longer half-life, allowing od doses. Neither reliably penetrates the cerebrospinal fluid. Fever in neutropenic patients is treated with glycopeptides when there is evidence of catheter infection or failure of empirical treatment. Vancomycin concentrations in serum can be monitored to maintain troughs of 10–15 mg/L to ensure a therapeutic level and avoid nephrotoxicity, particularly when used in combination with aminoglycosides. Teicoplanin does not require monitoring for toxicity, but to ensure therapeutic levels, for example, in staphylococcal endocarditis, when the trough should be over 20 mg/L, in renal failure, and in drug abusers. Ototoxicity and nephrotoxicity are rare using vancomycin alone, but there is a synergistic effect when it is combined with an aminoglycoside. Both glycopeptides can cause a rash.

Aminoglycosides

Aminoglycosides are bactericidal agents that bind to bacterial ribosomes. They are synergistic in combination with penicillins except when there is high-level resistance. Penetration into the lung is poor, but they are well concentrated in the urine. Their use is limited by nephrotoxicity and ototoxicity. Serum concentrations have to be assayed daily in the ICU to determine dosage. A course should be up to 3–5 days; longer courses should only be used exceptionally (e.g. endocarditis). In patients with normal renal function, administration of a large single daily dose (7 mg/kg) has been found to reduce toxicity without affecting efficacy [10]. A single assay is taken 6–14 hours after the dose to determine the next dosage interval. Aminoglycosides are used in severe infections when resistance to penicillins or cephalosporins is likely. Amikacin can be used in gentamicin-resistant infections.

Carbapenems

Imipenem is a carbapenem antibiotic with an extremely broad spectrum of activity. It is combined with cilastatin, which is an inhibitor of dehydropeptidase, an inactivating enzyme of the renal brush border, which ensures adequate urinary concentrations. Meropenem has similar activity, but does not require an enzyme inhibitor. The carbapenems are inducers of ß-lactamase and should not be combined with other ß-lactams. Penetration is good into most tissues. Excretion is predominantly renal. Bacteraemia, severe respiratory or urinary infections, febrile neutropenic episodes, and abdominal sepsis are common indications. Nausea and vomiting are common and fits develop in 1% of patients given imipenem. Patients allergic to penicillins may be allergic to carbapenems. Superinfection with resistant pseudomonads or fungi can develop.

Fluoroquinolones

Ciprofloxacin, levofloxacin, and ofloxacin are available for po or iv use. However, resistance is increasing, particularly in *Pseudomonas aeruginosa* and MRSA. Like the cephalosporins, some hospitals have

withdrawn them in the belief that avoidance will reduce *C. difficile* and MRSA rates. They inhibit bacterial DNA gyrase and are bactericidal. Excretion is via the kidney. They are used to treat complicated urinary infections and prostatitis, but should be avoided for community-acquired pneumonia. They are first-line agents in severe *Salmonella* and *Shigella* infections. Osteomyelitis and soft tissue infections caused by Gram-negative bacteria, and gonorrhoea are other indications. Gastrointestinal symptoms, rash, and occasionally convulsions occur. Quinolones are not recommended in children, unless there is no alternative, because of their potential effect on growing cartilage.

Macrolides

Erythromycin acts on protein synthesis at the ribosome. Erythromycin is excreted by the liver and should be avoided in severe liver disease. It is used in the treatment of mycoplasmal and chlamydial pneumonia, legionnaires' disease, whooping cough, diphtheria, and *Campylobacter* infections. Nausea and vomiting are common adverse effects. Cholestatic jaudice (with estolate) and reversible ototoxicity are reported. Clarithromycin and azithromycin are used in respiratory tract and sexually-transmitted infections. Gastrointestinal symptoms are less common than with erythromycin.

Clindamycin

Clindamycin inhibits ribosomal protein synthesis. Clindamycin penetrates tissues well, particularly bone and pleural fluid (but not the meninges) and is excreted by the liver. The dose should be reduced in liver failure. It is an alternative to metronidazole for abdominal sepsis and is used to treat osteomyelitis aspiration pneumonia and lung abscess. Necrotizing fasciitis and other severe infections caused by *Streptococcus pyogenes* can be treated with clindamycin. Diarrhoea is a well-recognized adverse effect.

Chloramphenicol

Chloramphenicol has a very wide spectrum of activity. It penetrates well into most tissues and is metabolized in the liver. Reversible bone marrow suppression can develop at dose of 4 g/day or on long courses. Serum concentrations should be measured in the very young and should not rise above 20 mg/L to avoid gray baby syndrome (vomiting, cyanosis, collapse). In rare cases (1 in 30,000) a fatal aplastic anaemia develops. The principle uses of chloramphenicol are treatment of meningitis in patients allergic to cephalosporins, brain abscess, and rickettsial infection.

Trimethoprim and trimethoprim-sulfamethoxazole (co-trimoxazole)

Trimethoprim and sulfamethoxazole act at different parts of the same pathway of synthesis of bacterial folate. Their long half-lives allow both to be given at 12-hour intervals. Trimethoprim can be used for urinary tract infections, but in hospital-acquired infections susceptibility needs first to be demonstrated. Rash, nausea, vomiting, and diarrhoea are common, and occasionally Stevens–Johnson syndrome occurs. Administration in pregnancy is contraindicated.

Tetracyclines

Tetracyclines are bacteriostatic antibiotics with a wide bacterial spectrum, but resistance is common. They are an alternative treatment for atypical pneumonia. Doxycycline has the longest half-life and is the only one that can be used in renal failure. Tetracyclines interfere with growth and development of bone, and must not be given in pregnancy or to children under 8 years old.

Metronidazole

Metronidazole is as well absorbed by the po or rectal route as by iv route. It should not be used in pregnancy. It is used to treat anaerobic bacteraemia, intra-abdominal sepsis, and brain abscess. Aspiration pneumonia can be treated by metronidazole with a cephalosporin, or clindamycin. Oral metronidazole is used to treat mild to moderate antibiotic-associated colitis. The dose should be reduced in severe renal or hepatic failure. Peripheral neuropathy may develop during prolonged courses.

Rifampin

Rifampin is a bactericidal antibiotic, which inhibits protein synthesis by binding RNA polymerase. Resistance will emerge rapidly if it is used in isolation. It is a first-choice agent in treating tuberculosis and *Mycobacterium avium intracellulare* complex disease. In staphylococcal endocarditis, rifampin may be used in combination with a glycopeptide with or without an aminoglycoside. Fever, rash, and hepatotoxicity are the most important adverse effects. The antibiotic antagonizes the effects of warfarin, cyclosporin, verapamil, and po hypoglycaemics.

Other antituberculosis agents

Isoniazid is metabolized in the liver and dosage is not reduced in renal failure. Hepatitis occurs in 1% of patients, but peripheral neuropathy can be prevented by giving pyridoxine. Pyrazinamide is often combined with rifampin and isoniazid. It is given po and can be used to treat meningitis. Hepatotoxicity can occur. Ethambutol is bacteriostatic and is widely distributed after po administration. The dose is reduced in renal failure. Optic neuritis (loss of colour vision) is an important adverse effect, which prevents its use in the unconscious. Streptomycin, like other aminoglycosides, is ototoxic and nephrotoxic, and serum levels must be assayed.

Antifungals

Amphotericin B

Amphotericin B remains the most common choice for the treatment of systemic fungal infection. It is a polyene, which acts by increasing the permeability of the fungal cell membrane. It is highly tissue bound, particularly in the liver, spleen, kidney, and lung. No dose modification is necessary in renal or hepatic failure. Amphotericin B is not removed by haemodialysis. Amphotericin is often used to treat acute cryptococcal meningitis. Adverse effects are renal failure, fever, chills, headache, hypotension, phlebitis, hypokalaemia, anaemia, and hepatitis. Liposomal, lipid complex, and colloidal dispersion amphotericin B have been produced to reduce toxicity. High doses can be given safely, but they are less potent than the original preparation.

Caspofungin

Echinocandins such as caspofungin are indicated in treatment of invasive candidiasis and *Aspergillus* if refractory or intolerant to amphotericin. They are not effective in fungal meningitis.

Imidazoles and triazoles

Voriconazole is the treatment of choice for aspergillosis, including central nervous system infection. Miconazole, ketoconazole, fluconazole, and itraconazole are active against most fungi except *Aspergillus* species. They act by inhibiting the production of the fungal cell membrane. Fluconazole is well absorbed po and can be given iv. Its long half-life allows od dosing. It penetrates most tissues and is excreted renally, largely unchanged. Dosage must be reduced in renal failure. Adverse effects are rare. It is highly effective in mucosal candidiasis. Itraconazole is given po and is distributed throughout the body except the cerebrospinal fluid. It is used to treat histoplasmosis, paracoccidiodomycosis, and blastomycosis, and can be given to patients with invasive aspergillosis in the presence of immune suppression.

Antivirals

Aciclovir

Aciclovir is an analog of guanosine. The iv route is most reliable and it is distributed to all tissues including the meninges. Aciclovir is excreted by the kidneys and dose reduction is necessary in renal failure, although it is removed by haemodialysis. For the immune-suppressed patient, aciclovir prevents dissemination and reduces shedding. It is effective in the treatment of herpes simplex encephalitis. Chickenpox in adults should be treated with aciclovir to reduce the morbidity associated with pneumonia. Phlebitis, reversible renal impairment, and elevation of transaminases are minor side-effects.

Foscarnet

Foscarnet is used to treat herpetic infection that does not respond to aciclovir. It is nephrotoxic.

Ganciclovir

Ganciclovir is usually administered parenterally and penetrates the lung and liver. Dose should be reduced in renal failure, but it is removed by haemodialysis. Ganciclovir is used to treat cytomegalovirus retinitis in AIDS patients and is also effective in cytomegalovirus gastrointestinal disease. The presence of cytomegalovirus in the lungs of AIDS patients may not be the cause of clinical disease and is usually not treated. Myelosuppression is common, and mucositis, fits, and rash can occur.

Oseltamavir and zanamivir

These agents inhibit viral neuraminidase of influenza A and B. They should be used within 48 hours of onset of symptoms to reduce the risk of complications in the elderly or those with chronic underlying illness.

References

1. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, and Schentag JJ. (1993). Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrobial Agents and Chemotherapy*, **37**, 1073–81.
2. Choi G, Gomersall CD, Tian Q, Joynt GM, Freebairn R, and Lipman J. (2009). Principles of antibacterial dosing in continuous renal replacement therapy. *Critical Care Medicine*, **37**, 2268–82.
3. Sandiumenge A, Diaz E, Rodriguez A, et al. (2006). Impact of diversity of antibiotic use on the development of antimicrobial resistance. *Journal of Antimicrobial Chemotherapy*, **57**, 1197–204.
4. Electronic Medicines Compendium. Available at: http://www.medicines.org.uk/EMC (accessed 15 May 2012).
5. British National Formulary (2012). No. 63 Available at: http://www.medicinescomplete.com/mc/bnf/current/index.htm (accessed 15 May 2012).
6. Shulman R, Thacker M, O'Farrell B, Kidd IM, and Borthwick M. (2001). UKCPA Antiviral management of influenza A (H1N1) in critical care. UKCPA Critical Care Group, vers 5. Dec 2011.
7. British HIV Association and British Infection Association. (2011). Guidelines for the treatment of opportunistic infection in HIV-seropositive individuals. *HIV Medicine*, **12**(Suppl. 2), 1–5.
8. Thomson AH, Staatz CE, Tobin CM, Gall M, and Lovering AM. (2009). Development and evaluation of vancomycin dosage guidelines designed to achieve new target concentrations. *Journal of Antimicrobial Chemotherapy*, **63**, 1050–7.
9. Neu H, Wilson APR, and Grüneberg RN. (1993). Amoxicillin/clavulanic acid: a review of its efficacy in over 38 500 patients from 1979 to 1992. *Journal of Chemotherapy*, 5, 67–93.
10. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, and Quintiliani R. (1995). Experience with a once daily aminoglycoside program administered to 2184 adult patients. *Antimicrobial Agents and Chemotherapy*, 39, 650–5.

CHAPTER 54

Steroids in critical illness

Didier Keh

Key points

- Critical illness-related corticosteroid insufficiency (CIRCI) is caused by adrenal insufficiency and tissue corticosteroid resistance. It is characterized by insufficient corticosteroid effect to counterbalance an exaggerated and protracted pro-inflammatory response.
- Moderate-dose hydrocortisone should be considered in severe septic shock with poor response to fluid and vasopressor therapy. Shock resolution is earlier and survival probably improves in patients with high risk of death.
- The indication for use should be based on clinical judgement and not on cortisol measurements.
- A continuous infusion and slow weaning from corticosteroids may be preferable to bolus applications and abrupt withdrawal to avoid side effects, such as rebound of inflammation and shock, glucose variability, or respiratory failure.
- There is some evidence of beneficial effect with prolonged moderate-dose methylprednisolone in early severe acute respiratory distress syndrome (ARDS), but further studies are needed for confirmation.

Introduction

The role of corticosteroids in systemic inflammatory diseases such as sepsis and/or acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is unclear. There is consensus that short therapy with high doses (up to 42 g hydrocortisone equivalent/day) is harmful. The benefit of prolonged use of moderate doses (200–300 mg/day hydrocortisone or 1–2 mg/kg/day methylprednisolone) remains controversial.

In response to inflammation, the hypothalamic-pituitary-adrenal (HPA) axis is stimulated to release cortisol (hydrocortisone), which protects against exaggerated inflammation. Cortisol or exogenous glucocorticoids activate cytoplasmic glucocorticoid receptors (GR), which positively or negatively regulate transcription of proteins (genomic effect), or modulate immune responses by non-genomic pathways, e.g. induction of endothelial nitric oxide production [1]. Glucocorticoids can attenuate inflammation very effectively by inhibition of nuclear factor kappa B (NF-κB), which regulates multiple cytokines, chemokines, adhesion molecules, effector cells, and other mediators.

In critical illness, the HPA-axis may become dysregulated. Triggered by cytokines and toxins, cortisol release and function may be impaired due to reduced corticotropin release, adrenal dysfunction, or resistance to corticosteroids. It has been recommended to describe the dysfunction of the HPA-axis as critical illness-related corticosteroid insufficiency (CIRCI), and to avoid terms like absolute or relative adrenal insufficiency [2]. The latter was used in patients with septic shock to describe poor adrenal response to 250 μg corticotropin stimulation [3,4]. Currently, the best cut-offs for diagnosis of adrenal dysfunction, which was found in about 60% of patients with severe sepsis and septic shock, are a delta cortisol <9 μg/dL ('non-responders') or a random total cortisol <10 μg/dL [2]. However, measuring cortisol is currently not recommended to define eligible patients for corticosteroid therapy [2,5]. There is uncertainty about assay-variability to measure cortisol in septic serum, or to define valid cut-offs for free (biological active) cortisol in the critical ill. CIRCI is not restricted to adrenal dysfunction, but describes an insufficient GR-mediated down-regulation of pro-inflammatory transcriptions factors, such as NF-kB, resulting in persistent inflammation. CIRCI may be transient during critical illness, caused by insufficient cortisol availability or resistance to corticosteroids due to fewer or low-affinity of GR-receptors, as known from chronic inflammatory diseases (e.g. chronic obstructive pulmonary disease). It has been postulated that the acute inflammation-induced resistance to glucocorticoids may be reversed by quantitatively adequate and prolonged glucocorticoid supplementation [2].

There is concern that moderate-dose corticosteroids suppress the immune system beyond the desired attenuation of inflammation. Currently, there is no evidence from immune-monitoring studies for severe immunosuppression or immunoparalysis. There is some evidence that moderate doses in acute systemic inflammation immunomodulating features. In septic shock, hydrocortisone was found to decrease pro-inflammatory interleukin 6 and 8, and inducible nitric oxide synthesis, but did not increase anti-inflammatory interleukin 10, or suppressed HLA-DR on monocytes (antigen presentation) [6]. There is also evidence from in vitro and in vivo studies that moderate doses support innate immune responses and improve opsonisation [2].

Uses

Sepsis

Based primarily on two larger randomized controlled trials, hydrocortisone should be considered only in adult septic shock patients who respond poorly to fluid resuscitation and vasopressor therapy [2,5].

In the French study (n = 299) a significant reduction of 28-day mortality (53% versus 63%, p = 0.04) was observed in

non-responders, but not in responders or in the whole population [3]. Similarly, a significantly faster shock resolution of about 3 days was observed in non-responders.

In the CORTICUS study (n = 499) there was no significant difference of 28-day mortality in the whole group treated with hydrocortisone or placebo (34 versus 32%), in non-responders (39 versus 36%), or in responders (29 versus 29%) [4]. There was a significantly faster shock resolution of about 2.5 days, but in contrast to the French study, irrespective of adrenal dysfunction.

There had been differences between both studies.: In the French trial, patients had a higher mortality in the control group (61 versus 31%), and a higher severity of septic shock. A post-hoc subgroup analysis of CORTICUS patients with similar shock severity revealed a comparable 11% reduction of 28-day mortality. The additional use of fludrocortisone had no effect on mortality in a recent trial [7].

In a meta-analysis of six studies (n = 965) in patients with septic shock, prolonged use of moderate-dose hydrocortisone did not reduce 28-day mortality (relative risk: 0.92, 95% CI, 0.79–1.06, p = 0.25). However, shock was reversed until day 7, irrespective of response to corticotropin stimulation (relative risk: 1.39, 95% CI, 1.24–1.55, $p < 0.0001$) [2]. In another meta-analysis of 12 studies (n = 1228), including patients with severe sepsis, 28-day mortality was reduced in patients who received prolonged moderate-dose corticosteroids (relative risk: 0.87, 95% CI, 0.77–0.98, p = 0.02). Survivors had a shorter length of stay in the intensive care unit (ICU) of about 4.5 days when treated with moderate-dose corticosteroids. Although the combined data suggest possible beneficial effects in severe sepsis, heterogeneity of study populations, small patient numbers in single studies, and different trial designs limit generalization. Due to lack of data from larger randomized controlled trials, use of hydrocortisone is currently not recommended for the treatment of patients with severe sepsis without shock [2,5].

ALI/ARDS

Moderate-dose glucocorticoids have been considered as a management strategy in early severe ARDS (PaO_2/FiO_2 < 200) and before day 14 in unresolving ARDS [2]. In a study of late (>7 days) ARDS (n = 180), 60-day-mortality was not reduced by 2 mg/kg/day methylprednisolone (both groups about 29%). However, patients treated before day 14 had a shorter time on mechanical ventilation and reduced mortality (36 versus 27%) [8]. In another study with early (<72 hours) ARDS (n = 91), patients treated with 1 mg/kg/day methylprednisolone had significantly improved lung function and significantly more ventilator-free days, shorter ICU stay, and reduced ICU-mortality (21 versus 43%) [9]. Combined data from five trials (n = 518) showed an improvement of lung function and reduction of ICU stay. Patients treated before day 14 and for at least 7 days had about 5–6 more ventilator-free days, and a significantly reduced mortality (relative risk; 0.62 95% CI, 0.43–0.90, p = 0.01) [2]. Another meta-analysis included four randomized controlled trials (n = 341) and 5 cohort studies (n = 307) of patients with ALI/ARDS [10]. There was a significant reduction of mortality in pooled data (relative risk: 0.62 95% CI, 0.43–0.91, p = 0.01), but not when cohort and randomized studies were analysed separately. Cohort studies had a higher weight on mortality reduction. There was a consistent improvement of lung function and reduction of organ dysfunction, duration of mechanical ventilation and ICU stay. Taken all together, there is evidence of beneficial effects of moderate-dose steroids in ALI/ARDS, but high heterogeneity of studies, small sample sizes, and subgroup analyses limit a definite conclusion. There is a need for confirmatory trials in early ALI/ARDS.

There are preliminary data suggesting beneficial effects of prolonged use of moderate doses of hydrocortisone in severe community-acquired pneumonia, liver failure, pancreatitis, cardiopulmonary bypass, weaning from mechanical ventilation, severe head injury, and trauma, however, further studies are needed for confirmation [2,11].

Dosages

In patients with septic shock, hydrocortisone should be given in a dose of 200 mg/day in four divided doses or as a bolus of 100 mg, followed by a continuous infusion at 10 mg/hour (240 mg/day), and for at least 7 days before tapering [2]. Although treatment for more than 1 week may be justified following the concept of ongoing inflammation, there is no experience from larger studies in patients with septic shock. With regard to side effects, a continuous infusion and tapering with stepwise reduction every 2–3 days seem preferable; if the clinical situation deteriorates due to tapering, increasing the dose again should be considered.

The best time to start therapy is uncertain. With regard to attenuation of inflammation, early therapy would be obvious. Interestingly, the time window until use of hydrocortisone was much shorter in the French trial (8 hours) [3] than in the CORTICUS trial (72 hours) [4]. In a recent cohort study, there was a significant difference in 28-day mortality between patients treated with hydrocortisone within 6 hours after onset of septic shock, compared with later therapy (32 versus 51%, p = 0.013) [12].

In patients with early ARDS, 1 mg/kg/day methylprednisolone as a continuous infusion for at least 14 days followed by slowly tapering is currently regarded as the optimal treatment procedure [2]. The recommendation is based on a study in which patients with ARDS received the aforementioned dosage early (<72 h) until day 14 followed by tapering up to day 28 [9].

Routes of administration

In critically-ill patients, glucocorticoids should be administered intravenously, either via a central catheter or peripheral access. Fludrocortisone has to be administered orally.

Side effects

Secondary infections

High doses of corticosteroids should be avoided since several trials have shown they were ineffective, harmful, or increased the risk of secondary infections in patients with septic shock, ALI/ARDS, pneumonia, or severe head injury [2,5,13,14].

Evaluating the risk of moderate doses is more challenging. A higher number of secondary infections, including new sepsis and septic shock in the analysis, was reported in the CORTICUS study (33 versus 26%; relative risk 1.27, 95% CI, 0.96–1.68) [4]. In other studies, patients with septic shock [3] and/or ALI/ARDS [8,9] had (significantly) less secondary infections when treated with corticosteroids. Four meta-analyses concluded moderate-dose corticosteroids did not increase the risk in severe

sepsis/septic shock [15], pneumonia or ALI/ARDS [10,13], and one Bayesian analysis of patients with septic shock described an increased risk [16]. Notably, in a trial with hospital-acquired pneumonia as the primary endpoint, patients with severe trauma who received hydrocortisone had a decreased risk of pneumonia (35.6 versus 51.3%; hazard ratio 0.51, 95% CI, 0.30–0.83, $p = 0.007$) [11]. There is currently no clear evidence that moderate-dose corticosteroids increase the risk of secondary infections. However, infection surveillance should be intensified when patients are treated with steroids [2].

Critical-illness polyneuromyopathy

Corticosteroids are often cited to induce critical-illness polyneuromyopathy (CIPNM), which may lead to weaning failure and prolonged mechanical ventilation. In a systematic review of 24 studies, the main risks factors for CIPNM were sepsis, multiple organ failure, and protracted mechanical ventilation (immobilization), but not corticosteroids [17]. Several studies in patients with ALI/ARDS [8–10] or trauma [11] reported more rapid ventilator-weaning with moderate-dose corticosteroids. That muscle weakness may be triggered by systemic inflammation is supported by the observation of high interleukin-6 levels as a risk factor for early myopathy [18]. A higher risk for muscle weakness was reported when patients with ARDS were treated late with higher doses than those currently recommended [8]. Overall, there is currently no clear evidence that early-administered moderate-dose corticosteroids induce CIPNM, whether inhibition of inflammation is protective requires further investigation. Notably, none of the recent studies emphasized CIPNM as a major outcome measure, probably underestimating the incidence of CIPNM. The combination of muscle relaxants and corticosteroids was associated with an increased risk of muscle weakness and should be avoided [2].

Other side effects

Moderate-dose corticosteroids may increase the risk of hyperglycaemia (relative risk 1.16, 95% CI, 1,07–1.25, $p < 0.001$) [15]. Beside the absolute glucose value, glucose variability gains increasing attention as a risk factor for mortality. A continuous infusion of corticosteroids may be advantageous to repetitive bolus applications, which were associated with more glucose undulation and staff workload to maintain an aspired glucose level [19,20]. Due to the intrinsic mineralocorticoid activity of hydrocortisone, there is an increased risk for hypernatraemia (relative risk 1.61, 95% CI, 1.26–2.06, $p < 0.001$) [15]. Abrupt cessation of corticosteroids may produce immunologic (inflammation) and haemodynamic (shock) rebound effects [6], and the need of re-intubation due to respiratory failure [2,8]. The risk of gastrointestinal bleeding is not increased [15].

References

1. Rhen T and Cidlowski JA. (2005). Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. *New England Journal of Medicine*, **353**(16), 1711–23.
2. Marik PE, Pastores SM, Annane D, et al. (2008). Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Critical Care Medicine*, **36**(6), 1937–49.
3. Annane D, Sebille V, Charpentier C, et al. (2002). Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *Journal of the American Medical Association*, **288**(0098–7484), 862–71.
4. Sprung CL, Annane D, Keh D, et al. (2008). Hydrocorticone therapy for patients with septic shock. *New England Journal of Medicine*, **358**(1533–4406) (Electronic), 111–24.
5. Dellinger RP, Levy MM, Rhodes A, et al. (2012). Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Medicine*, **39**, 165–228.
6. Keh D, Boehnke T, Weber-Carstens S, et al. (2003). Immunologic and hemodynamic effects of 'low-dose' hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *American Journal of Respiratory Critical Care Medicine*, **167**(1073–449X), 512–20.
7. COIITSS Study Investigators, Annane D, Cariou A, et al. (2010).Corticosteroid treatment and intensive insulin therapy for septic shock in adults: A randomized controlled trial. *Journal of the American Medical Association*, **303**(4), 341–8.
8. Steinberg KP, Hudson LD, Goodman RB, et al. (2006). Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *New England Journal of Medicine*, **354**(1533–4406), 1671–84.
9. Meduri GU, Golden E, Freire AX, et al. (2007). Methylprednisolone infusion in early severe ARDS: Results of a randomized controlled trial. *Chest*, **131**(0012–3692), 954–63.
10. Tang BM, Craig JC, Eslick GD, Seppelt I, and McLean AS. (2009). Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. *Critical Care Medicine*, **37**(5), 1594–603.
11. Roquilly A, Mahe PJ, Seguin P, et al. (2011). Hydrocortisone therapy for patients with multiple trauma: the randomized controlled HYPOLYTE study. *Journal of the American Medical Association*, **305**(12), 1201–9.
12. Park HY, Suh GY, Song JU, et al. (2012). Early initiation of low-dose corticosteroid therapy in the management of septic shock: a retrospective observational study. *Critical Care*, **16**(1), R3.
13. Lamontagne F, Briel M, Guyatt GH, Cook DJ, Bhatnagar N, and Meade M. (2010). Corticosteroid therapy for acute lung injury, acute respiratory distress syndrome, and severe pneumonia: A meta-analysis of randomized controlled trials. *Journal of Critical Care*, **25**(3), 420–35.
14. Roberts I, Yates D, Sandercock P, et al. (2004). Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet*, **364**(1474–547X), 1321–8.
15. Annane D, Bellissant E, Bollaert PE, et al. (2009). Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *Journal of the American Medical Association*, **301**(22), 2362–75.
16. Kalil AC and Sun J. (2011). Low-dose steroids for septic shock and severe sepsis: The use of Bayesian statistics to resolve clinical trial controversies. *Intensive Care Medicine*, **37**(3), 420–9.
17. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, and Needham DM. (2007). Neuromuscular dysfunction acquired in critical illness: A systematic review. *Intensive Care Medicine*, **33**(11), 1876–91.
18. Weber-Carstens S, Deja M, Koch S, et al. (2010). Risk factors in critical illness myopathy during the early course of critical illness: A prospective observational study. *Critical Care*, **14**(3), R119.
19. Loisa P, Parviainen I, Tenhunen J, Hovilehto S, and Ruokonen E. (2007). Effect of mode of hydrocortisone administration on glycemic control in patients with septic shock: a prospective randomized trial. *Critical Care*, **11**(1), R21.
20. Weber-Carstens S, Deja M, Bercker S, et al. (2007). Impact of bolus application of low-dose hydrocortisone on glycemic control in septic shock patients. *Intensive Care Medicine*, **33**(0342–4642), 730–3.

CHAPTER 55

Immunotherapy in critical illness

Hans-Dieter Volk and Levent Akyüz

Key points

- There is a clear need for immunological stratification of critically-ill patients for improved efficacy of immune modulation.
- Immunostimulation cannot be recommended without immune monitoring.
- Immune modulation is a promising approach, despite many disappointing results, particularly with anti-inflammatory approaches.
- Some immunostimulatory cytokines are able to restore the immunocompetence.
- The reduction of hyperinflammation by broad inhibition of key pro-inflammatory transcription factors is not very promising.

Immunotherapy

The immune system plays an important role in the treatment of critically-ill patients. Adequate immune response is essential for wound healing and control of invading pathogens and, consequently, reducing immunosuppression in critically-ill transplant patients suffering from severe infection/sepsis aids pathogen control. However, this can be a dangerous approach if no immune monitoring is used to guide adequate immunosuppression dependent on individual immune competence/failure ('immunoparalysis'). Moreover, there are some promising pilot studies on immunostimulation granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-gamma (IFN-g) in non-immunosuppressed septic patients with 'immunoparalysis' that require prospective validation in multicentre trials [1–3].

On the other hand, there is no doubt that overwhelming inflammation can result in multiple organ failure and shock [4]. Unfortunately, all approaches to target inflammation (steroids, anti-tumour necrosis factor (TNF) monoclonal antibody (mAb), etc.) have failed, probably because of failure to stratify patients immunologically. This also demonstrates that our animal models are poorly predictive for the clinical course.

The goal of immunotherapy is to readjust the patient´s individually imbalanced immunological responsiveness.

Presently, immunotherapy in critically-ill patients is at a clinical experimental level—no therapy is approved so far. The treatment can include enhancement, suppression, or induction of the immune system. The decision starts with the question whether the therapeutic selection matches the clinical (immunological) need. To develop a potential therapeutic strategy we need to know the pathogen, the immune status of the patient, and the interaction between the particular pathogen and immune cells. The right treatment at the correct time point is crucial for a better outcome and the best economic use of resources is a difficult decision.

The best personalized immunotherapy is dependent on the available biomarker for the selection of the right patient and the right time point. Therefore, future studies on new immunotherapeutic approaches in critically-ill patients can only be interpreted in combination with immunological biomarker analyses.

Enhancement of the immune system by immunostimulatory therapeutic drugs

Inhibition of hyperinflammation

Trauma, major surgery, stroke, and sepsis induce an inflammatory response by activating pattern recognition receptors (PRRs) on cells of the innate immune system (e.g. Toll receptors) that can be amplified by stimulation of lymphocytes. Lymphocytes can be triggered both antigen-specifically (via T-cell receptor) or non-specifically (bystander activation via cytokine receptors). In preclinical experiments TNF-α, interleukin-1 (IL-1), and downstream products play a key role in the pathogenesis of systemic inflammation, organ failure, and shock. Consequently, targeting hyperinflammation seems to be a promising option to improve septic multi-organ failure, further supported by promising in vivo preclinical data (in the wrong models). However, the results are very disappointing.

Systemic glucocorticoids block the cytokine response. Glucocorticoids cross the cell membrane and down-regulate inflammatory mediators by modifying the transcription factors NF-κB and activator protein-1. This can be mediated by direct and indirect interaction by stimulating inhibitory factors, like IκB, and by blocking the DNA-binding of transcription factors, respectively.

The production of inflammatory cytokines, such as TNF-α and IL-6 are thus diminished [5]. This physiological property with the capacity to counteract hyperinflammation was used in many clinical studies and the treatment of critically-ill patients. Studies with high doses of glucocorticoids show no benefit in mortality or adverse events [6]. The trend was even higher in mortality in steroid-treated groups. A link between high dose and higher mortality has been shown in meta-analyses [7]. Treatment with low dose hydrocorticoids is still suggested, but only to treat adverse effects without beneficial in survival.

Controlling the immunoresponse under hyperinflammatory conditions was the aim of several clinical studies. To summarize,

Table 55.1 Some anti-inflammatory agents used in clinical trials of ICU patients

Drugs	Routes of administration	Function	Target
Hydrocorticoid	iv	Reduction of local and systemic inflammation, restore haemodynamic stability	Various cells
Eculizumab	iv	Monoclonal antibodies against C5	Complement activation downstream C3b
Afelimomab, Adalimumab	iv	Monoclonal antibody against TNF-alpha	TNF-α
Anakinra	iv	IL-1 receptor antagonist	IL-1
Tocilizumab	iv	Monoclonal antibody against IL-6 receptor	IL-6

iv, intravenous.

the reduction of hyperinflammation by broad inhibition of key pro-inflammatory transcription factors is not very promising.

However, specific targeting of key cytokines TNF-alpha and IL-1, both key players in (not so relevant) preclinical models, by specific biologics (antibodies, fusion proteins) revealed similar disappointing results.

Targeting TNF-α as a therapeutically approach showed beneficial results in animal model studies [8]. However, the large human clinical studies with monoclonal antibodies or soluble TNF-receptor fusion proteins as well as IL-1RA, generally failed to improved survival [9].

Another approach is to modulate the host innate response by targeting pattern recognition receptor (PRRs), like Toll-like receptors (TLRs). TLRs sense bacterial compounds, like lipopolysaccharide (LPS) or microbial nucleic acids, as well as damaged cells to trigger the innate inflammatory response. Targeting TLR to reduce inflammation by blocking TLR-4, however, failed in septic patients [10,11].

Interestingly, promising results could be observed in a proof-of-concept trial using the selective immunoabsorption of LPS, IL-6 and complement-activation product 5a (C5a). Reducing these factors in critically-ill patients leads to an increased monocytic HLA-DR expression (recovery from 'immunoparalysis') and improved organ function. The beneficial outcome on survival in patients with sepsis has to be demonstrated in a larger well-controlled study [12]. Moreover, it is not clear whether the decrease in C5a alone or the combination of targeting C5a, LPS, and IL-6 was most important for the beneficial effects in this proof-of-concept trial. C5a seems to be a key player in mediating negative effects of systemic inflammation. Monoclonal antibodies, such as eculizumab, against C5 are a promising therapeutic tool to treat critically-ill patients infected with pathogens like enterohaemorrhagic *E. coli* (EHEC) or haemolytic uremic syndrome–associated enterohaemorrhagic *E. coli* (HUSEC) [13]. Guidelines suggest a plasmapheresis within 24 hours to remove complement components C5a or the treatment with the monoclonal antibody targeting C5, eculizumab (Table 55.1).

Restoration of immunocompetence

As suggested in Table 55.1, the phenomenon of immunodepression, sometimes called compensatory anti-inflammatory syndrome (CARS) with its most severe form, 'immunoparalysis', is well recognized in critically-ill patients. It has a major impact on the competence of pathogen defence, wound healing, and tissue regeneration. It can be detected by standardized immune parameters, such as quantitative monocytic HLA-DR expression, ex vivo Toll-receptor triggered cytokine response, ex vivo T-cell responsiveness, and recently revealed molecular markers. There are some immunostimulatory cytokines that are able to restore the immunocompetence.

Both IFN-g and GM-CSF recover the monocytic HLA-DR expression and cytokine release [14]. Proof-of-concept trials demonstrated the power of these cytokines for recovery from 'immunoparalysis' [2].

Immunostimulation cannot be recommended without immune monitoring. Dependent on the individual immune responsiveness, the treatment might be beneficial or harmful. Treatment with IFN-g or GM-CSF during the dominant hyper-inflammatory phase might result in amplification of inflammation associated with enhanced multiple organ failure. Treatment during the phase of an exhausted immune response ('immunoparalysis') might help to readjust the immune system. Therefore, stratification of patients is a key issue.

Stress response induces inhibition of the innate responsiveness (e.g. drop of monocytic HLA-DR and cytokine release) and targets an adaptive response by inhibiting type I T-cell response or

Table 55.2 Some candidates for immunostimulation tested in critically-ill patients

Drugs	Routes of administration	Function	Target	Side effects
IFN-g	sc, iv	Increased expression of MHCI and II, anti-viral activity, activation of macrophages	Various cells	Fever, diarrhoea, muscle soreness
GM-CSF	sc	Granulocytes recruitment, monocytes, and eosinophil differentiation	Stem cell	Bone pain, mylagia, alopecia, fever

sc, subcutaneous; iv, intravenous.

inducing T/B cell apoptosis. IFN-g can replace some of the missing T-cell functions, but there is no drug to reconstitute specifically adaptive immune systems. The beneficial effects of removing T-cell targeting drugs (like calcineurin inhibitors) in critically-ill transplant patients suffering from severe infection demonstrate the need of sufficient adaptive T-cell response for recovery. A novel approach might be adoptive transfer of specific T cells, as shown in murine stroke models, but the proof is still missing (Table 55.2).

To summarize, immune modulation is a promising approach, despite many disappointing results particularly with anti-inflammatory approaches. There is a clear need for immunological stratification of critically-ill patients for improved efficacy, and the search for new clinical endpoints in surviving patients with medical and health-economical impact.

References

1. Meisel C, Schefold JC, Pschowski R, et al. (2009). Granulocyte-macrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: a double-blind, randomized, placebo-controlled multicenter trial. *American Journal of Respiratory and Critical Care Medicine*, **180**(7), 640–8.
2. Volk HD, Reinke P, Krausch D, et al. (1996). Monocyte deactivation—rationale for a new therapeutic strategy in sepsis. *Intensive Care Medicine*, **22** (Suppl. 4), S474–81.
3. Döcke WD, Randow F, Syrbe U, et al. (1997). Monocyte deactivation in septic patients: restoration by IFN-gamma treatment. *Nature Medicine*, **3**(6), 678–81.
4. Hotchkiss RS and Nicholson DW. (2006). Apoptosis and caspases regulate death and inflammation in sepsis. *Nature Reviews Immunology*, **6**(11), 813–22.
5. Quante T, Ng YC, Ramsay EE, et al. (2008). Corticosteroids reduce IL-6 in ASM cells via up-regulation of MKP-1. *American Journal of Respiratory Cell and Molecular Biology*, **39**, 208–17.
6. Lefering R and Neugebauer EAM. (1995). Steroid controversy in sepsis and septic shock: a meta-analysis. *Critical Care Medicine*, **23**, 1294–303.
7. Minneci PC, Deans KJ, Banks SM, et al. (2004). Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. *Annals of Internal Medicine*, **141**, 47–56.
8. Tracey K, Fong Y, and Hesse DG. (1987). Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature*, **330**, 662–4.
9. Reinhart K, Menges T, Garlund B, et al. (2001). Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: the RAMSES Study. *Critical Care Medicine*, **29**, 765–9.
10. Rice TW, Wheeler AP, Bernard GR, et al. (2010). A randomized, double-blind, placebo-controlled trial of TAK-242 for the treatment of severe sepsis. *Critical Care Medicine*, **38**(8), 1685–94.
11. Tidswell M, Tillis W, Larosa SP, et al. (2010). Phase 2 trial of eritoran tetrasodium (E5564), a toll-like receptor 4 antagonist, in patients with severe sepsis. *Critical Care Medicine*, **38**(1), 72–83. Erratum: **38**(9), 1925–6.
12. Schefold JC, von Haehling S, Corsepius M, et al. (2007). A novel selective extracorporeal intervention in sepsis: immunoadsorption of endotoxin, interleukin 6, and complement-activating product 5a. *Shock*, **28**(4), 418–25.
13. Waters AM and Licht C. (2011). aHUS caused by complement dysregulation: new therapies on the horizon. *Pediatric Nephrology*, **26**(1), 41–57. [Review.]
14. Döcke WD, Höflich C, Davis KA, et al. (2005). Monitoring temporary immunodepression by flow cytometric measurement of monocytic HLA-DR expression: a multicenter standardized study. *Clinical Chemistry*, **51**(12), 2341–7.

PART 2.8

Fluids and diuretics

CHAPTER 56

Colloids in critical illness

Andrew Webb

Key points

- An adequate circulating volume must be provided before considering other methods of circulatory support.
- The use of fluid to restore circulating volume is essential before resorting to inotropes in the hypovolaemic patient.
- Smaller volumes of colloid than crystalloid are required for resuscitation leading to quicker resuscitation.
- No mortality benefit has been demonstrated between patients resuscitated with colloid or crystalloid.
- The volume required for correction of hypovolaemia can be determined by the haemodynamic effect of small aliquots of plasma substitute.

Introduction

Intravenous (iv) fluids used for volume replenishment in critical care practice encompass a range of crystalloids and colloids. Colloids include: albumin, dextran, gelatin, and hydroxyethyl starch.

Pharmacology

Colloid solutions are homogenous mixtures of large molecules suspended in a crystalloid solution. They intend to substitute some properties of plasma, particularly increasing the capillary colloid osmotic pressure, thus increasing the intravascular retention of plasma.

The efficacy of colloids as volume substitutes or expanders and length of effect are determined by their physicochemical properties, which determine the number of colloid particles in solution and their persistence.

Albumin

Albumin is the fraction of plasma that provides the major part of the circulation's colloid osmotic pressure, and therefore it has been used as a plasma substitute. Although it is naturally occurring, there is a certain amount of heterogeneity in circulating albumin. Albumin for infusion is virtually free from disease transmission since it is heated to 60°C for approximately 10 hours following fractionation. The fractionation process contributes further heterogeneity since the final product contains some dimers and longer-chain polymers. Storage of albumin solutions may produce further heterogeneity through the formation of unstable polymers, which may affect *in vivo* characteristics.

Albumin is the main provider of colloid osmotic pressure in the plasma. The solution has a net negative charge, which helps retain colloid molecules within the vascular space by repulsion from the capillary endothelium and enhances the colloid osmotic pressure by the Gibbs–Donnan effect [1]. Albumin has a number of other functions [2]:

- Transport of various molecules.
- Free-radical scavenging.
- Binding of toxins.
- Inhibition of platelet aggregation.

Human albumin solutions have been used successfully as plasma substitutes and, in view of their natural occurrence, are often considered as the standard with which synthetic plasma substitutes are compared. The major limitations to the use of human albumin solutions are their high production costs and limited supplies.

Gelatin solutions

Gelatin is a degradation product of animal collagen and, therefore, is inexpensive and readily available. Gelatin polypeptides are chemically modified to reduce the gel melting point, while retaining sufficient molecular size for intravascular retention. In the manufacture of urea-bridged gelatin (polygeline) polypeptides of molecular weight 12–15 kDa are formed by thermal degradation of cattle bone gelatin and, subsequently, cross-linked by hexamethyl di-isocyanate. In the manufacture of succinylated gelatin polypeptides of molecular weight approximately 23 kDa are produced by thermal degradation of calf skin collagen. These polypeptides are reacted with succinic acid anhydride to replace amino groups with acid carboxyl groups. No cross-links are formed, but the increased net negative charge on the molecule produces a conformational change to open coils, as well as an enhanced colloid osmotic pressure by the Gibbs–Donnan effect [1]. Although little increase in molecular weight is produced by this reaction, molecular size is increased, allowing better intravascular retention. Urea-bridged gelatin (polygeline) is a 3.5% solution and contains calcium (6.25 mmol/L). The calcium content prevents the use of the same administration set for blood transfusions. Succinylated gelatin is a 4.0% solution with a slightly longer effect. This and the lack of calcium in solution make this a more useful solution than polygeline for short-term plasma volume expansion. Gelatins are largely excreted unchanged via the kidneys with minimal metabolism by proteases.

Dextran solutions

Dextrans are high molecular weight polysaccharides. They are natural substances produced by the action of the enzyme dextran sucrase during the growth of various strains of the bacteria

Leuconostoc in media containing sucrose. After partial hydrolysis of raw dextran (molecular weight between 10^4 and 10^5 kDa), the resulting hydrolysate is fractionated to produce dextran molecules of average molecular weight 70–75 kDa. Since 1953, *Leuconostoc mesenteroides B512* has been the strain used for the manufacture of clinical dextrans. Other strains have been shown to produce dextran molecules with greater degrees of branching, and these molecules were associated with more immunological reactions. Over 90% of the branches in dextran molecules produced by *L. mesenteroides B512* are α1–6 glucosidic bonds, giving relatively few side-chains [3].

Dextran 70 is available as in an isotonic solution or a hypertonic saline solution intended for small volume resuscitation. Dextran 40 is hyperoncotic, but is largely excreted without metabolism.

Hydroxyethyl starch solutions

Unmodified starch is unsuitable as a plasma substitute since it is broken down rapidly by amylase. The hydroxyethylation of starch protects the polymer against breakdown by amylase. Waxy starches consisting of 98% amylopectin are used in the manufacture of most hydroxyethyl starches although potato starch, consisting of 75% amylopectin is used for manufacture of some tetrastarches [4]. After hydrolysis of amylopectin, which is a highly-branched polysaccharide resembling natural glycogen, to reduce viscosity, the solution is treated with ethylene oxide in the presence of sodium hydroxide as a catalyst. Thus, glucose units are substituted with hydroxyethyl groups at positions C2, C3, and C6. The characteristics of hydroxyethyl starch solutions are dependent on the range of molecular weights, the degree of substitution of glucose units by hydroxyethyl groups, and the ratio of C2–C6 substitution. In general, higher molecular weights, higher degrees of substitution, and a high ratio of C2–C6 substitution are associated with more prolonged effects. As experience has been gained with hydroxyethyl starch solutions a balance between the safety profile of solutions and effective volume expansion has been sought by reducing molecular weight and degree of substitution while maintaining higher C2:C6 substitution ratio [5]. Smaller hydroxyethyl starch molecules are excreted unchanged in the urine, but larger molecules must be metabolized by amylase first. As larger molecules are broken down the colloid osmotic effect is maintained, since it is dependent on the number of particles. However, a recent systematic review of trials of lower molecular weight hydroxyethyl starch versus human albumin or crystalloid in sepsis showed no advantage in safety [6].

Uses

Correction of hypovolaemia

Colloid solutions are generally used for the maintenance of plasma volume and acute replacement of plasma volume deficit. Early administration of fluid often corrects features of shock, such as hypotension or oliguria. Hypovolaemia must be treated urgently to avoid the serious complication of progressive organ failure. Indeed, milder degrees of hypovolaemia are associated with the pathophysiological changes leading, ultimately, to organ failure or dysfunction.

Most studies have failed to demonstrate a mortality advantage for resuscitation with colloid, rather than crystalloid and some have demonstrated additional morbidity with colloid [7–10]. However, the CRISTAL trial showed a 90-day mortality advantage for resuscitation with colloid in patients predominantly presenting with hypotension and lactaemia [11]. The ALBIOS trial also showed a mortality advantage in a post-hoc analysis in septic shock patients at 90 days [9]. Resuscitation by smaller volumes is quicker and easier. Plasma substitutes maintain plasma colloid osmotic pressure, but they contain no clotting factors or other plasma enzyme systems.

Where blood loss is the cause of hypovolaemia, it would seem logical to use blood as the replacement fluid. However, while whole blood would achieve an adequate increase in circulating volume, the high haematocrit of packed red cells will correct red cell volume with less effect on plasma volume. Therefore, it is appropriate to consider replacing the plasma volume deficit with a plasma substitute.

It should be noted that plasma substitutes are carried in 0.9% saline or balanced electrolyte so that the majority of critically-ill patients will not require salt-containing crystalloid infusions if colloid solutions are used.

The volume required for correction of hypovolaemia is determined by the haemodynamic effect of the fluid given. Most colloid solutions are subject to maximum limits suggested by the manufacturers on the basis of available research and safety data.

Fluid challenge

The fluid challenge is a method of safely restoring circulating volume [12]. The response of central venous pressure (CVP) and stroke volume should be monitored during a fluid challenge (Fig. 56.1). The change in CVP after a 200-mL fluid challenge depends on the starting blood volume. A significant rise in CVP (3 mmHg) is probably indicative of an adequate circulating volume. However, a positive response may sometimes occur in the vasoconstricted patient with a low blood volume. In addition, it is important to assess the clinical response—if it is inadequate, it is appropriate to monitor stroke volume response, a rise of 10% after a 200-mL fluid challenge being indicative of fluid responsiveness.

Other disease states

Colloids have been used in a number of specific disease states, although in most cases their use has not been justified by evidence.

Nutritional supplementation

Despite the association of hypoalbuminaemia and high morbidity [13], the Cochrane Injuries Group meta-analysis demonstrated an increased mortality in patients who received albumin supplementation to correct hypoalbuminaemia [14]. There is no evidence that maintenance of plasma albumin levels, as opposed to maintenance of plasma colloid osmotic pressure with artificial plasma substitutes, is advantageous [2].

Cirrhosis and acute liver failure

In cirrhotic liver disease there has long been a tendency to give iv albumin infusions during paracentesis. Studies have shown that this practice has no benefit over infusion of synthetic colloids [15]. In-patients with cirrhosis and spontaneous bacterial peritonitis, renal function frequently becomes impaired. This impairment is probably related to a reduction in effective arterial blood volume and is associated with a high mortality. A randomized controlled study patients with cirrhosis and spontaneous bacterial peritonitis showed a reduction in the incidence of renal impairment and death in patients who received iv albumin and antibiotics in comparison

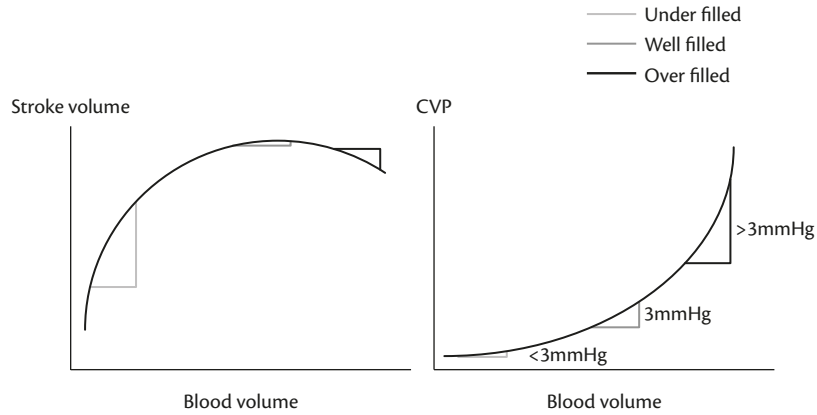


Fig. 56.1 The response of stroke volume and CVP to small-volume fluid challenges. In the hypovolaemic patient, an increase in stroke volume with no significant rise in CVP would be expected. In the optimally-filled patient a rise in CVP with no significant rise in stroke volume would be expected.

with patients who only received treatment with an antibiotic alone [16]. The mechanism by which albumin exerted such a beneficial effect is unclear. It remains possible that the effect of the albumin was simply expansion of the intravascular volume. Whether that effect is specific for albumin infusion or would be achieved with other fluids was not addressed.

Albumin is also used in the dialysate in extra-corporeal albumin dialysis for cirrhosis and acute liver failure. The procedure removes toxins bound to albumin in the blood as well as water-soluble, dialysable. The albumin in the dialysate is 'regenerated' by being passed through an anion exchange resin and activated charcoal. Although biochemical improvements have been demonstrated with the technique survival benefit has yet to be demonstrated [17].

Adverse effects

Adverse reactions include the infusion of excess volume, which may be associated with oedema. Oedema formation may occur despite infusion of apparently appropriate volumes, particularly in capillary leak states. Conversely, the consequences of the minor side-effect of oedema may be necessary to ensure adequate resuscitation.

Allergic phenomena are associated with all colloid fluids [18]. These may range from urticaria (the most common effect seen with gelatins) to severe anaphylaxis with cardiovascular collapse (more commonly seen with dextrans). Reactions may be classical IgE-mediated or complement-mediated and delayed in onset. The incidence of allergic reactions is low with any of the colloid solutions (0.01–0.15%). With longer-acting colloid solutions (e.g. high molecular weight hydroxyethyl starch), anaphylactoid reactions may require prolonged support.

Haemostatic defects include dilution coagulopathy associated with any plasma substitute. In addition, dextrans reduce the activities of factors V and VIII, fibrinogen, and prothrombin, decrease platelet adhesion, and prolong bleeding time. These effects are exploited in microsurgery, where dextran 40 is often used as an anticoagulant. Hydroxyethyl starch solutions also reduce factor VIII activity and platelet aggregation (rather than adhesion), again particularly with higher-molecular-weight fractions [7]. These effects are rarely associated with clinical bleeding.

Hydroxyethyl starch solutions have been associated with an increased incidence of acute kidney injury in sepsis, renal transplant and cardiac surgery patients [7,8]. Non-allergic pruritis has also been associated with tissue storage of hydroxyethyl starch, again more commonly with higher molecular weight fractions [7]. Both effects appear to be dose related.

References

1. Al-Khafaji A and Webb A. (2002). Colloid osmotic pressure. *Critical Care & Shock*, **5**, 178–83.
2. Al Khafaji A and Webb A. (2003). Should albumin be used to correct hypoalbuminaemia in the critically ill? No. *Transfusion Alternatives in Transfusion Medicine*, **5**, 392–6.
3. Mishler J. (1984). Synthetic plasma volume expanders, their pharmacology, safety and efficacy. *Clinics in Haematology*, **13**, 75–92.
4. Sommermeyer K, Cech F, and Shossow R. (2007). Differences in chemical structures between waxy maize- and potato starch-based hydroxyethyl starch volume therapeutics. *Transfusion Alternatives in Transfusion Medicine*, **9**, 127–33.
5. Westphal M, James M, Kozek-Langenecker S, Stocker R, Guidet B, and Van Aken H. (2009). Hydroxyethyl starches. *Anesthesiology*, **111**, 187–202.
6. Haase N, Perner A, Inkeri Hennings L, et al. (2013). Hydroxyethyl starch 130/0.38–0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *British Medical Journal*, **346**, f839.
7. Hartog C, Bauer M, and Reinhart K. (2010). The efficacy and safety of colloid resuscitation in the critically ill. *Anesthesia and Analgesia*, **112**, 156–64.
8. Myburgh J, Finfer S, Bellomo R, et al. (2012). Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *New England Journal of Medicine*, **367**, 1901–11.
9. Caironi P, Tognoni G, Masson S, et al. (2014). Albumin replacement inpatients with severe sepsis or septic shock. *New England Journal of Medicine*, **370**, 1412–21.
10. The SAFE investigators. (2004). A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *New England Journal of Medicine*, **350**, 2247–56.
11. Annane D, Siami S, Jaber S, et al. (2013). Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL trial. *Journal of the American Medical Association*, **310**, 1809–17.
12. Webb A. (2001). Recognising hypovolaemia. *Minerva Anestesiologica*, **67**, 185–9.

13. Reinhardt G, Myscofski W, Wilkens D, Dobrin P, Mangan J, and Stannard R. (1980). Incidence and mortality of hypoalbuminemic patients in hospitalized veterans. *Journal of Parenteral and Enteral Nutrition*, **4**, 357–9.
14. Cochrane Injuries Group. (1998). Human albumin administration in critically ill patients: systematic review of randomized trials. *British Medical Journal*, **317**, 235–40.
15. Salerno F, Badalamenti S, Lorenzano E, Moser P, and Incerti P. (1991). Randomized comparative study of hemaccel vs. albumin infusion after total paracentesis in cirrhotic patients with refractory ascites. *Hepatology*, **13**, 707–13.
16. Sort P, Navasa M, Arroyo V, et al. (1999). Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *New England Journal of Medicine*, **341**, 403–9.
17. Karvellas C, Gibney N, Kutsogiannis D, Wendon J, and Bain V. (2007). Bench-to-bedside review: current evidence for extracorporeal albumin dialysis systems in liver failure. *Critical Care*, **11**, 215–22.
18. Watkins J. (1991). Allergic and pseudoallergic reactions to colloid plasma substitutes: which colloid? *Care of the Critically Ill*, **7**, 213–17.

CHAPTER 57

Crystalloids in critical illness

Karthik Raghunathan and Andrew Shaw

Key points

- A revised Starling model describes fluid distribution across body compartments with the endothelial glycocalyx playing a central role in determining fluid disposition.
- Crystalloids produce important negative consequences with both inadequate and excessive resuscitation.
- During critical illness, crystalloid dose may be based on functional measures such as pulse pressure variation.
- Balanced crystalloid solutions may be advantageous over 'normal' (isotonic) saline.
- Crystalloids may have significant effects on immune and renal function, beyond their direct effects on cardiovascular function.

Background and epidemiology

Fluids are central to the management of critical illness, yet are rarely afforded the same degree of consideration as other drugs in the intensive care unit (ICU). Current estimates, based on a recent survey across 25 countries, suggest close to 40% of ICU patients receive resuscitation fluids each day [1]. Practice patterns show wide variations in the type and volume of fluid used in ICUs [1].

'Crystalloid' conventionally refers to solutions of crystalline substances that can pass through a semipermeable membrane and distribute widely in body fluid compartments. Typical solutions include isotonic 'normal' (0.9%) saline or fractions of 'normal' saline (such as half or quarter normal saline, 0.45 or 0.225% saline, respectively) with or without glucose, and other physiological or balanced solutions with electrolyte concentrations closer to plasma.

The 'crystalloid versus colloid' debate has raged for decades. Most large randomized controlled studies [2] have consistently found no survival advantage with colloids. However, the recently published CRISTAL trial reported that colloids may indeed have an advantage when used for resuscitation in acutely hypovolaemic patients [3]. However, ICU surveys prior to this have shown that colloids were administered to more patients during more resuscitation episodes than crystalloids [1] and this practice variation reflected local preferences, rather than differences in the patient-mix. Recent evidence [4,5] suggests the efficacy of volume expansion (i.e. the fraction of infused fluid retained within circulation that potentially augments cardiac output) depends on the underlying volume status, capillary pressures, and/or the patient's pathophysiological state. Optimal ICU outcomes often result from interventions beginning well before ICU admission. Pre-emptive haemodynamic optimization in patients undergoing major surgery favours colloids [6], since direct comparisons between goal-directed colloid therapy versus goal-directed crystalloid therapy are limited. Crystalloids tend to load the interstitial space in this setting. However, during resuscitation in shock states there is little apparent benefit of colloid use. Crystalloids have been shown to be equivalent and in several settings (e.g. traumatic brain injury) superior to colloids. In addition, crystalloids have variable electrolyte concentrations, volumes of distribution, and consequently have variable effects on plasma pH. The strong ion difference for various crystalloid solutions may vary widely ranging from 0 through 50. Since within-group differences may exceed between-group differences global crystalloid-colloid comparisons are inappropriate.

Pathophysiology

According to the classic Starling model, total body water (TBW) accounts for 60% of the lean body weight (LBW) in adults and is proportioned into: intracellular (IC, 40%) and extracellular (EC, 20%) spaces. EC volume is further divided into intravascular (5% of LBW) and interstitial fluid (ISF) compartments (15% LBW). Crystalloids are expected to distribute across these compartments proportionately, based on their composition. Transvascular exchange is based on the balance of opposing hydrostatic and oncotic forces acting across semi-permeable barriers. Net filtration occurs based on these pressure differentials as per the Starling–Landis equation:

$$J_v = k_f\left[\left(P_c - P_i\right) - \sigma\left(\pi_c - \pi_i\right)\right]$$

where J_v is net fluid movement, k_f is the capillary filtration coefficient, $P_c - P_i$ is the capillary hydrostatic pressure—ISF hydrostatic pressure, σ is the reflection coefficient and $\pi_c - \pi_i$ is the capillary oncotic pressure—ISF oncotic pressure]). Based on these assumptions, only about 7% of an infusion of electrolyte-free water (glucose solutions) should remain intravascular and if an isotonic saline solution is used, the expected efficacy of plasma volume expansion is about 20%. The classic Starling model might allow for fluid recruitment into the vascular compartment from the ISF, if capillary oncotic pressures are adequate to overcome the outward hydrostatic gradient. Colloids might also be predicted to be superior for the resuscitation of hypoalbuminaemic critically-ill patients. However, observations of fluid behaviour during critical illness are not consistent with these predictions [2,5].

To address inconsistencies, a revised Starling model has been developed incorporating a central role for the endothelial surface layer (ESL). This interface between blood and the capillary

wall resists fluid and solute filtration to varying degrees depending on the continuity of and fenestrations in the endothelium [5]. Different types of tissue capillary arrangements exist with sinusoidal tissues essentially continuous with plasma (marrow, spleen, and liver), glomerular filtration occurring via open fenestrated capillaries and continuous non-fenestrated capillaries acting as intact barriers to filtration in most tissue (muscle, lung, connective tissue). The glycocalyx, a key part of the ESL, is semi-permeable with an oncotic gradient across it, rather than across the vessel wall. Plasma proteins, including albumin, leak into the ISF via a relatively small number of large pores. There is *no* net fluid *absorption* across the capillary wall and filtered fluid is returned into circulation as lymph. Transvascular filtration is based on capillary pressures and is determined, in part, by the underlying volume status of the patient. With supranormal capillary pressures, crystalloid infusions will lower oncotic pressures (secondary to a dilutional effect) with resulting greater transvascular filtration into compliant ISF spaces. Therefore, in the presence of an intact endothelial glycocalyx layer (EGL) and euvolaemia, colloid infusions may sustain plasma expansion better (e.g. with pre-emptive goal-directed optimization in surgical patients). At lower capillary pressures during hypovolaemia, volume expansion with crystalloids is effective since transvascular filtration decreases linearly. Also, crystalloids may be more efficient plasma expanders than expected because the actual EC space available for equilibration is limited (by rigid structures or fibrous capsules). Crystalloid retention increases during hypovolaemic states, while the clearance is significantly reduced. Lower arterial pressures also reduce crystalloid clearance, while infusions of alpha-adrenergic agonists significantly accelerate this clearance. Overall, this revised model supports crystalloid utilization in most critical care settings where the ESL is disrupted and supports limiting colloid use to euvolaemic resuscitation at higher capillary pressures with an intact ESL [5].

During critical illness or with systemic inflammation, the ESL is compromised with increased vascular permeability and significant transcapillary escape of albumin [7,8]. There is 'no net absorption' explaining why attempts to raise the capillary oncotic pressure—with the aim of 'recruiting' interstitial fluids into circulation—are not successful. Crystalloid accumulation occurs in compliant loose connective tissues, such as with extravascular lung water (EVLW) and, in muscles or gastrointestinal mesentery, but not in other non-compliant tissues (marrow, liver, spleen, kidney). When the ESL is damaged, colloids are not retained within the intravascular space and would not offer any significant haemodynamic advantage. Thus, the context in which crystalloids are used is a key determinant of its disposition. When hypotension is a result of heart failure or vasoplegia, continued crystalloid use, as opposed to appropriate inotrope or vasopressor use, will result in decreasing clearance and increasing fluid sequestration. Thus, the continued administration of crystalloids in a volume non-responder is especially deleterious.

'Volume kinetics', based on the mathematical modelling of fluid disposition analogous to drug pharmacokinetics, describes the peak effects, distribution, and clearance of crystalloids. A two-compartment model has been developed and appears to fit observed kinetics. Three model parameters are described—volume of distribution, inter-compartmental transfer, and an elimination constant. From a clinical perspective, the elimination of a large, rapidly infused volume of saline is independent of the infused volume. The implication is that rapid crystalloid accumulation occurs after large fluid boluses are administered and the use of fluids under disrupted ESL conditions will result in undesirable accumulation (e.g. EVLW). The relationship between volume overload and poor ICU outcomes is well recognized. Consequently, the titration of crystalloid therapy based on functional dynamic parameters is warranted.

Dosing

The key to dosing crystalloids in the ICU is to address ongoing losses and the need for circulatory support (avoiding under-resuscitation), while continually assessing the need for 'routine maintenance' avoiding the replacement of unmeasured presumed fluid deficits (avoiding over-resuscitation). Threshold central venous pressure (CVP) values continue to be advocated in critical care settings (particularly in septic patients) as targets for early goal-directed fluid therapy in mechanically-ventilated and spontaneously breathing populations [9]. Such CVP-guided crystalloid therapy may be inappropriate and even harmful [10]. Decision-making regarding fluid therapy should be based on objectively-defined individualized functional dynamic parameters, such as the pulse pressure variation (PPV) [11,12] or flow-based/cardiac output related measures [12]. These measures can distinguish between volume responders and non-responders in mechanically-ventilated patients, and resuscitation and de-resuscitation can be guided by such measures in a 'gray zone' approach [11]. Fluids may be given or withheld based on the relative position of each patient on their Frank–Starling curve and the clinical context. Crystalloids dosed in this manner are based on individual assessment of left ventricular pre-load responsiveness balancing 'too little' against 'too much'. Patients may receive diuretics when appropriate, for instance, in the mechanically-ventilated patient with acute lung injury in a normal sinus rhythm with a PPV below 10%. The accumulation of crystalloids as in EVLW may be reduced with this approach. Conversely, early in sepsis a PPV of 12% or higher might indicate the continued need for aggressive crystalloid boluses [11]. Formulaic crystalloid administration especially in surgical populations (such as hourly maintenance rates, based on actual body weight) should be rejected in favour of minimal crystalloids for the replacement of measured losses. Post-operative replacement of 'third space losses' following major abdominal surgery with large volume hourly maintenance crystalloid infusions is especially detrimental.

Key limitations of PPV should be acknowledged including its lack of discriminant ability in spontaneously-breathing patients, in patients with significant arrhythmias, or in those receiving low tidal volume ventilation with reduced lung compliance. In such scenarios, the use of minimally-invasive techniques (such as oesophageal Doppler measures, echocardiographic measures of inferior vena cava collapsibility, etc.) coupled with reversible volume challenge manoeuvres, such as passive leg raising (PLR) might uncover 'recruitable stroke volume'. Cardiac output may be appropriately maximized with crystalloid therapy if PLR manoeuvres or mini-fluid challenges augment circulation. Optimal timing needs to be defined as well. Randomized trials suggest that early crystalloid resuscitation (i.e. within 6 hours of the onset of systemic inflammatory response syndrome) [9] with late restriction and 'de-resuscitation' (beyond 72 hours into critical illness) improves outcomes [13].

Composition

Plasma pH, according to Stewart's approach to acid-base disorders, is influenced by the composition of the crystalloids administered. In this sense, crystalloid administration is an acid-base intervention. Crystalloid loading causes dilution of plasma weak acids raising the plasma pH (alkalosis). On the other hand, crystalloids with a low strong ion difference (SID, approximated by the difference between sodium and chloride concentrations) will narrow the plasma SID driving the pH down (acidosis). Crystalloids with higher SID will tend to minimize this acidotic effect. Although no major clinical trials in the critically ill have compared different types of crystalloids (with SID differences) head-to-head, pre-clinical and observational data suggest that solutions with a low SID and high chloride concentrations (isotonic saline or its variations) may be associated with worse outcomes than balanced solutions. Balanced crystalloids will allow the plasma SID to fall just enough (causing acidosis) to counteract the alkalotic effects of plasma weak acid dilution [14].

In shock states, plasma SID is decreased with metabolic acidosis caused by lactataemia. Isotonic saline has a chloride concentration 1.5 times higher than plasma and has a SID = 0. Resuscitation with saline might be predictably lower the plasma SID resulting in further acidosis. When isotonic saline is given as the primary resuscitation fluid, the result is a predictable hyperchloraemic metabolic acidosis. Such acidosis may give rise to adverse effects including immune [15], gastrointestinal [16], and renal dysfunction [16]. Electrolyte abnormalities are seen more commonly in saline-treated patients and significant fluid replacement with saline (such as during trauma resuscitation) may induce sufficient changes in plasma acid-base balance to affect the immune response. Hyperchloraemia induces intrarenal vasoconstriction in humans and decreased renal function is associated with neutrophil dysfunction and decreased bacterial clearance [17]. A large observational study comparing patients undergoing major open abdominal surgery receiving exclusively saline versus a calcium-free balanced crystalloid on the day of surgery, found greater resource utilization, and risk of infectious and renal complications in the saline group [18]. These differences were especially marked in those undergoing emergent surgery, a population that typically receives care in the ICU post-operatively. Worsening acidosis, due to a saline-based resuscitation strategy, may be mistaken for inadequate tissue perfusion in the setting of septic shock [19]. Unwarranted corrective measures may involve further aggressive volume loading to remedy the presumed perfusion deficit. Such misguided attempts to reverse or correct acidosis may result in increased morbidity and mortality. In summary, there are plausible adverse effects of hyperchloraemic acidosis from saline administration. The routine use of saline for resuscitation and favour the use of alternate balanced solutions with a strong ion difference closer to plasma is cautioned against. It is suggested that saline use be restricted to co-administration with blood products, for the treatment of hydrochloric acid loss and of brain injured patients, as there is evidence that using colloidal solutions or hypotonic solutions results in suboptimal outcomes in this population [20]. Regardless of the chloride concentration, crystalloid solutions with SID (such as glucose-containing solutions, saline, 'half-normal saline', etc.) are going to lower plasma pH. The use of solutions that are closer to plasma in electrolyte concentration and SID are likely to be associated with better outcomes. Thus, the goal of crystalloid use must be to administer the right type of crystalloid at the right time and in the right amount.

References

1. Finfer S, Liu B, Taylor C, et al. (2010).Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Critical Care*, **14**(5), R185.
2. Finfer S, Bellomo R, Boyce N, et al. (2004). A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *New England Journal of Medicine*, **350**(22), 2247–56.
3. Annane D, Siami S, Jaber S, et al. (2013). Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *Journal of the American Medical Association*, **310**(17), 1809–17.
4. Corcoran T, Rhodes J, Clarke S, et al. (2012). Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesthesia and Analgesia*, **114**, 640–51.
5. Woodcock TE and Woodcock TM. (2012). Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. *British Journal of Anaesthesia*, **108**, 384–94.
6. Giglio MT, Marucci M, Testini M, et al. (2009). Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. *British Journal of Anaesthesia*, **103**, 637–46.
7. Steppan J, Hofer S, Funke B, et al. (2011). Sepsis and major abdominal surgery lead to flaking of the endothelial glycocalix. *Journal of Surgical Research*, **165**, 136–41.
8. Johansson PI, Stensballe J, Rasmussen LS, et al. (2011). A high admission syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with inflammation, protein C depletion, fibrinolysis, and increased mortality in trauma patients. *Annals of Surgery*, **254**, 194–200.
9. Dellinger RP, Levy MM, Carlet JM, et al. (2008). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Critical Care Medicine*, **36**, 296–327.
10. Boyd JH, Forbes J, Nakada TA, Walley KR, and Russell JA. (2011). Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Critical Care Medicine*, **39**, 259–65.
11. Cannesson M, Le Manach Y, Hofer CK, et al. (2011). Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a 'gray zone' approach. *Anesthesiology*, **115**, 231–41.
12. Hamilton MA, Cecconi M, and Rhodes A. (2011). A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesthesia and Analgesia*, **112**, 1392–402.
13. Wiedemann HP. (2008). A perspective on the fluids and catheters treatment trial (FACTT). Fluid restriction is superior in acute lung injury and ARDS. *Cleveland Clinic Journal of Medicine*, **75**(1), 42–8.
14. Morgan TJ. (2005). The meaning of acid-base abnormalities in the intensive care unit: part III—effects of fluid administration. *Critical Care*, **9**(2), 204–11.
15. Kellum JA, Song M, and Li J. (2004). Science review: extracellular acidosis and the immune response: clinical and physiologic implications. *Critical Care*, **8**(5), 331–6.
16. Williams EL, Hildebrand KL, McCormick SA, and Bedel MJ. (1999). The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. *Anesthesia and Analgesia*, **88**(5), 999–1003.
17. Zarbock A, Schmolke M, Spieker T, Jurk K, Van Aken H, and Singbartl K. (2006). Acute uremia but not renal inflammation attenuates aseptic acute lung injury: a critical role for uremic neutrophils. *Journal of the American Society of Nephrology*, **17**(11), 3124–31.

18. Shaw AD, Bagshaw SM, Goldstein SL, et al. (2012). Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Annals of Surgery*, **255**(5), 821–9.
19. Kellum JA. (2004). Metabolic acidosis in patients with sepsis: epiphenomenon or part of the pathophysiology? *Critical Care Resuscitation*, **6**(3), 197–203.
20. Myburgh J, Cooper DJ, Finfer S, et al. (2007). Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *New England Journal of Medicine*, **357**(9), 874–84.

CHAPTER 58

Diuretics in critical illness

Marlies Ostermann and Ruth Y. Y. Wan

Key points

- There is no role for diuretics to improve renal function or outcome in patients with acute kidney injury, although an increase in urine output may be achieved, which may be beneficial in patients who are fluid overloaded.
- Diuretics are often prescribed to patients with acute heart failure, but may be harmful since many patients are not fluid overloaded despite the presence of pulmonary oedema.
- Combination therapy with different diuretics is often necessary in resistant oedema, including advanced heart failure and chronic liver disease.
- In chronic kidney disease, the thiazide metolazone is commonly prescribed with furosemide to maintain fluid balance, but there is little data to suggest a mortality or morbidity benefit.
- Effective diuresis is easier to achieve with continuous infusion of loop diuretics compared with bolus therapy, but there is no evidence of better outcome.

Introduction

Diuretics are most commonly used in conditions characterized by fluid overload (including heart failure, acute and chronic kidney disease, nephrotic syndrome, and chronic liver disease) and chronic hypertension. Despite their frequent use, there is uncertainty regarding optimal dosing, route of administration (oral (po) versus intravenous (iv) bolus versus infusion) and the role of combination therapy, especially in the critical care setting.

Types of diuretics

Diuretics can be classified in terms of their site of action and behaviour along the nephron (Table 58.1). Diuretics act from within the tubular lumen. With the exception of spironolactone and mannitol, they are protein bound and are delivered to their site of action by secretion via organic anion transporters in the proximal tubular cells. The intrinsic secretory capacity of the proximal tubule controls the quantity of diuretic that enters the tubule. Patients with an estimated glomerular filtration rate (GFR) of 15 mL/min/1.73 m^2 secrete only 10–20% of the amount of loop diuretic that is secreted into tubular fluid in patients with a normal GFR receiving similar doses. As a result, they need a higher dose to elicit a similar diuretic response. In addition, a reduction in GFR reduces the filtered load of extracellular fluid and Na^+, which also limits the maximum achievable response to any diuretic.

Other factors that influence tubular secretion and drug availability include actual dose administered, absolute bioavailability (for orally administered drugs), renal blood flow, and potential competition for tubular secretion due to metabolic acidosis or co-administration of drugs.

Indications for diuretics

Acute kidney disease

Experimental data suggest that furosemide reduces the oxygen and metabolic requirements of tubular cells, and increases oxygen concentration in the medulla [1]. This led to the hypothesis that furosemide may be beneficial in early acute kidney injury (AKI), and prevent progression and/or reduce its severity. Three meta-analyses concluded that the use of diuretics in established AKI did not improve renal function, speed up recovery, or change mortality, but carried a significant risk of side-effects, including electrolyte derangement, ototoxicity, and vestibular dysfunction [2–4]. There is also no evidence that diuretics are effective in restoring renal function in patients on renal replacement therapy (RRT) [5]. However, diuretics may have a role when treating patients with AKI and significant fluid overload, especially if RRT is not immediately available.

Most of these data stem from small studies. A large randomized controlled trial is currently recruiting patients to evaluate the role of furosemide in AKI (SPARK Study) [6]. The aims of this study are to compare the efficacy and safety of a continuous infusion of furosemide versus placebo in early AKI on progression of kidney injury. Secondary endpoints include fluid balance, the need for RRT, electrolyte and acid-base balance, total duration of AKI, rate of renal recovery, and mortality. Pending the results of this study, there is no evidence in favour of the use of diuretics to treat AKI.

Chronic kidney disease

Patients with chronic kidney disease (CKD) are often (not always) characterized by progressive sodium and water retention. Patients vary in the amounts of urine produced independently of CKD stage. Diuretic therapy usually starts with furosemide as the preferred loop diuretic, since thiazide diuretics (with the exception of metolazone) cease to be effective when estimated GFR falls to <30 mL/min/1.73 m^2. Metolazone is still effective in worsening CKD, but as renal function deteriorates and patients respond less well, RRT may need to be considered for management of fluid overload.

In the critically ill with acute on chronic kidney injury, iv furosemide is widely used. As with AKI, there is no evidence that this strategy improves renal recovery or shortens the duration of AKI.

Table 58.1 Characteristics of different diuretics

Type of diuretic	Site of action	Physiological effect	Most common indication(s)	Most important side effects
Loop diuretics: organic anions	Thick ascending limb loop of Henlé	Blockade of $Na^+/K^+/Cl^-$ cotransport system Inhibition of Na^+ reabsorption	Acute kidney injury, chronic kidney disease, acute heart failure, congestive heart failure, and chronic liver disease	Otoxicitiy Hyperuricaemia Electrolyte disorders Drug hypersensitivity
Thiazides: organic anions	Distal tubule, in the case of metolazone affects the loop of Henlé also	Blockade of Na^+/Cl^- transport system Inhibition of Na^+ reabsorption	Hypertension, chronic kidney disease (metolazone)	Hyperglycaemia Drug hypersensitivity Cholestatic jaundice, hepatitis Agranulocytosis
Aldosterone antagonists	Aldosterone receptors in the distal tubule	Prevention of aldosterone induced Na retention	Mobilization of ascites in chronic liver disease Congestive heart failure	Gynaecomastia Gastrointestinal Drug hypersensitivity Agranulocytosis
Osmotic agents: e.g. mannitol	Filtered in the glomerulus and not reabsorbed along the whole nephron	Reduced passive reabsorption of water	Cerebral oedema ?Rhabdomyolysis	Skin necrosis (in case of extravasation) Renal failure Seizures
Carbonic anhydrase inhibitors: e.g. acetazolamide	Proximal tubule	Inhibition of carbonic anhydrase Increased HCO_{3-} excretion, followed by increased Na^+, K^+ and water excretion	Correction of severe metabolic alkalosis Glaucoma	Drug hypersensitivity Metabolic acidosis Agranulocytosis
Potassium sparing diuretics: e.g. amiloride, triamterene	Late portion of the distal tubule and cortical collecting duct	Inhibition of K^+ secretion	To minimize K^+ loss with loop diuretics or thiazides	Hyperkalaemia
ANP/BNP: e.g. nesiritide	Afferent and efferent glomerular arterioles	Increase in GFR by dilation of afferent glomerular arteries and constriction of efferent arteries	?Acute heart failure	Renal failure Skin necrosis (in case of extravasation)

GFR, glomerular filtration rate; ANP, atrial natriuretic peptide; BNP, B type natriuretic peptide.

Acute decompensated heart failure

Most patients with acute decompensated heart failure present with symptoms related to fluid overload, which may be complicated by concomitant renal dysfunction. For decades, the administration of iv loop diuretics has been the mainstay of therapy to reduce congestion, decrease ventricular filling pressures, and improve clinical symptoms. However, many patients with acute heart failure are not substantially volume overloaded despite the presence of pulmonary or peripheral oedema [7,8]. In these cases, removing volume may reduce the necessary preload of a poorly functioning heart and may actually be harmful. There are other theoretical risks with administering loop diuretics in this situation, including the risk of neurohormonal activation, systemic vasoconstriction, electrolyte disturbances, and impairment of renal function.

Nesiritide (B type natriuretic peptide) has an effect on renin-angiotensin-aldosterone system resulting in smooth muscle relaxation [9]. Despite the potentially beneficial effects, there are currently little data to support its use in acute heart failure.

Congestive heart failure

Appropriate diuretic therapy controls fluid in most patients with mild to moderate chronic heart disease, leading to the resolution of pulmonary and peripheral oedema. Although diuretics may induce a decrease in ventricular filling and fall in cardiac output, this is usually not clinically important unless the patient is over-diuresed. A Cochrane review concluded there was evidence from 14 controlled studies (n = 525 patients) that conventional diuretics in congestive heart failure reduced the risk of worsening heart failure and death when compared with placebo [10]. Diuretics also increased the ability to exercise by 28–33% compared with other drugs. However, most studies had small numbers with a follow-up period of only 4–24 weeks and the use of diuretics was not standardized.

Patients with advanced heart failure may become less responsive to conventional oral doses of a loop diuretic due to reductions in renal perfusion and increased secretion of sodium-retaining hormones (i.e. aldosterone, angiotensin II), and may need increasing doses of diuretics or combination therapies.

Chronic liver disease

Spironolactone is used in escalating doses for the removal of ascites with the usual starting po dose of 100 mg daily. There are two therapeutic strategies for large-volume ascites—paracentesis and the administration of diuretics at increasing doses (maximal doses, 400 mg of spironolactone per day and 160 mg of furosemide per

day) until loss of ascitic fluid is achieved. The results of randomized trials comparing these two approaches support paracentesis as the method of choice [11]. Although there is no difference between the two strategies with respect to long-term mortality, large-volume paracentesis is faster, more effective, and associated with fewer adverse events than diuretic therapy. Regardless of the strategy used, diuretics should be included in the maintenance therapy to prevent recurrence of ascites.

A common complication of both acute and chronic liver failure is hepatic encephalopathy presenting with raised intracranial pressure. Treatment with mannitol boluses 1 g/kg has been shown to improve survival in liver patients with cerebral oedema and normal renal function [12]. More commonly, a dose of 0.5 g/kg is used as a bolus (100 mL 20% mannitol) and repeated after an hour, if necessary. The resulting hypovolaemia can paradoxically cause an increase in intracerebral pressure. Plasma osmolality should be maintained at <320 mOsomol/L, while a mildly hyperosmotic state should be targeted to minimize cerebral oedema. Accordingly, serum sodium should be maintained at least within high normal limits. Hypertonic saline administered to achieve serum Na 145–155 mmol/L may be considered in patients with intracranial hypertension refractory to mannitol [13].

Rhabdomyolysis

The main reason for considering diuretics in rhabdomyolysis is to remove myoglobin from the tubular lumen. However, the use of any diuretic in this situation remains controversial and should be restricted to patients who are not fluid deplete. As an osmotic agent, mannitol may increase urinary flow, promote the flushing of nephrotoxic agents through the renal tubules, and facilitate the shift of fluid from injured muscles into the vascular space. Mannitol is also a free-radical scavenger.

No randomized controlled trial has supported the evidence-based use of mannitol in humans. In addition, high accumulated doses of mannitol (>200 g/day or accumulated doses of >800 g) have been associated with AKI due to renal vasoconstriction and tubular toxicity.

If mannitol is used to prevent and treat rhabdomyolysis-induced AKI and to relieve compartmental pressure [14], plasma osmolality and the osmolal gap should be monitored, and therapy discontinued if adequate diuresis is not achieved or if the osmolal gap rises above 55 mOsmol/kg. Loop diuretics also increase urinary flow and may decrease the risk of myoglobin precipitation, but no study has shown a clear benefit in patients with rhabdomyolysis.

Hypertension

In chronic hypertension, diuretics are one of the dominant drug classes used. However, diuretics should be used with caution during a hypertensive crisis in the critically ill, as volume depletion may already be present in these conditions, putting the patient at risk of AKI. Furthermore, in acute hypertensive crises, there is a role for stronger antihypertensives than diuretics.

Management of resistant oedema

Combination of diuretics

Combinations of different diuretics may be necessary and may avoid side effects from a single drug given at high dose.

In chronic liver disease, dose titration of spironolactone to 300 mg daily is limited by hyperkalaemia. For this reason, loop diuretics are often added to aid faster mobilization of moderate ascites. Maximum doses of spironolactone 400 mg daily and furosemide 160 mg daily is achievable in combination. Amiloride (10–40 mg/day) can be substituted in patients suffering from spironolactone-induced gynaecomastia, although amiloride is less effective. Eplenerone, a newer aldosterone receptor blocker without the side effect of gynaecomastia has not been studied in the setting of cirrhosis and ascites. Other combinations include triamterene, metolazone, and hydrochlorothiazide [15].

In patients with congestive heart failure, the RALES (Randomized Aldactone Evaluation) trial showed that spironolactone (25–50 mg daily), in combination with an ACE inhibitor and a loop diuretic, with or without digoxin was associated with a significantly reduced mortality at 24 months and significant reduction in hospitalization for heart failure [16].

In CKD, the thiazide metolazone is commonly added with furosemide to maintain fluid balance. However, there is little data to suggest any mortality or morbidity benefit when using this combination.

In patients with cerebral oedema, aldosterone antagonists such as spironolactone or potassium canreonate (canrenone) have been used in conjunction with mannitol to minimize the risk of cardiac arrhythmias precipitated by hypokalaemia [17].

Intravenous bolus versus continuous infusion therapy

A randomized controlled trial comparing furosemide infusion versus bolus administration in 59 critically-ill patients with fluid overload, showed patients in the bolus group needed a significantly higher total dose to achieve target diuresis [18]. Mean urine output was significantly higher in the infusion group, but there was no difference in hospital mortality, the number of patients requiring ventilatory support, change in serum creatinine, or change in estimated GFR. Current data suggest diuresis is easier to achieve with a continuous infusion, but there is no evidence of better outcomes.

Combination with albumin

In situations of fluid overload associated with severe hypoalbuminaemia, such as nephrotic syndrome or advanced chronic liver disease, diuretic resistance can occur. Albumin is considered to be necessary to deliver furosemide to the kidney, and severe hypoalbuminaemia is associated with impaired furosemide secretion into the tubular lumen. Diuretics bind to albumin in the tubular fluid, which decreases the amount of unbound, active drug that is available to interact with the tubular receptor. When urinary concentrations of albumin are >4 g/L, up to 65% of the diuretic that reaches the tubular fluid is bound to albumin.

A mixture of loop diuretic and albumin is occasionally used if the patient is severely hypoalbuminaemic (serum albumin <20 g/L). Data to support this strategy are conflicting. In a study including patients with cirrhosis and ascites, the administration of premixed loop diuretic and albumin (40 mg of furosemide and 25 g of albumin) did not enhance the natriuretic response [19]. In contrast, a randomized controlled crossover study in 24 patients with CKD and hypoalbuminaemia showed a significant increase in the increment of urine volume with furosemide and albumin [20]. However, at 24 hours, there were no longer any significant differences.

References

1. Brezis M, Agmon Y, and Epstein FH. (1994). Determinants of intrarenal oxygenation. I. Effects of diuretics. *American Journal of Physiology*, **267**, F1059–62.
2. Ho KM and Sheridan DJ. (2006). Meta-analysis of frusemide to prevent or treat acute renal failure. *British Medical Journal*, **333**, 420.
3. Bagshaw SM, Delaney A, Haase M, Ghali WA, and Bellomo R. (2007). Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis. *Critical Care Resuscitation*, **9**, 60–8.
4. Sampath S, Moran JL, Graham PL, Rockliff S, Bersten AD, and Abrams KR. (2007). The efficacy of loop diuretics in acute renal failure: assessment using Bayesian evidence synthesis techniques. *Critical Care Medicine*, **35**, 2516–24.
5. Van der Voort PH, Boema EC, Koopmans M, et al.(2009). Furosemide does not improve renal recovery after hemofiltration for acute renal failure in critically ill patients: a double blind randomized controlled trial. *Critical Care Medicine,* **37**, 533–8.
6. Bagshaw SM, Gibney RTN, McAlister FA, and Bellomo R. (2010). The SPARK Study: a phase II randomized blinded controlled trial of the effect of furosemide in critically ill patients with early acute kidney injury. *Trials*, **11**, 50.
7. Cotter G, Metzkor E, Kaluski E, et al. (1998). Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet*, **351**, 389–93.
8. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *New England Journal of Medicine*, **364**, 797–805.
9. O'Connor CM, Starling RC, Hernandez AF, et al. (2011). Effect of Nesiritide in patients with acute decompensated heart failure. *New England Journal of Medicine*, **365**, 32–43.
10. Faris RF, Flather M, Purcell H, Poole-Wilson PA, and Coats AJS. (2012). Diuretics for heart failure. *Cochrane Database Systematic Reviews*, **2**, CD003838.
11. Runyon BA. (2009). AASLD Practice guidelines. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology*, **49**, 2087–107.
12. Canalese J, Gimson AE, Davis C, Mellon PJ, Davis M, and Williams R. (1982). Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. *Gut*, **23**, 625–9.
13. Stravitz RT, Kramer AH, Davern T, et al. (2007). Acute liver failure study group. Intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. *Critical Care Medicine*, **35**, 2498–508.
14. Brown CV, Rhee P, Chan L, Evans K, Demetriades D, and Velmahos GC. (2004). Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? *Journal of Trauma*, **56**, 1191–6.
15. Sica DA and Gehr TW. (1996). Diuretic combinations in refractory oedema states. *Clinical Pharmacokinetics*, **30**, 229–49.
16. Pitt B, Zannad F, Remme WJ, et al. (1999). The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *New England Journal of Medicine*, **341**, 709–17.
17. Bilotta F, Giovannini F, Aghilone F, et al. (2012). Potassium sparing diuretics as adjunct to mannitol therapy in neurocritical care patients with cerebral edema: effects on potassium homeostasis and cardiac arrhythmias. *Neurocritical Care*, **16**(2), 280–5.
18. Ostermann M, Alvarez G, Sharpe MD, and Martin CM. (2007). Frusemide administration in critically ill patients by continuous compared to bolus therapy. *Nephron Clinical Practice*, **107**, c70–6.
19. Chalasani N, Gorski JC, Horlander JC, et al. (2001). Effects of albumin/furosemide mixtures on responses to furosemide in hypoalbuminemic patients. *Journal of the American Society of Nephrology*, **12**, 1010–16.
20. Phakdeekitcharoen B and Boonyawat K. (2012). The added-up albumin enhances the diuretic effect of furosemide in patients with hypoalbuminemic chronic kidney disease: a randomized controlled study. *BMC Nephrology*, **13**, 92.

SECTION 3

Resuscitation

PART 3.1

Respiratory management

CHAPTER 59

Airway management in cardiopulmonary resuscitation

Jerry P. Nolan and Jasmeet Soar

Key points

- In the context of cardiopulmonary resuscitation (CPR), airway obstruction is common.
- The most appropriate strategy for managing the airway depends on the skills of the rescuer.
- Tracheal intubation is generally accepted as the optimal method for securing the airway, but only when undertaken by a highly skilled individual.
- In the absence of a skilled intubator, insertion of a supraglottic airway device (SAD) is probably the best way of managing the airway during CPR.
- Use of waveform capnography is mandatory whenever tracheal intubation is attempted, but will also provide useful information about the effectiveness of CPR, and an early indication of return of spontaneous circulation (ROSC) even when used with a SAD.

Introduction

Establishing and maintaining a clear airway is a fundamental component of cardiopulmonary resuscitation (CPR), but there is some controversy about precisely how this should be achieved [1]. Patients requiring resuscitation often have an obstructed airway, usually caused by loss of consciousness, but occasionally it may be the primary cause of cardiac arrest. Immediate restoration of airway patency enables ventilation of the lungs and oxygenation of the blood. Without adequate oxygenation it may be impossible to restore a perfusing cardiac rhythm. Tracheal intubation is generally considered to be the optimal method for maintaining a clear airway, but this is likely to be true only when undertaken by individuals highly skilled in the technique. In the absence of a skilled intubator, use of a supraglottic airway device (SAD) will provide a more reliable airway than simply using a bag-mask and oropharyngeal airway.

Causes of airway obstruction

Airway obstruction can occur at any level from the nose and mouth down to the level of the carina and bronchi. In unconscious patients, the commonest site of airway obstruction is at the soft palate and epiglottis. Vomit, blood, or foreign bodies can also cause airway obstruction. Laryngeal obstruction may be caused by oedema from burns, inflammation, or anaphylaxis. Upper airway stimulation or inhalation of foreign material may cause laryngeal spasm. Obstruction of the airway below the larynx is less common, but may be caused by excessive bronchial secretions, mucosal oedema, bronchospasm, pulmonary oedema, or aspiration of gastric contents. Extrinsic compression of the airway may also occur above or below the larynx, e.g. as a result of trauma, haematoma, or tumour.

Recognition of airway obstruction

In partial airway obstruction, air entry is diminished and usually noisy—inspiratory stridor is caused by obstruction at the laryngeal level or above, and expiratory wheeze suggests obstruction of the lower airways, which tend to collapse and obstruct during expiration. Signs of complete airway obstruction in a patient who is making respiratory efforts include paradoxical chest and abdominal movement (see-saw breathing), use of accessory muscles of respiration, intercostal and subcostal recession, and tracheal tug. Airway obstruction must be relieved rapidly otherwise irreversible brain injury will start to occur within a few minutes. High concentration oxygen is given during attempts to relieve airway obstruction because this will increase arterial blood oxygen saturation (SaO_2) values more rapidly once airway patency is restored.

Basic techniques for opening the airway

The head tilt, chin lift (Fig. 59.1), and jaw thrust (Fig. 59.2) can be used to relieve upper airway obstruction.

Airway manoeuvres in a patient with suspected cervical spine injury

If spinal injury is suspected the head, neck, chest, and lumbar region are maintained in the neutral position during resuscitation. When there is a risk of cervical spine injury, establish a clear upper airway by using jaw thrust or chin lift in combination with manual in-line stabilization (MILS) of the head and neck. Establishing a patent airway takes priority over concerns about a potential cervical spine injury.

Fig. 59.1 Head tilt and chin lift.
This photograph is reproduced with kind permission by Michael Scott and the Resuscitation Council (UK).

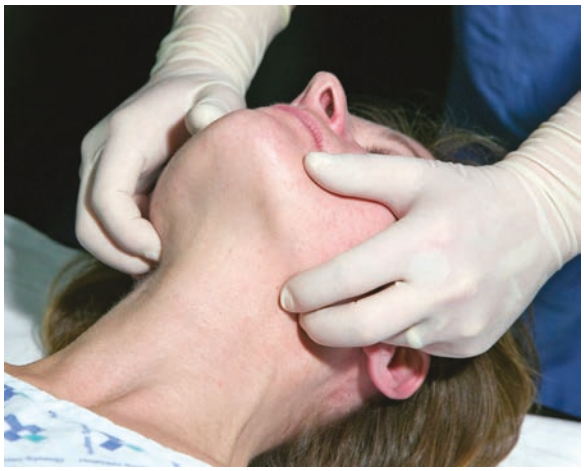


Fig. 59.2 Jaw thrust.
This photograph is reproduced with kind permission by Michael Scott and the Resuscitation Council (UK).

Adjuncts to basic airway techniques

Oropharyngeal and nasopharyngeal airways will overcome soft palate obstruction and backward tongue displacement in an unconscious patient, but head tilt and jaw thrust may also be required. The appropriate size for an oropharyngeal airway corresponds to the vertical distance between the patient's incisors and the angle of the jaw. In patients who are not deeply unconscious, a nasopharyngeal airway is better tolerated than an oropharyngeal airway—sizes 6–7 mm are suitable for adults.

Oxygen

During CPR, the lungs are ventilated with 100% oxygen until return of spontaneous circulation (ROSC) is achieved. After ROSC is achieved, high-flow oxygen is given until the oxygen saturation of arterial blood (SaO_2) can be measured reliably. Animal data indicate an association between high SaO_2 (hyperoxaemia) after ROSC and worse neurological outcome [2], but clinical data from observational studies are conflicting [3,4]. Current recommendations are that when blood oxygen saturation can be measured reliably, oxygen saturations should be maintained between 94% and 98%; or between 88 and 92% if the patient has chronic obstructive pulmonary disease [5].

Ventilation

A detailed discussion on ventilation during resuscitation, including use of a bag-mask device, is covered in Chapter 60.

Supraglottic airway devices

In comparison with bag-mask ventilation, use of SADs may enable more effective ventilation and reduce the risk of gastric inflation. They are also easier to insert than a tracheal tube and can generally be positioned without interrupting chest compressions. Alternative airway devices are used generally by those unskilled in tracheal intubation or as part of a back-up plan if a skilled operator is unable to intubate. Once a SAD has been inserted it is often possible to ventilate the patient's lungs without pausing the chest compressions—this reduces the 'no flow' time (when there is no blood flow to vital organs).

Laryngeal mask airway

Successful use of the laryngeal mask airway (LMA) by nursing, paramedical, and medical staff during resuscitation has been documented, although these are generally observational studies. The need to resterilize the reusable LMA Classic™ makes single-use LMAs more suitable for resuscitation, but the performance of some single-use devices is inferior to the Classic version. In the presence of high airway resistance or poor lung compliance, there is a risk of hypoventilation caused by a significant leak around the cuff. Once an LMA is inserted it is reasonable to attempt continuous compressions (i.e. not pausing the chest compressions during inspiration) initially, but abandon this if persistent leaks and hypoventilation occur.

The LMA ProSeal®

The LMA ProSeal® is a modified LMA: it has an additional posterior cuff, a gastric drain tube (enabling venting of liquid regurgitated gastric contents from the upper oesophagus and passage of a gastric tube to drain liquid gastric contents), and incorporates a bite block. There are no studies of its performance during CPR, but it enables ventilation at higher airway pressures (up to 35–40 cm H_2O), which may enable adequate ventilation during uninterrupted chest compressions. A disposable version, the LMA Supreme (Fig. 59.3), has been used very successfully during resuscitation following out of hospital cardiac arrest [6].

i-gel® airway

The i-gel® has a preformed cuff that does not require inflation. The stem of the i-gel incorporates a bite block and a narrow oesophageal drain tube (Fig. 59.4). Its ease of insertion and favourable leak pressure (20–24 cmH_2O) make it theoretically very attractive as a resuscitation airway device for those inexperienced in tracheal intubation. It has been introduced widely into United Kingdom ambulance services [7] and is about to be compared with tracheal intubation in out of hospital cardiac arrest in a large cluster randomised controlled trial.

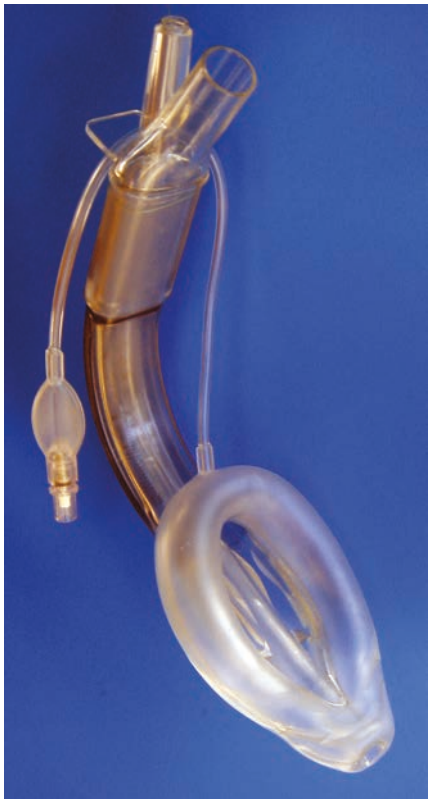


Fig. 59.3 LMA Supreme™.
This photograph is reproduced with kind permission by Michael Scott and the Resuscitation Council (UK).

Fig. 59.4 I-gel®.
This photograph is reproduced with kind permission by Michael Scott and the Resuscitation Council (UK).

Laryngeal tube

The laryngeal tube (LT) is a single-lumen tube with both an oesophageal and pharyngeal cuff (Fig. 59.5), which are inflated simultaneously via a single pilot balloon. A double lumen LT with an oesophageal vent, and a disposable version are available. There are several observational studies that document successful use of the LT by nurses and paramedics during prehospital cardiac arrest.

Outcomes with supraglottic airway devices

There are no high-quality randomised controlled trials powered for mortality comparing SADs with either tracheal intubation or mask and oropharyngeal airway. Several large observational studies that have documented the association between outcome after out-of-hospital cardiac arrest (OHCA) and use of a variety of SADs. The results of such studies are mixed with some showing better outcome associated with use of a SAD, while others show better outcome with tracheal intubation. Most observational studies show an association between the use of any advanced airway device (SAD or tracheal intubation) and worse outcome after OHCA compared with those patients managed with a bag-mask airway [8]. A large study from North America has also documented lower long-term survival among those OHCA patients with a SAD compared with a tracheal tube [9]. The problem with observational studies is that, no matter how sophisticated the risk adjustment, the possibility of significant confounders remain; for example, some SADs are inserted only when attempts at tracheal intubation have failed. More commonly, a SAD is used as part of a stepwise approach to airway management making it very difficult to ascertain the contribution of any particular airway to outcome after cardiac arrest [7,10]. There are very few data relating to airway management during in-hospital cardiac arrest and it is likely that extrapolation from OHCA studies is invalid; for example, patients with in-hospital cardiac arrest are much more likely to have respiratory disease, and an airway or breathing problem as the cause of their cardiac arrest.

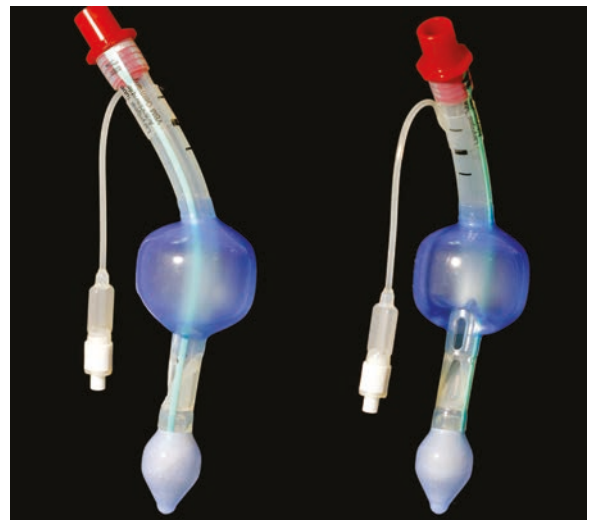


Fig. 59.5 Laryngeal tube.
This photograph is reproduced with kind permission by Michael Scott and the Resuscitation Council (UK).

Tracheal intubation

Tracheal intubation should be attempted during resuscitation only by personnel who are able to carry out the procedure with a high level of skill and competence. No prospective study has shown improved outcome with tracheal intubation compared with bag-mask after cardiac arrest. Some observational studies document an association between tracheal intubation and worse outcome [11].

The perceived advantages of tracheal intubation over bag-mask ventilation include maintenance of a patent airway, which is protected from aspiration of gastric contents or blood from the oropharynx, the ability to provide an adequate tidal volume reliably even when chest compressions are uninterrupted, the potential to free the rescuer's hands for other tasks, and the ability to suck-out airway secretions. The use of a bag-mask is more likely to cause gastric distension, which is, theoretically, more likely to cause regurgitation and the risk of aspiration. This theoretical risk has yet to be proven in randomized clinical trials.

The perceived disadvantages of tracheal intubation over bag-mask ventilation include the risk of an unrecognized misplaced tracheal tube (up to 17% in some OCHA studies, although a recent high-quality Scottish study documented a rate of 2.4%) [12], a prolonged time without chest compressions while tracheal intubation is attempted, and a comparatively high failure rate. In one study involving prehospital intubation of 100 cardiac arrest patients by paramedics, the first intubation attempt accounted for a median interruption in CPR of 45 seconds and in one third of cases it exceeded 1 minute [13].

Personnel skilled in advanced airway management should be able to undertake laryngoscopy without stopping chest compressions. A brief pause in chest compressions will be required only as the tube is passed through the vocal cords. Alternatively, to avoid any interruptions in chest compressions, the intubation attempt may be deferred until ROSC. Attempted tracheal intubation should not interrupt chest compressions for more than 5 seconds, otherwise, bag-mask or bag-SAD ventilation is recommenced. After tracheal intubation, tube placement must be confirmed and the tube secured adequately.

Confirmation of correct tracheal tube placement

Unrecognized oesophageal intubation is the most serious complication of attempted tracheal intubation. Routine use of primary and secondary techniques to confirm correct placement of the tracheal tube will reduce this risk.

Clinical assessment

Primary assessment includes observation of chest expansion bilaterally, auscultation over the lung fields bilaterally in the axillae and over the epigastrium. Secondary confirmation of tracheal tube placement by use of a colorimetric carbon dioxide detector or waveform capnography will reduce the risk of unrecognized oesophageal intubation.

Carbon dioxide detectors

Unless cardiac arrest has been very prolonged (more than 30 minutes), chest compressions will produce sufficient pulmonary blood flow to produce detectable exhaled carbon dioxide (CO_2) concentrations. Following a tracheal intubation attempt, if exhaled CO_2 is not detected, the tube is probably in the oesophagus. Carbon dioxide detector devices measure the concentration of exhaled carbon dioxide from the lungs. There are broadly three types:

- Disposable colorimetric end-tidal carbon dioxide ($ETCO_2$) detectors use a litmus paper to detect CO_2, and these devices generally give readings of purple ($ETCO_2$ <0.5%), tan ($ETCO_2$ 0.5–2%), and yellow ($ETCO_2$ > 2%).
- Non-waveform electronic digital $ETCO_2$ devices measure $ETCO_2$ using an infrared spectrometer and display the results with a number.
- End-tidal CO_2 detectors that include a waveform graphical display (capnograph) are the most reliable for verification of tracheal tube position during cardiac arrest.

When tracheal intubation is undertaken <30 minutes after the onset of cardiac arrest, waveform capnography has 100% (95% CI 98–100%) sensitivity and 100% (95% CI 97–100%) specificity to verify placement of the tube in a major airway. The Royal College of Anaesthetists and Difficult Airway Society National Audit Project 4 (NAP4) included a case of unrecognized oesophageal intubation in which a flat capnograph trace was interpreted as being due to cardiac arrest [14,15]. If tracheal intubation is delayed by >30 minutes, pulmonary blood flow can be so low during CPR that CO_2 is undetectable, despite the tracheal tube being correctly placed [5]. Waveform capnography is the most sensitive and specific way to confirm and continuously monitor the position of a tracheal tube in victims of cardiac arrest, but will not discriminate between tracheal and bronchial placement of the tube—careful auscultation is essential.

During CPR, the use of waveform capnography is also valuable to provide feedback on the quality of chest compressions (better chest compressions will generate higher end-tidal CO_2 values) [16], to predict which patients are likely to achieve ROSC (those with an end-tidal CO_2 value >10 mmHg) [17], and to provide an early indication of ROSC (if the end-tidal CO_2 increases suddenly during CPR) [18]. Waveform capnography works best in the presence of a tracheal tube, but can also be used during ventilation with a SAD [6] or a bag-mask. End-tidal CO_2 values will vary if an inadequate seal causes a leak.

Existing portable monitors make capnographic initial confirmation and continuous monitoring of tracheal tube position feasible in almost all settings, including out-of-hospital, emergency department, and in-hospital locations where tracheal intubation is performed. Ideally, waveform capnography should be available wherever tracheal intubation is performed.

Cricothyroidotomy

Occasionally, it will be impossible to ventilate an apnoeic patient with a bag-mask, or to pass a tracheal tube or other airway device. This may occur in patients with extensive facial trauma or laryngeal obstruction caused by oedema, e.g. anaphylaxis. In these circumstances, a surgical cricothyroidotomy provides a definitive airway that can be used to ventilate the patient's lungs until semi-elective intubation or tracheostomy is performed. Needle cricothyroidotomy is a much more temporary procedure providing only short-term oxygenation. It requires a wide-bore, non-kinking cannula, a high-pressure oxygen source and may cause serious barotrauma. It is also prone to failure because of kinking of the cannula, and is unsuitable for patient transfer. The NAP4 study documented a high failure rate (60%) when airway rescue was attempted with needle cricothyroidotomy [14,19]. In contrast, all surgical cricothyroidotomies achieved access to the trachea.

References

1. Nolan JP and Soar J. (2013). Airway techniques and ventilation strategies. *Current Opinion in Critical Care*, **19**, 181–7.
2. Pilcher J, Weatherall M, Shirtcliffe P, Bellomo R, Young P, and Beasley R. (2012). The effect of hyperoxia following cardiac arrest—a systematic review and meta-analysis of animal trials. *Resuscitation*, **83**, 417–22.
3. Kilgannon JH, Jones AE, Shapiro NI, et al. (2010). Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *Journal of the American Medical Association*, **303**, 2165–71.
4. Bellomo R, Bailey M, Eastwood GM, et al. (2011). Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. *Critical Care*, **15**, R90.
5. Soar J, Nolan JP, Bottiger BW, et al. (2005). European Resuscitation Council Guidelines for Resuscitation 2015 Section 3. Adult advanced life support. *Resuscitation*, **95**, 100–47.
6. Bosch J, de Nooij J, de Visser M, et al. (2014). Prehospital use in emergency patients of a laryngeal mask airway by ambulance paramedics is a safe and effective alternative for endotracheal intubation. *Emergency Medical Journal*, **31**, 750-3. .
7. Duckett J, Fell P, Han K, Kimber C, Taylor C (2014). Introduction of the i-gel supraglottic airway device for prehospital airway management in a UK ambulance service. *Emergency Medical Journal*, **31**, 505-7.
8. Fouche PF, Simpson PM, Bendall J, et al (2014). Airways in out-of-hospital cardiac arrest: systematic review and meta-analysis. *Prehospital Emergency Care*, **18**, 244-56.
9. Wang HE, Szydlo D, Stouffer JA, et al. (2012). Endotracheal intubation versus supraglottic airway insertion in out-of-hospital cardiac arrest. *Resuscitation*, **83**, 1061–66.
10. Voss S, Rhys M, Coates D, et al. (2014). How do paramedics manage the airway during out of hospital cardiac arrest? *Resuscitation*, **85**, 1662–6.
11. Studnek JR, Thestrup L, Vandeventer S, et al. (2010). The association between prehospital endotracheal intubation attempts and survival to hospital discharge among out-of-hospital cardiac arrest patients. *Academy of Emergency Medicine*, **17**, 918–25.
12. Lyon RM, Ferris JD, Young DM, McKeown DW, Oglesby AJ, and Robertson C. (2010). Field intubation of cardiac arrest patients: a dying art? *Emergency Medicine Journal*, **27**, 321–23.
13. Wang HE, Simeone SJ, Weaver MD, and Callaway CW. (2009). Interruptions in cardiopulmonary resuscitation from paramedic endotracheal intubation. *Annals of Emergency Medicine*, **54**, 645–52 e1.
14. Cook TM, Woodall N, Harper J, and Benger J. (2011). Major complications of airway management in the UK: results of the fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. *British Journal of Anaesthesia*, **106**, 632–42.
15. Nolan JP and Kelly FE. (2011). Airway challenges in critical care. *Anaesthesia*, **66**(Suppl. 2), 81–92.
16. Heradstveit BE, Sunde K, Sunde GA, Wentzel-Larsen T, and Heltne JK. (2012). Factors complicating interpretation of capnography during advanced life support in cardiac arrest-A clinical retrospective study in 575 patients. *Resuscitation*, **83**, 813–18.
17. Grmec S, Lah K, and Tusek-Bunc K. (2003). Difference in end-tidal CO2 between asphyxia cardiac arrest and ventricular fibrillation/pulseless ventricular tachycardia cardiac arrest in the prehospital setting. *Critical Care*, **7**, R139–44.
18. Pokorna M, Necas E, Kratochvil J, Skripsky R, Andrlik M, and Franek O. (2010). A sudden increase in partial pressure end-tidal carbon dioxide (P(ET)CO(2)) at the moment of return of spontaneous circulation. *Journal of Emergency Medicine*, **38**, 614–21.
19. Cook TM, Woodall N, and Frerk C. (2011). Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: anaesthesia. *British Journal of Anaesthesia*, **106**, 617–31.

CHAPTER 60

Artificial ventilation in cardiopulmonary resuscitation

Jasmeet Soar and Jerry P. Nolan

Key points

- Cardiopulmonary resuscitation (CPR) should be started with chest compressions.
- The need for ventilation during CPR is determined by both patient and rescuer factors.
- Rescuers who are unable or unwilling to provide effective ventilation, whilst awaiting expert help should use compression-only CPR.
- Ventilations are necessary during CPR in children and those with a primary respiratory cause of cardiac arrest.
- A high inspired oxygen concentration should be given during CPR, but once circulation has been restored, inspired oxygen should be adjusted to maintain normoxaemia.

Introduction

Traditionally, as soon as possible after cardiorespiratory arrest occurs, artificial ventilation (rescue breathing) is started as part of the ABC (Airway, Breathing Circulation) approach in order to maintain adequate oxygenation and remove carbon dioxide (CO_2). Current guidance advocates starting cardiopulmonary resuscitation (CPR) with chest compressions first. The provision of ventilation is determined by the training of rescuers, their ability, and willingness to provide rescue breaths, patient characteristics, and the underlying cause of the cardiac arrest. There is a greater urgency and need for ventilation when cardiac arrest results from a primary respiratory problem; in such cases it may be impossible to restore a perfusing cardiac rhythm without adequate ventilation and oxygenation. This chapter addresses the need for ventilation, how much ventilation and oxygen to give, ventilation techniques, safe use of oxygen during defibrillation, and how to monitor ventilation during CPR. Ventilation requires an open airway, and techniques for airway opening and maintenance are described in Chapter 59.

Are ventilations needed during CPR?

When performed by laypersons chest compression-only CPR during the first few minutes of a primary cardiac arrest can result in equivalent or superior survival to standard CPR [1]. In primary cardiac arrest arterial blood can remain saturated with oxygen for several minutes [2]. If CPR is started early, myocardial and cerebral oxygen delivery is determined by cardiac output rather than lack of oxygen in the arterial blood. Also, rescuers are often unwilling or unable to provide effective mouth-to-mouth ventilations. Even if they provide effective mouth-to-mouth ventilations, the typical prolonged pause in chest compressions when ventilations are given can reduce the chances of survival. Importantly, ventilations are needed for the treatment of cardiac arrest in children [3], when the arrest is from a primary respiratory cause or during a prolonged cardiac arrest [4]. However in adults, chest compression-only CPR is better than no CPR if a rescuer is untrained in CPR, is untrained and receiving instructions over a telephone from an ambulance dispatcher, or is unwilling or unable to perform rescuer breaths [2].

In the presence of an open airway, chest compressions generate air-flow into and out of the lungs although the measured tidal volumes are small and generally no more than the anatomical dead space [5]. Airway opening and high-flow face-mask oxygen and passive ventilation chest compressions for the first 6 minutes of CPR is used by some ambulance services for primary adult cardiac arrests. Improved outcomes have been reported with this 'minimally interrupted' CPR approach although further study is needed [6].

How much ventilation?

Current guidelines recommend two ventilations after every 30 chest compressions in adults, and after every 15 compressions in children [2]. Once the airway is secured with a tracheal tube, ventilations should be given at 10 breaths/min without any pause in chest compressions. Pauses in chest compressions for ventilations and other interventions reduce coronary and brain perfusion, and worsen the chances of survival [7]. High ventilation rates increase intrathoracic pressure and decrease coronary perfusion during CPR [8]. In clinical practice, rescuers often ventilate patients' lungs at much higher rates. In a single centre US study of in-hospital cardiac arrest, the observed ventilation rate was above 20/min over 61% of the time [9].

The optimal ventilation strategy during CPR is not known and current recommendations are based on limited evidence. As lung blood flow is reduced during CPR, a lower minute ventilation

is needed to maintain an adequate ventilation-perfusion ratio. A larger tidal volume (e.g. 1 L) in patients with unprotected airways produces more gastric distension than a smaller tidal volume (e.g. 500 mL). Effective oxygenation and ventilation can be maintained during CPR with a tidal volume of approximately 500 mL given over an inspiratory time of 1 second.

After a brief duration of cardiac arrest patients usually recover consciousness, maintain their airway safely, breathe adequately, and do not require ventilator support. Patients who remain comatose or agitated with a decreased conscious level, and those with respiratory compromise will require tracheal intubation and mechanical ventilation. In these patients, once return of spontaneous circulation (ROSC) has been achieved ventilation should be adjusted to achieve a normal partial pressure of carbon dioxide ($PaCO_2$) guided by arterial blood gas analysis and capnography. Hypocapnia is associated with decreased cerebral blood flow, and increased excitatory amino acid release causing neurotoxicity [10].

How much oxygen?

Rescuers should give supplemental oxygen in as high a concentration as possible during CPR in order to rapidly correct tissue hypoxia. Once ROSC has been achieved the inspired oxygen should be adjusted to maintain arterial oxygen saturation between 94 and 98% [11,12]. Recent observational studies in adults and children suggest that both hypoxaemia and hyperoxaemia in the first few hours after ROSC are associated with worse survival and neurological function [13,14]. Hyperoxaemia is thought to worsen free radical-induced mitochondrial injury during neuronal perfusion.

Ventilation techniques

The ventilation technique used during CPR and after ROSC will depend on the skills and training of rescuers and the equipment available.

Mouth-to-mouth ventilation

The expired oxygen concentration is only 16–17%, but mouth-to-mouth ventilation has the benefit of not requiring any equipment. Rescuers are often reluctant to perform mouth-to-mouth ventilation due to panic, fear of harming the patient, risk of infection, presence of vomit, blood, or the victim being unkempt. There are very few reports of individuals acquiring infections after providing CPR. Tuberculosis and severe acute respiratory distress syndrome (SARS) infections have been reported [15]. Mouth-to-mouth ventilation is rarely used in clinical settings as current guidelines recommend CPR is started with chest compressions alone. This allows time for airway and ventilation equipment to arrive.

Pocket mask

The pocket resuscitation mask is similar to an anaesthetic face mask and enables mouth-to-mask ventilation through a unidirectional valve (Fig. 60.1). Some masks have a port for the addition of oxygen. If oxygen is available, it should be added via the port at a flow of 10 L/min. If there is no oxygen port, supplemental oxygen can be given by placing oxygen tubing underneath one side and ensuring an adequate seal.

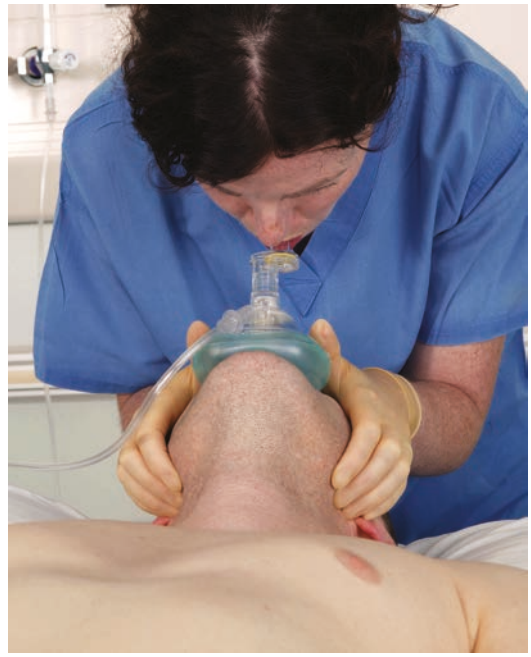


Fig. 60.1 Pocket mask ventilation.
This photograph is reproduced with kind permission by Michael Scott and the Resuscitation Council (UK).

Self-inflating bag

A self-inflating bag can be connected to a face mask, tracheal tube, or supraglottic airway device to enable positive pressure ventilation when the bag is squeezed (Fig. 60.2). On release, expired gas is diverted to the atmosphere via a one-way valve. The bag

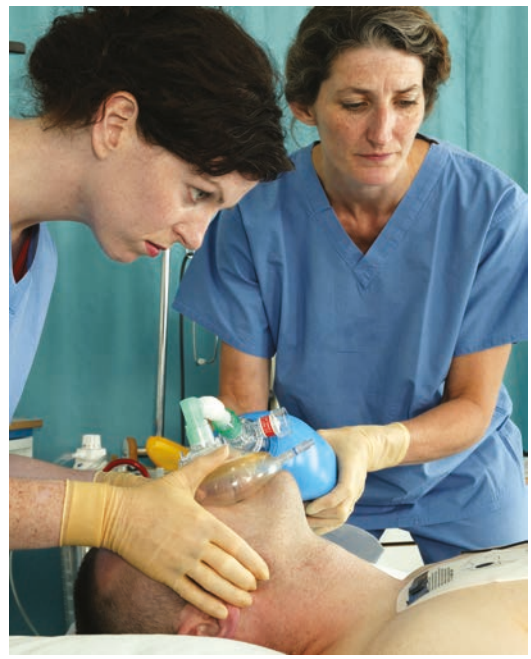


Fig. 60.2 Ventilation with self-inflating bag and facemask.
This photograph is reproduced with kind permission by Michael Scott and the Resuscitation Council (UK).

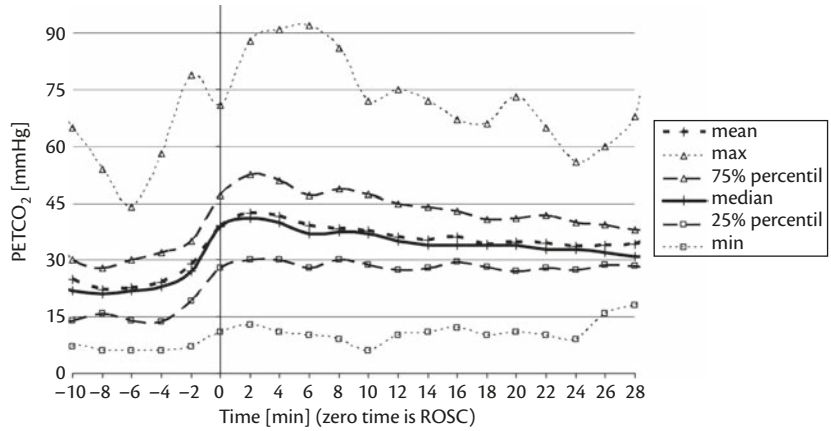


Fig. 60.3 End-tidal carbon dioxide ($PETCO_2$) values recorded before and after ROSC in 59 patients.
Reprinted from *Journal of Emergency Medicine*, **38**, 5, Pokorná M et al., 'A sudden increase in partial pressure end-tidal carbon dioxide (PETCO2) at the moment of return of spontaneous circulation', pp. 614–21, Copyright 2010 with permission from Elsevier and the American Academy of Emergency Medicine.

then refills automatically via an inlet at the opposite end. Without supplemental oxygen, the bag ventilates the patient's lungs with ambient air. Inspired oxygen concentration can be increased to about 45% by attaching high flow oxygen directly to the bag. An inspired oxygen concentration of approximately 85% can be achieved if a reservoir system is attached and the oxygen flow is maximally increased. As the bag re-expands it fills with oxygen from both the reservoir and the continuous flow from the attached oxygen tubing.

Oxygen safety during defibrillation

Sparking from a defibrillator can cause fire and patient burns in an oxygen-enriched atmosphere. The use of self-adhesive pads for defibrillation instead of manual paddles decreases this risk. The Resuscitation Council (UK) recommends the following precautions to minimize risk of fire during defibrillation [16]:

- Remove any oxygen mask, nasal cannulae, or disconnected ventilation bag and place them at least 1 m away from the patient's chest.
- Leave a ventilation bag connected to the tracheal tube or supraglottic airway device, no increase in oxygen concentration occurs in the zone of defibrillation, even with an oxygen flow of 15 L/min.
- If the patient is connected to a ventilator, leave the ventilator tubing connected to the tracheal tube during defibrillation. If the ventilator tubing is disconnected, ensure that it is kept at least 1 m from the patient. Better still switch the ventilator off.

Monitoring ventilation during CPR

Prompts and, or feedback devices can be used to ensure correct ventilation during CPR [17]. Ventilation rate can be monitored by recording changes in the transthoracic impedance through adhesive defibrillation electrodes [18].

Waveform capnography is now recommended to monitor correct tracheal tube placement during CPR [19]. In addition, it can be used to help guide ventilation rate during CPR. Increased depth and quality of chest compression will increase end-tidal CO_2, and a sudden steep rise in the end-tidal CO_2 may be an indicator of ROSC during CPR (Fig. 60.3) [20].

References

1. Hupfl M, Selig HF, and Nagele P. (2010). Chest-compression-only versus standard cardiopulmonary resuscitation: a meta-analysis. *Lancet*, **376**(9752),1552–7.
2. Koster RW, Sayre MR, Botha M, et al. (2010). Part 5: Adult basic life support: 2010 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Resuscitation*, **81**(Suppl. 1), e48–70.
3. Ogawa T, Akahane M, Koike S, Tanabe S, Mizoguchi T, and Imamura T. (2011). Outcomes of chest compression only CPR versus conventional CPR conducted by lay people in patients with out of hospital cardiopulmonary arrest witnessed by bystanders: nationwide population based observational study. *British Medical Journal*, **342**, c7106.
4. Kitamura T, Iwami T, Kawamura T, et al. (2010). Conventional and chest-compression-only cardiopulmonary resuscitation by bystanders for children who have out-of-hospital cardiac arrests: a prospective, nationwide, population-based cohort study. Lancet, **375**(9723), 1347–54.
5. Safar P, Brown TC, and Holtey WJ. (1962). Failure of closed chest cardiac massage to produce pulmonary ventilation. *Diseases of the Chest*, **41**, 1–8.
6. Bobrow BJ, Ewy GA, Clark L, et al. (2009). Passive oxygen insufflation is superior to bag-valve-mask ventilation for witnessed ventricular fibrillation out-of-hospital cardiac arrest. *Annals of Emergency Medicine*, **54**(5), 656–62 e1.
7. Berg RA, Sanders AB, Kern KB, et al. (2001). Adverse hemodynamic effects of interrupting chest compressions for rescue breathing during cardiopulmonary resuscitation for ventricular fibrillation cardiac arrest. *Circulation*, **104**(20), 2465–70.
8. Aufderheide TP, Sigurdsson G, Pirrallo RG, et al. (2004). Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation*, **109**(16), 1960–5.

9. Abella BS, Alvarado JP, Myklebust H, et al. (2005). Quality of cardiopulmonary resuscitation during in-hospital cardiac arrest. *Journal of the American Medical Association*, **293**(3), 305–10.
10. Curley G, Kavanagh BP, and Laffey JG. (2010). Hypocapnia and the injured brain: more harm than benefit. *Critical Care Medicine*, **38**(5), 1348–59.
11. O'Driscoll BR, Howard LS, and Davison AG. (2008). BTS guideline for emergency oxygen use in adult patients. *Thorax*, **63**(Suppl. 6), vi1–68.
12. Deakin CD, Nolan JP, Soar J, et al. (2010). European Resuscitation Council Guidelines for Resuscitation 2010 Section 4. Adult advanced life support. *Resuscitation*, **81**(10), 1305–52.
13. Kilgannon JH, Jones AE, Parrillo JE, et al. (2011). Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest. *Circulation*, **123**(23), 2717–22.
14. Ferguson LP, Durward A, and Tibby SM. (2012). Relationship between arterial partial oxygen pressure after resuscitation from cardiac arrest and mortality in children. *Circulation*, **126**(3), 335–42.
15. Soar J, Mancini ME, Bhanji F, et al. (2012). Part 12: Education, implementation, and teams: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*, **81**(Suppl. 1), e288–330.
16. Nolan J. (2015). *Advanced Life Support*, 7th edn. London: Resuscitation Council (UK).
17. Yeung J, Meeks R, Edelson D, Gao F, Soar J, and Perkins GD. (2009). The use of CPR feedback/prompt devices during training and CPR performance: a systematic review. *Resuscitation*, **80**(7), 743–51.
18. Edelson DP, Eilevstjonn J, Weidman EK, Retzer E, Hoek TL, and Abella BS. (2010). Capnography and chest-wall impedance algorithms for ventilation detection during cardiopulmonary resuscitation. *Resuscitation*, **81**(3), 317–22.
19. Cook TM, Woodall N, Harper J, and Benger J. (2011). Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. *British Journal of Anaesthesia*, **106**(5), 632–42.
20. Pokorna M, Necas E, Kratochvil J, Skripsky R, Andrlik M, and Franek O. (2010). A sudden increase in partial pressure end-tidal carbon dioxide (P(ET)CO(2)) at the moment of return of spontaneous circulation. *Journal of Emergency Medicine*, **38**(5), 614–21.

PART 3.2

Circulatory management

CHAPTER 61

Pathophysiology and causes of cardiac arrest

Peter Thomas Morley

Key points

- Sudden cardiopulmonary arrest (CPA) is the commonest cause of death globally.
- Most CPAs are due to cardiac causes, except in children where respiratory causes are more common.
- Identification and treatment of reversible causes of CPAs (4 Hs and 4 Ts) during the arrest appears to improve survival.
- CPAs due to primary arrhythmias, especially in young adults or children, may represent a genetic/familial cause.
- Survivors of CPAs develop an inflammatory response that can result in adverse effects in many organ systems.

Introduction

Sudden cardiopulmonary arrest (CPA) is the commonest cause of death around the world. Sporadic attempts at resuscitation of sudden unexpected deaths have been reported for thousands of years, especially for neonates and victims of drowning. Initial attempts at resuscitation were limited to replacing or restoring breathing, as apnoea was the observed pathology, and it was assumed that restarting the heart was not possible. Establishing the aetiology of sudden death is usually difficult without an obvious cause (e.g. trauma, drowning, or electrocution). In the past, as now, the observed causes of CPA have driven the search for better treatment and prevention. The past 200 years has seen a shift in focus from trauma and drowning to deaths under anaesthesia, electrical injury, and most recently myocardial ischaemia.

Understanding the aetiology of cardiopulmonary arrests

Sudden CPA can occur anywhere, but the location of arrest is usually categorized as out-of-hospital or in-hospital, each of which have similarities and differences. The likelihood of CPA has driven a more targeted approach to training in basic life support and cardiopulmonary resuscitation (CPR). The CPA itself is due to rhythms that are either shockable (ventricular fibrillation (VF) or pulseless ventricular tachycardia), or not shockable (asystole and pulseless electrical activity (PEA); previously known as electro-mechanical dissociation or EMD). All of these rhythms require early basic life support followed by advanced life support. The requirement for early shocks in shockable rhythms has resulted in widespread distribution of automated external defibrillators (public access defibrillation). The majority of CPA in both out-of-hospital and in-hospital settings appear to be of cardiac origin, but the actual underlying causes, presenting rhythms and co-morbidities vary significantly among populations and between studies.

Out-of-hospital CPA

Approximately 75% of deaths from CPA occur in the prehospital setting. Cardiac arrests in the community occur at approximately 50–150/100,000 person years [1]. The incidence of CPA (and their outcomes) is significantly affected by the denominator used, e.g. including all cardiac arrests (89/100,000 person years) versus including only those with a presumed cardiac cause where resuscitation was attempted (31/100,000 person years) [2]. In addition to this, the incidence is variable depending on the reporting area of interest (e.g. between cities and between countries) [3]. In adults, the incidence of CPA increases with increasing age [1]. Perinatal asphyxia is obviously a unique situation, and will not be discussed here in any detail.

Apart from obvious causes (such as trauma or drowning), determining the actual aetiology of the out-of-hospital CPA can be very difficult.

Out-of-hospital CPA in children

Large registries are now providing insights into CPA in the out-of-hospital setting in children. The incidence of CPA is highest in infants (< 1 year; 73/100,000 person years); this is higher than for children (1–11 years; 4/100,000 person years), or adolescents (12–19 years; 6/100,000 person years) [4]. In this study, the overall rate of return of spontaneous circulation in the field was 10% and overall 6.4% survived to hospital discharge (3.3% for infants, 9.1% for children, and 8.9% for adolescents) [4]. The majority of paediatric CPAs are due to respiratory causes (including drowning). Other causes identified include cardiac (including congenital heart disease), trauma, neurological conditions, drug overdose/toxicity, and electrolyte disorders.

The majority of deaths in young adults are due to accidents and trauma, with only 15–20% due to cardiac causes [5].

Out-of-hospital CPA in adults

The incidence of out-of-hospital CPA in the published literature in adults has been quite variable (50–150/100,000 person years). The large Resuscitation Outcomes Consortium epistry reported

a range of incidences from 71.8–159.0 per 100,000 person years (median 96.8), with survival to hospital discharge ranging from 3.0–16.3% (median 8.4%) [6]. The incidence of CPA is reported to be higher in the poorer metropolitan neighbourhoods of the US and Canada. In addition, in the United States, Latinos and blacks are at higher risk for non-shockable rhythms, with their inherent worse prognosis.

A common way of reporting CPA outcomes is to use the Utstein benchmark (cases of attempted resuscitation following adult, witnessed CPA, with an initial rhythm of VF/pulseless ventricular tachycardia). Using this definition, survival to 28 days for out-of-hospital CPA has been reported to range from 4.5–37.7% [3].

Cardiac causes of out-of-hospital CPA in adults

The majority (60–80%) of adult out-of-hospital CPAs are due to cardiac disease [3,7]. Obviously the term 'cardiac causes' includes a large number of subcategories. The commonest cardiac cause in adults is ischaemic heart disease [1], where an identified coronary occlusion is detected in most patients with recent CPA (including at least 25% of those without ST-elevation) [7]. Other specific cardiac causes include cardiomyopathy, valvular abnormalities, and primary cardiac arrhythmias (both brady-arrhythmias and tachyarrhythmias) [1]. The group of primary arrhythmias is of special interest because of the implications for genetic counselling [1,5] and for the specific potential benefits of anti-arrhythmic drugs, electrophysiological ablation techniques, or implantable defibrillators.

Non-cardiac causes of out-of-hospital CPA in adults

There are a large number of conditions, involving a myriad of organ systems, which can result in CPA (see Box 61.1). The teaching surrounding cardiac arrest management has evolved to focus on the detection and correction of potential causes of cardiac arrests, and a number of educational approaches have been used to help rescuers consider these causes. These approaches include the commonly used 'Hs and Ts' [8] (see Box 61.2) advocated by many resuscitation councils, the simple zig-zag technique [9] and the use of ultrasound. The most important justification for identifying or excluding these causes is that the use of individualized specific treatment may be lifesaving [8].

Box 61.1 Non-cardiac causes of cardiopulmonary arrest [10]

- Pulmonary (including pulmonary emboli).
- Aortic dissection/rupture.
- Intoxication/adverse drug reactions.
- Hypovolemia/exsanguination.
- Electrolytes/metabolic.
- Neurological.
- Sepsis.
- Accidental hypothermia.
- Other and unknown causes.

Reprinted from *Resuscitation*, **83**, 10, Wallmuller C et al., 'Causes of in-hospital cardiac arrest and influence on outcome', p. 1206, Copyright 2012, with permission from Elsevier and the European Resuscitation Council.

Box 61.2 4 Hs and 4 Ts (www.resus.org.au)

- Hypoxaemia.
- Hypovolaemia.
- Hyper/hypokalaemia and metabolic disorders.
- Hypo/hyperthermia.
- Tension pneumothorax.
- Tamponade.
- Toxins/poisons/drugs.
- Thrombosis—pulmonary/coronary.

Data from www.resus.org.au<http://www.resus.org.au>.

In-hospital cardiopulmonary arrest

It is estimated that the total number of in-hospital CPA where resuscitation is attempted, is similar to the number seen in the out-of-hospital setting. Patients may be in-hospital for a number of reasons, including for minor procedures, but in general hospitalized patients have more comorbidities and are sicker than the general population.

In-hospital CPA in children

In-hospital CPA in children is very uncommon ranging from 0.11/1000 admissions [11], to approximately 3/1000 admissions [12]. The majority of these cases appear due to cardiac causes (including congenital heart disease). The survival rates are better with shockable rhythms, and appear to be improving over time with all rhythms [13]. These survival rates are higher than those seen in the out-of-hospital setting [13], despite the fact that the in-patients have more comorbidities.

In-hospital CPA in adults

The vast majority of in hospital deaths occur in settings where they are expected, and resuscitation attempts are not made [14,15]. The reported incidence of in-hospital CPA in adults where resuscitation is attempted ranges from 3.8–13.1 per 1000 admissions [12]. Outcomes again seem to be critically dependent on the underlying rhythm at the time of the arrest [10,12], with the best outcomes seen with shockable rhythms, and in hospitals with a higher cardiac arrest volume. Registry data have reported improvements in survival over the past decade [12]. In-hospital CPAs that are actively treated are associated with a higher survival than out-of-hospital CPA, especially for non-shockable rhythms. This is probably due to a combination of early recognition, early advanced life support, and the detection and treatment of reversible causes (given the access to a wider range of investigative and treatment options) [8]. Arrests in patients that are witnessed (or monitored) also appear to have better outcomes [12].

The majority of in-hospital CPA seem to be related to cardiac causes, but other causes include: respiratory (e.g. pulmonary emboli, hypoxia), vascular (e.g. aortic rupture), intoxications and adverse drug effects, blood loss, metabolic causes (e.g.

hyperkalaemia and hypokalaemia), and others (including neurological, sepsis, complications of interventions, and accidental hypothermia) [8,10].

Those patients with cardiac causes for CPA had better outcomes than those with non-cardiac causes. The best survival outcomes from any CPA (near 100%) occur in the electro-physiology laboratory, where VF is often deliberately induced.

A lot is known about the antecedents to in-hospital CPA [12,16], and rapid response systems have been developed to intervene well before CPA ensues.

In patients aged 65 years or older, factors associated with lower odds of survival included older age, male sex, chronic disease burden, and black or other non-white race [15]. Cardiac arrests were also more frequent for black and other non-white patients [15].

Specific situations

Anaesthesia

The incidence of anaesthesia-related CPA appears to be decreasing. In patients undergoing non-cardiac surgery the reported incidence ranges from 0.2–1.1 per 10,000 adults and from 1.4–2.9 per 10,000 children [17]. The overwhelming majority of patients are in non-shockable rhythms at the time of arrest, and the CPA appear to be related to pre-existing medical or surgical disease [17]. The other key aetiological factors can be grouped into the categories of anaesthetic technique (including drug-related) and those associated with the surgical procedure. Airway and ventilatory causes of arrest have decreased since the introduction of improved monitoring (e.g. pulse oximetry, capnography, ventilator alarms), and guidelines and training around management of the difficult airway [17].

Intensive care

A large, but variable proportion of reported in-hospital CPA occur in the intensive care setting, where significant monitoring and interventions are already in place. In one series the published survival to hospital discharge after nearly 50,000 cardiac arrests in critically patients was 15.9%, but this was much lower in patients receiving vasopressors at the time of arrest [18].

Pathophysiology of CPA

The actual CPAs are due to either shockable or non-shockable rhythms. Irrespective of the initiating rhythm, the end result of a CPA is inadequate delivery of oxygenated blood to the tissues. This process, combined with the underlying cause of the arrest, result in a large number of changes within the body. These include the activation of a number of mechanisms that result in a systemic inflammatory response, as well as irreversible damage to those organs at particular risk. A three-stage approach has been proposed to describe the sequential activation of various biochemical pathways: an electrical phase, a circulatory phase, and a metabolic phase. Tissue injury can occur from any of the compounding effects of local ischaemia, global ischaemia, and reperfusion. The changes in levels of oxygen free radicals, endotoxin, cytokines, interleukins, and tumour necrosis factor, as well as a number of other immunological effects, are similar to those seen with systemic sepsis. The resultant organ system damage (post-cardiac arrest syndrome) has been divided into, post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, and the systemic ischaemia/reperfusion response [12,19]. The occurrence of all of these phenomena has resulted in the tailoring of post-arrest therapy in a way to minimize the damage done, and speed recovery of function [12].

Ischaemic organ damage

Organs at particular risk of direct ischaemic damage include the brain, the heart, and the kidneys. The brain is at particular risk, because of its high oxygen consumption (and hence intolerance of ischaemia) and its response to reperfusion. Specific potential mechanisms for neuronal injury include excitotoxicity, disrupted calcium homeostasis, free radical formation, pathological protease cascades, and the activation of cell death signalling pathways [19]. Specific areas of the brain at risk include the hippocampus, the cortex, the cerebellum, the corpus striatum, and the thalamus [19].

Conclusion

The increasing understanding of the epidemiology and pathophysiology of cardiac arrests has resulted in improved outcomes over the last decade. Continued focus on prevention, early detection and individualized treatment will hopefully result in ongoing improvements.

References

1. Deo R and Albert CM. (2012). Epidemiology and genetics of sudden cardiac death. *Circulation*, **125**(4), 620–37.
2. Finn JC, Jacobs IG, Holman CD, and Oxer HF. (2001). Outcomes of out-of-hospital cardiac arrest patients in Perth, Western Australia, 1996–1999. *Resuscitation*, **51**(3), 247–55.
3. Fridman M, Barnes V, Whyman A, et al. (2007). A model of survival following pre-hospital cardiac arrest based on the Victorian Ambulance Cardiac Arrest Register. *Resuscitation*, **75**(2), 311–22.
4. Atkins DL, Everson-Stewart S, Sears GK, et al. (2009). Epidemiology and outcomes from out-of-hospital cardiac arrest in children: the Resuscitation Outcomes Consortium Epistry-Cardiac Arrest. *Circulation*, **119**(11), 1484–91.
5. Morrow W, Berger S, Jenkins K, et al. (2012). Pediatric sudden cardiac arrest. *Pediatrics*, **129**(4), e1094–102.
6. Nichol G, Thomas E, Callaway CW, et al. (2008). Regional variation in out-of-hospital cardiac arrest incidence and outcome. *Journal of the American Medical Association*, **300**(12), 1423–31.
7. Kern KB. (2012). Optimal treatment of patients surviving out-of-hospital cardiac arrest. *JACC Cardiovascular Interventions*, **5**(6), 597–605.
8. Saarinen S, Nurmi J, Toivio T, Fredman D, Virkkunen I, and Castren M. (2012). Does appropriate treatment of the primary underlying cause of PEA during resuscitation improve patients' survival? *Resuscitation*, **83**(7), 819–22.
9. Kloeck WG. (1995). A practical approach to the aetiology of pulseless electrical activity. A simple 10-step training mnemonic. *Resuscitation*, **30**(2), 157–9.
10. Wallmuller C, Meron G, Kurkciyan I, Schober A, Stratil P, and Sterz F. (2012). Causes of in-hospital cardiac arrest and influence on outcome. *Resuscitation*. **83**(10), 1206–11.
11. Tibballs J, Kinney S, Duke T, Oakley E, and Hennessy M. (2005). Reduction of paediatric in-patient cardiac arrest and death with a medical emergency team: preliminary results. *Archives of the Diseases of Childhood*, **90**(11), 1148–52.
12. Morrison LJ, Neumar RW, Zimmerman JL, et al. (2013). Strategies for improving survival after in-hospital cardiac arrest in the United States: 2013 consensus recommendations: a consensus statement from the American Heart Association. *Circulation*, **127**(14), 1538–63.
13. Kleinman ME, Chameides L, Schexnayder SM, et al. (2010). Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines

for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*, **122**(18, Suppl. 3), S876–908.
14. Chen J, Flabouris A, Bellomo R, Hillman K, and Finfer S. (2008). The Medical Emergency Team System and not-for-resuscitation orders: results from the MERIT study. *Resuscitation*, **79**(3), 391–7.
15. Ehlenbach WJ, Barnato AE, Curtis JR, et al. (2009). Epidemiologic study of in-hospital cardiopulmonary resuscitation in the elderly. *New England Journal of Medicine*, **361**(1), 22–31.
16. Churpek MM, Yuen TC, and Edelson DP. (2013). Predicting clinical deterioration in the hospital: The impact of outcome selection. *Resuscitation*, **84**(5), 564–8.
17. Zuercher M and Ummenhofer W. (2008). Cardiac arrest during anesthesia. *Current Opinion in Critical Care*, **14**(3), 269–74.
18. Tian J, Kaufman DA, Zarich S, et al. (2010). Outcomes of Critically Ill Patients Who Received Cardiopulmonary Resuscitation. *American Journal of Respiratory and Critical Care Medicine*, **182**, 501–6.
19. Nolan JP, Neumar RW, Adrie C, et al. (2008). Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. *Resuscitation*, **79**(3), 350–79.

CHAPTER 62

Cardiac massage and blood flow management during cardiac arrest

Gavin D. Perkins

Key points

- The quality of cardiopulmonary resuscitation (CPR) is critical to outcome from cardiac arrest.
- Optimal CPR quality is defined by compressions of adequate depth, rate, and avoidance of both leaning and interruptions to chest compressions.
- Compression only CPR is useful during dispatcher assisted CPR and if a CPR provider is unable or unwilling to perform ventilation.
- Mechanical chest compression devices can be helpful when it is difficult or unsafe to perform manual CPR.
- Vasoactive drugs improve haemodynamics and short term patient outcomes, but may worsen long term outcomes.

Introduction

When cardiac arrest occurs, meaningful blood flow ceases within seconds, leading to loss of consciousness and a decline in oxygen delivery to the vital organs. Without intervention, energy stores are depleted within minutes and a cascade of biochemical reactions occur, which culminate in death.

The birth of modern cardiopulmonary resuscitation (CPR) is widely attributed to a report in the *Journal of the American Medical Association* in 1960 [1]. External chest compressions were applied to a group of 20 patients in cardiac arrest—14 were successfully resuscitated and survived to hospital discharge. The authors concluded that 'Anyone, anywhere, can now initiate cardiac resuscitative procedures. All that is needed are two hands' [1].

At best, external chest compressions achieve approximately one-third of the normal cardiac output. Since the early descriptions of chest compressions, considerable information has emerged to define the optimal characteristics of chest compressions.

Optimal chest compression characteristics

Compression depth

Most animal models show a linear relationship between chest compression depth and cardiac output, coronary perfusion pressure and flow, although some suggest this effect plateaus at higher compression depths. In humans, increasing compression force raises aortic systolic pressure and end-tidal carbon dioxide, although there is no effect on aortic diastolic pressure [2]. Observational studies found deeper chest compressions are associated with defibrillation success, return of spontaneous circulation and survival to hospital admission [3]. In a cohort of 9136 adult patients receiving resuscitation from out of hospital cardiac arrest chest compression depth >38 mm was associated with better outcome [4]. For each 5 mm increment in compression depth the adjusted odds ratios were 1.06 (95% CI 1.04–1.08) for return of spontaneous circulation, 1.05 (95% CI 1.03–1.08) for 1-day survival and 1.04 (95% CI 1.00–1.08) for survival to discharge. Covariate-adjusted spline curves revealed that the maximum survival is at a depth of 45.6 mm (optimal range 40.3 and 55.3 mm) with no differences between men and women.

Chest compression rate

Higher compression rates are linked to better outcomes. The ILCOR review of science (2015) concluded that compression rates should be between 100–120/min [4]. Observational and experimental studies show that compression rates exceeding 120/min impact on other compression quality parameters (e.g. compression depth, leaning, decay) [5]. Data from recent human studies suggest a threshold effect with compression rates greater than 120/min are linked to worse outcomes [6].

Duty cycle

Duty cycle refers to the proportion of the chest compression cycle spent in the compression phase relative to the relaxation phase. Forward coronary blood flow occurs during the decompression phase of a chest compression cycle. Mathematical and animal models suggest a duty cycle of 50% is optimal.

Leaning

Failing to fully release pressure from the chest between sequential chest compressions is known as leaning. Observational studies indicate that leaning is relatively common during resuscitation. In animal models, even small amounts of leaning are associated with reduced mean arterial blood pressure, coronary perfusion pressure, cardiac output, and myocardial blood flow [7]. Guidelines recommend ensuring that pressure is fully released between sequential chest compressions.

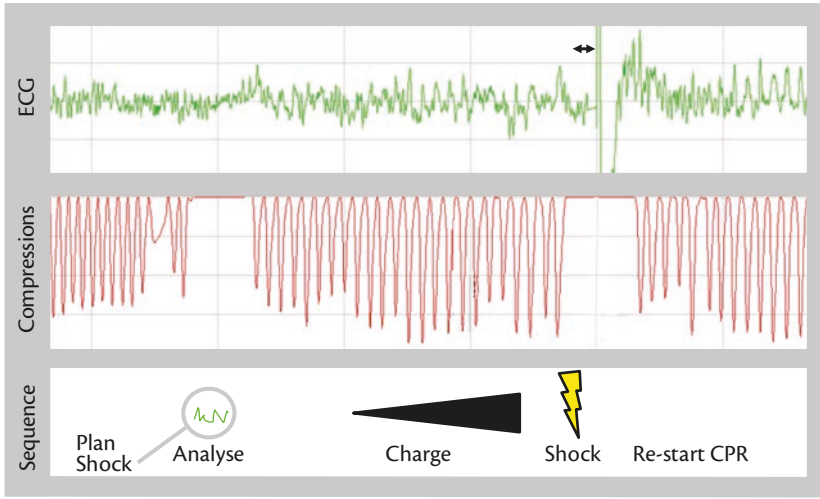


Fig. 62.1 Defibrillation sequence to minimize interruptions in CPR before a shock.
Reproduced from *Heart*, Perkins GD, et al., 'Out-of-hospital cardiac arrest: recent advances in resuscitation and effects on outcome', **98**(7), pp. 529–38, copyright 2011 with permission from BMJ Publishing Group Ltd.

Interruptions in chest compressions

Interruptions in chest compressions are common. Analysis of the reasons for interruptions identifies airway interventions, rhythm analysis, operating the defibrillator, switching chest compression provider, and poor team dynamics as causative factors. Interruptions in chest compressions are harmful, particularly around the time of attempted defibrillation. Interruptions just before a shock reduce the likelihood of shock success. In a series of 2006 cases, analyses adjusted for Utstein variables found that pre-shock pauses of < 10 sec and peri-shock pauses of < 20 sec improved survival to hospital discharge [8]. Pausing chest compressions briefly to check rhythm and then restarting chest compressions while the defibrillator is charged (Fig. 62.1) can minimize preshock pauses to less than 2 seconds [9].

Chest compression fraction

Compression fraction is the proportion of the resuscitation time during which compressions are performed; the higher the compression fraction, the better the outcome. In an observational study in 506 in-hospital cardiac arrests, the adjusted odds ratio for survival was 1.11 (95% CI, 1.01–1.21) for every 0.1 increase in compression fraction. Higher compression to ventilation ratios are linked to higher compression fractions; the current recommended ratio of compressions to ventilations of 30:2 is associated with higher chest compression fractions than previous ratios of 5:1 or 15:2. Asynchronous ventilation and continuous chest compressions minimize interruptions in CPR and are possible once the airway is secured with an endotracheal tube or supraglottic airway device.

Compression-only CPR

During the first few minutes after cardiac arrest due to a cardiac cause, there is likely to be sufficient oxygen within the lungs to maintain oxygenation during CPR. Randomized controlled trials provide convincing evidence that ambulance dispatcher telephone instructions should focus on compression only CPR [10]. Compression-only CPR is certainly better than no CPR in the event that a rescuer was unable or unwilling to do full CPR. However, there are certain specific situations where compressions-only CPR (without ventilation) is harmful; these include arrest secondary to asphyxia, cardiac arrest in children, and during prolonged resuscitation attempts.

Adjuncts and alternatives to CPR

Impedance threshold device

The impedance threshold device (ITD) [11] is a one-way valve that is placed at the airway to limit airflow into the lungs during chest recoil between compressions. This reduces intrathoracic pressure and increases venous return to the heart. Although most animal studies show improved haemodynamics during CPR with the ITD, clinical trials have produced conflicting results.

Active compression decompression

The active compression–decompression CPR (ACD-CPR) device is a hand-held manually-operated device that incorporates a suction cup to enable the chest to be lifted actively during decompression. Active decompression reduces intrathoracic pressure, which increases venous return to the heart and enabling increased cardiac output and increases coronary and cerebral perfusion pressures during the compression phase. However, a Cochrane review of ten trials found no evidence for improved patient-centred outcomes [12].

CPR feedback devices

CPR feedback and prompt devices allow real time feedback in training and clinical settings. Devices range from a simple metronome or flashing light that guide compression rate to more complex devices that monitor and provide feedback about actual CPR performance. The more complex devices allow data download at the end of the event for subsequent performance review, audit, and/or debriefing. The ILCOR systematic review of CPR feedback and prompt devices concluded that there is good evidence supporting the use of CPR feedback/prompt devices during CPR training to improve CPR skill acquisition and retention

[13]. Their use in clinical practice as part of an overall strategy to improve the quality of CPR may be beneficial.

Mechanical compression devices

Mechanical compression devices automate the process of manual chest compression. Most experimental studies show improved haemodynamics with mechanical CPR [14]. Additional advantages of mechanical compression devices are that they provide CPR of a consistent quality and can be deployed in situations where manual chest compressions are difficult (e.g. in an ambulance or during a percutaneous coronary intervention procedure) [14]. Despite theoretical advantages 3 large randomised trials have failed to show improved long-term outcomes [15–18]. ILCOR therefore recommends against the routine use of mechanical CPR devices. Mechanical CPR may be considered in situations where manual CPR is impractical or may compromise provider safety. Such situations may include ambulance transport, during cardiac catheterisation and prolonged resuscitation attempts.

Vasoactive drugs

Adrenaline (epinephrine) has been an integral component of advanced resuscitation algorithms since the early 1960s. Initial guidelines recommended intracardiac adrenaline (0.5 mg) or high dose intravenous adrenaline (10 mg). Adrenaline increases the rate of return of spontaneous circulation but impairs cerebral blood flow and increases cardiovascular instability [19]. This creates the paradox of an increase in initial survival, but worse survival and greater brain injury by the time of hospital discharge [20]. The need for randomized, placebo-controlled trials has been indentified by the International Liaison Committee for Resuscitation.

Extracorporeal Resuscitation

Extracorporeal membrane oxygenation (E-CPR) has been used as a rescue therapy in refractory cardiac arrest. A growing number of observational studies report survivors amongst patients who would otherwise have had resuscitation attempts terminated [20]. From the limited literature available, it is too early to draw definitive conclusions as to the effectiveness of this intervention for which patient selection is likely to be the key to the success. Identification of patients with limited co-morbidities, a reversible cause of cardiac arrest, and other good prognostic factors (e.g. witnessed arrest, early bystander CPR) and initating ECPR within 60 minutes of cardiac arrest is likely to be central to whether the treatment is found to clinically and cost effective [20].

References

1. Kouwenhoven WB, Jude JR, and Knickerbocker GG. (1960). Closed-chest cardiac massage. *Journal of the American Medical Association*, **173**, 1064–7.
2. Ornato JP, Levine RL, Young DS, Racht EM, Garnett AR, Gonzalez ER. (1989) The effect of applied chest compression force on systemic arterial pressure and end-tidal carbon dioxide concentration during CPR in human beings. *Annals Emergency Medicine*, **18**, 732–7.
3. Perkins GD, Travers AH, Berg RA, et al. (2015). Part 3: Adult basic life support and automated external defibrillation: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*, 2015, **95**, e43–69.
4. Stiell IG, Brown SP, Nichol G et al. (2014). What is the optimal chest compression depth during out-of-hospital cardiac arrest resuscitation of adult patients? *Circulation,* **130**, 1962–70.
5. Field RA, Soar J, Davies RP, Akhtar N, Perkins GD. (2012). The impact of chest compression rates on quality of chest compressions—a manikin study. *Resuscitation*, **83**, 360–4.
6. Idris AH, Guffey D, Pepe PE, et al. (2015). Chest compression rates and survival following out-of-hospital cardiac arrest *Critical Care Medicine*, **43**(4), 840–8.
7. Zuercher M, Hilwig RW, Ranger-Moore J, et al. (2010). Leaning during chest compressions impairs cardiac output and left ventricular myocardial blood flow in piglet cardiac arrest. *Critical Care Medicine*, **38**, 1141–6.
8. Cheskes S, Schmicker RH, Verbeek PR, et al. (2014). The impact of peri-shock pause on survival from out-of-hospital shockable cardiac arrest during the Resuscitation Outcomes Consortium PRIMED trial. *Resuscitation,* **85**, 336–42.
9. Perkins GD, Davies RP, Soar J, and Thickett DR. (2007). The impact of manual defibrillation technique on no-flow time during simulated cardiopulmonary resuscitation. *Resuscitation*, **73**, 109–14.
10. Hupfl M, Selig HF, and Nagele P. (2010). Chest-compression-only versus standard cardiopulmonary resuscitation: a meta-analysis. *Lancet*, **376**, 1552–7.
11. Wang CH, Tsai MS, Chang WT, *et al.* (2015). Active Compression-Decompression Resuscitation and Impedance Threshold Device for Out-of-Hospital Cardiac Arrest: A Systematic Review and Metaanalysis of Randomized Controlled Trials. *Critical Care Medicine,* **43***, 889–96*
12. Lafuente-Lafuente C and Melero-Bascones M. (2013). Active Chest Compression-Decompression for Cardiopulmonary Resuscitation. *Cochrane Database of Systemic Reviews*, CD002751.
13. Yeung J, Meeks R, Edelson D, Gao F, Soar J, and Perkins GD. (2009). The use of CPR feedback/prompt devices during training and CPR performance: a systematic review. *Resuscitation*, **80**, 743–51.
14. Couper KM, Smyth MS, Perkins GD. (2015). Mechanical chest-compression devices: to use or not to use. *Current Opinions in Critical Care*, **21**, 188–94.
15. Rubertsson S, Lindgren E, Smekal D *et al.* (2014). Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial. *Journal American Medical Association*, **311**, 53–61.
16. Wik L, Olsen JA, Persse D et al. (2014) Manual vs. integrated automatic load-distributing band CPR with equal survival after out of hospital cardiac arrest. The randomized CIRC trial. *Resuscitation*, **85**, 612–16.
17. Perkins GD, Lall R, Quinn T, et al. (2015). Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. *Lancet*, **385**, 947–55.
18. Perkins GD, Cottrell P, and Gates S. (2014). Is adrenaline safe and effective as a treatment for out of hospital cardiac arrest. *British Medical Journal*, **348**, g2435.
19. Larabee TM, Liu KY, Campbell JA, and Little CM. (2012). Vasopressors in cardiac arrest: a systematic review. *Resuscitation*, **83**(8), 932–9.
20. Fagnoul D, Combes A, De Backer D, (2014). Extracorporeal cardiopulmonary resuscitation. *Curr Opin Crit Care*, **20**(3):259–65.

CHAPTER 63

Defibrillation and pacing during cardiac arrest

Charles D. Deakin

Key points

- Defibrillation should not be allowed to interrupt external chest compressions for more than 5 seconds.
- Biphasic waveforms are more effective than the older monophasic waveform.
- In adults, biphasic shocks should commence at 150 J, with subsequent shocks being given at the same or greater energy levels.
- In children (<8 years), all shocks should be delivered at 4 J/kg.
- External pacing is ineffective for asystole, but should be considered for bradyarrhythmias refractory to pharmacological therapy.

Defibrillation

Defibrillation is the passage of an electrical current across the myocardium in order to change the electrical activity of the heart from a chaotic to organized rhythm. It is a term usually used in relation to the treatment of ventricular fibrillation (VF) or ventricular tachycardia (VT); when used for the treatment of atrial fibrillation (AF) or atrial flutter, it is usually termed 'cardioversion'.

History

Although the Danish physician Abildgaard described the use of electricity to stun and revive chickens in 1775, it was not until 1899 when Prevost and Batelli demonstrated that electric shocks could terminate VF in dogs that a more scientific understanding of defibrillation began. The first successful human defibrillation was performed in 1947 by Beck, using internal cardioversion, followed nine years later by Zoll using external defibrillation. Direct current defibrillation soon replaced alternating current as it was shown to result in less myocardial stunning and fewer post-shock arrhythmias.

Mechanisms of action

The precise mechanism of defibrillation remains unknown and the existence of several hypotheses suggests that a complex mechanism underlies the ability of electrical impulses to restore organized electrical activity in the heart [1].

Critical mass hypothesis

Proposes that only a critical mass of myocardium must be depolarized, rather than the entire myocardium. Activation fronts not terminated by the shock in the remaining myocardium are not sufficient to maintain fibrillation and soon extinguish. The critical mass has been estimated as 75–90% of myocardial mass.

Upper limit of vulnerability hypothesis

Proposes that to successfully defibrillate, a shock must:

- Halt the activation fronts of fibrillation by either directly activating the myocardium or by rendering it refractory to stimulation just ahead of these activation fronts.
- Prevent re-initiation of new activation fronts, which could propagate away from the border of the directly excited region and re-initiate fibrillation [2].

Refractory period extension hypothesis

Proposes that because successful defibrillation shock extends the refractory period of action potentials in excitable myocardium, VF wave fronts are terminated by blocking their propagation throughout the ventricles.

Synchronized repolarization hypothesis

Proposes that a defibrillation shock creates an additional phase of depolarization from just after completion of the upstroke (phase 0) to a nearly maximal repolarization time (late phase 3), of the fibrillating action potentials. As a result, the myocardium repolarizes at a constant time after the shock irrespective of its pre-shock fibrillating electrical activity. This creates an iso-electric window during which synchronized electrical activity can resume.

Virtual electrode polarization hypothesis

Defibrillation shocks can produce simultaneous areas of depolarization and hyperpolarization. Depolarization can result in prolongation of the action potential if the tissue is refractory, or activation if the tissue is excitable. Conversely, hyperpolarization can shorten the action potential and completely repolarize the tissue to restore excitability [3].

Technical aspects of defibrillation

Waveforms

Biphasic defibrillators have become established as the defibrillators of choice, and very few monophasic defibrillators remain in clinical use. Unfortunately, defibrillators are not marked as to their waveform and the highest possible energy levels should be used if the operator is unsure which type of waveform the defibrillator delivers.

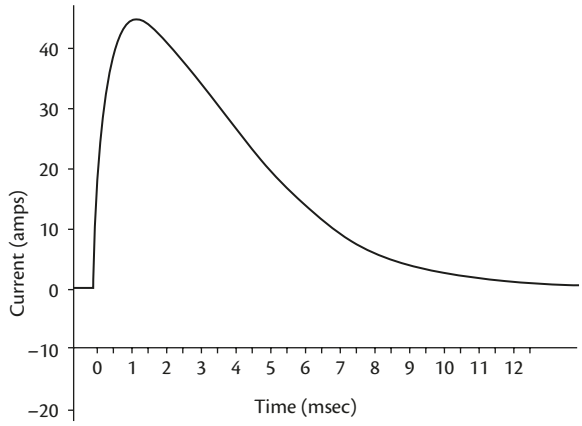


Fig. 63.1 Monophasic damped sinusoidal waveform.

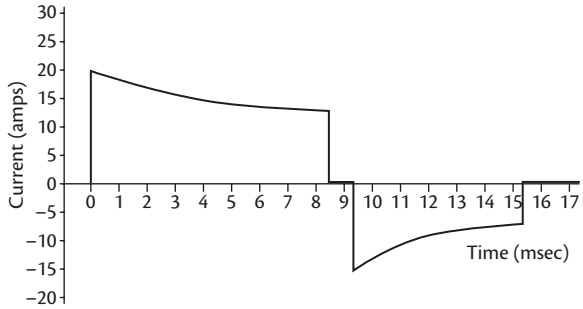


Fig. 63.2 Biphasic truncated exponential waveform.

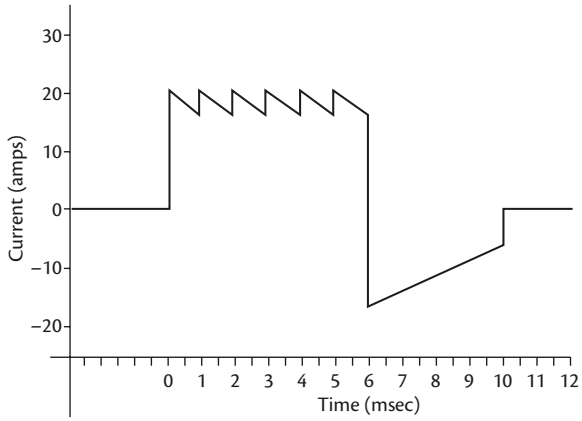


Fig. 63.3 Rectilinear biphasic waveform.

The commonest monophasic waveform is the damped sinusoidal (MDS) waveform, which gradually returns to zero current flow (Fig. 63.1). Monophasic waveforms are very susceptible to variation in transthoracic impedance (TTI); small patients with low TTI would receive an excessive transmyocardial current, and large patients with a high TTI risked receiving a broadened waveform that failed to reach sufficient peak current to achieve successful defibrillation. Monophasic waveforms are of limited efficacy, delivering first shock success rates of 50–70%.

There are two main types of biphasic waveform: the biphasic truncated exponential (BTE) (Fig. 63.2) and the rectilinear biphasic

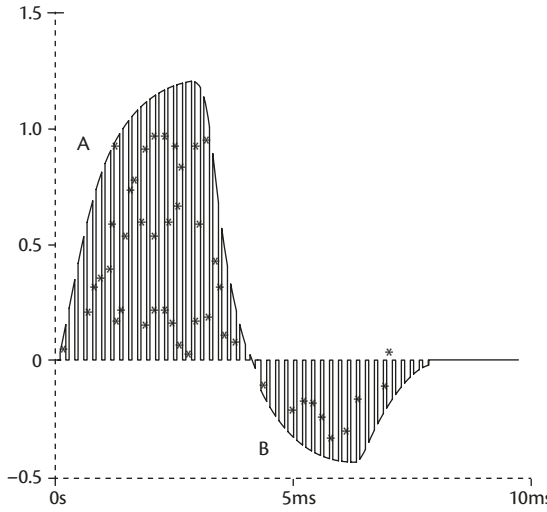


Fig. 63.4 Multiphase biphasic waveform.

(RLB) waveform (Fig. 63.3). Computer modelling suggests that the role of the first positive phase of a biphasic defibrillation waveform is to hyperpolarize the cardiac cell membrane from its most negative potential of approximately –65 mV during fibrillation back to its resting transmembrane voltage of –90mV. This decrease in transmembrane potential is hypothesized to allow Na^+ channels to recover, thus allowing easier tissue stimulation during the second negative phase of the biphasic waveform.

Biphasic defibrillators compensate for variations in transthoracic impedance by electronically adjusting the waveform to optimize its magnitude and duration. Biphasic waveforms typically deliver only half the current associated with monophasic waveforms, but achieve a greater first shock success rate of 90–95%. However, use of biphasic waveforms have not been shown to be associated with greater survival than monophasic waveforms. Because of the significantly lower current, biphasic waveforms are associated with reduced post-shock burns, fewer post-shock arrhythmias, and reduced electrocardiogram (ECG) injury potential.

The newest waveform in clinical use is the multiphasic waveform, in which a multiphase waveform is incorporated into a biphasic waveform. A recent study has demonstrated similar efficacy rates to those seen with biphasic waveforms (Fig. 63.4).

Triphasic, and quadriphasic waveforms are showing promise for delivering effective defibrillation at even lower currents and other novel waveforms such as those that form a spinning thoracic current are also under investigation as potentially effective waveforms.

Safety

Oxygen concentrations as high as 60% have been measured in enclosed environments using oxygen-powered medical devices [4], 24% oxygen doubles the rate of combustion and 30% oxygen increases combustion rate 10-fold. In an oxygen-enriched atmosphere, sparking from poorly applied defibrillator paddles in an oxygen-enriched environment can cause a catastrophic fire.

The risk of fire during attempted defibrillation can be minimized by taking the following precautions:

- Remove any oxygen mask or nasal cannulae and place ≥ 1 m away from the patient's chest.

- Leave any bag-valve device connected to a tracheal tube or other airway adjunct (e.g. laryngeal mask airway, Combitube, or laryngeal tube). Alternatively, disconnect any bag-valve device from the tracheal tube (or other airway adjunct), and remove it ≥ 1 m from the patient's chest during defibrillation.
- If the patient is connected to a ventilator, leave the ventilator tubing (breathing circuit) connected to the tracheal tube during defibrillation [5].

Application of defibrillation electrodes

Self-adhesive defibrillation pads are generally replacing defibrillation paddles. They improve safety by avoiding the need to lean over the patient during defibrillation and provide better electrical contact with the skin compared with the flat metal plates of defibrillation paddles, minimizing the risk of electrical arcing and fire.

Optimal electrode position is one that results in greatest current flow across the myocardium. The standard position to achieve this is the sternal electrode placed to the right of the sternum, immediately below the clavicle and the apical paddle placed in the mid-axillary line (Fig. 63.5), level with the V6 ECG electrode position. Acceptable alternative positions include:

- Bi-axillary.
- **Anterior (left sternal edge)**: posterior (between the left clavicle and spine).
- **Posterior (behind the right clavicle)**: apical [5].

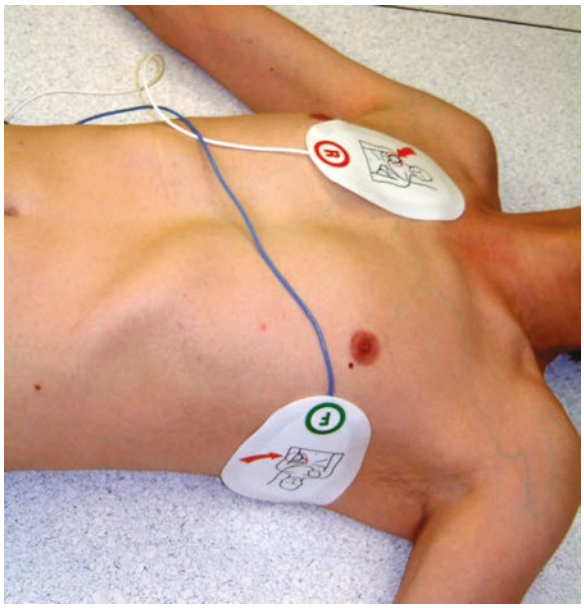


Fig. 63.5 Anterior-apical defibrillation electrode placement.
Reproduced with permission of Charles Deakin © 2012.

Clinical aspects of defibrillation

Defibrillation is one of the few interventions that have been shown to improve survival from cardiac arrest and it is therefore a key link in the chain of survival (Fig. 63.6). The probability of successful defibrillation and neurologically-intact survival to hospital discharge is time critical, with every minute that passes between collapse and defibrillation resulting in an increase in mortality of 7–10%, this increase is slowed marginally in patients receiving bystander resuscitation.

In order to reduce delays in defibrillation, the introduction of public access defibrillators in areas of high population density (e.g. airports, shopping centres, railways stations, etc.) has resulted in significantly improved survival rates, particularly in some urban areas. In more rural areas rapid activation of trained community responders is also contributing to early defibrillation.

CPR versus defibrillation as the initial treatment

Although early studies suggested that a period of cardiopulmonary resuscitation (CPR) for 1–3 minutes prior to defibrillation increased the defibrillation success rate, subsequent larger studies failed to repeat these observations. It is now recommended that when treating both in- and out-of-hospital cardiac arrest, rescuers should provide good-quality CPR, while a defibrillator is quickly applied and charged, but routine preshock CPR (e.g. 2 or 3 minutes) is no longer recommended.

One shock versus three shock sequence

With first shock efficacy of biphasic waveforms exceeding 90%, failure to successfully defibrillate is more likely to suggest the need for a period of CPR, rather than a further shock. The previous recommendations for up to three shocks before resuming CPR have now been superseded by a single shock sequence.

Only on the rare occasion of a monitored VF/non-pulsatile VT arrest, it is acceptable to deliver three stacked shocks using a

Fig. 63.6 Chain of survival.
Reproduced with permission from Laerdal Medical.

manual defibrillator before commencing 2 minutes of external chest compression and ventilation if necessary. Automatic external defibrillators (AEDs) are all programmed to deliver a single shocks before recommencing the 2-minute CPR cycle [5].

Energy levels

First shock efficacy of the BTE waveform using 150–200 J has been reported as 86–98% and of the RLB waveform using 120 J as 85% [6]. The initial biphasic shock should be no lower than 120 J for RLB waveforms and 150 J for BTE waveforms. Ideally, the initial biphasic shock energy should be at least 150 J for all waveforms when defibrillating ventricular arrhythmias.

If the first shock is unsuccessful, there is no evidence to suggest that either a fixed or escalating energy protocol is more effective. However, although an escalating strategy reduces the number of shocks required to restore an organized rhythm compared with fixed-dose biphasic defibrillation, rates of return of spontaneous circulation or survival to hospital discharge are not significantly different between strategies. Both fixed or escalating strategies are acceptable, but when using a manual defibrillator, it is reasonable to increase the energy for subsequent shocks.

The lower efficacy of the monophasic waveform means the initial and all subsequent monophasic shocks should be delivered at 360 J [5].

Detrimental effects of defibrillation

Interruptions to chest compressions adversely affect the outcome of a resuscitation attempt. One of the commonest causes of these interruptions is defibrillation, due to pre-shock and post-pauses in chest compressions associated with ECG analysis, delivery of the shock and a pulse check.

In order to minimize interruptions to chest compressions associated with defibrillation, it is now recommended to continue chest compressions whilst the defibrillator is charged. Immediate resumption of chest compressions following defibrillation is also emphasised, without pausing for a pulse check, which should only then take place after 2 minutes of CPR [7]. Defibrillation should be achievable with an interruption in chest compressions of no more than 5 seconds [8].

Defibrillation in children

Shockable rhythms occur in only 7–15% of paediatric and adolescent arrests with a much lower percentage than in adult cardiac arrest. Common causes of VF in these children include trauma, congenital heart disease, drug overdose, and hypothermia.

Ideally, paediatric self-adhesive pads with electrical attenuators should be used for children aged less than 8 years, but when these are not available, adult pads are acceptable, as long as there is no direct contact between the two electrodes.

The recommended energy levels for both monophasic and biphasic defibrillation are 4 J/kg for the initial and all subsequent shocks [9].

Internal defibrillation

When using internal paddles during a cardiac arrest, a 10–20 J shock is considered optimal [10].

Pacing

In emergencies, pacing is usually limited to delivery through external pads (placed in similar position to that for defibrillation), unless an internal system (endocardial or epicardial) has been placed previously.

External pacing delivers a pulsed transmyocardial impulse that causes ventricular depolarization and myocardial contraction. It is usually delivered in a demand mode because a fixed mode does not sense the QRS complex and risks pacing on the T-wave, with the potential to induce VF. The relatively high current can cause chest muscle contractions and cutaneous pain under the electrode. Using the lowest output setting necessary to achieve capture will minimize this discomfort, but sedation and/or analgesia may be necessary.

Pacing is of no proven effectiveness for asystole unless P waves are present, but it should be considered for:

- Patients with symptomatic bradycardia refractory to anti-cholinergic drugs or other second line therapy.
- Conduction blocks at or below the His-Purkinje level.

If transthoracic pacing is ineffective, consider transvenous pacing which requires central venous access and pacing wire insertion under X-ray guidance or through an appropriate pulmonary artery catheter [5].

References

1. Dosdall DJ, Fast VG, and Ideker RE. (2010). Mechanisms of defibrillation. *Annual Review of Biomedical Engineering*, **12**, 233–58.
2. Walcott GP, Walcott KT, and Ideker RE. (1995). Mechanisms of defibrillation. Critical points and the upper limit of vulnerability. *Journal of Electrocardiology*, **28**, Suppl. 1–6.
3. Efimov IR, Aguel F, Cheng Y, Wollenzier B, and Trayanova N. (2000). Virtual electrode polarization in the far field: implications for external defibrillation. *American Journal of Physiology—Heart and Circulatory Physiology*, **279**, H1055–70.
4. Deakin CD, Paul V, Fall E, Petley GW, and Thompson F. (2007). Ambient oxygen concentrations resulting from use of the Lund University Cardiopulmonary Assist System (LUCAS) device during simulated cardiopulmonary resuscitation. *Resuscitation*, **74**, 303–9.
5. Sunde K, Jacobs I, Deakin CD, et al. (2010). Part 6: defibrillation: 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Resuscitation*, **81**(Suppl. 1), e71–85.
6. Jacobs I, Sunde K, Deakin CD, et al. (2010). Part 6: defibrillation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*, **122**, S325–37.
7. Deakin CD, Nolan JP, Soar J, et al. (2010). European Resuscitation Council Guidelines for Resuscitation 2010 Section 4. Adult advanced life support. *Resuscitation*, **81**, 1305–52.
8. Nolan JP, Hazinski MF, Billi JE, et al. (2010). Part 1: Executive summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Resuscitation*, **81**(Suppl. 1), e1–25.
9. Biarent D, Bingham R, Eich C, et al. (2010). European Resuscitation Council Guidelines for Resuscitation 2010 Section 6. Paediatric life support. *Resuscitation*, **81**, 1364–88.
10. Soar J, Perkins GD, Abbas G, et al. (2010). European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: Electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. *Resuscitation*, **81**, 1400–33.

CHAPTER 64

Therapeutic strategies in managing cardiac arrest

John Field

Key points

- Updated resuscitation guidelines emphasize the need for minimally interrupted high quality chest compressions as a prerequisite for successful resuscitation outcome.
- Resuscitation involves the integration of complex systems and the interdisciplinary coordination of multispecialty emergency and critical care providers.
- The immediate period following return of spontaneous circulation (ROSC) is crucial and is dominated by the presence of two critical goals—identification of the pathophysiological cause, and the assessment and initiation of time-dependent interventions, directed at preventing recurrent arrest, and improving immediate and long-term outcome.
- There is no vasopressor or anti-arrhythmic agent whose use is associated with improved outcome at discharge. In-hospital resuscitation should focus on the provision of high quality chest compressions and the search for immediate treatable precipitants of the arrest in those patients who achieve ROSC.
- A systematic checklist may aid in the systematic evaluation of patients following ROSC.

Introduction

Traditional care of the cardiac arrest patient has emphasized two treatment components: basic life support (BLS) and advanced cardiac life support (ACLS). An algorithmic approach to resuscitation emphasizes the 'chain of survival'. However, successful resuscitation and optimal patient outcome require a broader interdisciplinary approach that includes immediate post-cardiac arrest care. This topic will focus on the important components and interventions of care to achieve return of spontaneous circulation (ROSC) and immediately stabilize a patient while positioning them for optimal long-term recovery. Important components of basic and advanced life support are summarized. Comprehensive details can be reviewed in recent 2010 updates of Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care [1,2].

During resuscitation: optimizing success for return of spontaneous circulation

Basic life support

Immediate by-stander CPR predicts improved survival and outcome from cardiac arrest. However, the traditional focus on complex training and treatment sequences failed to emphasize simple skills and focus on major determinants of patient survival—high quality chest compressions and very early defibrillation. Failure to perform high quality minimally interrupted chest compressions is associated with decreased response to defibrillation attempts, decreased ROSC and, ultimately, decreased survival of patients with good neurological outcome. 'Push hard, push fast' is now the core skill in BLS and very early defibrillation is the major intervention emphasized. A new circular American Heart Association (AHA) algorithm highlights the importance of continuous uninterrupted chest compressions (Fig. 64.1).

Very early defibrillation

Early defibrillation in conjunction with high quality minimally interrupted chest compressions is critical to survival following sudden cardiac arrest. Survival rates decrease 7–10% with each minute that passes without defibrillation and an initial shockable rhythm of ventricular fibrillation (VF) will then deteriorate into pulseless electrical activity (PEA) and asystole.

It is important however, to realize that early defibrillation alone does not usually improve survival and that integration of high quality minimally interrupted chest compressions is essential for optimal outcome. For example, the National Registry of CPR (NRCPR) observed that the use of an automatic external defibrillator (AED) was not associated with improved survival for in-hospital cardiac arrest in patients presenting with VF as the initial rhythm [3].

Advanced life support

For patients in refractory VF, PEA, or asystole, advanced life support (ALS) measures are initiated and include intravenous access, pharmacological therapy, mechanical adjuncts for circulatory support together with airway support and intervention. However, no ALS technique has been demonstrated in randomized controlled trials to improve outcomes defined as discharged alive and neurologically intact. The European Resuscitation Council Advanced

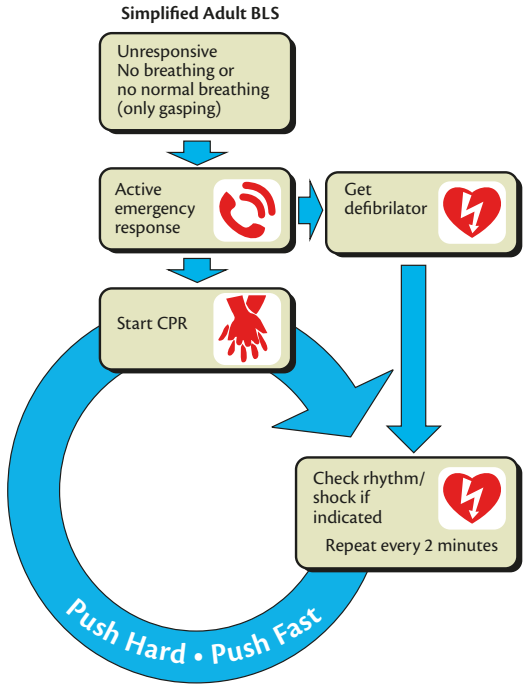


Fig. 64.1 AHA simplified basic life support algorithm.
Reprinted with permission 2010 American Heart Association Guidelines For CPR and ECC. Part 9: Post-Cardiac Arrest Care. *Circulation*, 2010, **122**(Suppl. 3), S768-86. ©2010, American Heart Association, Inc.

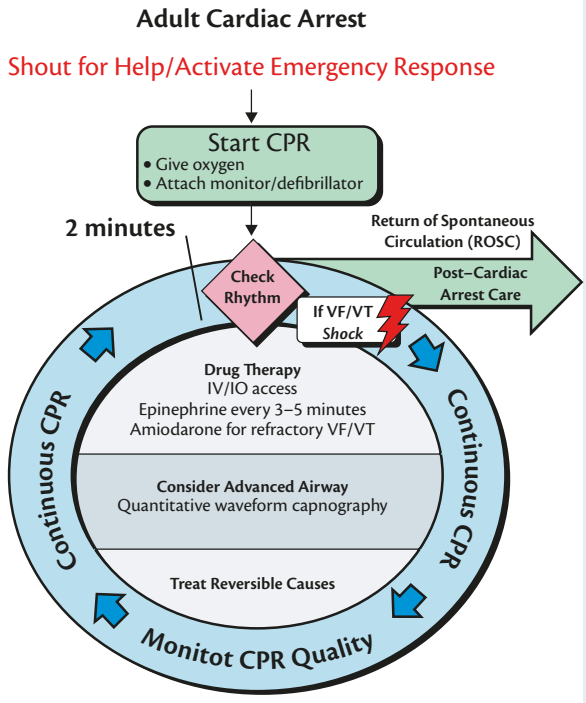
Life Support algorithm emphasizes the essential components of ALS including core high quality CPR and immediate post-cardiac arrest treatment (Fig. 64.2). Current guidelines have decreased the emphasis on advanced airway interventions and pharmacological therapy during adult sudden cardiac arrest. Airway management is discussed in Chapter 59, 'Airway Management in Cardiopulmonary Resuscitation'.

Pharmacological therapy

Historically, significant efforts and resuscitation goals focused on the administration of drugs during CPR largely based on animal data and non-randomized clinical trials. Pharmacological agents have proved disappointing and no specific drug has improved outcome following cardiac arrest. Vasopressors and anti-arrhythmic agents are included in current guidelines, but their administration should not delay or interrupt high quality chest compressions or attempts at defibrillation. However, possible confounding parameters for pharmacologic efficacy are time to administration and quality of chest compressions permitting delivery of drugs to the circulation.

Vasopressors

The vasopressors epinephrine and vasopressin have been studied in animal models and randomized clinical trials. To date, no placebo-controlled trials have shown that any vasopressor administered during management of VF/VT, asystole, or PEA improves survival to hospital discharge. Epinephrine was initially the preferred vasopressor largely based on animal experiments. Peripheral selective alpha-2 adrenergic stimulation and improvement in aortic diastolic pressure and coronary perfusion pressure improved



CPR Quality
- Push hard (≥2 inches [5 cm]) and fast (≥100/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes
- If no advanced airway, 30:2 compression-ventilation ratio
- Quanititave waveform capnography
  – If P_{ETCO_2} <10 mm Hg, attempt to improve CPR quality
- Intra-arterial pressure
  – If relaxation phase (diastolic) pressure <20 mm Hg, attempt to imprve CPR quality

Return of Spontaneous Circulation (ROSC)
- Pulse and blood pressure
- Abrupt sustained increase in P_{ETCO_2} (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Shock Energy
- **Biphasic:** Manufacturer recommendation (120–200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic:** 360 J

Drug Therapy
- **Epinerphrine IV/IO Dose:** 1 mg every 3–5 minutes
- **Vasopressin IV/IO Dose:** 40 units can replace first or second dose of epinerphrine
- **Amiodarone IV/IO Dose:** First dose: 300 mg bolus. Second dose: 150 mg.

Advanced Airway
- Supraglottic advanced airway or endortracheal intubation
- Waveform capnograpghy to confirm and monitor ET tube placement
- 8–10 breaths per minute with continuous chest compressions

Reversible Causes
- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pnuemothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

Fig. 64.2 European Resuscitation Council Adult Advanced Cardiac Life Support.
Reprinted from *Resuscitation*, **81**, 10, Nolan JP et al., 'European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary', pp. 1219–76. Copyright 2010, with permission from European Resuscitation Council.

ROSC, but associated alpha-1 and beta-2 adrenergic stimulation is potentially detrimental. However, pure alpha-vasoconstrictors failed to prove beneficial as compared to epinephrine [4]. Beta blockade during cardiac arrest was promising in animal models, but clinical trials in humans demonstrating efficacy remain to be performed [5].

Vasopressin was introduced as a non-adrenergic vasoconstrictor increasing both coronary and cerebral blood flow while avoiding the inotropic and chronotropic beta-2 adrenergic stimulation of epinephrine. However, randomized clinical trials have failed to show vasopressin to be superior to epinephrine [6].

Anti-arrhythmia agents

Although anti-arrhythmic agents are used routinely during refractory VT/VF cardiac arrest, lidocaine, and amiodarone have not been demonstrated to improve survival to discharge. Amiodarone improves admission to hospital when administered for refractory out-of-hospital VT/VF [7,8]. Available evidence suggests that the routine use of atropine for PEA/asystole is not associated with improved outcome and atropine has been eliminated from recent resuscitation algorithms for these rhythms.

Return of spontaneous circulation and differential diagnosis

Following sudden arrest, ROSC is defined as the presence of an organized rhythm and a palpable pulse. The immediate period following ROSC is crucial and is dominated by the presence of two critical goals. The first goal attempts to define the trigger or aetiology for the cardiac arrest (Fig. 64.2 and Table 64.1) and, concurrently, the second goal incorporates the assessment and initiation of time-dependent interventions directed at preventing recurrent arrest and improving immediate and long term outcome (Fig. 64.3). It is important in this context to realize that resuscitation continues following ROSC and is called post-cardiac arrest care.

Immediate decisions following ROSC

Both during refractory cardiac arrest and immediately following ROSC a quick check list helps to identify comorbidities that have contributed to the arrest and serve to position the patient for recurrent arrest, haemodynamic compromise and serious arrhythmias. Common pathophysiological conditions have been described as the H's and the T's and serve as a useful checklist during and immediately after ROSC (Table 64.1). Specific diagnostic and laboratory tests are prioritized to help establish a differential diagnosis in the minutes following ROSC. Most helpful are tests to assess the metabolic status of the patient, a 12-lead electrocardiogram, chest X-ray, and cardiac ultrasonography (Table 64.2).

Table 64.1 The Hs and the Ts (modified). Immediately following ROSC a checklist differential diagnosis using the pneumonic 'H's and T's' can guide post-cardiac arrest assessment. The checklist is prioritized as additional patient history is integrated into consideration. Indicated and expedited laboratory and diagnostic testing is ordered targeting correctable causes and comorbidities of cardiac arrest

Hs	Ts
☐ Hypoxia	☐ Thrombosis (coronary)
☐ Hypo/hypervolaemia (CHF)	☐ Thrombosis (PTE)
☐ Hydrogen ion (acidosis)	☐ Tear (aorta)
☐ Hypo/hyperkalaemia	☐ Tamponade (cardiac)
☐ Hypothermia	☐ Tension pneumothorax
☐ Head (stroke/haemorrhage)	☐ Toxins

Data from www.resus.org.au

Table 64.2 ROSC Laboratory and Diagnostic Checklist. A checklist can guide and prioritize laboratory and diagnostic testing following ROSC to identify the cause of the cardiac arrest or comorbidity compromising stability or impacting on optimal outcome

Lab/metabolic	Diagnostic
☐ Electrolytes	☐ Focused clinical exam
☐ Haemoglobin/haematocrit	☐ 12-lead electrocardiogram
☐ Arterial blood gas	☐ Chest X-ray
☐ Lactate	☐ Cardiac ultrasound
☐ Core temperature	☐ Indicated CT scans

Stabilization and immediate decisions post-cardiac arrest

Following ROSC important time-dependent decisions must be made (Fig. 64.3). Following initial haemodynamic and respiratory stabilization, consideration of targeted temperature management (TTM), triage for coronary angiography (if indicated), and transfer to an appropriate critical care unit with comprehensive post-cardiac arrest care protocols and resources are essential [9,10]. Bundled, goal directed therapy has been shown to reduce early haemodynamic instability and subsequent morbidity and mortality from cardiovascular, neurologic, metabolic, and other reversible pathology [11].

Initiation of targeted temperature nanagement (induced hypothermia)

Two small randomized trials [12,13] reported that induced hypothermia improved neurological outcome following resuscitation from cardiac arrest. These trials reported improved neurological outcome in comatose patients with out-of-hospital VF. More recently a much larger high quality trial led by the Scandinavian Critical Care Trials Group reported no difference in outcome when the target temperature was either 33°C or 36°C [14]. Following that trial the International Liason Committee on Resuscitation considers temperature management targeting either 33°C or 36°C to be appropriate treatment following ROSC. Although the efficacy and optimal time-to-target temperature is undefined, many systems initiate temperature management as early as possible during emergency medical services (EMS) transport and coronary angiography.

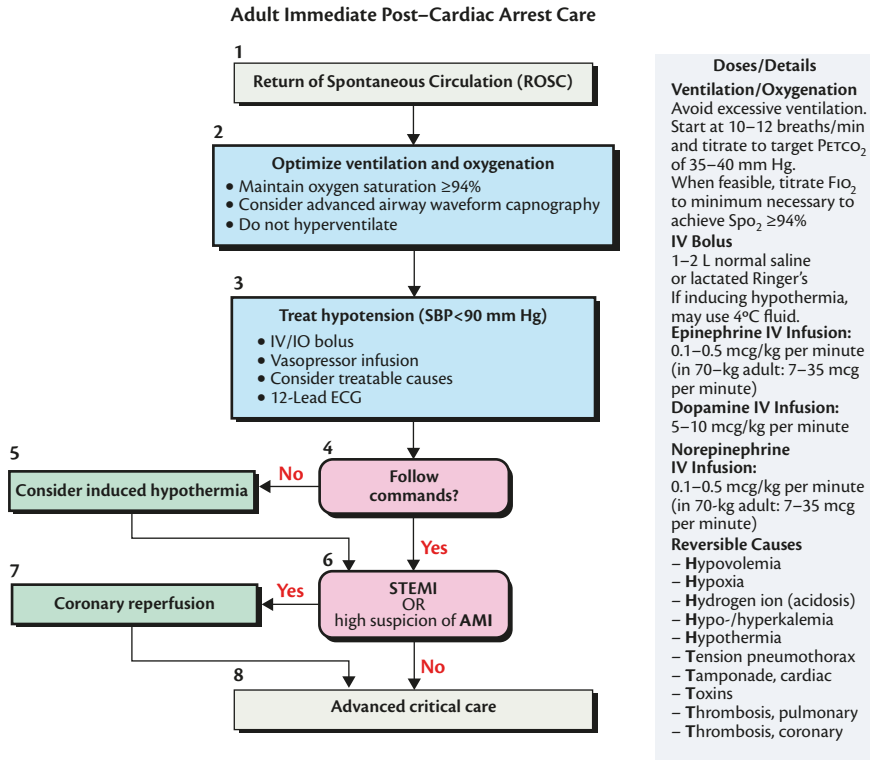


Fig. 64.3 AHA Adult Immediate Post-Cardiac Arrest Care Algorithm.

Reprinted with permission 2010 American Heart Association Guidelines For CPR and ECC. Part 9: Post-Cardiac Arrest Care. *Circulation*, 2010, **122**(Suppl. 3), S768-86. ©2010, American Heart Association, Inc.

Triage for coronary angiography and percutaneous coronary intervention

The majority of adult out-of-hospitals cardiac arrests (OHCA) occur in the setting of an acute coronary syndrome and adult patients with no obvious cause for OHCA may be considered for triage to percutaneous coronary intervention (PCI) facilities. Despite the lack of randomized data the performance of PCI following ROSC has been associated with favourable outcomes [15–17] and survivors of cardiac arrest with ST-segment elevation myocardial infarction (STEMI) have a particularly good neurological outcome [18]. Importantly, comatose patients should not be excluded from consideration of angiography and therapeutic hypothermia can be successfully initiated or continued during PCI [19].

Patients with STEMI should be triaged to PCI capable facilities. The electrocardiogram (ECG) is specific for STEMI following cardiac arrest, but the recording may be insensitive and patients with other ECG patterns may also benefit [17]. If indicated induced hypothermia can be initiated successfully during transport to and within hospital and during cardiac catheterization.

Conclusion

Strategies for management of cardiac arrest are time-sensitive and immediate successful ROSC requires prompt recognition, high quality minimally interrupted chest compressions and, when indicated, early defibrillation. Airway interventions, drug administration, and other interventions during management of cardiac arrest should not delay defibrillation and avoid interrupting high quality chest compressions. Following ROSC, a critical period exists when appropriate triage and use of time-dependent treatments with coordinated interdisciplinary care can improve both short-term outcome and long-term functional recovery.

References

1. Field JM, Hazinski MF, Sayre MR, et al. (2010). Part 1: executive summary: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*, **122**(18, Suppl. 3), S640–56.
2. Nolan JP, Soar J, Zideman DA, et al. (2010). European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary. *Resuscitation*, **81**(10), 1219–76.
3. Chan PS, Krumholz HM, Spertus JA, et al. (2010). Automated external defibrillators and survival after in-hospital cardiac arrest. *Journal of the American Medical Association*, **304**(19), 2129–36.
4. Olson DW, Thakur R, Stueven HA, et al. (1989). Randomized study of epinephrine versus methoxamine in prehospital ventricular fibrillation. *Annals of Emergency Medicine*, **18**(3), 250–3.
5. de Oliveira FC, Feitosa-Filho GS, and Ritt LE. (2012). Use of beta-blockers for the treatment of cardiac arrest due to ventricular fibrillation/pulseless ventricular tachycardia: A systematic review. *Resuscitation*, **83**(6), 674–83.
6. Aung K and Htay T. (2005). Vasopressin for cardiac arrest: a systematic review and meta-analysis. *Articles on Internal Medicine*, **165**(1), 17–24.
7. Kudenchuk PJ, Cobb LA, Copass MK, et al. (1999). Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *New England Journal of Medicine*, **341**(12), 871–8.

8. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, and Barr A. (2002). Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *New England Journal of Medicine*, **346**(12), 884–90.
9. Laurent I, Monchi M, Chiche JD, et al. (2002). Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *Journal of the American College of Cardiology*, **40**(12), 2110–16.
10. Skrifvars MB, Pettila V, Rosenberg PH, and Castren M. (2003). A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation. *Resuscitation*, **59**(3), 319–28.
11. Neumar RW, Nolan JP, Adrie C, et al. (2008). Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. *Circulation*, **118**(23), 2452–83.
12. HACA. (2002). Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *New England Journal of Medicine*, **346**(8), 549–56.
13. Bernard S, Buist M, Monteiro O, and Smith K. (2003). Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. *Resuscitation*, **56**(1), 9–13.
14. Nielsen N, Wetterslev J, Cronberg T, et al. (2013) Targeted temperature management at 33°C versus 36°C after cardiac arrest. *New England Journal of Medicine*, **369**, 2197–206.
15. Garot P, Lefevre T, Eltchaninoff H, et al. (2007). Six-month outcome of emergency percutaneous coronary intervention in resuscitated patients after cardiac arrest complicating ST-elevation myocardial infarction. *Circulation*, **115**(11), 1354–62.
16. Spaulding CM, Joly LM, Rosenberg A, et al. (1997). Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *New England Journal of Medicine*, **336**(23), 1629–33.
17. Dumas F, Cariou A, Manzo-Silberman S, et al. (2010). Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. *Circulation Cardiovascular interventions*, **3**(3), 200–207.
18. Hosmane VR, Mustafa NG, Reddy VK, et al. (2009). Survival and neurologic recovery in patients with ST-segment elevation myocardial infarction resuscitated from cardiac arrest. *Journal of the American College of Cardiology*, **53**(5), 409–15.
19. Batista LM, Lima FO, Januzzi JL, Jr., Donahue V, Snydeman C, and Greer DM. (2010). Feasibility and safety of combined percutaneous coronary intervention and therapeutic hypothermia following cardiac arrest. *Resuscitation*, **81**(4), 398–403.

CHAPTER 65

Post-cardiac arrest arrhythmias

Marwan F. Jumean and Mark S. Link

Key points

- Global ischaemia and reperfusion injury are the hallmarks of post-arrest myocardial dysfunction.
- In patients with recurrent arrhythmias, every effort should be made to correct the underlying precipitating factors that led to the arrest.
- Early coronary revascularization should be considered in all patients with recurrent ventricular arrhythmias.
- Amiodarone is a relatively safe anti-arrhythmic agent and should be used in recurrent ventricular arrhythmia once underlying causes have been treated.
- ICD placement is recommended in all patients with ventricular arrhythmia with the exception of those within 48 hours of an ST elevation myocardial infarction.

Introduction

There has been increasing emphasis in recent years on understanding the pathophysiology and management of the post-cardiac arrest syndrome that follows the return of spontaneous circulation (ROSC) [1,2]. The importance of post-arrest care and its impact on survival has been highlighted by the addition of the 5th link in the chain of survival in the American Heart Association (AHA) resuscitation guidelines [2]. Following ROSC, a variety of measures should be undertaken in an attempt to halt or reverse pathologic processes that occur at the time of and following cardiac arrest. ROSC initiates a cascade of ischaemic reperfusion injury to the myocardium that is mediated in part by oxygen free radicals and high levels of circulating cytokines [3]. These processes create a state of electrical instability in the 24–72-hour period after ROSC, which may give rise to a wide spectrum of arrhythmias ranging from atrial fibrillation and premature ventricular complexes to intractable ventricular tachycardia (VT) or ventricular fibrillation (VF). The focus of this chapter is to explore the arrhythmias that can develop after cardiac arrest, and understand the pathophysiology, prevention, and management of such arrhythmias.

Post-arrest arrhythmias

Sustained ventricular tachycardia and ventricular fibrillation

VT (Fig. 65.1) is an organized monomorphic wide complex tachycardia, while VF (Fig. 65.2) is a disorganized polymorphic wide complex tachycardia. Some experts argue for dividing VF into subtypes of polymorphic VT, torsades (Fig. 65.3), or standard VF, but generally all subtypes appear to be of similar morphology when they initiate (course and undulating) and all will degenerate into more standard VF if they continue. Recurrent VT or VF following ROSC is most commonly due to an acute coronary syndrome, particularly ST segment elevation myocardial infarction (STEMI). In the fibrinolytic era, 10% of patients presenting with STEMI had ventricular arrhythmias and in the percutaneous coronary intervention (PCI) era 6% had VT or VF within the first 48 hours [4–5]. The development of VT usually correlates with a larger infarct size [7]. There may be a familial genetic component to the increased risk of VT and VF in patients presenting with acute coronary syndrome (ACS) [8]. Following out of hospital cardiac arrest, recurrent VF has been reported in as many as 61–79% of patients with ROSC [6].

The development of recurrent VT or VF within 48 hours of an acute coronary syndrome is associated with increased in-hospital mortality. However, the data on long-term mortality risk following early (less than 48 hours) VT is inconclusive, whereas for patients with VF, long-term mortality beyond 30 days does not appear to be significantly increased [4,7].

In addition to myocardial ischaemia, uncorrected electrolyte disturbances, particularly hypokalaemia and hypomagnesaemia, can predispose to VF by a decrease in current flow of the rapid component of the delayed rectifier potassium current (IKr) leading to prolonged QT interval. This effect may be potentiated by the use of drugs known to prolong QTc, including most anti-arrhythmic agents, certain antibiotics (azithromycin, erythromycin), anti-emetics (droperidol), and antipsychotic medications (chlorpromazine, haloperidol).

Accelerated Idioventricular rhythm

Accelerated idioventricular rhythm (AIVR) (Fig. 65.4), also known as slow VT, was first described in 1910, and is usually observed in patients with acute coronary syndromes. AIVR is defined as a wide complex arrhythmia originating in the ventricle at a rate less than 120 bpm. In the era of thrombolytic therapy, AIVR was felt to be a marker of successful reperfusion. However, this has not generally been observed in the PCI era [9]. AIVR results from increased automaticity or triggered activity. It is often facilitated by sinus bradycardia, and does not usually cause haemodynamic instability unless significant myocardial dysfunction exists. AIVR is not associated with increased short or long term mortality.

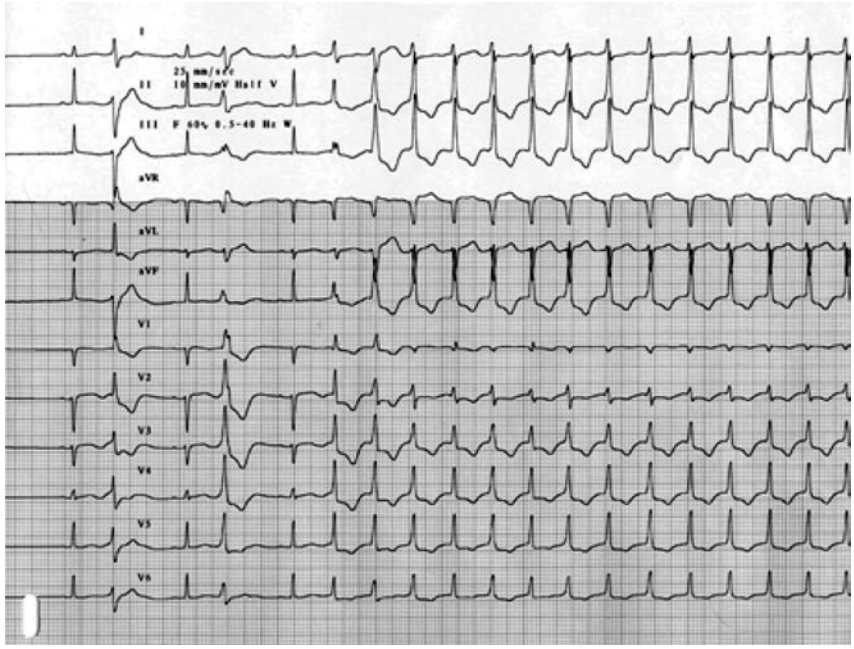


Fig. 65.1 Monomorphic ventricular tachycardia due to ischaemic cardiomyopathy

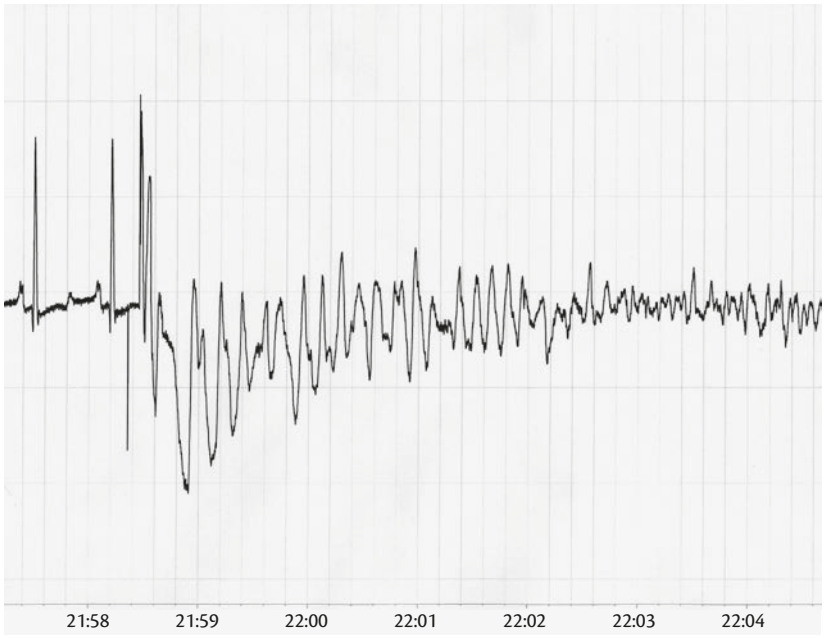


Fig. 65.2 Ventricular fibrillation in an animal model of commotio cordis. The initiation of ventricular fibrillation appears to be polymorphic ventricular tachycardia which quickly degenerates into ventricular fibrillation.

Atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general public, yet there are no published studies that assessed the prevalence or mechanisms of AF following ROSC. AF, even in the setting of haemodynamic instability, rarely leads to cardiac arrest with the exception of patients with Wolff–Parkinson–White syndrome (WPW). AF following ROSC is multifactorial, often triggered by the interplay between the neuro-hormonal milieu in the post-arrest period, increased catecholamine levels, frequent use of inotropes, vasopressors, the patient's underlying comorbid conditions, and the cause of the arrest. There are no published mortality data on patients with AF following ROSC.

Mechanism

There are several factors that place cardiac arrest patients at a higher risk of cardiac arrhythmia following ROSC, particularly in the first few days that follow the arrest. These factors include persistence of

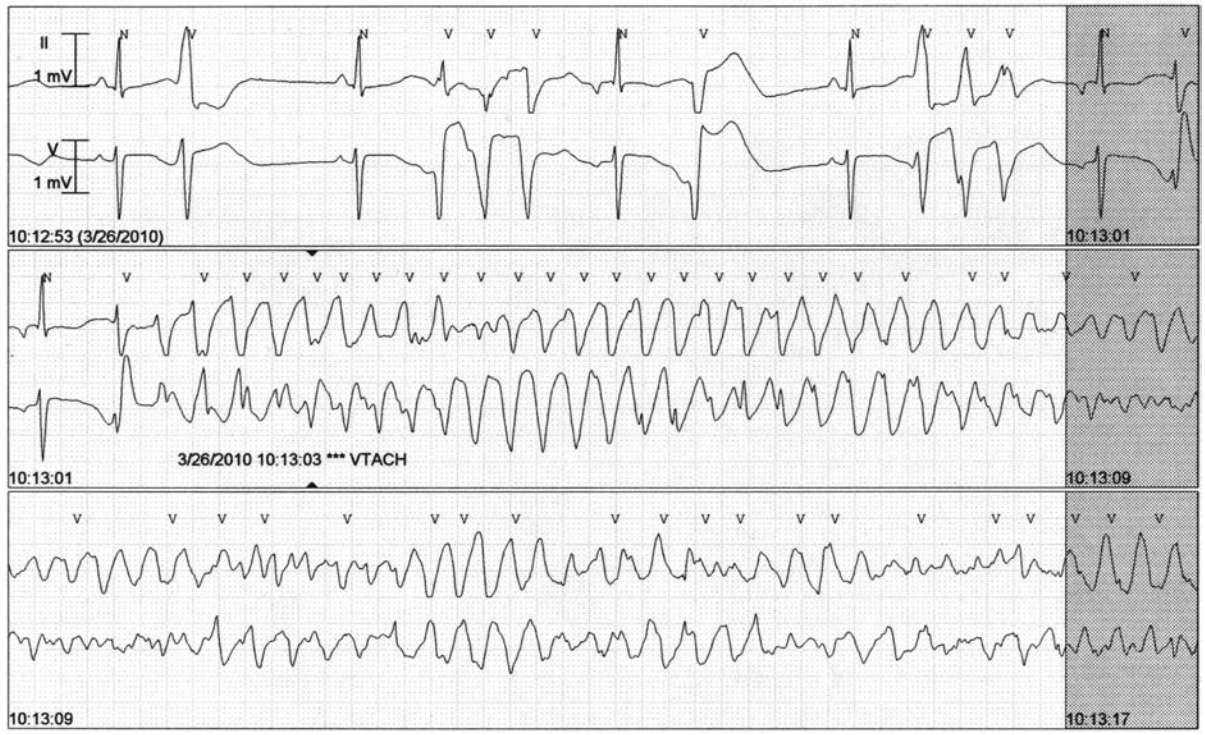


Fig. 65.3 Torsades de pointes or polymorphic ventricular tachycardia in a 28-year-old patient treated with fluconazole and nortryptiline. Note the prolonged QTc and the R on T beat in the upper panel. In the middle panel, torsades de pointes initiates and then degenerates into ventricular fibrillation.

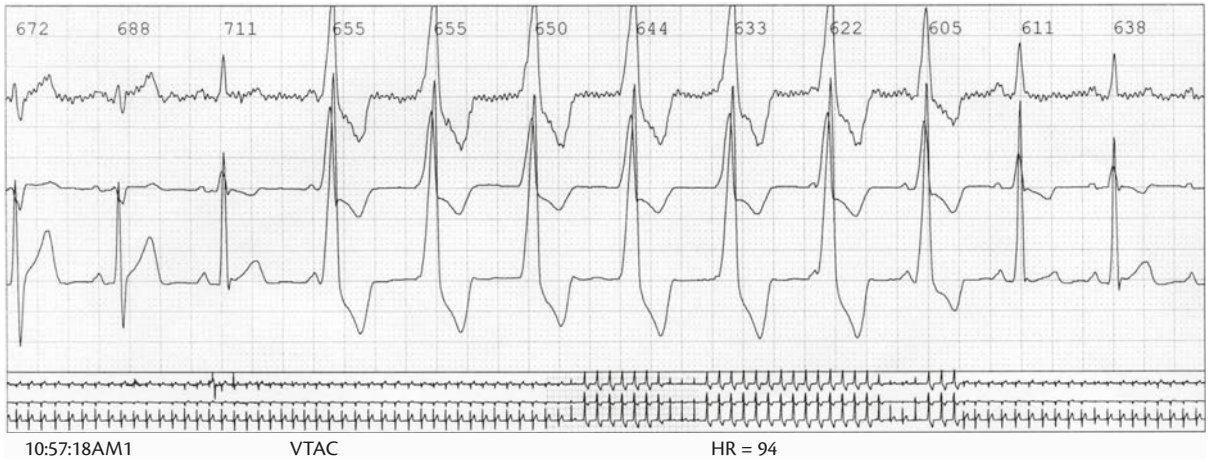


Fig. 65.4 Accelerated idiopathic ventricular tachycardia. This wide complex ventricular rhythm is barely more rapid than the normal sinus rhythm.

uncorrected precipitating factor(s) that led to the arrest, changes in the neuro-hormonal milieu following the arrest, and the development of post-arrest myocardial dysfunction. Precipitating factors of persistent electrical instability post-arrest include persisting coronary artery lesions with unstable plaque or fresh thrombus in patients presenting with ACS; chronic ischaemic, dilated, restrictive, congenital, or hypertrophic cardiomyopathies, large pulmonary emboli, uncorrected severe electrolyte and acid-base disturbances, or toxins. During cardiopulmonary resuscitation, the delivery of electrical defibrillation may contribute to post-arrest myocardial dysfunction [10]. Following ROSC a number of factors contribute to a state of cardiac electrical instability, These include elevated endogenous catecholamine levels, the lingering effects of vasoactive agents such as vasopressin and epinephrine administered during the arrest, the subsequent use of inotropic agents and vasopressors. These factors increase left ventricular afterload, may induce coronary vasospasm, and an increase in myocardial oxygen demand all of which predispose to arrhythmias [1]. Furthermore, therapeutic hypothermia implemented to minimize hypoxic brain injury often leads to bradycardia and prolongs QTc which predisposes to polymorphic VT and VF [11]. Lastly, emerging evidence suggests that both acute systolic and diastolic left ventricular dysfunction due to myocardial stunning is common following cardiac arrest, this also predisposes to recurrent arrhythmias [12].

Management

With few exceptions, the management of post-arrest arrhythmias should not differ from the acute management of the initial arrhythmias that led to the arrest. Every effort should be made to correct and treat precipitating factors and reversible causes, with particular emphasis on coronary revascularization in those presenting with VF.

Ventricular fibrillation and tachycardia

The use of beta-blockers and anti-arrhythmic drugs is an effective approach for the treatment of recurrent ventricular arrhythmias following ROSC. VF, torsades de points, and polymorphic VT are not organized rhythms and never maintain haemodynamic stability. Thus VF should be treated immediately with early, high energy defibrillation following established ACLS protocols.

Since the most common cause of recurrent ventricular arrhythmias is ongoing myocardial ischaemia, reducing adrenergic drive and myocardial ischaemia by use of beta blockers, the use of intra-aortic balloon counter pulsation, and early coronary revascularization should be considered [13,14].

If VT or VF is persistent or recurrent, amiodarone may be used. Two randomized clinical trials initiated in the 1990s, the ARREST and ALIVE trials, demonstrated that following out-of-hospital cardiac arrest more patients survive to hospital admission with the use of amiodarone compared with lidocaine [15,16]. However neither trial demonstrated a survival advantage to hospital discharge.

Observational studies suggest that polymorphic ventricular tachycardia associated with a long QTc in normal sinus rhythm (sometimes subtyped as torsades de pointes) may be prevented with IV magnesium [17] and polymorphic ventricular tachycardia associated with bradycardia can be prevented by increasing heart rate with ventricular pacing and/or isoproterenol or epinephrine.

VT can be effectively treated with anti-arrhythmic agents. The lack of negative inotropic effect and the low rate of pro-arrhythmic effects makes the class III drug amiodarone an attractive agent in many cases of recurrent ventricular arrhythmias, particularly as new or pre-existing myocardial dysfunction is commonly present following ROSC, and the use of other anti-arrhythmic agents may be detrimental due to their negative inotropic effects. However, in head to head comparisons intravenous procainamide has a higher rate of conversion of VT compared with amiodarone [17]. Lidocaine and sotalol are alternative agents if amiodarone is unavailable or proves ineffective.

Atrial fibrillation

In the setting of haemodynamic instability, synchronized electrical cardioversion is the treatment of choice. In the setting of haemodynamic stability a rate control strategy to target a heart rate of less than 100 beats per minute with beta-blockers, non-dihydropyridine Ca channel blockers, or amiodarone may be acceptable. Procainamide should be utilized for patients with AF in the setting of WPW. Anti-coagulation should be considered in patient in whom AF persists [18].

Long term treatment of survivors of VT/VF cardiac arrest

With the exception of patients who have VF/VT within 48 hours of an acute ST elevation myocardial infarction, current European Society of Cardiology and AHA guidelines recommend the placement of implantable cardioverter-defibrillator (ICD) for secondary prevention in patients suffering a cardiac arrest [19]. A recent meta-analysis of three major trials: CASH, CIDS, and AVID demonstrated a 25% reduction in overall mortality in patients with an ICD compared with treatment with anti-arrhythmic drugs. The difference was driven largely by a reduction in sudden cardiac death [20]. The long-term adjunctive use of anti-arrhythmic drugs should be reserved to those patients with recurrent ventricular arrhythmias.

References

1. Neumar RW, Nolan JP, Adrie C, et al. (2008). Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation*, **118**, 2452–83.
2. Peberdy MA, Callaway CW, Neumar RW, et al. (2010). Part 9: post cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*, **122**, S768-S78.
3. Adrie C, Laurent I, Monchi M, Cariou A, Dhainaou JF, and Spaulding C. (2004). Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? *Current Opinion in Critical Care*, **10**, 208–12.
4. Newby KH, Thompson T, Stebbins A, Topol EJ, Califf RM, and Natale A. (1998). Sustained ventricular arrhythmias in patients receiving thrombolytic therapy: incidence and outcomes. The GUSTO Investigators. *Circulation*, **98**, 2567–73.
5. Mehta RH, Starr AZ, Lopes RD, et al. (2009). Incidence of and outcomes associated with ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention. *Journal of the American Medical Association*, **301**, 1779–89.
6. vanAlem AP, Post J, and Kroster RW. (2003). VF recurrence: characteristics and patient outcome in out-of-hospital cardiac arrest. *Resuscitation*, **59**, 182–8.
7. Mont L, Cinca J, Blanch P, et al. (1996). Predisposing factors and prognostic value of sustained monomorphic ventricular tachycardia in the early phase of acute myocardial infarction. *Journal of the American College of Cardiology*, **28**, 1670.
8. Kaikkonen KS, Kortelainen ML, Linna E, and Huikuri HV. (2006). Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. *Circulation*, **114**, 1462–7.
9. Terkelsen CJ, Sørensen JT, Kaltoft AK, et al. (2009). Prevalence and significance of accelerated idioventricular rhythm in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *American Journal of Cardiology*, **104**(12), 1641–6.
10. Xie J, Weil MH, Sun S, et al. (1997). High-energy defibrillation increases the severity of postresuscitation myocardial dysfunction. *Circulation*, **96**, 683–8.
11. Boddicker KA, Zhang Y, Zimmerman MB, Davies LR, and Kerber RE. (2005). Hypothermia improves defibrillation success and

resuscitation outcomes from ventricular fibrillation. *Circulation*, **111**, 3195–201.
12. Xu T, Tang W, Ristagno G, Wang H, Sun S, and Weil MH. (2008). Postresuscitation myocardial diastolic dysfunction following prolonged ventricular fibrillation and cardiopulmonary resuscitation. *Critical Care Medicine*, **36**, 188–92.
13. Cronier P, Vignon P, Bouferrache K, et al. (2011). Impact of routine percutaneous coronary intervention after out-of-hospital cardiac arrest due to ventricular fibrillation. *Critical Care*, **15**(3), R122.
14. Antman EM, Anbe DT, Armstrong PW, et al. (2004). ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation*, **110**, e82.
15. Kudenchuk PJ, Cobb LA, Copass MK, et al. (1999). Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *New England Journal of Medicine*, **341**, 871–8.
16. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, and Barr A. (2002). Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *New England Journal of Medicine*, **346**, 884–90.
17. Neumar RW, Otto CW, Link MS, et al. (2010). Part 8: Adult advanced cardiovascular life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*, **122**, S729–67.
18. Singer DE, Albers GW, Dalen JE, et al. (2008). Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians evidence-based clinical practice guidelines (8th edn). *Chest*, **133**, 546S.
19. Epstein AE, DiMarco JP, Ellenbogen KA, et al. (2008). ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Anti-arrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation*, **117**, e350.
20. Lee DS, Green LD, Liu PP, et al. (2003). Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. *Journal of the American College of Cardiology* , **41**, 1573–82.

CHAPTER 66

Management after resuscitation from cardiac arrest

Jerry P. Nolan and Michael J. A. Parr

Key points

- Following return of spontaneous circulation, the quality of the treatment provided in the post-arrest period influences outcome.
- Most patients resuscitated after a prolonged period of cardiac arrest will develop the post-cardiac arrest syndrome.
- All survivors of out-of-hospital cardiac arrest should be considered for urgent coronary angiography unless the cause of cardiac arrest was clearly non-cardiac or continued treatment is considered futile.
- Several interventions may impact on neurological outcome; the most significant of these is targeted temperature management.
- In patients remaining comatose after resuscitation from cardiac arrest, prediction of the final outcome in the first few days may be unreliable. Prognostication should normally be delayed until at least 3 days after return to normothermia and should involve more than one mode (e.g. clinical examination combined with another investigation).

Introduction

Interventions applied after return of spontaneous circulation (ROSC) impact significantly on the quality of survival. There is considerable variation in post–cardiac arrest treatment and patient outcome between hospitals [1]. Based on updated data from the UK Intensive Care National Audit and Research Centre, approximately 35% of patients admitted to an intensive care unit (ICU) after out of hospital cardiac arrest will survive to be discharged from hospital [2] and most of these will have a good neurological outcome [3].

Post-cardiac arrest syndrome

Systemic ischaemia during cardiac arrest and the subsequent reperfusion response after ROSC causes the post-cardiac arrest syndrome (PCAS) [4]. The severity of this syndrome is determined by the cause and duration of cardiac arrest, and has four key clinical components (Box 66.1).

All components of the PCAS need to be addressed if outcome is to be optimized and post-cardiac arrest care should start immediately after ROSC has been achieved, irrespective of location. An 'ABCDE' (Airway, Breathing, Circulation, Disability, Exposure) systems approach is used to identify and treat physiological abnormalities and organ injury.

Airway and breathing with controlled re-oxygenation

After a brief period of cardiac arrest (e.g. single successful shock for witnessed ventricular fibrillation (VF) arrest) patients usually recover consciousness, maintain their airway safely, and breathe adequately without the need for tracheal intubation. Patients who remain comatose or agitated with a decreased conscious level, and those with breathing difficulties will require sedation, tracheal intubation, and mechanical ventilation. The duration of ventilation may be determined by the use of therapeutic hypothermia, and the extent of the neurological injury.

Increasing evidence suggests that hyperoxaemia after ROSC is harmful and worsens outcomes [5]. Current guidelines recommend that the inspired oxygen concentration immediately after ROSC should be adjusted to achieve a normal arterial oxygen saturation (94–98%) when measured by pulse oximetry or arterial blood gas analysis [6]. Adjust ventilation to achieve normocarbia and monitor using end-tidal CO_2 with waveform capnography, and arterial blood gases. Avoid hyperventilation, which will cause cerebral vasoconstriction and possible cerebral ischaemia.

Box 66.1 Key components of the post-cardiac arrest syndrome

- Post-cardiac arrest brain injury—this manifests as coma and seizures.
- Post-cardiac-arrest myocardial dysfunction—this can be severe and usually recovers after 48–72 hours.
- Systemic ischaemia/reperfusion response—tissue reperfusion can cause programmed cell death (apoptosis) effecting all organ systems.
- Persisting precipitating pathology—coronary artery disease is the commonest precipitating cause after OHCA.

Circulation

About 80% of sudden out-of-hospital cardiac arrests (OHCAs) are caused by coronary artery disease. Early reperfusion therapy is indicated for ST elevation myocardial infarction (STEMI) and this is achieved most effectively with primary percutaneous intervention (PCI) as long as a first medical contact-to-balloon time of less than 90 minutes can be achieved. If not, fibrinolysis (thrombolysis) may be preferable. In the past, patients in a coma after a cardiac arrest were often denied PCI in the expectation that few would make a good neurological recovery. There is now a trend towards considering immediate coronary artery angiography in all OHCA patients without an obvious non-cardiac cause of arrest regardless of ECG changes. This is because the early post-resuscitation 12-lead electrocardiogram (ECG) is less reliable for diagnosing acute coronary occlusion than it is in non-arrest patients. About 25% of patients without an obvious non-cardiac cause for their cardiac arrest and no evidence of STEMI on their initial 12-lead ECG will have a coronary lesion on angiography that is amenable to stenting [7].

After cardiac arrest, patients often develop reversible myocardial dysfunction ('myocardial stunning') causing haemodynamic instability and arrhythmias. The severity increases with the duration of the arrest and in those with pre-existing myocardial dysfunction. Echocardiography enables the extent of myocardial dysfunction to be quantified; it usually shows global impairment of both systolic and diastolic dysfunction. Although systemic vascular resistance (SVR) may be high initially, the release of inflammatory cytokines associated with the PCAS will then result in a low SVR [4]. Treatment with fluids, inotropes, and vasopressors is guided by blood pressure, heart rate, urine output, and rate of plasma lactate clearance, central venous oxygen saturations, and cardiac output monitoring. In patients with severe cardiogenic shock intra-aortic balloon counterpulsation may be used. There are no proven evidence-based targets for post-cardiac arrest patients, although the use of a goal directed protocol may improve outcomes.

Patients who survive a cardiac arrest caused by VF/pulseless ventricular tachycardia (pVT) and who have no evidence of a disease that can be effectively treated (e.g. coronary revascularization) should be considered for an implantable cardioverter-defibrillator before leaving hospital.

Brain (disabilty)

Neurological injury is the cause of death in about two-thirds of OHCAs and a quarter of in-hospital cardiac arrests (IHCAs) admitted to ICU [8]. Aneurysmal subarachnoid haemorrhage is a potential cause of OHCA and should be excluded in comatose victims with ROSC who do not have an obvious cardiac cause for their cardiac arrest, because the use of thrombolytics will be contraindicated [9]. Strategies to improve neurological outcome are described in the remainder of this section

Targeted temperature management

Pyrexia associated with a systemic inflammatory response is common in the first 72 hours after cardiac arrest, and is associated with worse outcome. Mild hypothermia (32–36°C) improves outcome after a period of global cerebral hypoxia-ischaemia. Cooling suppresses many of the pathways associated with ischaemia-reperfusion injury, including apoptosis (programmed cell death), and the harmful release of excitatory amino acids and free radicals. Hypothermia also decreases the cerebral oxygen requirements (6% for each 1°C reduction in temperature), although this is not thought to be a primary mechanism for its impact on outcome.

Indications for post-arrest cooling

Several animal studies have shown that mild hypothermia applied after ROSC improves neurological outcome. Two randomized studies showed improved neurological outcome at hospital discharge or at 6 months in comatose patients after out-of-hospital VF cardiac arrest [10,11]. Cooling was initiated within hours after ROSC and a target temperature of 32–34ºC was maintained for 12–24 hours. The use of hypothermia for non-shockable rhythms and after in-hospital cardiac arrest is supported mainly by observational data. Despite this, many centres use hypothermia irrespective of initial cardiac arrest rhythm or location. In the Targeted Temperature Management (TTM) trial, 950 all-rhythm OHCA patients were randomized to 24 hours of temperature control at either 33°C or 36°C [12]. Strict protocols were followed for assessing prognosis and for withdrawal of life-sustaining treatment (WLST). There was no difference in the primary outcome—all cause mortality, and neurological outcome at 180 days was also similar. Importantly, patients in both arms of this trial had their temperature well controlled so that fever was prevented even in the 36°C group. There is no international consensus on the optimal target temperature and clinicians will need to decide locally which target temperature to adopt in their post-resuscitation protocol. Clearly, if there are problems with attaining a target of 33°C it is rational to aim for 36°C instead. In any case, the TTM trial does not support abandoning temperature control.

Cooling techniques

Targeted temperature management comprises induction of hypothermia, maintenance at a constant temperature in the range 32–36°C, and rewarming while preventing hyperthermia. Infusion of 30 mL/kg of 4°C 0.9% sodium chloride or Hartmann's solution decreases core temperature by approximately 1.5°C. A recent study documented increased rates of re-arrest and pulmonary oedema with this technique when used in the prehospital setting, but use under close monitoring in-hospital is still considered safe.

Following induction with cold iv fluids, ice packs and/or wet towels can be used to maintain hypothermia, but fluctuations in temperature are common when using techniques that do not include temperature feedback control and automatic temperature regulation. Several surface cooling devices that include temperature feedback control are also available [13]. There are several intravascular cooling systems that provide tight temperature control via a cooling catheter in a large vein (usually femoral), but they produce no better neurological outcome than the external cooling systems. Initial cooling is facilitated by concomitant neuromuscular blockade with sedation to prevent shivering. Animal evidence indicates that outcomes are better the earlier cooling is started, but so far, this has not been proven conclusively in humans. By starting cooling in the prehospital phase, it is possible to achieve the target temperature more rapidly. Nasopharyngeal cooling, achieved by instilling perflurocarbon via nasal prongs (cooling is produced by evaporation), enables induction of hypothermia during cardiac arrest.

The optimal duration of induced hypothermia is unknown. Although current guidelines suggest 12–24 hours, some experts are using longer periods of hypothermia (at least 24 hours and sometimes up to 72 hours) especially when there has been a long

Box 66.2 Complications associated with therapeutic hypothermia

- **Shivering**: reduced with sedation, neuromuscular blockers and magnesium.
- **Dysrhythmias**: bradycardia is the most common.
- **Diuresis**: may cause hypovolaemia and electrolyte abnormalities.
- **Electrolyte abnormalities**:
  - Hypophosphataemia.
  - Hypokalaemia.
  - Hypomagnesaemia.
  - Hypocalcaemia.
- **Decreased insulin sensitivity and insulin secretion**: hyperglycaemia.
- Impaired coagulation and increased bleeding.
- **Impairment of the immune system**: increased infection rates, e.g. pneumonia.
- Increased plasma amylase concentration.
- **Reduced drug clearance**: clearance of sedative and neuromuscular blocking drugs is reduced by up to 30% at a temperature of 34ºC.

duration of cardiac arrest. Rewarming should be controlled at 0.25–0.5°C per hour and potentially harmful rebound hyperthermia avoided. The complications of therapeutic hypothermia are listed in Box 66.2 [14]. Many of these should be more accurately described as normal physiological response to mild hypothermia.

Sedation

Patients are sedated during treatment with therapeutic hypothermia, because this reduces oxygen consumption, prevents shivering, and facilitates cooling [14]. Short-acting sedatives and opioids (e.g. propofol, alfentanil, remifentanil) will enable earlier neurological assessment after rewarming. Clearance of many drugs is reduced by about one third at 34°C and this must be considered carefully before making decisions about prognosis.

Cerebral perfusion

Autoregulation of cerebral blood flow is impaired after cardiac arrest and cerebral perfusion is dependent on an adequate blood pressure. Brain oedema can occur transiently after ROSC following asphyxial cardiac arrest, but sustained intracranial hypertension is rare. Aim to maintain a normal mean arterial pressure for that particular patient.

Control of seizures

Seizures, myoclonus, or both occur in about 24% of those who remain comatose and are cooled after cardiac arrest [15]. Ideally, continuous electroencephalography (EEG) monitoring is used in patients receiving neuromuscular blocking drugs to ensure seizures are not missed. Seizures are associated with a fourfold increase in mortality, but good neurological recovery has been documented in 17% of those with seizures [15]. Seizures should be treated with benzodiazepines, phenytoin, sodium valproate, propofol, or a barbiturate. Clonazepam, sodium valproate, levetiracetam, and propofol may be used to treat myoclonus; phenytoin is often ineffective.

Glucose control

Both hyperglycaemia and hypoglycaemia after ROSC are associated with a poor neurological outcome [15]. Based on the available data and expert consensus, following ROSC, maintain blood glucose between 4–10 mmol/L.

Prognostication

Predicting outcome in patients remaining comatose after cardiac arrest is challenging. Previous guidelines on prognostication [16] were derived from data collected before the introduction of therapeutic hypothermia and are now known to be unreliable. This may reflect a direct effect of hypothermia on the progress of neurological recovery and/or the residual effects of sedatives and opioids, which tend to be used in larger doses and take longer to clear after hypothermia, confounding neurological assessment. Several studies have shown that a Glasgow Coma Scale (GCS) motor score of 1 or 2 on day 3 is highly unreliable as a predictor of poor outcome in patients who have been cooled. Furthermore, amongst these studies, there are several examples of good outcomes despite absent pupil or absent corneal reflexes on day 3, and in one series good outcomes were documented among 9% of patients with myoclonus [17]. The absence of EEG background reactivity to a stimulus (e.g. tracheal suction) is a strong predictor of a poor outcome, although most of the studies on this prognosticator have been undertaken by the same group. Serum neuron-specific enolase (NSE) values above 60 μg/L measured at 48–72 hours from ROSC are very rarely associated with a good outcome.

Two systematic reviews [18,19] summarize all the science supporting updated guidance on prognostication in comatose survivors of cardiac arrest, which has been published by the European Resuscitation Council and the European Society of Intensive Care Medicine (Fig. 66.1) [20].

The current consensus is that a multimodal approach should be used for prognostication in comatose patients after cardiac arrest. This generally means a combination of neurological examination and assessment using one or more of: electrophysiology, biomarkers, or imaging [20]. The ERC-ESICM prognostication algorithm is entered if the patient is unconscious with a motor score of 1 or 2 and after excluding residual sedation. This will be at least 72 hours after ROSC, but more usually 72 h after return to normothermia.

Organ donation

Up to 16% of patients who achieve sustained ROSC after cardiac arrest fulfil criteria for brain death and can be considered for organ donation. Transplant outcomes for organs from donors who have suffered a cardiac arrest are similar to those achieved with organs from other beating-heart donors.

Cardiac arrest centres

Post-cardiac arrest patients are likely to have improved outcomes if they are cared for in a hospital that offers a comprehensive package

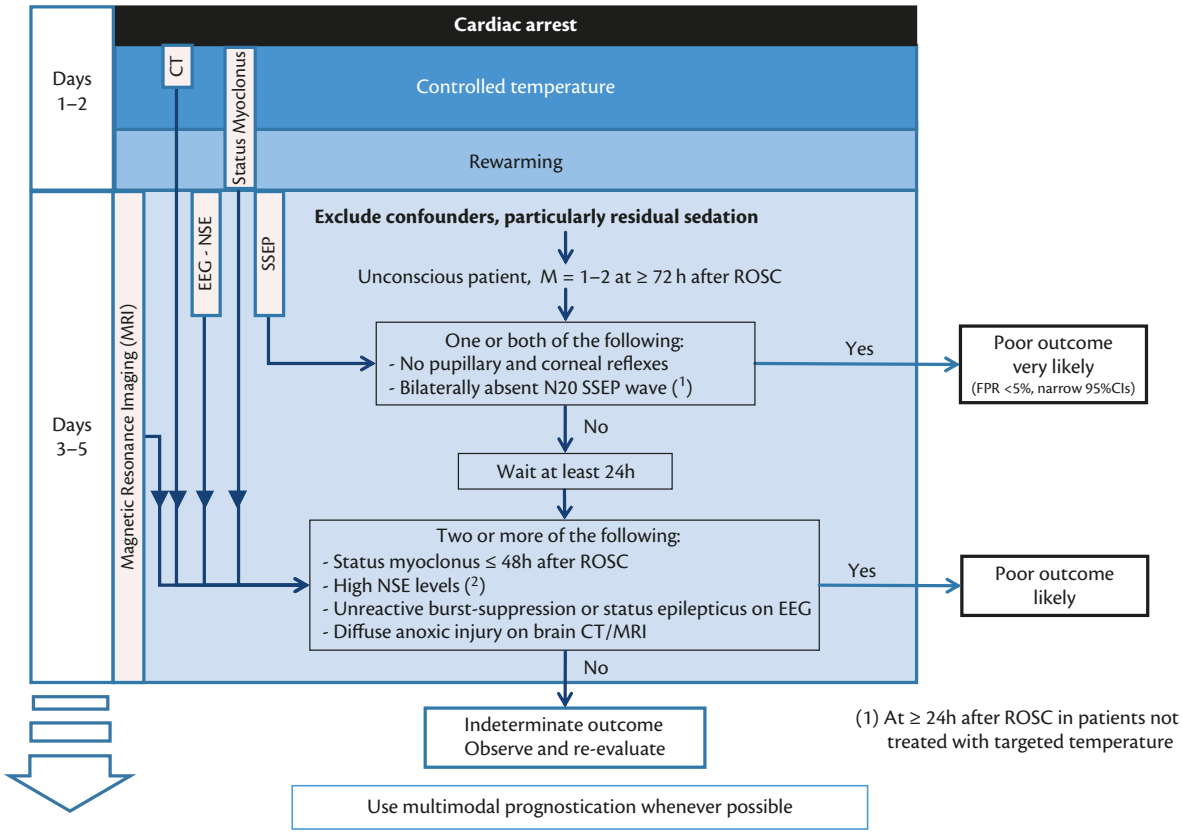


Fig. 66.1 European Resuscitation Council and European Society of Intensive Care Medicine algorithm for prognostication in comatose survivors of cardiac arrest.
ROSC, return of spontaneous circulation; SSEP, somatosensory evoked potential; NSE, neuron specific enolase.
Reprinted from Resuscitation, 12, Sandroni C et al., 'Prognostication in comatose survivors of cardiac arrest: An advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine', pp. 1779–1789, Copyright 2014, with permission from Elsevier.

of care that includes PCI and targeted temperature management. In some observational studies, hospitals that offer a post-cardiac arrest 'care bundle' have shown improved good quality survival. There may be a volume effect, whereby hospitals treating the most post-cardiac arrest patients achieve the best outcomes, but this has not been proven conclusively.

References

1. Carr BG, Kahn JM, Merchant RM, Kramer AA, and Neumar RW. (2009). Inter-hospital variability in post-cardiac arrest mortality. *Resuscitation*, **80**, 30–4.
2. Nolan JP, Laver SR, Welch CA, Harrison DA, Gupta V, and Rowan K. (2007). Outcome following admission to UK intensive care units after cardiac arrest: a secondary analysis of the ICNARC Case Mix Programme Database. *Anaesthesia*, **62**, 1207–16.
3. Elliott VJ, Rodgers DL, and Brett SJ. (2011). Systematic review of quality of life and other patient-centred outcomes after cardiac arrest survival. *Resuscitation*, **82**, 247–56.
4. Nolan JP, Neumar RW, Adrie C, et al. (2008). Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. *Resuscitation*, **79**, 350–79.
5. Neumar RW. (2011). Optimal oxygenation during and after cardiopulmonary resuscitation. *Current Opinions in Critical Care*, **17**, 236–40.
6. Deakin CD, Nolan JP, Soar J, et al. (2010). European Resuscitation Council Guidelines for Resuscitation 2010 Section 4. Adult advanced life support. *Resuscitation*, **81**, 1305–52.
7. Dumas F, Cariou A, Manzo-Silberman S, et al. (2010). Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. *Circulation and Cardiovascular Intervention*, **3**, 200–7.
8. Laver S, Farrow C, Turner D, and Nolan J. (2004). Mode of death after admission to an intensive care unit following cardiac arrest. *Intensive Care Medicine*, **30**, 2126–8.
9. Inamasu J, Miyatake S, Tomioka H, et al. (2009). Subarachnoid haemorrhage as a cause of out-of-hospital cardiac arrest: a prospective computed tomography study. *Resuscitation*, **80**, 977–80.
10. The Hypothermia after Cardiac Arrest Study Group. (2002). Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *New England Journal of Medicine*, **346**, 549–56.
11. Bernard SA, Gray TW, Buist MD, et al. (2002). Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *New England Journal of Medicine*, **346**, 557–63.
12. Nielsen N, Wetterslev J, Cronberg T, et al. (2013). Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *New England Journal of Medicine*, **369**, 2197–206.
13. Holzer M. (2010). Targeted temperature management for comatose survivors of cardiac arrest. *New England Journal of Medicine*, **363**, 1256–64.
14. Polderman, K. H. and Herold, I. (2009). Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical

considerations, side effects, and cooling methods. *Critical Care Medicine*, **37**, 1101–20.
15. Nielsen N, Sunde K, Hovdenes J, et al. (2011). Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. *Critical Care Medicine*, **39**, 57–64.
16. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, and Wiebe S. (2006). Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, **67**, 203–10.
17. Seder DB, Sunde K, Rubertsson S, et al. (2015). Neurologic outcomes and postresuscitation care of patients with myoclonus flowing cardiac arrest. *Critical Care Medicine*, **43**(5), 965–72.
18. Sandroni C, Cavallaro F, Callaway CW, et al. (2013). Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 1: Patients not treated with therapeutic hypothermia. *Resuscitation*, **84**, 1310–23.
19. Sandroni C, Cavallaro F, Callaway CW, et al (2013). Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 2: Patients treated with therapeutic hypothermia. *Resuscitation*, **84**, 1324–38.
20. Sandroni C, Cariou A, Cavallaro F, et al. (2014). Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. *Resuscitation*, **85**, 1779–89.

CHAPTER 67

Ethical and end-of-life issues after cardiac arrest

Carolyn Benson and G. Bryan Young

Key points

- Accurate prognostication following cardiac arrest requires the presence of two or more negative prognosticators, especially following treatment with therapeutic hypothermia.
- Poor prognosis is generally defined as severe disability with full dependency, vegetative state, or death.
- Negative prognosticators include:

  Day 1: presence of axial myoclonus, **Day 3**: absence of pupillary light reflex or corneal reflex, **Day 6**: extensor posturing or no motor response, **Days 1–3**: bilateral absent N20 response on somatosensory-evoked potentials (SSEPs), Diffusion restriction on MRI, EEG non-reactive, isoelectric, or status epilepticus.
- Early contact with family or surrogate decision makers, the involvement of medical experts, and clear explanation of both prognosis and the limitations of intensive care can help reduce the provision of medically futile care.
- In discussion with families about the level of care to be provided to the patient autonomy is often considered of the foremost importance.

Introduction

Out-of-hospital cardiac arrest represents a major cause of morbidity and mortality in developed countries. Despite advances in the management of these patients, overall mortality rates continue to exceed 90%. In survivors, anoxic-ischaemic brain injury is of particular concern and predicting neurological outcome at an early stage becomes important for directing medical care. Early discussions with families and surrogate decision makers may address further resuscitation and whether to continue with intensive care. Establishing the neurological prognosis is the first essential step in arriving at goals of care.

Prognostic determination

Studies evaluating predictors of neurological recovery following cardiac arrest aim to reliably predict Glasgow outcome scores (GOS) of three or less (vegetative state, defined as wakefulness with no conscious awareness, or severe disability with total dependency), at six months post-arrest. As prediction of this degree of disability often results in withdrawal of life-sustaining treatments, it is important that the combination of clinical, radiographic and electrophysiological tests used have a very low (close to zero) false positive rates for determining poor prognosis.

The clinical examination following cardiac arrest should ideally include assessment of pupillary reaction to light, corneal reflex and motor response to noxious stimuli. The presence of axial myoclonus, defined as bilateral synchronous jerks of the proximal limbs, trunk or face, should be noted. Axial myoclonus may be accompanied by status epilepticus on electroencephalogram (EEG) or originate from the brainstem and have no EEG correlation. It is important to distinguish axial myoclonus from tonic-clonic activity and multifocal, asynchronous myoclonus, both of which may occur during passive rewarming and have limited prognostic value. It is difficult to assess the function of the cerebral cortex in a comatose patient, but as the brainstem is more resilient to anoxic-ischaemic injury, dysfunction of the brainstem post-arrest suggests the cerebral cortex has suffered severe anoxic injury.

For many years, prediction of neurological outcome has been based on the work by Levy and colleagues [1]. In 2006, the American Academy of Neurology (AAN) published practice parameters based on a systematic review of the literature and provided clinicians with guidelines to identify patients who would have poor neurological outcomes following cardiac arrest [2]. Clinical features indicating poor outcome included presence of myoclonic status epilepticus on day one, and absence of either pupillary responses or corneal reflexes or extensor posturing as the best motor response on day 3. Bilateral absence of N20 response on somatosensory-evoked potentials (SSEPs) performed on day 1–3 and serum neuron-specific enolase (NSE) >33 μg/L also predicted negative outcome with an acceptable false positive rate (FPR). It is important to note that the guidelines identify patients who will have poor outcomes, but many patients will remain severely impaired from anoxic brain injury in the absence of unfavourable prognostic signs. A major issue with the AAN guidelines is that they were based on studies conducted prior to widespread use of therapeutic hypothermia which followed two landmark studies published in 2002 that reported therapeutic hypothermia (TH) could improve neurological outcome following cardiac arrest. Recent evidence suggests that different standards may be needed in patients who have been treated with hypothermia as established prognostic indicators are unreliable in patients who have been treated with hypothermia [3]. Rossetti and colleagues conducted a prospective study to validate the AAN guidelines in

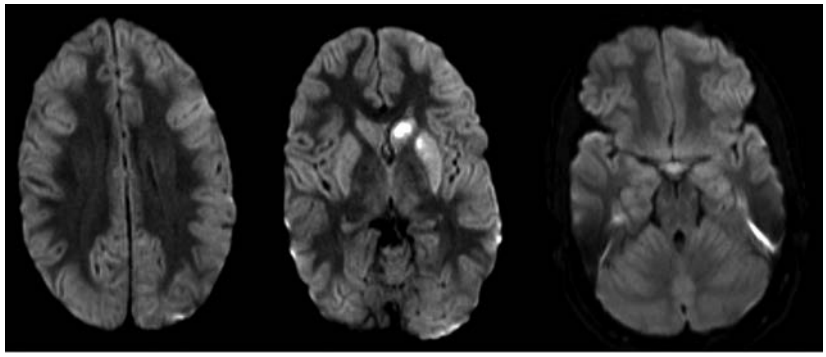


Fig. 67.1 MRI of a post-arrest patient demonstrating diffusion restriction in the cortex and basal ganglia.

patients treated with hypothermia. They found that when assessed within 72 hours of cardiac arrest the following variables had higher FPRs for mortality than reported in the AAN guidelines: absent brainstem reflexes (FPR 4%), myoclonus (FPR 3%), and absent motor response to pain (FPR 24%). The presence of at least two negative prognosticators (absent brain stem reflexes, myoclonus, unreactive EEG, and bilaterally absent N20 on SSEPs) had a positive predictive value of 100% for poor neurological outcome [4]. The presence of axial myoclonus was considered uniformally fatal prior to the use of hypothermia and continues to carry a negative prognosis. However, recent reports of good neurological recovery in patients with axial myoclonus following cardiac arrest due to cardiac pathology, emphasize the importance of having multiple negative prognosticators [5–7].

Longer anoxia time (time between collapse and initiation of cardiopulmonary resuscitation (CPR)) and longer duration of CPR intuitively lead to poorer outcomes. The Brain Resuscitation Clinical Trial and Study Group confirmed that anoxia time exceeding 5 minutes and CPR time exceeding 20 minutes were independent predictors of mortality. However, some patients with prolonged anoxia times and longer duration of CPR had good neurological outcome meaning that these factors alone are insufficient to predict unfavourable neurological outcome [8].

Electrophysiological tests, which include SSEPs and EEG, can help to assess cortical function post-arrest. Bilateral absence of the N20 response (the response from the primary somatosensory cortex that occurs 20 msec after electrical stimulation of the median nerve at the wrist) on SSEPs has a specificity as high as 100% for unfavourable outcome [9]. Electrodes placed over the brachial plexus and upper cervical cord result in responses at 9 and 13 msec, respectively, and confirm that that the sensory pathway is intact from the wrist to the brainstem, reducing FPR (Fig. 67.1).

EEG patterns associated with poor outcomes post-arrest include generalized suppression, burst suppression, and epileptic discharges, including status epilepticus and generalized periodic epileptiform discharges on a flat background [10]. The presence of reactivity, meaning a change in frequency and/or amplitude in response to an external stimulus, is a favourable sign. Lack of reactivity on EEG has been associated with poor neurological outcome, but with a FPR of 7% [4]. The EEG does not have a sufficient positive predictive value to be used alone for prognostication and is susceptible to many confounders including sedation, multi-organ failure, and hypothermia.

Early after cardiac arrest a cranial computed tomography (CT) scan is usually negative, but in the presence of severe anoxic injury may show loss of gray–white differentiation and cerebral oedema [11]. Diffusion-weighted magnetic resonance imaging (MRI) is sensitive for early ischaemic changes and may be useful for prognostication when the cranial CT is normal and clinical examination is equivocal (Fig. 67.2).

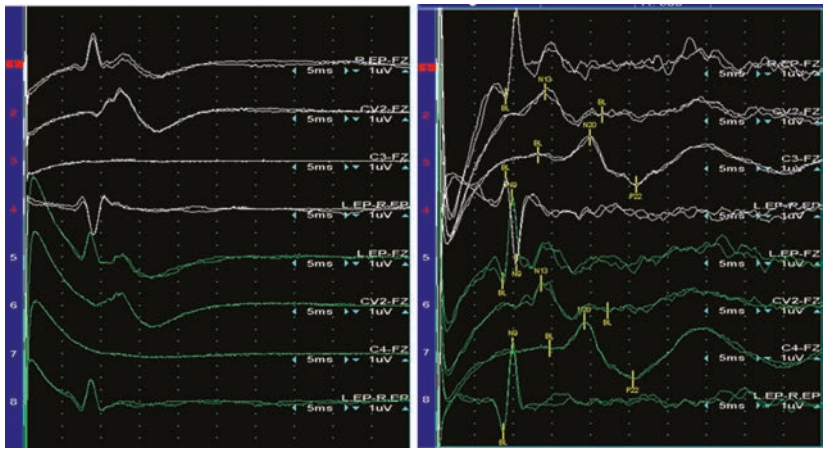


Fig. 67.2 SSEPs. The figure on the right demonstrates normal SSEPs with bilaterally present N20 responses. In contrast, the figure on the left demonstrates bilaterally absent N20 responses (channels 3 and 7).

Several biomarkers have shown potential to identify patients who will have poor neurological outcome. NSE is a cytoplasmic enzyme found in neurons and neuroectodermal cells. Neuronal damage results in NSE release into the cerebrospinal fluid and blood, with a half-life of 24 hours. Although the AAN guidelines found a NSE above 33 μg/L to be reliably predictive of poor outcome, these results do not seem to apply to patients treated with hypothermia in who NSE concentrations greater than 90 μg/L may be recorded in patients who subsequently regain consciousness [12,13].

S100B is a calcium-binding protein with a half-life of 2 hours found predominantly in astroglial cells. Depending on time of measurement, cut-off measurements from 0.7–5.2 μg/L have been shown to have 100% specificity for poor neurological outcome [13]. The measurement of such biomarkers is not available at many medical centres and more research is needed to determine a serum cut-off measurement with 100% specificity.

In addition to treatment with hypothermia, other confounders of the neurological examination include organ failure, specifically hepatic and renal dysfunction, cardiogenic shock, metabolic acidosis, other metabolic derangements, and treatment with sedatives and neuromuscular blocking agents. As many as 83% of patients are still treated with sedative agents on day 3 post-arrest, and the receipt of a sedating drug within 12 hours of the 72-hour neurological examination increases the risk of false-positive predictions [14]. Hypothermia can result in increased serum drug concentrations, increased duration of action, and decreased clearance. Relevant drugs commonly used in patients treated with hypothermia include fentanyl, midazolam, propofol, and neuromuscular blocking agents.

The use of at least two established predictors of poor outcome markedly improves the predictive value and allows the use of some predictors, e.g. EEG, MRI, and axial myoclonus, that by themselves have good, but not perfect predictive values. At the same time, it is useful to consider factors that indicate a favourable outcome. These include EEG reactivity, serum biomarkers, the presence of purposeful limb movements, e.g. localization, and imaging findings, such as minimal to no diffusion restriction on magnetic resonance imaging (MRI) and an intact default mode network on resting functional magnetic resonance imaging (fMRI). Further research is needed to improve parameters for poor prognostication in patients treated with hypothermia and also to discriminate patients who will have full recovery from those who will be left with moderate and severe disability.

Prognostication following cardiac arrest remains a medical, ethical, and socioeconomic challenge. A number of errors occur when doctors provide prognoses without sufficient evidence and it remains difficult to predict a patient's neurological prognosis with certainty. Published literature guides physicians by providing the FPR of physical signs and diagnostic tests. However, it also reports cases of miraculous recovery. The socioeconomic pressure to determine prognosis in the very early post-arrest period, in order to ensure appropriate use of scarce medical resources, may lead to false prediction of an unfavourable outcome and premature withdrawal of life-sustaining treatments. Perman and colleagues retrospectively reviewed the medical records of patients admitted following cardiac arrest and found 57% of patients had documentation of poor prognosis during hypothermia or within 15 hours of normothermia and some patients had withdrawal of life support prior to rewarming [15]. While other factors, for example, other terminal disease or pre-existing disability, may influence decision-making, accurate prognostication is not reliable during hypothermia, and is probably best delayed until 72 hours or longer after the arrest.

Ethic principles and end-of-life decision making

Discussions regarding prognosis and management of patients who remain unresponsive after resuscitation from cardiac arrest must be conducted in a professional manner and show respect for the individuals involved, their culture and religion. It is vital that the physician who is 'breaking bad news' explain the condition and prognosis in lay terms, be honest and open, show respect and acknowledge the emotional responses that follow. Often more than one meeting is necessary to allow friends and relatives to fully understand the situation, to communicate with each other and to consider the options for future treatment. The prognosis should be presented in an evidence-based manner, using statistical probabilities when feasible, and using terms that lay persons can understand.

The object of the discussion with substitute decision makers is to arrive at an informed decision about the level of care that is appropriate for the patient. Possible levels of care include:

- Full intensive care including ventilator support, treatment of infections, haemodynamic support and providing CPR if another cardiac arrest were to occur.
- Full intensive care, but without CPR.
- Limitations of support, which could include providing ventilator support, but restricting investigations and some treatments.
- Withdrawal of life-sustaining therapy with the object being to prevent distress or the appearance of distress. This usually includes withdrawal of ventilator support, but can also include withdrawal of hydration and nutrition.

The Beauchamp–Childress system of medical ethics recognizes four guiding principles:

- Respect for autonomy or self-determination.
- Non-maleficence or avoidance of harm.
- Beneficence or promoting what is good or beneficial.
- Distributive justice or respect for societal values and principles.

In discussion with families about the level of care to be provided to the patient autonomy is often considered of the foremost importance. When a patient is mentally competent, he or she can decide the level of care acceptable to them based on the expected outcome, which includes the withdrawal of life-sustaining treatments. Following cardiac arrest most patients will not be mentally competent, but some will have an advance directive giving written instructions directing treatment in the event of incapacity certain prognoses or written designation of proxy decision-makers in the event of incapacity. The advance directive is the most powerful assertion of the patient's wishes and should be respected. In the event that specific directives were not given, it is essential to emphasize to the surrogate decision maker(s) that they should act according to what they feel the patient would have wanted, based on previous conversations, values, and beliefs.

Medical futility

With increasing available technology to support critically-ill patients, a particularly difficult ethical dilemma arises when decision makers request the continuation or initiation of treatments that the health professional team believes to be futile. Defining medical futility is fraught with controversy. Schneiderman defines medical futility as the 'unacceptable likelihood of achieving an effect that the patient has the capacity to appreciate as a benefit' [16]. Medical futility can be divided into quantitative and qualitative components. Quantitative futility is the extreme unlikelihood of accomplishing a desired physiological effect and is linked to the basic ethical principle of beneficence. Qualitative futility is the unlikelihood of improving a patient's life in a meaningful way and must be assessed on an individual basis. There are several reasons families may insist on pursing treatment deemed medically futile by the treating team. Cultural and religious reasons can compel families and surrogate decision makers to continue intensive care, even against their own judgment of what the patient would want. Lack of understanding of the limitations and complications of intensive care has also been cited as a reason for continuing medically futile care. Early and open communication, being as definitive as possible with the prognosis, exploring patient values, and where necessary the involvement of medical ethicists may help families and health professional teams reach common ground and agree on appropriate levels of care. While reaching such an agreement is preferable it is not always possible and it may sometimes be necessary to resort to 'Consent and Capacity Boards' (or a similar independent body that is legally empowered to hold hearings) or courts of law to arrive at a decision regarding treatment to be provided or to withhold life-sustaining treatments.

References

1. Levy DE, Caronna JJ, Singer BH, Lapinski RH, Frydman H, and Plum F. (1985). Predicting outcome from hypoxic-ischemic coma. *Journal of the American Medical Association*, **253**, 1420–6.
2. Wijdicks EFM, Hijdra A, Young GB, Bassetti CL, and Wiebe S. (2006). Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, **67**, 203–10.
3. Al Thenayan EA, Savard M, Sharpe M, Norton L, and Young B. (2008). Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. *Neurology*, **71**, 1535–7.
4. Rossetti AO, Oddo M, Logroscino G, and Kaplan PW. (2010). Prognostication after cardiac arrest and hypothermia: A prospective study. *Annual of Neurology*, **67**, 301–7.
5. Chen CJ, Coyne PJ, Lyckhom LJ, and Smith TJ. (2012). A case of inaccurate prognostication after the ARCTIC protocol. *Journal of Pain and Symptom Management*, **43**, 1120–5.
6. Lucas JM, Cocchi MN, Salciccioli J, et al. (2012). Neurologic recovery after hypothermia in patients with post-cardiac arrest myoclonus. *Resuscitation*, **83**, 265–9.
7. Rossetti AO, Oddo M, Liaudet L, and Kaplan PW. (2009). Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. *Neurology*, **72**, 744–9.
8. Rogove HJ, Safar P, Sutton-Tyrrell K, and Abramson NS. (1995). Old age does not negate good cerebral outcome after cardiopulmonary resuscitation: analyses from the brain resuscitation clinical trials. The Brain Resuscitation Clinical Trial I and II Study Groups. *Critical Care Medicine*, **23**(1), 18–25.
9. Tiainen M, Kovala TT, Takkunen OS, and Roine RO. (2005). Somatosensory and brainstem auditory evoked potentials in cardiac arrest patients treated with hypothermia. *Critical Care Medicine*, **33**(8), 1736–40.
10. Rossetti AO, Urbano LA, Delodder F, Kaplan PW, and Oddo M. (2010). Prognostic value of continuous EEG monitoring during therapeutic hypothermia after cardiac arrest. *Critical Care*, **14**(5), R173.
11. Metter RB, Rittenberger JC, Guyette FX, and Callaway CW. (2011). Association between a quantitative CT scan measure of brain edema and outcome after cardiac arrest. *Resuscitation*, **82**(9), 1180–5.
12. Daubin C, Quentin C, Allouch S, et al. (2011). Serum neuron-specific enolase as predictor of outcome in comatose cardiac-arrest survivors: a prospective cohort study. *BMC Cardiovascular Disordors*, **11**, 48–61.
13. Shinokzaki K, Oda S, Sadahiro T, et al. (2009). S-100B and neuron-specific enolase as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation: a systematic review. *Critical Care*, **13**(4), R121.
14. Samaniego EA, Mlynash M, Finley Caulfield A, Eyngorn I, and Wijman CAC. (2011). Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. *Neurocritical Care*, **15**(1), 113–19.
15. Perman SM, Kirkpatrick JN, Reitsma AM, et al. (2012). Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia. *Critical Care Medicine*, **40**(3), 719–24.
16. Schneiderman LJ. (2011). Defining medical futility and improving medical care. *Journal of Bioethical Inquiry*, **8**(2), 123–31.

PART 3.3

Fluid management

CHAPTER 68

Physiology of body fluids

Anthony Delaney

Key points

- In health, approximately 60% of body weight is water, 66% of this is intracellular fluid, 33% is extracellular fluid. The extracellular fluid is distributed approximately 20% in the intravascular or plasma space and 80% in the interstitial space.
- The endothelial glycocalyx layer appears to play an important role in determining the movement of fluid between the vascular compartment and the interstitial compartment.
- Intracellular fluid volume is largely determined by changes in osmolarity.
- Extracellular fluid volume is largely determined by total body sodium.
- Consideration of the physiological nature of fluid losses will allow appropriate fluid replacement.

Introduction

An understanding of the physiology of body fluids is essential in the consideration of appropriate fluid resuscitation and fluid replacement therapy in critically ill patients. This chapter will provide an overview of the body fluid compartments and forces that govern the distribution of fluids between compartments, and the regulation of body fluid status.

Body fluid compartments

The human body, in health, is composed of approximately 60% water. This proportion declines with age [1] and increasing obesity [2], and is lower in females compared to males [3]. The measurement of total body water can be performed via indicator dilution techniques using Deuterium oxide (^2H_2O), tritium oxide (^3H_2O), or ^{18}O-labelled water [4], or more recently via bioelectrical impedance analysis [2].

Total body water is classically described as being distributed between an intracellular fluid compartment, and extracellular fluid compartment. The extracellular fluid compartment can be further divided into an intravascular or plasma component, an interstitial component and a transcellular component [5], as shown in Fig. 68.1.

Intracellular fluid compartment

The intracellular component of total body water is generally estimated from the difference between total body water and extracellular fluid space [2]. Approximately 60% of total body water is in the intracellular fluid compartment and thus the intracellular fluid compartment makes up approximately 35% of total body weight. While the composition of intracellular fluid varies greatly between tissues and organs, the approximate electrolyte composition of the intracellular fluid is shown in Table 68.1.

Extracellular fluid compartment

The extracellular fluid compartment, composed of all the fluid external to cells, can be divided into an intravascular or plasma component, an interstitial component and a transcellular component. The extracellular fluid volume can be measured by indicator dilution using non-ionic substances such as inulin, mannitol, or sucrose, or ionic substances such as bromide, chloride, or sulphate. The extracellular fluid composes approximately 20% of total body weight. The approximate electrolyte composition of the extracellular fluid compartment is shown in Table 68.1.

Intravascular fluid compartment

The intravascular compartment is composed of a cellular component (largely filled by the red cell mass, but also the other cellular components of blood) and the plasma volume. The plasma volume can be estimated by an indicator dilution technique using Evans blue or radiolabelled albumin. The plasma contains a number of proteins: albumin, globulins and fibrinogen and clotting proteins. These proteins have specific physiologic roles, such as hormone transport, buffering, immune function, and in clotting, as well as maintaining the plasma colloid osmotic pressure.

Interstitial fluid compartment

The interstitial fluid compartment is difficult to measure and its volume is estimated by the difference between the extracellular fluid volume and the plasma volume. The interstitial fluid compartment has an electrolyte composition that is similar to that of plasma and the rest of the extracellular fluid compartment, as shown in Table 68.1. The protein content of the interstitial fluid is only approximately 40% of that of the plasma [7].

Transcellular fluid compartment

The transcellular fluid compartment consists of all fluid that is formed by the transport activity of cells. This includes the fluids found in the gastrointestinal tracts, biliary tree, salivary glands, the eye, and the cerebrospinal fluid. In health these volumes total approximately 1000 mL, although in disease states (such as bowel obstruction), the volume may be considerably more. The electrolyte composition of the transcellular fluid varies according to the tissue where it is produced.

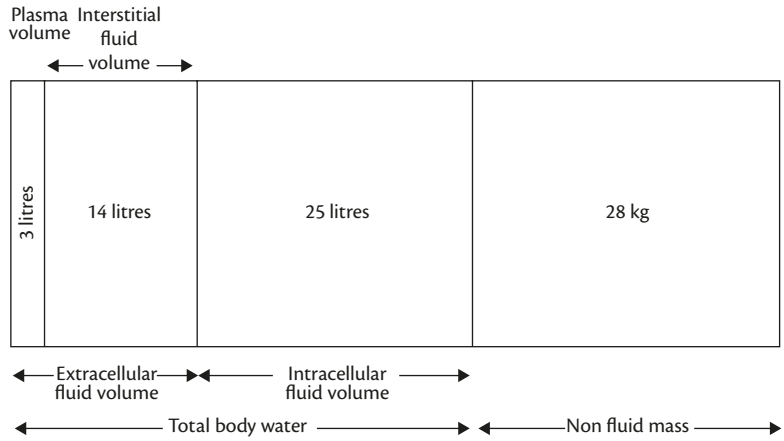


Fig. 68.1 Body fluid compartments.
This figure was published in the *American Journal of Medicine*, **27**, Edelman IS, et al., 'Anatomy of body water and electrolytes', pp. 256–77, Copyright Elsevier and Alliance for Academic Internal Medicine 1959.

Table 68.1 Average electrolyte composition of body fluid compartments

Electrolyte	ICF (mmol/L)	ECF (mmol/L)	Plasma interstitial
Sodium	10	140	145
Potassium	155	3.7	3.8
Chloride	3	102	115
Bicarbonate	10	28	30
Calcium (ionized)	<0.01	1.2	1.2
Magnesium	10	0.8	0.8
Phosphate	105	1.1	1.0

ICF, intracellular fluid compartment; ECF, extracellular fluid compartment.

This table was published in the *American Journal of Medicine*, **27**, Edelman IS, et al., 'Anatomy of body water and electrolytes', pp. 256–77, Copyright Elsevier and Alliance for Academic Internal Medicine 1959.

Forces governing movement of fluid between compartments

Forces governing the movement of fluid to and from the intravascular fluid compartment, and the interstitial fluid compartment

The movement of fluid between the plasma and the interstitial space is classically governed by Starling forces [8]. The Starling equation summarizes these forces:

$$J_v = K[(P_c - P_i) - \sigma(\pi_c - \pi_i)],$$

where J_v is the fluid flux across the capillary membranes, K = is the filtration coefficient, P_c is the capillary hydrostatic pressure, P_i is the interstitial hydrostatic pressure, σ is the reflection coefficient and π_c is the capillary osmotic pressure and π_i is the interstitial osmotic pressure [9].

The capillary hydrostatic pressure is determined by the pressure inside the capillaries and is higher at the arterial end of the capillary bed compared to the venous end, leading to a net movement of fluid out of the capillary at the arterial end and a net movement of fluid back into the capillary at the venous end. The interstitial hydrostatic pressure is maintained at a slightly negative value by the action of the lymphatics actively removing fluid from this space. The plasma osmotic pressure is due to the osmotic action of the plasma proteins, in particular albumin, but also due to the additional effect of the sodium, potassium, and other cations that are held with the plasma proteins, an effect known as the Donnan effect. The osmotic pressure in the interstitial space is due to proteins that have leaked through pores in the capillary membrane.

Under normal circumstances there is a small net force that leads to approximately 2 ml/min of fluid moving from the capillaries to the interstitium to be returned to the circulation via the lymphatics [7], as shown in Fig. 68.2.

In more recent times, the classic Starling hypothesis and equation have been questioned and the endothelial glycocalyx layer, a web of glycoproteins and proteoglycans that are bound on the luminal side of the vascular endothelial cells, has assumed increased importance in theories regarding the movement of fluid between the vascular and interstitial spaces. There is little evidence to support the hypothesis that fluid resorption occurs at the venous end of most capillary beds [10], rather most filtered fluid returns to the circulation via the lymphatic system. The endothelial glycocalyx covers the endothelial intercellular clefts, and as such separates the plasma from a region below the glycocalyx, the sub-glycocalyx space. This

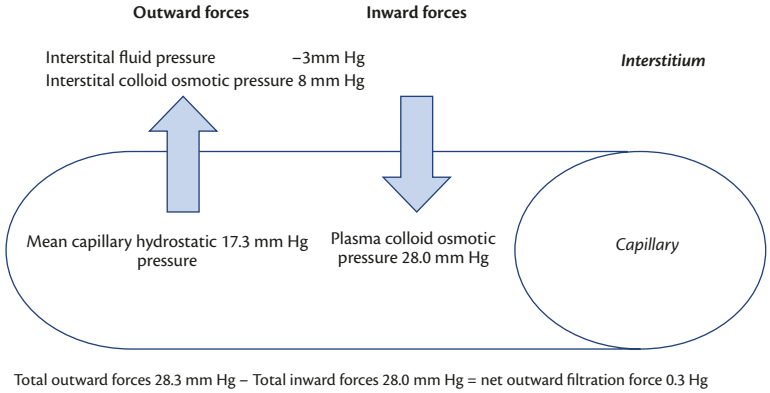


Fig. 68.2 Forces governing the movement of fluid across capillary membranes.

space, which is almost protein free, determines the flow of fluid across the capillary membrane from the plasma to the interstitial space [11].

This revised model provides an explanation of why isotonic saline solutions result in similar plasma volume expansion as colloids [12] when capillary pressure is low. Disruption of the endothelial glycocalyx layer, which can occur with rapid infusion of fluids, acute hyperglycaemia, surgery, and sepsis, can alter the functioning of this barrier [11], and in part explains why fluid distribution differs in various disease states.

Forces governing the movement of fluid to and from the interstitial fluid compartment, and the intracellular fluid compartment

As water is able to pass freely across cell membranes, the major determinant of fluid movement into or out of cells is the relative osmolarity of the intracellular and interstitial fluid compartments. The internal composition of cells is maintained via a number of active transport mechanisms [13] including volume sensitive chloride channels [14]. Thus changes in interstitial osmolarity are most responsible for changes in intracellular fluid volume.

The regulation of body fluid status

Body fluid status is governed by the difference between the intake and outputs. Fluid intake in health is regulated by thirst, which in turn determines the osmolarity of the internal environment, and plays a crucial role in regulating intracellular fluid status. Fluid output largely consists of losses from the gastrointestinal tract [15], and insensible losses [16], as shown in Table 68.2; the renal system regulates sodium and water balance, with an obligatory fluid loss to enable excretion of metabolic waste.

The regulation of intracellular fluid status

The major factor regulating the intracellular fluid volume is the relative osmolarity of the interstitial fluid which is determined by the balance between water intake and excretion. Osmoreceptors in the lamina terminalis in the posterior pituitary gland detect of systemic osmolarity and once plasma osmolarity is greater than 284 mOsm/L, there is a linear increase in the secretion of antidiuretic

Table 68.2 Approximate daily volume and electrolyte composition of body fluid losses

	Volume (ml/day)	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)	$HCO3^-$ (mmol/L)
Gastrointestinal tract					
Saliva	500–1000	30	20	10–35	0–15
Stomach	1000–2500	60	10	100–120	0
Bile	500	140	5–10	100	40–70
Pancreatic	750	140	5–10	70	40–70
Intestine	2000–4000	110	5–10	100	25
Other					
Respiration	300–500	0	0	0	0
Sweat	800–1200	30–60	5–10	30–50	0

Data from Worthley LI, '*Fluid and electrolytes*', Synopsis of Intensive Care Medicine, First edition, Edinburgh: Churchill Livingstone, 1994; and Cox P, 'Insensible water loss and its assessment in adult patients: a review', *Acta anaesthesiologica Scandinavica*, 1987, **31**(8), pp. 771–6. Epub 1987/11/01.

hormone (ADH), accompanied by a corresponding increase in thirst [17]. Systemic hypotension and activation of baroreceptors may also trigger these responses. As well as increasing thirst, ADH causes water retention in distal tubule of the kidney via increased expression of aquasporins mediated by V_2 receptors.

The integration of thirst and ADH secretion maintain plasma osmolarity within the narrow range of 284–295 mOsm/L [17]. The maximal ADH response occurs at 295 mOsm/L, and as there is an obligatory urine volume required to excrete metabolic waste, further water conservation is not possible. Thus, unless water intake is increased, hyperosmolarity and intracellular volume depletion result. Conversely, at plasma osmolarity of below 284 mOsm/L ADH secretion is suppressed. Maximal renal water excretion is 15–20 L/day, and if water intake exceeds this, then hypo-osmolarity will follow with consequent increase in intracellular water, and cell swelling [17].

The regulation of extracellular volume status

The regulation of extracellular volume status is inextricably linked to the regulation of sodium, the predominant electrolyte in extracellular fluid. The human body has a number of well-described mechanisms to avoid hypovolaemia, and to deal with total body sodium overload or hypervolaemia.

In addition to the cardiovascular responses to hypovolaemia, neurohumoral responses include activation of baroreceptors with increase secretion of ADH, activation of the renin-angiotensin-aldosterone system, and the release of endogenous corticosteroids all of which promote the retention of sodium and water.

References

1. Schoeller DA. (1989). Changes in total body water with age. *The American Journal of Clinical Nutrition*, **50**(5 Suppl.) 1176–81; discussion 231–35.
2. Ritz P, Vol S, Berrut G, Tack I, Arnaud MJ, and Tichet J. (2008). Influence of gender and body composition on hydration and body water spaces. *Clinical nutrition (Edinburgh, Scotland)*, **27**(5), 740–6.
3. Chumlea WC, Guo SS, Zeller CM, et al. (2001). Total body water reference values and prediction equations for adults. *Kidney international*, **59**(6), 2250–8.
4. Chumlea WC, Schubert CM, Sun SS, Demerath E, Towne B, and Siervogel RM. (2007). A review of body water status and the effects of age and body fatness in children and adults. *Journal of Nutrition, Health & Aging*, **11**(2), 111–18.
5. Edelman IS and Leibman J. (1959). Anatomy of body water and electrolytes. *American Journal of Medicine*, **27**, 256–77.
7. Hall JE. (2011). *The Microcirculation and Lymphatic System: Capillary Fluid Exchange, Interstitial Fluid and Lymph Flow. Guyton and Hall Textbook Of Medical Physiology*, 12th edn. London: Saunders.
8. Starling EH. (1896). On the absorption of fluids from the connective tissue spaces. *Journal of Physiology*, **19**(4), 312–26.
9. Vercueil A, Grocott MP, and Mythen MG. (2005). Physiology, pharmacology, and rationale for colloid administration for the maintenance of effective hemodynamic stability in critically ill patients. *Transfusion Medicine Reviews*, **19**(2), 93–109.
10. Levick JR and Michel CC. (2010). Microvascular fluid exchange and the revised Starling principle. *Cardiovascular Research*, **87**(2), 198–210.
11. Woodcock TE and Woodcock TM. (2012). Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. *British Journal of Anaesthesia*, **108**(3), 384–94.
12. The SAFE Study Investigators. (2004). A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *New England Journal of Medicine*, **350**(22), 2247–56.
13. Pasantes-Morales H, Lezama RA, Ramos-Mandujano G, and Tuz KL. (2006). Mechanisms of cell volume regulation in hypo-osmolality. *American Journal of Medicine*, **119**(7 Suppl. 1), S4–11.
14. Okada Y. (2004). Ion channels and transporters involved in cell volume regulation and sensor mechanisms. *Cell Biochemistry and Biophysics*, **41**(2), 233–58.
15. Worthley LI. (1994). *Fluid and Electrolytes. Synopsis of Intensive Care Medicine*. Edinburgh: Churchill Livingstone.
16. Cox P. (1987). Insensible water loss and its assessment in adult patients: a review. *Acta anaesthesiologica Scandinavica*, **31**(8), 771–6.
17. Ball SG. (2007). Vasopressin and disorders of water balance: the physiology and pathophysiology of vasopressin. *Annals of Clinical Biochemistry*, **44**(5), 417–31.

CHAPTER 69

Choice of resuscitation fluid

John Myburgh and Naomi E. Hammond

Key points

- On current evidence, isotonic crystalloids should be considered the first-choice resuscitation fluids for almost all patients.
- On the balance of evidence, that colloids do not confer any clinically meaningful advantage over crystalloids.
- Albumin is contraindicated for the resuscitation of patients with recent severe traumatic brain injury.
- Resuscitation with hydroxyethyl starch (HES) is associated with increased risk of death and use of renal replacement therapy in critically-ill patients, especially those with severe sepsis and septic shock.
- Current evidence does not support the use of other semi-synthetic colloids for resuscitation.

Introduction

Fluid resuscitation, the administration of fluid to increase or maintain intravascular volume, is a ubiquitous intervention in acute medicine, used in almost all patients undergoing anaesthesia, following severe trauma and burns. It is used extensively in the emergency department and the intensive care unit (ICU).

The first use of an intravenous alkalinized saline solution for resuscitation was described during the cholera pandemic in 1832. The use of asanguinous fluid resuscitation accelerated following the development of blood fractionation in the 1940s and has effectively replaced blood-based resuscitation, except in patients with active haemorrhage.

Despite the widespread use of resuscitation fluids, there is a wide variation in fluid resuscitation practice, with little consensus over the best fluid in many situations. Until recently there were very few high-quality trials to guide clinical practice.

The principal aim of administering fluid for resuscitation is to rapidly and effectively restore intravascular volume to restore vital organ perfusion and function.

The ideal resuscitation fluid should therefore be one that:

- Is retained within the intravascular space.
- Produces a predictable and sustained increase in intravascular volume.
- Is physiologically constituted as close as possible to extracellular fluid.
- Is metabolized and completely excreted without accumulation.
- Does not produce transient biochemical or metabolic adverse effects.
- May be used safely and effectively in all patient populations.

At present there is no such ideal fluid available for clinical use. Resuscitation fluids are broadly categorized into crystalloid and colloid solutions.

Crystalloids

Crystalloids are solutions of ions that are capable of passing through semi-permeable membranes. They are inexpensive, have a long shelf life and are usually supplied in plastic containers. The constituents and physicochemical properties of commonly used crystalloid solutions are shown in Table 69.1.

Commonly used crystalloid resuscitation solutions contain sodium and chloride that determines the tonicity of the fluid relative to extracellular fluid. Tonicity refers to the ability of the solution to exert osmotic pressure across the cellular membrane. These two physicochemical properties are important determinants of both the efficacy of volume expansion and potential for toxicity.

All crystalloids produce a transient increase in intravascular volume before equilibrating with the extracellular fluid, generally within 1 hour after administration. Compared to colloid solutions, greater volumes of crystalloids are required to achieve an equivalent increase in intravascular volume. As a consequence, crystalloid administration is more likely to be associated with the development of interstitial oedema that depends on the rate and volume of fluid administered and on endothelial permeability. A common clinical manifestation is acute pulmonary oedema, although interstitial oedema with resultant organ dysfunction may occur in the brain, myocardium, intestines, and kidney, particularly when endothelial permeability is altered. Excessive administration of crystalloids may also cause a dilutional coagulopathy.

Crystalloid solutions in common clinical use

'Normal' (0.9%) saline

Normal saline, which is isotonic due to its high sodium concentration, is the most common crystalloid solution prescribed for fluid resuscitation. It is recommended for fluid resuscitation of patients following trauma, particularly those with traumatic brain injury, in patients who are hypovolaemic due to upper gastrointestinal losses and in patients with diabetic ketoacidosis.

As sodium and chloride are present in the same concentrations, the strong ion difference in normal saline is zero. As a result the

Table 69.1 Crystalloid solutions (per litre)

Solution	Osmolarity (mOsmol/L)	pH	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)	Ca^{2+} (mmol/L)	HCO_3^- (mmol/L)	Other (mmol/L)
Normal (0.9%) saline	308	5.0	154	—	154	—	—	—
Compounded sodium lactate (Hartmann's)	280.6	5.0–7.0	131	5.4	111	2.0	—	Lactate: 29
Ringer's lactate	273	6.5	130	4	109	2.7	—	Lactate: 28
Ringers acetate	304	4.6–5.4	140	4	127	2.5	—	Acetate: 24 Malate: 5.0 Magnesium: 1.0
Plasmalyte A	294	7.4	140	5	98	—	—	Acetate: 27 Gluconate: 23 Magnesium: 3.0
5% Glucose in water	277	3.5–6.5	—	—	—	—	—	—
4% Glucose in 0.18% saline	284	3.5–6.5	31	—	31	—	—	—

rapid administration of large volume results in the generation of a hyperchloraemic metabolic acidosis [1]. Adverse effects attributed to this metabolic acidosis include impaired renal and splanchnic function, hypotension, and coagulopathy, although whether the acidosis is clinically harmful or not is unclear. Normal saline is also the crystalloid vehicle for many colloid solutions, including some preparations of albumin and hydroxyethyl starch.

'Balanced' salt solutions

Crystalloids with a chemical composition that approximates to that of extracellular fluid have been termed 'balanced' or 'physiological' solutions. Of these, Hartmann's solution which was originally used in the 1940s for rehydration of children with severe gastro-enteritis, was the prototype. However, none of the proprietary solutions are either truly balanced or physiological. Balanced salt solutions are relatively hypotonic as they have a lower sodium concentration than extracellular fluid. The predominant anions in extracellular fluid are chloride and bicarbonate. However, due to the instability of bicarbonate-containing solutions in plastic containers, alternative anions such as lactate, acetate, gluconate, and malate have been used to substitute for bicarbonate.

Excessive administration of balanced salt solutions may result in hyperlactataemia, metabolic alkalosis, hypotonicity (compound sodium lactate), and cardiotoxicity (acetate). In addition, if solutions containing calcium are co-administered with citrated red blood cells microthrombi may form during administration. Hypotonic crystalloids are also relatively contraindicated in patients with traumatic brain injury, because of the potential to worsen cerebral oedema.

Balanced salt solutions are increasingly recommended as first line resuscitation fluids in surgical patients, trauma, and burns.

Despite increased use and recommendations, there have been no large scale trials to establish the safety and efficacy of 'balanced' salt solutions or to compare their safety and efficacy with that of normal saline. The evidence that balanced salt solutions confer any benefit over saline is limited to data from observational studies.

Hypertonic crystalloid solutions

The concern regarding sodium and water overload with crystalloid resuscitation has resulted in the concept of 'small volume' crystalloid resuscitation using hypertonic saline (3%, 5%, 7.5% sodium chloride) solutions. The early use of hypertonic saline, particularly in patients with traumatic brain injury, is theoretically attractive, but the most definitive trial to date did not demonstrate a significant advantage for hypertonic saline [2].

Consequently, hypertonic fluids are not recommended or established in current practice, although hypertonic saline may still be used as part of osmotherapy protocols for the control of intracranial hypertension in selected patients

Hypotonic crystalloids

With the exception of dehydrated patients with hypernatraemia hypotonic or 'salt free' crystalloids (for example, 5% glucose in water, 4% glucose in 0.18% saline) have no substantial role in fluid resuscitation. These solutions are commonly used as 'maintenance' fluids or for correction of insensible or 'third space' losses. This practice is increasingly questioned with the recognition that it contributes to water overload and pathological interstitial oedema [3].

Colloid solutions

Colloid solutions are suspensions of plasma-derived or semi-synthetic molecules that do not pass through semi-permeable membranes under normal physiological conditions. An international survey published in 2010 reported that colloid solutions were more commonly used for fluid resuscitation than crystalloids and that hydroxyethyl starch was the most common colloid solution used for fluid resuscitation [4]. The theoretical advantage of colloids is that they stay within the intravascular compartment longer due to their increased molecular weight, as a result less volume is needed

Table 69.2 Colloid solutions (per litre)

Solution	Osmolarity (mOsmol/L)	pH	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)	Ca^{2+} (mmol/L)	Other
Albumin 4% (Albumex 4®)	250	7.0	140	—	128	—	Octanoate 6.4 mmol/L
Albumin 20% (Albumex 20®)	130	7.0	48–100	—	—	—	Octanoate 32 mmol/L
6% Hydroxyethyl starch (130/0.4) in saline (Voluven®)	308	4.0–5.5	154	—	154	—	—
6% Hydroxyethyl starch (130/0.4) in balanced salt solution (Volulyte®)	286	5.7–5.5	137	4	110	—	Acetate 34 Magnesium 1.5
6% Hydroxyethyl starch (130/0.42) in balanced salt solution (Tetraspan®)	296	5.6–6.4	140	4.0	118	2.5	Acetate 24 Malate 5 Magnesium 1.0
Succinylated gelatin (Gelofusin 4%®)	274	7.4	154	—	120	—	—
Polygeline (Hemaccel 3.5%®)	301	7.3	145	5.1	145	6.25	—

Albumex is a trademark of CSL Bioplasma, Broadmedows, Victoria, Australia. Other preparations of albumin may contain different constituents and preservatives.

for the same effect and there is therefore less potential to produce interstitial oedema. However, the duration of intravascular effect is variable and dependent on the rate of metabolism and clearance of the different solutions. Generally, plasma derivatives have a longer duration of effect (4–6 hours) than synthetic colloids (1–4 hours), although this may vary substantially within and between patients.

Traditional teaching is that 3 L of isotonic crystalloid is needed to expand plasma volume by the same amount as 1 L of colloid. However, recent blinded trials suggest that only 1.4 L of isotonic crystalloid is needed for the same effect as 1.0 L of colloid; this reduces considerably the theoretical advantage of colloid solutions [5,6].

A recent open-label randomized-controlled trial compared resuscitation with crystalloids to colloids in severely hypovolaemic critically-ill patients and demonstrated no difference in the a priori primary outcome of 28-day mortality [7].

Off set against the potential volume sparing effect of colloids is their greater potential for toxicity.

The constituents and concentrations of some commonly used colloid preparations are shown in Table 69.2.

Plasma derivatives

Human albumin

Under normal conditions albumin is the predominant plasma protein and the predominant determinant of plasma colloid osmotic pressure. Its normal biological half-life is 15 days. Solutions for therapeutic use are produced by fractionation of blood and heat treated to prevent transmission of pathogenic viruses. 4–5% albumin is considered to be the reference colloid solution. More concentrated solutions (20 or 25%) are sometimes referred to as 'salt-poor' as they contain less sodium per gram of albumin. The more concentrated solutions are available as hypertonic preparations.

Albumin is used widely as a resuscitation fluid. Although a Cochrane Injuries Group meta-analysis suggested that administration of albumin was harmful [8], a large randomized trial found that overall it had equivalent effects to normal saline in adult ICU patients [6] and subsequent meta-analyses have concluded that its use is safe. The exception to this is in patients with severe traumatic brain injury where resuscitation with albumin soon after injury is associated with a significant increase in mortality, primarily due to the development of increased intracranial pressure [9,10].

Albumin may have a beneficial role in reducing mortality in patients with severe sepsis/septic shock, both as a resuscitation fluid [11] and as an infusion to maintain a serum albumin of 30 g/L [12], although this has not been conclusively demonstrated in specific randomized controlled trials.

Potential limitations of albumin are that most commercial preparations are supplied in glass bottles and compared to other fluids it is expensive. This is of particular concern in low income countries. The role of albumin (and saline) for bolus resuscitation of febrile children with impaired perfusion has been questioned following a large randomized trial conducted in Africa that showed increased mortality with bolus resuscitation with both albumin and saline compared to avoiding boluses of fluid [13]. The applicability of these results to other health care settings is not currently known. While hypoalbuminaemia is associated with increased mortality in critically-ill patients, there is no convincing evidence that routine albumin supplementation to correct hypoalbuminaemia reduces mortality [14].

Given these limitations, the role of albumin for resuscitation remains uncertain and there is currently no definitive evidence of benefit of albumin over crystalloid resuscitation [15,16].

Semi-synthetic colloids

Given the relative expense and limited availability of albumin, a number of semi-synthetic colloids have been developed as alternative colloid solutions.

Hydroxyethyl starches

HES are the most commonly used semi-synthetic colloids and are produced by hydroxyethyl substitution of amylopectin obtained from sorghum, maize, or potatoes. HES solutions are supplied in normal saline or 'balanced' salt solutions, in plastic containers.

The pattern of hydroxyethyl substitution of glucose influences the susceptibility of the HES molecules to hydrolysis by non-specific amylases in the blood. A high degree of substitution protects against enzymatic breakdown thereby prolonging plasma volume expansion and also the potential for HES to accumulate in the reticulo-endothelial system.

Older HES preparations, specifically pentastarch (10%) have a high molecular weight (>200 kD) and high degree of substitution (>0.6). Their use has been linked with an increased risk of acute renal injury and failure [17] pruritis and prolongation of clotting times. In general they have been superseded by newer less concentrated and less substituted preparations. Hydroxyethyl starch (6%) with a molecular weight of 130 kD and molar substitution of around 0.4 is currently extensively used as a resuscitation fluid, particularly in anaesthetic practice and in patients with trauma and sepsis. Its use is more widespread and more common in Europe than in other parts of the world.

Recent high quality randomized trials have demonstrated increased risk of death and increased use of renal replacement therapy in patients resuscitated with 6% HES (130/0.42) in Ringer's acetate in patients with severe sepsis and septic shock [5], and an increase in the use of renal replacement therapy in ICU patients in general with the use of 6% HES (130/0.4) in saline [18].

Given these findings and the relative expense compared to crystalloids, the use of HES as a resuscitation fluid in critically-ill patients is now being questioned [19].

Gelatins

Gelatins are prepared by hydrolysis of bovine or porcine collagen. The commonly available preparations are succinylated gelatin and urea-linked gelatin-polygeline. They are supplied in saline in plastic containers.

Gelatin has a relatively low molecular weight (30–35 kD) and expands plasma volume for only 1–2 hours. It is then metabolized and excreted via the kidney. Gelatins have a long shelf life, but a recognized incidence of anaphylaxis and their use may increase the risk of acute renal injury [20]. There have been no large scale trials comparing efficacy and safety of gelatins with other resuscitation fluids and therefore their role as resuscitation fluids has not been clearly defined.

Dextrans

Dextrans are polysaccharides, enzymatically synthesized from sucrose by bacteria that produce lactic acid as the major end-product of carbohydrate fermentation. Resuscitation fluids containing dextrans are typically described by the average molecular weight of the dextran molecules they contain, although the molecular weights of the dextran molecules in the solution are highly variable with 80% of the molecules having a molecular weight ranging from 10–90 kD. A number of dextran preparations are available and are supplied in glucose or saline in plastic containers.

High molecular weight dextrans (average molecular weight >60 kD) are slowly excreted. They expand plasma volume for 6–8 hours, but remain in the circulation for weeks following administration. Lower molecular weight dextrans (average molecular weight <40 kD) are primarily used as antithrombotic agents, but their use may be associated with acute renal injury. The use of dextrans for resuscitation has been superseded by other fluids and there is no robust evidence to support their ongoing use as resuscitation fluids.

Clinical applications of resuscitation fluids

General principles to consider when selecting a resuscitation fluid

The volume (i.e. dose) and rate of administration of the fluid bolus needs to be carefully considered, particularly once recognizable fluid deficits have been corrected. No single clinical index reliably represents the degree of volume deficit. Clinical and biochemical signs of hypovolaemia vary widely in different disease states and within patients over the course of the critical illness.

Specific indications

In patients who are actively bleeding, blood and blood component transfusion should be commenced as soon as practical.

Hypovolaemia should be corrected using the most pragmatic fluid available usually a crystalloid such as a balanced salt solution or normal saline.

While the selection of resuscitation fluids is influenced by clinician preference, institution protocol and fluid availability, other important considerations include serum sodium (or osmolality), pH, renal function, and coagulation status.

There are few evidence-based indications for specific resuscitation fluids in specific settings and little evidence that colloids confer any advantage over crystalloids. Rather, certain resuscitation fluids may be considered relatively or absolutely contra-indicated in certain patient populations, for example:

- Albumin in patients with recent severe traumatic brain injury.
- HES in patients with severe sepsis or septic shock.
- HES in patients at risk of acute kidney injury.
- Bolus resuscitation with albumin or saline in children with compensated shock in Africa and other resource-poor settings.

References

1. Morgan TJ, Venkatesh B, and Hall J. (2004). Crystalloid strong ion difference determines metabolic acid-base change during acute normovolaemic haemodilution. *Intensive Care Medicine*, **30**, 1432–37.
2. Cooper DJ, Myles PS, McDermott FT, et al. (2004). Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. *Journal of the American Medical Association*, **291**, 1350–57.
3. Corcoran T, Rhodes JE, Clarke S, Myles PS, and Ho KM. (2012). Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesthesia & Analgesia*, **114**, 640–51.

4. Finfer S, Liu B, Taylor C, et al. (2010). Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Critical Care*, **14**, R185.
5. Perner A, Haase N, Guttormsen AB, et al. (2012). Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *New England Journal of Medicine*, **367**, 124–34.
6. SAFE Study Investigators. (2004). A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *New England Journal of Medicine*, **350**, 2247–56.
7. Annane D, Siami S, Jaber S, et al. (2013). Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock. *Journal of the American Medical Association*, **310**, 1809–17.
8. Cochrane Injuries Group Albumin Reviewers, (1998). Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *British Medical Journal*, **317**, 235–40.
9. Cooper DJ, Myburgh J, Finfer S, et al. (2012). Albumin resuscitation for traumatic brain injury: is intracranial hypertension the cause of increased mortality? *Journal of Neurotrauma.*
10. SAFE Study Investigators. (2007). Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *New England Journal of Medicine*, **357**, 874–84.
11. The SAFE Study Investigators (2011). Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Medicine*, **37**, 86–96.
12. Caironi P, Tognoni G, Masson S, et al. (2014). Albumin replacement in patients with severe sepsis or septic shock. *New England Journal of Medicine*, **370**, 1412–21.
13. Maitland K, Kiguli S, Opoka R, et al. (2011). Mortality after fluid bolus in African children with shock. *New England Journal of Medicine*, **364**(26), 2483–95.
14. Finfer S, Bellomo R, McEvoy S, et al. (2006). Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study. *British Medical Journal*, **333**, 1044.
15. Bunn F, and Trivedi D. (2012). Colloid solutions for fluid resuscitation. Cochrane. Database. Syst. Rev. 7, CD001319.
16. Perel P, and Roberts I. (2012). Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane. Database. Syst. Rev. 6, CD000567.
17. Brunkhorst FM, Engel C, Bloos F, et al. (2008). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *New England Journal of Medicine*, **358**, 125–39.
18. Myburgh JA, Finfer S, Bellomo R, et al. (2012). Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. *New England Journal of Medicine*, **367**, 1901–11.
19. Myburgh JA, and McIntyre L. (2013). New insights into fluid resuscitation. *Intensive Care Medicine*, **39**(6), 998–1001.
20. Bayer O, Reinhart K, Sakr Y, et al.(2011). Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: a prospective sequential comparison. *Critical Care Medicine*, **39**, 1335–42.

CHAPTER 70

Therapeutic goals of fluid resuscitation

Bashar S. Staitieh and Greg S. Martin

Key points

- Central venous pressure and pulmonary capillary wedge pressure are poor predictors of fluid responsiveness.
- Downstream markers of tissue perfusion (lactic acid, base deficit, and central venous oxygen saturations) are helpful but relatively late and non-specific.
- A conservative fluid strategy is recommended in ARDS.
- Early fluid resuscitation followed by a conservative fluid strategy is recommended in septic shock.
- Arterial waveform analysis is a useful method of predicting fluid responsiveness.

Introduction

By far the most common goal of fluid resuscitation is to optimize tissue perfusion, generally through improved stroke volume and cardiac output. Knowing how well patients have responded to intravenous (iv) fluid administration has, however, become one of the more vexing problems in critical care medicine. Because traditional variables such as blood pressure, heart rate, capillary refill, and urine output are poor markers of perfusion and the adequacy of resuscitation, clinicians are increasingly turning to surrogate markers of adequate tissue perfusion. These measures can be divided into upstream, which assess the macrocirculation, and downstream, which assess the microcirculation (Table 70.1 shows the therapeutic targets for haemodynamic monitoring). Here, we review these markers, offer an overview of the available methods to assess response to fluid administration, and present guidance on the endpoints of resuscitation.

Upstream markers

Central venous pressure

Central venous pressure (CVP), transduced from a vascular catheter in the great vessels of the chest, has the advantage of being relatively simple to obtain. Owing largely to the advent of early goal-directed therapy for septic shock, CVP has become a common surrogate for preload and volume status in the critically ill. Despite that, abundant historical data are reinforced in a recent systematic review [1] confirming an exceedingly poor relationship between CVP and blood volume and showing that changes in CVP are unhelpful in predicting a patient's response to a fluid challenge. Its dependence on a wide range of factors, (including patient position, intrathoracic pressures, and venous compliance), makes it difficult to interpret, but the fact remains that CVP, particularly at extreme values, is still frequently used as a metric in critically-ill patients to indicate hypo- or hypervolaemia.

Pulmonary capillary wedge pressure

Pulmonary capillary wedge pressure (PCWP), which requires a pulmonary artery catheter (PAC) to obtain, provides an indirect measurement of left atrial pressure, which is a common surrogate for preload or intravascular volume. The catheter can also provide additional physiological information including cardiac output and mixed venous oxygen saturation. It is frequently cited as the gold standard for haemodynamic monitoring. However, two landmark studies [2,3] published in the last several years found that PAC-guided therapy did not improve outcomes in critically-ill patients. Despite their different approaches, the data from those two studies and several others have led to a drastic reduction in the use of PACs in the critical care setting.

Cardiac output

There are several different methods available at the bedside to assess cardiac output (CO). Traditional PAC-based thermodilution has given way to thermodilution-calibrated systems that use continuous arterial blood pressure waveforms to derive CO. Furthermore, non-calibrated systems using arterial waveform analysis have shown increasing accuracy in the past decade. Bioimpedance systems have given way to more accurate bioreactance systems, although both have limitations in critically-ill patients. Echocardiography also offers a bedside assessment of cardiac function and can estimate pulmonary artery pressures through the study of valvular flow. Less invasive and increasingly portable transthoracic echocardiography equipment permits dynamic assessment of cardiac output in response to fluid or inotrope administration. However, comprehensive training is required to use echocardiography for such discrete monitoring and many critical care providers lack that training [4].

Predictors of fluid responsiveness

Conceptually, stroke volume variation (SVV) and pulse pressure variation (PPV) rely on the basic physiology of patient-ventilator interactions [5]. A breath delivered via mechanical ventilation decreases the preload of the right ventricle (RV) by decreasing

venous return and increases the afterload of the RV by increasing transpulmonary pressure. These two factors combine to decrease RV stroke volume at the end of inspiration. 2–3 cardiac cycles later, this reduction in RV stroke volume results in a decrease in LV filling and a decrease in LV stroke volume (which is at its lowest during expiration). The magnitude of that decrease provides an indication of biventricular preload dependence. A recent systematic review found that measurements of SVV and PPV are highly sensitive and specific in predicting which mechanically-ventilated patients would respond to a fluid challenge with an increase in stroke volume. Measurement of PPV and SVV generally involve arterial catheters and can be accomplished with several commercially-available systems.

Systolic pressure variation (SPV) relies on similar physiologic concepts to the SVV and PPV. The SPV is the difference between the maximum and minimum systolic blood pressure over a single respiratory cycle. As with SVV and PPV, several studies have shown that increased SPV correlates with hypovolaemia.

Fluid challenge

The traditional method of assessing preload responsiveness with a fluid challenge has come under scrutiny for two main reasons [6]. First, many haemodynamically unstable patients will not respond to a fluid bolus, and the time spent waiting for a response may delay other necessary therapies. Second, and more importantly, excess volume may cause direct injury to patients. The risks involved in excessive fluid administration have popularized the passive leg raise (PLR) as an alternative to the traditional fluid challenge for assessing actual response to additional volume. PLR involves a passive transfer of blood from the lower extremities to the central circulation to determine whether increased preload will increase cardiac output [7]. When the legs are returned to the horizontal position, the autotransfusion returns to the lower extremities. Several clinical trials have confirmed its utility in the critical care setting.

Downstream markers

Base deficit

Base deficit (BD) is derived from the values obtained in an arterial blood gas analysis. It is typically thought to represent the presence of unmeasured anions and viewed as a surrogate for lactic acidosis. It has been studied in surgical populations as an independent marker for mortality. But other metabolic derangements leading to acidosis can influence the BD and not be specifically related to tissue ischaemia, and thus not related to mortality risk [8]. Trends of the BD may be useful in demonstrating the effects of resuscitation, but it is not a particularly specific marker.

Central venous and mixed venous oxygenation ($ScvO_2$ and SvO_2)

Practically, the measurement of mixed venous oxygen saturation (SvO_2) has been hampered by declining PAC use. As a surrogate, a thoracic central venous catheter can permit measurement of central venous oxygen saturation ($ScvO_2$), which generally correlates well with SvO_2 [9]. The $ScvO_2$ and SvO_2 are essentially measures of the amount of oxygen left over after the body has extracted oxygen from the systemic circulation. They are thus related to both oxygen delivery and oxygen consumption. As a target for fluid resuscitation, they have been used most often in the management of septic shock and its utility is currently being investigated in 3 large multicenter trials. Ensuring a $ScvO_2$ of at least 70% or a SvO_2 of at least 65% guarantees an appropriate amount of oxygen is being delivered to the tissues. However, whether the tissues are able to make use of that delivered oxygen relates more to the severity and type of the disease process.

Lactate

Lactic acid, an end-product of anaerobic metabolism, has been found to be a useful, albeit insensitive, marker of tissue dysoxia. Elevation of serum lactate during critical illness has prognostic implications, and a decreasing level is an appropriate target for resuscitation in critical illness. That said, as a result of the imbalance between lactate production and utilization, lactate levels can also be elevated outside critical illness, particularly after a seizure or strenuous exercise. In such settings, lactate levels do not carry a specific mortality risk, which can confound its use in the critical care setting [10].

Safety endpoints

Traditionally, knowing went to stop fluid administration in the critically ill involved recognition of the side effects of excess fluids. Pulmonary oedema can result from over-aggressive fluid resuscitation, particularly in the setting of left ventricular dysfunction or kidney injury. In addition, changes in pulmonary capillary permeability in conditions such as acute respiratory distress syndrome (ARDS), can result in pulmonary oedema even in the absence of LV failure. Other side effects of excessive fluid administration include acid-base disturbances, particularly hyperchloraemic acidosis from normal saline administration and hypotonicity from Lactated Ringer's administration.

Extravascular lung water

Extravascular lung water (EVLW) is an emerging safety endpoint that has been shown to aid in the resuscitation of the critically ill. The measurement of EVLW allows the characterization of patients with increased pulmonary oedema and in turn allows the determination of appropriate end-points of resuscitation (i.e., the point at which additional fluid increases pulmonary oedema without a concomitant benefit in blood pressure or stroke volume) [11]. Results of several key studies have demonstrated an increase in ventilator-free days and a reduction in mortality when using EVLW to guide fluid therapy in pulmonary oedema, but larger trials and wider access are both necessary before it achieves more general use.

Therapeutic goals in specific cases

Table 70.2 shows the therapeutic targets for specific disease states.

Post-cardiac arrest syndrome

As discussed in recent consensus guidelines [12], post-arrest myocardial dysfunction and consequent hypotension are well-described and frequently reversible. Preload should be optimized, although limited data exists to help direct management. In one study, 3.5–6.5 L of iv crystalloid was required to maintain right atrial pressures between 8 and 13 mmHg. If iv fluids are insufficient to support haemodynamic stability, vasopressors should be

Table 70.1 Therapeutic targets for haemodynamic monitoring

Upstream markers	Advantages	Disadvantages
CO	Most direct measurement of volume responsiveness	Difficult to determine optimal cardiac output in individual patients. Accuracy varies by measurement technique
CVP	Easily obtainable through central venous line	Not predictive of intravascular volume, fluid responsiveness, or cardiac output
PCWP	Familiarity, and historically considered the gold standard of volume assessment	Not predictive of intravascular volume, fluid responsiveness, or cardiac output; increased complications compared with CVP
Arterial blood pressure waveform analysis	Accurate assessment of volume responsiveness	Limited availability, requires arterial catheter placement
Fluid challenge	Rapid assessment of volume responsiveness	Fluid administration carries inherent risks
Passive leg raise	Rapid assessment of volume responsiveness without disadvantages of inappropriate fluid administration	Requires personnel to stand at the bedside for several minutes each time
Downstream markers		
Base deficit	Data support usage in surgical populations	Non-specific marker. Abnormal in scenarios other than hypoperfusion
$ScvO_2$	Easily obtainable through central venous line. Data supports use in septic shock resuscitation	Non-specific marker of oxygen delivery and consumption. Does not ensure adequate tissue perfusion
SvO_2	More accurate than $ScvO_2$ for measuring the balance between oxygen delivery and consumption	Requires pulmonary artery catheterization. Non-specific marker of oxygen delivery and consumption. Does not ensure adequate tissue perfusion
Lactic acid	Data support usage in septic shock. Easily obtainable	Non-specific marker of end-organ perfusion

initiated. Downstream measures of perfusion such as lactate clearance and mixed venous oxygen saturation can be used to guide therapy, as can other non-invasive cardiac monitors (Table 70.2). In addition, although elevations of intracranial pressure in the post-arrest period are uncommon, if present, mean arterial pressure should be increased (potentially with vasopressor therapy) to ensure a cerebral perfusion pressure of at least 60 mm Hg.

ARDS

Understanding and manipulating the Starling forces present at the alveolar-capillary membrane have been the primary goals in determining an optimal fluid strategy in ARDS. Although pulmonary oedema accumulates due to capillary injury and not to an increase in hydrostatic pressure per se, an impaired alveolar-capillary barrier mitigates oncotic pressure as an oedema-protective mechanism and thus small alterations in hydrostatic pressure have larger effects on oedema production [13]. Restricting the amount of fluid given to these patients should therefore aid in lung function recovery. Balanced against that fact is the reality that many patients with ARDS have concomitant critical issues that necessitate fluid resuscitation to ensure adequate organ perfusion. A few trials have compared fluid management strategies in patients with ARDS. The largest study to date found that a conservative fluid strategy resulted in more ventilator and intensive care unit (ICU)-free days than a liberal fluid strategy with no increase in shock or in renal dysfunction [14]. In that study, the conservative fluid management group was around 150 mL net negative, while the liberal fluid management group was around 6 L net positive. Although that study used CVP and PCWP to target management, they were often unable to meet their set goals. More importantly, based on the available data on filling pressures and their relationship to fluid responsiveness, CVP or PCWP-driven protocols are now inadvisable. That said, management in ARDS should involve minimizing fluid administration while using other available haemodynamic monitoring tools to ensure adequate organ perfusion.

Severe sepsis and septic shock

Historically, determining appropriate endpoints for fluid resuscitation in severe sepsis and septic shock has been challenging, but efforts were aided by the advent of early goal-directed therapy. Data from a landmark trial in critical care suggest that targeting a CVP of 8–12 (10–14 if the patient is intubated) and a SvO_2 of 70% resulted in an absolute reduction in hospital mortality of 16% for patients who present in septic shock or severe sepsis with an elevated lactate (>4 mEq/L) [15]. The study has come under scrutiny for several reasons, and several recent multi-centre trials have called into question the importance of protocolized sepsis care versus a focus on early identification and antibiotic administration. In addition, other recent data suggest that a significantly positive fluid balance at three-days is harmful, particularly with regard to lung function [16]. Overall, a strategy of rapid volume expansion at diagnosis followed by consideration of diuresis once haemodynamic stability

Table 70.2 Therapeutic targets for specific disease states

Disease state	Target
Post-cardiac arrest syndrome	Data limited. Attempt to optimize preload and maintain RAP 8–13 mmHg if able. May require inotropic or vasopressor support.
ARDS	Minimize fluid administration, while using haemodynamic monitoring tools to ensure adequate organ perfusion.
Sepsis	Early targeted fluid resuscitation. May follow EGTD protocol using CVP or $ScvO_2$, but focus primarily on early identification and antibiotics. Target negative fluid balance at 72 hours as able.
Burns	Data limited. Target urine output 0.5 mL/kg, 1 mL/kg if rhabdomyolysis or electrical injury present. Caveat that excessive fluid administration carries risks.
Trauma	Data limited. Emphasis on permissive hypotension prior to control of bleeding. Favour use of blood products for resuscitation over iv fluids. APP may be a useful metric in patients with IAH.

has been achieved appears to be a sound strategy in the management of septic shock in the ICU.

Burns

The historical dogma that fluid resuscitation in burns should be targeted to urine output has given way to more invasive monitoring techniques and a balance to avoid 'fluid creep,' the concept that over-resuscitation carries significant risks, including pulmonary oedema, increased likelihood of tracheostomy, and compartment syndromes. The traditional concept of intravenous fluid resuscitation involves the Parkland formula: volume of Lactated Ringer's solution given in the first 24 hours after injury = 3–4 mL/kg/% total body surface area. Half of the volume should be given in the first 8 hours, the second half in the following 16 hours. Urine output should be targeted at 0.5 mL/kg/hour under normal circumstances, and at 1 mL/kg/hour in cases of crush injuries with rhabdomyolysis and high voltage electrical burns. The recognition that urine output is not representative of adequate intravascular volume has led to a greater emphasis on more invasive monitoring [17].

Trauma

In cases with uncontrolled traumatic bleeding, the emphasis in fluid management should be to avoid over-resuscitating patients until the bleeding is under control. In trauma, this concept is known as 'permissive hypotension,' and rests on the premise that bleeding will worsen if blood pressure is elevated prior to control of the bleeding source. A trial comparing delayed intraoperative fluid resuscitation to early prehospital intervention in hypotensive patients with uncontrolled bleeding due to thoraco-abdominal stab or gunshot wounds found that prehospital resuscitation resulted in both a higher mortality rate and a higher rate of post-operative complications compared with patients in the delayed resuscitation group. This concept does not apply to patients whose bleeding can be brought under control prior to definitive surgical intervention. In those cases, the use of iv fluid to restore a normal blood pressure is still recommended, with the caveat that relying more heavily on blood products is advisable in an effort to break the cycle of acidosis, coagulopathy, and hypothermia that iv fluid itself may exacerbate [18].

Another metric that may prove useful is the abdominal perfusion pressure (APP), which is calculated by subtracting the intra-abdominal pressure (IAP, obtained at the bedside from bladder pressure) from the mean arterial pressure. A study of surgical patients with intra-abdominal hypertension (defined as IAP > 15 mmHg) found that an APP > 50 mmHg was more predictive of survival than other traditional markers of resuscitation [19]. More data are needed to determine whether using the APP as a resuscitation goal offers a survival advantage.

Patients with traumatic brain injury present a special case, as they are exquisitely sensitive to episodes of hypotension. As a result, most advocate a more aggressive fluid resuscitation strategy in these cases. This strategy must be balanced against the risks of increasing intracranial pressure (ICP). Striking this balance has led some to advocate the use of hypertonic saline as a resuscitation fluid, since it has been shown to lower ICP significantly when compared to isotonic resuscitation fluids, while still increasing systemic blood pressure. The ICP and mean arterial blood pressure are generally targeted to a cerebral perfusion pressure of approximately 60 mmHg.

References

1. Marik PE, Baram M, and Vahid B. (2008). Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest*, **134**(1), 172–8.
2. Wiedemann HP, Wheeler AP, Bernard GR, et al. (2006). Clinical trials network. pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *New England Journal of Medicine*, **354**(21), 2213–24.
3. Richard C, Warszawski J, Anguel N, et al. (2003). Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. *Journal of the American Medical Association*, **290**(20), 2713–20.
4. Marik PE and Baram M. (2007). Noninvasive hemodynamic monitoring in the intensive care unit. *Critical Care Clinic*, **23**, 383–400.
5. Cannesson M, de Backer D, and Hofer CK. (2011). Using arterial pressure waveform analysis for the assessment of fluid responsiveness. *Expert Review of Medical Devices*, **8**(5), 635–46.

6. Vincent J-L and Weil MH. (2006). Fluid challenge revisited. *Critical Care Medicine*, **34**(5), 1333–7.
7. Cavallaro F, Sandroni C, Marano C, et al. (2010). Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive Care Medicine*, **36**, 1475–83.
8. Engleharta MS and Schreiberb MA. (2006). Measurement of acid–base resuscitation endpoints: lactate, base deficit, bicarbonate or what? *Current Opinions in Critical Care*, **12**, 569–74.
9. Walley KR. (2011). Use of Central Venous Oxygen Saturation to Guide Therapy. *American Journal of Respiratory Critical Care Medicine*, **184**, 514–20.
10. Fall PJ and Szerlip HM. (2005). Lactic acidosis: from sour milk to septic shock. *Journal of Intensive Care Medicine*, **20**, 255–71.
11. Cribbs SK and Martin GS. (2009). Fluid balance and colloid osmotic pressure in acute respiratory failure: optimizing therapy. *Expert Reviews in Respiratory Medicine*, **3**(6), 651–62.
12. Neumar RW, Nolan JP, Adrie C, et al. (2008). Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation. *Circulation*, **118**(23), 2452–83.
13. Roch A, Guervilly C, and Papazian L. (2011). Fluid management in acute lung injury and ARDS. *Annals of Intensive Care*, **1**(1), 16.
14. Wiedemann HP, Wheeler AP, Bernard GR, et al. (2006). Comparison of Two Fluid-Management Strategies in Acute Lung Injury. *New England Journal of Medicine*, **354**(24), 2564–75.
15. Rivers E, Nguyen B, Havstad S, et al. (2001). For the Early Goal-Directed Therapy Collaborative Group. *New England Journal of Medicine*, **345**(19), 1368–77.
16. Murphy CV, Schramm GE, Doherty JA, et al. (2009). The Importance of Fluid Management in Acute Lung Injury Secondary to Septic Shock. *Chest*, **136**(1), 102–9.
17. Tricklebank S. (2009). Modern trends in fluid therapy for burns. *Burns*, **35**, 757–67.
18. Ertmer C, Kampmeier T, Rehberg S, and Lange M. (2011). Fluid resuscitation in multiple trauma patients. *Current Opinions on Anaesthesiology*, **24**(2), 202–8.
19. Cheatham ML, White MW, Sagraves SG, Johnson JL, and Block EF. (2000). Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. *Journal of Trauma*, **49**(4), 621–6.

SECTION 4

The respiratory system

PART 4.1

Physiology

CHAPTER 71

Normal physiology of the respiratory system

Göran Hedenstierna and João Batista Borges

Key points

- Functional residual capacity (FRC) is lowered in supine position and reduced further by anaesthesia. Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) goes with very low lung volume, frequently below 1 L.
- Compliance of the lung is increased in emphysema, but reduced in lung fibrosis and during anaesthesia, the latter because of reduced ventilated lung volume. ALI/ARDS are found with very low lung compliance and frequently with low chest wall compliance.
- Airway resistance is increased in obstructive lung disease, but also during anaesthesia and in ALI/ARDS because of reduced lung volume with decreased airway dimensions.
- Inspired air goes mainly to lower, dependent lung regions, but a shift to upper lung can be seen during anaesthesia and in ALI/ARDS, because of low lung volume promoting airway closure in dependent regions.
- Lung blood flow goes mainly to dependent lung regions and more so with increase in alveolar gas pressure. Besides a gravitational perfusion distribution there is also a non-gravitational perfusion inhomogeneity that may possibly exceed gravitational inhomogeneity.

Lung volumes and ventilation

The lungs contain 2–300 million alveoli with a total surface area, for gas exchange, of approximately 140 m^2. The alveoli are reached via 23 generations of airways with a rapidly increasing total surface area from 2.5 cm^2 at the trachea to 70 cm^2 in the 14th generation that enters the acinus, to 0.8 m^2 (8000 cm^2) in the 23rd generation [1]. Gas flow velocity decreases as the area increases. For an ordinary breath, the average velocity of gas in the trachea is around 0.7 m/sec, but at the alveolar surface it is no higher than 0.001 mm/sec (Fig. 71.1, left part). This is much slower than the diffusion rate of O_2 and CO_2. Transport of O_2 and CO_2 is therefore accomplished by diffusion in the peripheral airways and in the alveoli, not by convective flow.

The gas volume in the lung after a maximum inspiration is called **total lung capacity** (TLC) and is typically 6–8 L [2]. TLC can increase in patients with chronic obstructive pulmonary disease (COPD), and decrease in fibrosis and other restrictive disorders.

Even after a maximum expiratory effort, some air is left in the lung, preventing collapse. This remaining gas volume is called **residual volume** (RV) and amounts to 2–2.5 L. The maximum volume that can be inspired and expired is called **vital capacity** (VC), and is around 4–6 L. It is reduced in restrictive lung diseases, frequently before a decrease in RV. What may not be equally clear is that VC is also reduced in obstructive lung disease. This is an effect of the chronic 'air trapping' that increases RV, mainly at the expense of VC [2].

The volume in the lungs after an ordinary expiration is called functional residual capacity (FRC) and is approximately 3–4 L [2]. It is increased in obstructive lung disease and reduced in restrictive disorders. It is reduced by 0.7–0.8 L when supine compared with an upright position and by another 0.4–0.5 L by anaesthetics, muscle relaxants, and possibly sedatives (lowered muscle tone) [3].

All inspired air does not reach the alveoli. Approximately 100–150 mL will be confined in the airways and does not participate in gas exchange. This 'anatomical deadspace' is approximately 30% of tidal volume; that is, the V_D/V_T ratio is 0.3 [4]. The remaining part of ventilation reaches the alveoli and respiratory bronchioles (with some alveoli tapered on the airway wall). Thus, 'alveolar ventilation' is around 5 L/min, similar to cardiac output, which is also approximately 5 L/min. Accordingly, the overall alveolar ventilation-perfusion ratio is 1.

Ventilation through a mouthpiece, facemask, or tubings adds an apparatus deadspace of 25 to a few hundred millilitres. Intubation of the trachea reduces anatomic dead space almost to half, 70–80 mL. Pulmonary emboli and obstructive lung disease increase deadspace by ventilation of alveoli that are not perfused or ventilated in excess of perfusion ('alveolar dead space'). The sum of the anatomic and alveolar dead spaces is called 'physiological dead space'.

Compliance of the respiratory system

The lung recoils like an elastic rubber balloon. The pressure needed to keep the lung inflated at a certain volume is pleural minus alveolar pressure, or 'transpulmonary pressure' (Ptp) [5]. Oesophageal pressure (Pes) is for technical and safety reasons substituted for pleural pressure. A change in lung volume (ΔV) divided by the concomitant change in Ptp gives lung compliance. Normally, it is around 0.2–0.3 L/cmH_2O (2–3 L/kPa). It is increased in emphysema, but reduced in fibrotic lung disease and during anaesthesia, the latter being a consequence of reduced ventilated lung volume [6]. It can be markedly reduced in acute lung injury (ALI, ARDS) [7]. If a lung is resected, the measured compliance is reduced, despite the fact that the remaining lung tissue is unaltered (a compensatory expansion may occur).

The chest wall also exerts elastic impedance to breathing that goes undetected during spontaneous breathing because the chest wall is part of the pump itself. During muscle relaxation, on the other hand, the separate compliances of the lung and the chest wall can be measured by dividing ΔV with ΔPtp (lung) and ΔV with ΔPes (chest wall). Compliance of the chest wall is approximately the same magnitude as compliance of the lungs, around 0.2 L/cmH_2O. It may go down in obesity and in ALI/ARDS, especially in so called 'extra-pulmonary ARDS' [7].

Resistance of the respiratory system

Pressure is required to force gas flow (V') through the airways during respiration. In addition, movement of lung tissue and chest wall during inspiration and expiration exerts resistance (R) [8]. In the mechanically-ventilated subject airway, lung tissue, and chest wall resistances are mostly measured together as R_{tot} = (peak airway–end-inspirtory airway pressure):V', but techniques are available for recording of the individual components.

In larger airways, gas flow is turbulent and proportional to the square of the pressure. In smaller airways, flow is laminar and is linearly related to pressure. Thus, most of the energy or pressure involved in creating flow of gas is expended on overcoming resistance in the larger airways [8]. Only about 20% of the measured airway resistance, in a normal subject, is located in the small bronchi [9].

Airflow resistance is normally around 1 cmH_2O/L/sec. Since airway dimensions vary with lung volume, resistance goes up with decrease in volume. At RV resistance may be 4–6 cmH_2O/L/sec, similar to that in moderate asthma [10]. Breathing through a size 8 endotracheal tube causes a resistance of 5 cmH_2O/L/sec at a flow of 1 L/sec and size 7 tube increases resistance to 8 cmH_2O/L/sec [11].

The resistance of lung tissue and the chest wall has been studied to a lesser extent. Lung tissue resistance amounts to around 1 cmH_2O/L/sec in normal cases, but can be increased three- to four-fold in chronic lung disease. Even less has been studied regarding chest wall resistance. However, the sum of lung tissue and chest wall resistance is markedly increased in acute respiratory failure, demanding mechanical ventilation [12].

Distribution of inspired gas

During quiet breathing, inspired air goes mainly to the lower, dependent regions—basal, diaphragmatic areas in the upright or sitting position, dorsal units in the supine position, and left lung in left lateral position [9]. The reason for this seemingly gravitational orientation of something as light as gas is the combined effect of the curved pressure–volume relationship of the lung tissue and the increasing pleural pressure down the lung (Fig. 71.1, upper right).

With increasing flow rate, more inspired air goes to the upper, non-dependent lung regions [13]. This is because the airways are more expanded in the upper than in the lower regions and resistance becomes increasingly important with increasing gas flow.

Airway closure

Airways become narrower during expiration, as can be inferred from the previous discussion. If the expiration is deep enough, airways in dependent regions will eventually close. The volume above RV at which airways begin to close during expiration is called the **closing volume** (CV), and the sum of RV and CV is called **closing capacity** (CC) [14]. Airway closure is a normal physiological phenomenon and is caused by increasing pleural pressure during

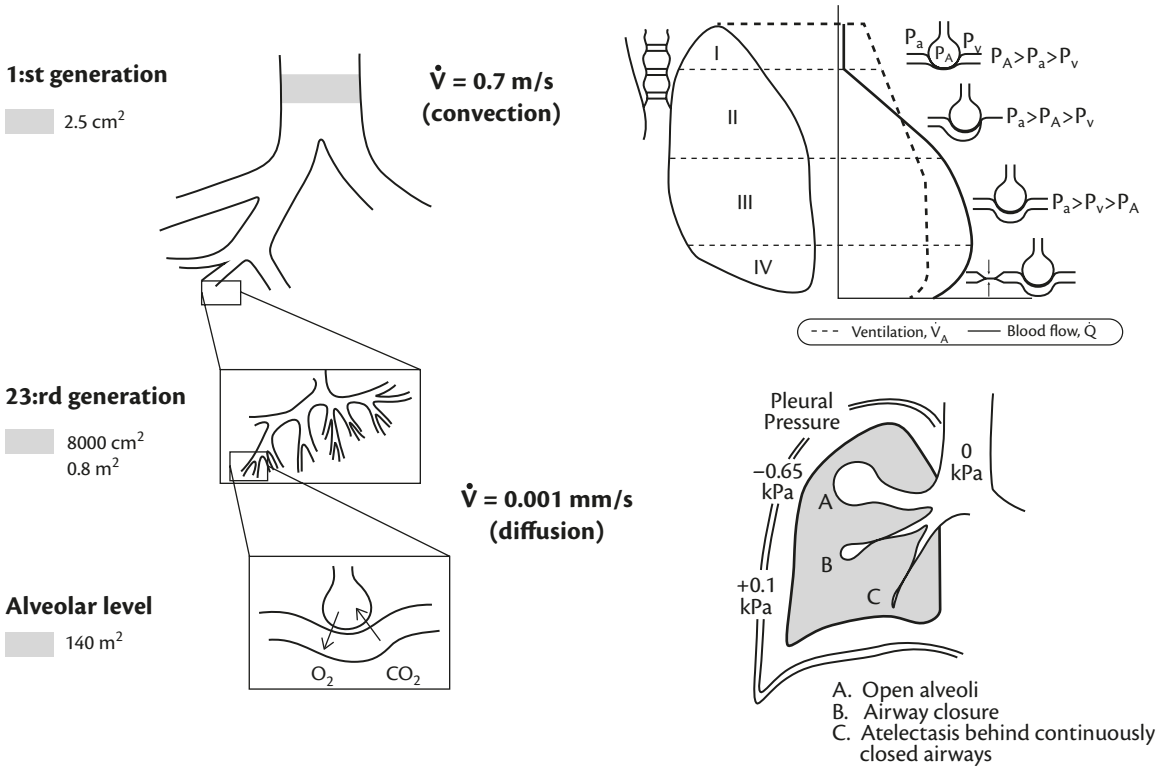


Fig. 71.1 The airway tree from generation 1 (trachea) to generation 23 (terminal bronchioli) (left panel), the vertical distributions of ventilation and blood flow (upper right) and airway closure and alveolar collapse (lower right).

expiration. When pleural pressure exceeds atmospheric pressure it will compress the airway and close it. Because pleural pressure is higher in dependent regions than higher up, closure of airways begins in the bottom of the lung. With increasing age, pleural pressure is 'positive' at higher lung volume, and at an age of 65–70 years, airway closure may occur above FRC [14].

Airway closure plays an even greater role in the supine position, because FRC is reduced, whereas CC is not. Closure of airways may occur above FRC, even at an age of 45–50 years. Airway closure is more common during anaesthesia because of the decrease in FRC, whereas CC seems to be unaltered [6]. If the anaesthetized patient is ventilated with a high concentration of O_2, the alveoli will collapse behind continuously closed airways, thus producing atelectasis (see Fig. 71.1, lower right) [6]. Airway closure is also more common in obstructive lung disease [14].

Diffusion of gas

Oxygen diffuses passively from the alveolar gas phase into plasma and red cells, where it binds to haemoglobin. Carbon dioxide diffuses in the opposite direction, from plasma to the alveoli. The amount that can diffuse over the membranes for a given period is determined by:

- The surface area available for diffusion.
- The thickness of the membranes.
- The pressure difference of the gas across the barrier.
- The molecular weight of the gas.
- The solubility of the gas in the tissues that it has to traverse.

Diffusion limitation is of importance in lung fibrosis and in emphysema, but seems not to be an important issue in anaesthesia and intensive care. For further details, see ref. [15].

Pulmonary perfusion: pressure–flow relationship

The pulmonary circulation is a low-pressure system with a pulmonary artery pressure of approximately 20/8 mmHg. The lower pressure is an effect of larger vascular diameter and shorter distance of the pulmonary vessels than the systemic ones. As a consequence of the lower resistance, pulmonary capillary blood flow is pulsatile, contrary to the steady flow in systemic capillaries [16]. Another consequence of the low pressure is that the capillary and alveolar walls can be made very thin without causing any leakage of plasma, and this facilitates diffusion of O_2 and CO_2, but also of oedema formation if the vascular pressure goes up.

Distribution of lung blood flow

The 'classical' model of lung blood flow distribution is related to gravity [17]. Pulmonary artery pressure (PAP) increases down the lung by 1 cmH_2O/cm distance. This causes a PAP difference between the upper and lower regions of 11–15 mmHg, depending on the height of the lung. There is thus less driving pressure to the top of the lung. If alveolar pressure is increased, as during positive-pressure ventilation, it may exceed PAP and compress the pulmonary capillaries and prevent blood flow (so called zone I). Further down, arterial pressure exceeds alveolar pressure and blood flow will be established. The increasing PAP down the lung and the constant alveolar pressure increase blood flow down this 'zone II'. Further down the lung, both arterial and venous pressures exceed that in the alveoli (zone III). Despite similar increase in arterial and venous pressure, perfusion increases down this zone, by increasing dilation of vessels. In the bottom of the lung perfusion decreases, presumably because of increasing interstitial pressure (zone IV; Fig. 71.1, upper right).

There is also accumulating evidence that there are morphological or functional differences (or both) between lung vessels that—and perhaps more importantly than gravity—determine blood flow distribution with more inhomogeneity in a horizontal than vertical plane ('fractal distribution') [18].

Hypoxic pulmonary vasoconstriction

Hypoxic pulmonary vasoconstriction (HPV) reduces blood flow in hypoxic lung regions. A major stimulus for HPV is low alveolar oxygen tension, whether caused by hypoventilation or by breathing gas with a low PO_2. The stimulus of mixed venous PO_2 is much weaker [19]. The strength of the constriction is also dependent on the size of the lung segment exposed to the hypoxia, being stronger the smaller the region is.

Chronic lung disease with hypoxaemia also causes HPV, but the slow progress of the disease allows time for remodelling of the pulmonary vascular wall, with thickening of the wall preventing oedema formation [19].

References

1. Haefeli-Bleuer B and Weibel ER. (1988). Morphometry of the human pulmonary acinus. *Anatomical Record*, **220**, 401–14.
2. Quanjer PH, Tammeling GJ, Cotes JE, et al. (1993). Lung volumes and forced ventilatory flows. Report Working Party 'Standardization of Lung Function Tests.' European Community for Steel and Coal. *European Respiratory Journal Supplement*, **16**, 5–40.
3. Wahba RWM. (1991). Perioperative functional residual capacity. *Canadian Journal of Anaesthesia*, **38**, 384–400.
4. Astrom E, Niklason L, Drefeldt B, et al. (2000). Partitioning of dead space—a method and reference values in the awake human. *European Respiratory Journal*, **16**, 659–64.
5. Grassino AE and Roussos C. (1997). Static properties of the lung and chest wall. In: Crystal RG, West JB, Weibel ER, and Barnes PJ (eds) *The Lung: Scientific Foundations*, 2nd edn, pp. 1187–202. Philadelphia: Lippincott-Raven.
6. Hedenstierna G, Edmark L. (2005). The effects of anesthesia and muscle paralysis on the respiratory system. *Intensive Care Medicine*, **31**, 1327–35.
7. De Chazal I and Hubmayr RD. (2003). Novel aspects of pulmonary mechanics in intensive care. *British Journal of Anaesthesia*, **91**, 81–91.
8. Pedley TJ and Kamm RD. (1997). Dynamics of gas flow and pressure-flow relationships. In: Crystal RG, West JB, Weibel ER, Barnes PJ (eds) *The Lung: Scientific Foundations*, 2nd edn, pp. 1365–80. Philadelphia: Lippincott-Raven.
9. Milic Emili J. (2005). Ventilation distribution. In: Hammid Q, Shannon J, Martin J (eds) *Physiologic Bases of Respiratory Disease*, pp. 131–41. Hamilton, Ontario: BC Decker.
10. Jonson B. (1970). Pulmonary mechanics in normal men studied with the flow regulator method. *Scandinavian Journal of Clinical and Laboratory Investigations*, **25**, 363–73.
11. Holst M, Striem J, and Hedenstierna G. (1990). Errors in tracheal pressure recording in patients with a tracheostomy tube—a model study. *Intensive Care Medicine*, **16**, 384–9.
12. Tantucci C, Corbeil C, Chasse M, et al. (1992). Flow and volume dependence of respiratory system flow resistance in patients with adult respiratory-distress syndrome. *American Reviews of Respiratory Diseases*, **145**, 355–60.

13. Bake B, Wood L, Murphy B, et al. (1974). Effect of inspiratory flow-rate on regional distribution of inspired gas. *Journal of Applied Physiology*, **37**, 8–17.
14. Milic-Emili J, Torchio R, and D'Angelo E. (2007). Closing volume: a reappraisal (1967–2007). *European Journal of Applied Physiology*, **99**, 567–83.
15. Hughes JMB and Bates DV. (2003). Historical review: the carbon monoxide diffusing capacity (Dlco) and its membrane (D-M) and red cell (Theta.Vc) components. *Respiratory Physiology & Neurobiology*, **138**, 115–42.
16. Dawson CA and Linehan JH. (1997). Dynamics of blood flow and pressure-flow relationships. In: Crystal RG, West JB, Weibel ER, and Barnes PJ (eds) *The Lung: Scientific Foundations*, 2nd edn, pp. 1503–22. Philadelphia: Lippincott-Raven.
17. Hughes M and West JB. (2008). Gravity is the major factor determining the distribution of blood flow in the human lung. *Journal of Applied Physiology*, **104**, 1531–3.
18. Glenny R. (2008). Gravity is not the major factor determining the distribution of blood flow in the human lung. *Journal of Applied Physiology*, **104**: 1533–6.
19. Sylvester JT, Shimoda, LA, Aaronson, PI, and Ward Jeremy PT. (2012). Hypoxic pulmonary vasoconstriction. *Physiological Reviews* **92**, 367–520.

PART 4.2

Respiratory monitoring

CHAPTER 72

Blood gas analysis in the critically ill

Gavin M. Joynt and Gordon Y. S. Choi

Key points

- Oxygenation is assessed by measuring PaO_2 and SaO_2 in the context of the inspired oxygen concentration, haemoglobin concentration, and the oxyhaemoglobin dissociation curve.
- Ventilation is assessed by measuring the $PaCO_2$ in the context of systemic acid-base balance.
- Acid base assessment requires the integration of clinical findings and a systematic interpretation of arterial blood gas parameters.
- For clinical use, traditional acid base interpretation rules based on the bicarbonate buffer system or standard base excess estimations, and the interpretation of the anion gap, are substantially equivalent to the physicochemical method of Stewart.
- The presence of a metabolic acidosis or alkalosis, and its influence on compensatory respiratory responses is important to recognize.

Introduction

Arterial blood gases provide information that allows the assessment of patient oxygenation, ventilation and acid-base status. Usually, modern blood gas machines directly measure pH, and the partial pressures of carbon dioxide ($PaCO_2$) and oxygen (PaO_2) dissolved in arterial blood. These values are then used to calculate the arterial oxygen saturation (SaO_2), bicarbonate (HCO_3^-) concentration and base excess (BE). The addition of a co-oximeter allows the direct estimation of haemoglobin content, haemoglobin oxygen saturation (SaO_2), and carbon monoxide (COHb) and methaemoglobin (MetHb) saturation. More sophisticated and expensive machines can measure electrolyte concentrations including sodium, potassium, chloride, magnesium, and calcium. Commonly measured parameters and their significance are listed in Table 72.1.

Assessment of oxygenation

The PaO_2 and SaO_2 are used to assess oxygenation. These values should be interpreted in conjunction with the fractional inspired oxygen concentration (FIO_2). Hypoxaemic respiratory failure is characterized by PaO_2 lower than 60 mmHg (8.0 kPa) when breathing room air at sea level. In critically-ill patients, it is usually not necessary or desirable to remove oxygen supplementation to interpret blood gases with the patient breathing room air. Hypoxaemic respiratory failure in the critically ill can be most simply expressed in terms of the PaO_2/FIO_2 or PF ratio. With the PaO_2 measured in mmHg (kPa), the normal PF ratio is approximately 450 (60) and a PF ratio < 200 (25) indicates severe hypoxaemic respiratory failure.

Major pathophysiological mechanisms leading to hypoxaemia include a reduction of inspired oxygen tension, hypoventilation, ventilation–perfusion mismatch, right-to-left shunting, and diffusion impairment. Causes may be elucidated by determining the alveolar–arterial oxygen gradient (A–a PO_2) where:

$$PaO_2 = (P_B - P_{H_2O}) \times FIO_2 - (PaCO_2 / R) \quad \text{[eqn 1]}$$

where P_B = barometric pressure, 760 mmHg (101kPa) at sea level, P_{H_2O} = partial pressure of fully saturated water vapour, 47 mmHg (6.3 kPa) at 37°C, $PaCO_2$ = partial pressure of alveolar carbon dioxide ~ $PaCO_2$ because of the ease of exchange of carbon dioxide, R = respiratory quotient (R = 0.8 for a 'normal' diet).

The normal (A–a PO_2) gradient varies with age and ranges from 7 to 14 mmHg (0.9–1.9 kPa) when breathing room air, but increases with age [1], where:

$$(A - a\ PO_2) = 2.5 + 0.21 \times \text{age (in years), in mmHg} \quad \text{[eqn 2]}$$

$$(A - a\ PO_2) = 0.3 + 0.03 \times \text{age, in kPa} \quad \text{[eqn 3]}$$

Solving the alveolar gas equation helps distinguish whether hypoxaemia is caused by hypoventilation, or is the result of ventilation perfusion mismatch, and/or diffusion abnormalities. In hypoventilation, there will be a normal gradient between alveolar and arterial blood, while other abnormalities result in an increased A–a PO_2. Mixed abnormalities often occur, such as in a patient with chronic obstructive airways disease (causing alveolar hypoventilation) and lobar collapse (causing a decreased ventilation perfusion ratio or shunt).

The following formula illustrates that the amount of dissolved oxygen in the blood, measured by PaO_2, is relatively small, and the oxygen content of blood is primarily determined by the haemoglobin concentration and the haemoglobin-bound O_2 (HbO_2), expressed as a saturation.

$$\text{Blood } O_2\text{content (mL/100 mL)} = Hb(g/dL) \times SaO_2 \times 1.306 + PaO_2(mmHg) \times 0.003 \quad \text{[eqn 4]}$$

Table 72.1 Common parameters reported on an arterial blood gas

Parameter	Normal values	Significance
pH (m)	7.35–7.45	**Measurement of hydrogen ion [H^+]:** *Acidaemia*: arterial pH < 7.35 *Alkalaemia*: arterial pH > 7.45 *Acidosis*: an abnormal process or condition that would lower arterial pH *Alkalosis*: an abnormal process or condition that would raise arterial pH (if there were no secondary changes in response to the primary aetiological factor)
$PaCO_2$ (m)	35–45 mmHg (4.7–6 kPa)	**Partial pressure of CO_2 in arterial blood**: $PaCO_2$ > 45 mmHg (6 kPa) indicates respiratory acidosis $PaCO_2$ < 35 mmHg (4.7 kPa) indicates respiratory alkalosis
HCO_3^- (c)	22–26 mmol/L	**The amount of buffer base in arterial blood**: <22 mmol/L indicates metabolic acidosis >26 mmol/L indicates metabolic alkalosis
Standard base excess (c)	−2 to +2 mmol/L	The amount of acid (in mmol/L) required to restore 1 L of tested blood to a pH of 7.4
SaO_2 (m or c)	93–98%	The percentage of oxygen bound to haemoglobin
PaO_2 (m)	80–100 mmHg (10.7–13.3 kPa)	**Partial pressure of oxygen in arterial blood**: Hypoxaemia is defined as PaO_2 < 60 mmHg (8 kPa)

Measured parameters are designated (m) and calculated parameters designated (c).

The PaO_2 should thus always be interpreted in the context of the relationship between PaO_2 and HbO_2. The oxyhaemoglobin dissociation curve describes this relationship (Fig. 72.1). If the measured saturation is not what you would expect from the PaO_2 it may indicate a shift in the oxyhaemoglobin dissociation curve. The PaO_2 at which saturation is 50% (P_{50}) is usually used as a reference point. If P_{50} is increased, it indicates a shift to the right and vice versa. Possible causes of shift are shown in Fig. 72.1. Note that in clinical practice, saturations of <88–90% are considered risky, because below this saturation the content of oxygen carried by arterial blood decreases substantially with relatively small decreases in PaO_2, risking tissue hypoxia. When SaO_2 is not measured by co-oximetry, but calculated by the blood gas machine on the basis of the oxyhaemoglobin dissociation curve, inaccuracies in SaO_2 estimations are likely, especially when PaO_2 is relatively low (as occurs in venous samples). Also related to the shape of the curve, saturations greater than 90–92% will increase oxygen content by relatively small amounts. Co-oximetry also allows the quantitative measurement of abnormal haemoglobin complexes, such as COHb and MetHb, both of which can substantially reduce blood oxygen content when present in high concentrations.

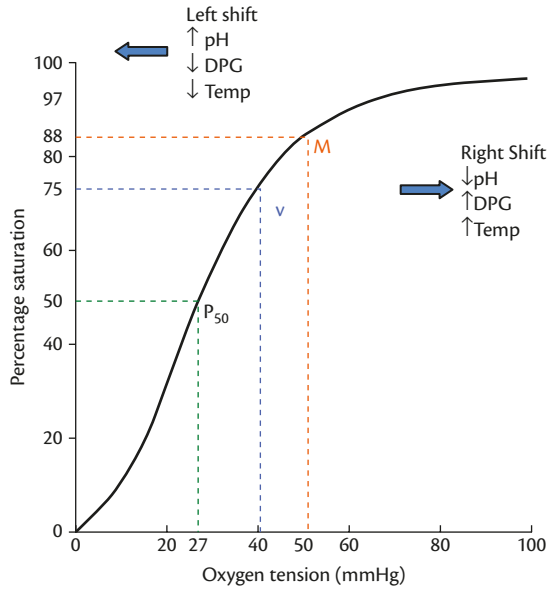


Fig. 72.1 The normal oxyhaemoglobin dissociation curve with causes of left and right shift. Relationships at key points are shown; the partial pressure at which saturation is 50% (P_{50}), mixed venous oxygen tension (v), and the inflection point of the oxyhaemoglobin dissociation curve known as the minimum saturation point (M). Below M a small reduction in PaO_2 will result in a large decrease in oxygen saturation and oxygen content. To convert to kPa, divide by 7.5 DPG, 2,3-diphosphoglycerate.

Reproduced by permission of G. Joynt/G. Choi, for ICU Web http://aic-server4.aic.cuhk.edu.hk/web8/

Assessment of ventilation and acid-base disturbances

Ventilation should always be assessed in combination with acid-base status, as ventilation forms an integral part of acid-base homeostasis. A rise in $PaCO_2$ indicates alveolar hypoventilation, while a decrease indicates alveolar hyperventilation. Given the requirement to maintain a normal pH, functioning homeostatic mechanisms result in metabolic acidosis triggering a compensatory hyperventilation, and metabolic alkalosis a compensatory reduction in ventilation. Similarly, when primary alveolar hypoventilation generates a respiratory acidosis, it results in a compensatory increase in serum bicarbonate that is achieved, in part, by kidney bicarbonate retention. In the same way, respiratory alkalosis induces kidney bicarbonate loss.

It may happen that more than one 'primary' abnormality exists, for example, respiratory alkalosis and metabolic acidosis can be

Box 72.1 Systematic Interpretation Rules for the Arterial Blood Gas

- **Step 1: assess the pH**. Acidosis or alkalosis is present if the pH value indicates acidaemia or alkalaemia, respectively. If pH is normal then *either* there is no acid-base disorder *or* a compensating disorder is present (e.g. a disorder with alkalosis compensating for the acidosis).
- **Step 2: determine whether the primary disturbance is metabolic or respiratory**. Clinical assessment, and/or the relationship between the direction of changes in the pH, bicarbonate (HCO_3^-) and $PaCO_2$ may indicate the origin of the disorder. In primary metabolic disorders the pH and $PaCO_2$ change in the same direction, but in primary respiratory disorders, the pH and $PaCO_2$ change in **opposite** directions.

Metabolic acidosis	pH ↓	HCO_3^- ↓	$PaCO_2$ ↓
Metabolic alkalosis	pH ↑	HCO_3^- ↑	$PaCO_2$ ↑
Respiratory acidosis	pH ↓	HCO_3^- ↑	$PaCO_2$ ↑
Respiratory alkalosis	pH ↑	HCO_3^- ↓	$PaCO_2$ ↓

Note: Respiratory compensation for primary metabolic acidosis does not restore the pH to normal and the presence of a normal pH in a patient with a perceived primary metabolic acidosis should raise suspicion of a concomitant primary alkalosis (e.g. severe sepsis presenting with hypoperfusion and a primary respiratory alkalosis). A mixed disorder cannot be completely excluded when both the HCO_3^- and $PaCO_2$ changes in the same direction, but a mixed disorder must be present if the HCO_3^- and $PaCO_2$ move in an opposite direction.

- **Step 3: use either the Boston or Copenhagen bedside rules to assess the appropriateness of the compensatory response**. If the observed compensation is not in the range of the expected normal compensation, it is likely that more than one primary acid-base disorder is present (e.g. if an acidaemic patient with a low [HCO_3^-] has a $PaCO_2$ higher than the expected compensatory range, a coexisting primary respiratory acidosis should be suspected, such as might occur in a patient with diabetic ketoacidosis and chronic obstructive pulmonary disease). Note the greater allowance for the compensatory response in chronic disorders, as renal buffering and some transcellular responses are time dependent.

Boston rules

Disorder	Primary change	Compensatory change
Metabolic acidosis	[HCO_3^-] < 22 mmol/L	$PaCO_2$ (mmHg) = 1.5 × (HCO_3^-) + 8 $PaCO_2$ (kPa) = [(HCO_3^-)/5] + 1
Metabolic alkalosis	[HCO_3^-] > 26 mmol/L	$PaCO_2$ (mmHg) = 0.7 × (HCO_3^-) + 21 $PaCO_2$ (kPa) = [(HCO_3^-)/10] + 2.6
Respiratory acidosis (acute)	$PaCO_2$ > 45 mmHg (6.0 kPa)	HCO_3^- (mmHg) = [($PaCO_2$ – 40)/10] ×1 +24 HCO_3^- (kPa) = [($PaCO_2$ – 5.3)/4] ×3 +24
Respiratory acidosis (chronic)	$PaCO_2$ > 45 mmHg (6.0 kPa)	HCO_3^- (mmHg) = [($PaCO_2$ – 40)/10] ×4 +24 HCO_3^- (kPa) = ($PaCO_2$ – 5.3) ×3 +24
Respiratory alkalosis (acute)	$PaCO_2$ < 35 mmHg (4.7 kPa)	HCO_3^- (mmHg) = 24 – [(40 – $PaCO_2$)/10] × 2 HCO_3^- (kPa) = 24 – 1.5 × (5.3 –$PaCO_2$)
Respiratory alkalosis (chronic)	$PaCO_2$ < 35 mmHg (4.7 kPa)	HCO_3^- (mmHg) = 24 – [(40 – $PaCO_2$)/10] × 5 HCO_3^- (kPa) = 24 – 4 × (5.3 –$PaCO_2$)

Copenhagen rules

Disorder	Primary change	Compensatory change
Metabolic acidosis	SBE < −5 mmol/l	$PaCO_{2\,(mmHg)} = 40 + SBE$ $PaCO_{2\,(kPa)} = 5.3 + 0.13 \times SBE$
Metabolic alkalosis	SBE > +5 mmol/l	$PaCO_{2\,(mmHg)} = 40 + 0.6 \times SBE$ $PaCO_{2\,(kPa)} = 5.3 + 0.08 \times SBE$
Respiratory acidosis (acute)	$PaCO_2$ > 45 mmHg (6.0 kPa)	SBE = 0 $PCO_2 = 40 + 0.6 \times SBE$ $PCO_2 = 5.3 + 0.08 \times SBE$
Respiratory acidosis (chronic)	$PaCO_2$ > 45 mmHg (6.0 kPa)	SBE (mmHg) = 0.4 × ($PaCO_2$ − 40) SBE (kPa) = 3 × ($PaCO_2$ − 5.3)
Respiratory alkalosis (acute)	$PaCO_2$ < 35 mmHg (4.7 kPa)	SBE = 0
Respiratory alkalosis (chronic)	$PaCO_2$ < 35 mmHg (4.7 kPa)	SBE (mmHg) = 0.4 × ($PaCO_2$ − 40) SBE (kPa) = 3 × ($PaCO_2$ − 5.3)

- **Step 4: if metabolic acidosis exists, calculate the anion gap (AG):**

$$AG = [Na^+] + [K^+] - \left([Cl^-] + [HCO_3^-]\right)$$

Because of electrochemical neutrality requirements, total [cations] must equal total [anions]. The difference must indicate the presence of unmeasured anions and a 'normal' anion gap is approximately 12 ± 4 mmol/L. Albumin (a weak acid) accounts for the major part of unmeasured anions and therefore the anion gap and the following correction is required. AG_{corr} = AG + (40 – measured albumin/4).

If an increased anion gap is present, it is strongly supportive of the presence of a primary metabolic acidosis and is often a useful pointer to the cause of metabolic acidosis, e.g. the presence of lactate or keto-acids.

- **Step 5: re-consider all the evidence** from the history, examination, additional investigations, and systematic blood gas analysis to formulate a complete acid-base diagnosis.

caused simultaneously by salicylate poisoning, and diagnosis of combined disorders like this can be challenging. Therefore to assess acid-base and ventilatory disturbances it is necessary to have at least a basic understanding of acid-base physiology, and a systematic approach to the interpretation of the arterial blood gas.

Systematic blood gas interpretation methods

Three commonly used systematic approaches exist to this end [2]. The two traditional, established methods use the arterial blood value of pH as a measure of the degree of acidity or alkalinity, $PaCO_2$ as a marker of the respiratory component and bicarbonate concentration (HCO_3^-) or BE as a marker of the non-respiratory or metabolic component of acid-base balance.

The first approach is based mainly on the interpretation of the Henderson–Hasselbach equation:

$$CO_2 + H_2O <> H_2CO_3 <> H^+ + HCO_3^- \quad \text{[eqn 5]}$$

Rearranged this gives:

$$pH = pK + \log\left\{\left[HCO_3^-\right]/\left[H_2CO_3\right]\right\} \quad \text{[eqn 6]}$$

where pK is the dissociation constant for carbonic acid.

This can further be expressed as:

$$pH = pK + \log\left\{[HCO_3^-]/[0.03 \times pCO_2]\right\} \quad \text{[eqn 7]}$$

According to this construct, changes in arterial pH occur as a result of changes in either $[HCO_3^-]$ or $PaCO_2$. Primary disorders occur with initial changes in either of the two parameters. Metabolic acidosis occurs with a reduction in $[HCO_3^-]$, whereas an increase in $[HCO_3^-]$ occurs with metabolic alkalosis. An increase in $PaCO_2$ is indicative of respiratory acidosis, while a reduction in $PaCO_2$ indicates respiratory alkalosis.

Homeostasis, however, demands a normal, or near normal, pH and in this system the bicarbonate buffering system accomplishes this goal. The most immediate response is simply that as $PaCO_2$ increases, the law of mass action will result in more $[HCO_3^-]$ production. However, this response by itself may be insufficient so there are additional responses in the kidney that increase $[HCO_3^-]$ production. It is, however, well known that 'hidden' buffers like haemoglobin, albumin, and phosphates also buffer excess protons and minimize alterations in pH. One way of addressing this complexity has been to observe normal compensatory changes in humans and animals exposed to acid base disorders, and quantify them in terms of changes in pH, $PaCO_2$ and $[HCO_3^-]$. This data has provided empirical limits for normal compensation and observed aberrations outside these compensatory limits are assumed to be the result of the presence of other primary abnormalities. Much of this work was completed in Boston, hence, the term 'Boston Rules' when this approach is used [3]. Box 72.1 provides a guide for using this approach in the clinical setting.

Despite widespread use of the 'Boston' method, theoretical limitations are the assumption that $PaCO_2$ and $[HCO_3^-]$ are independent of one another, and that all buffering of metabolic acids is by HCO_3^-. An alternative method of interpretation deals with these theoretical limitations. The 'standard bicarbonate' is a CO_2-independent index of the HCO_3^- concentration of a sample when the partial pressure CO_2 has been adjusted to 40 mmHg (5.3 kPa) at a temperature of 37°C. Buffer base was introduced as a measure of the concentration of all the buffers present in either plasma or blood, and BE as a measure of how far buffer base has changed from its normal value. BE is defined as the amount of strong acid or base required to return the pH of 1 L of whole blood to 7.4, assuming $PaCO_2$ of 40 mmHg (5.3 kPa), a temperature of 37°C. BE is routinely reported by most blood gas analysing machines. Thus, BE is proposed as a measure of the magnitude of the metabolic disorder, because it assesses all the extracellular buffers (in the blood sample) and is independent of $PaCO_2$. As haemoglobin is a buffer, but is not distributed throughout the extracellular fluid (ECF), BE is calculated for a haemoglobin concentration of 30 or 50 g/L, instead of the actual haemoglobin, allowing the whole ECF buffering capacity (and not just whole blood) to be estimated. With this adjustment, known as standard BE, the differences between in vitro and in vivo behaviour are largely eliminated [4]. It is BE variation from normal that forms the basis of the second traditional method of systematic arterial blood gas analysis. The 'Copenhagen' rules are usually used in a similar context to the Boston rules (Box 72.1).

More recently, an alternative method developed by Stewart used the physical-chemical principles of electrical neutrality, conservation of mass, and laws of dissociation of electrolytes to explain hydrogen ion disturbances [5]. In this model $[H^+]$ and $[HCO_3^-]$ are dependent variables and within the system, the concentration of $[H^+]$ changes only as a result of the degree of dissociation of water. The degree of dissociation is significantly influenced by three independent factors:

- **The strong ion difference (SID)**: the difference between strong (always dissociated) cations and strong anions.
- **The total non-volatile weak acids (A_{TOT})**: mainly albumin and phosphate (existing in dissociated (A^-) and non-dissociated (AH) forms).
- The $PaCO_2$.

Thus, it is the electrochemical forces produced by changes in SID, A_{TOT} and $PaCO_2$ that alter the $[H^+]$. Stewart solved a series of simultaneous mathematical equations describing the relationship between the factors listed above and $[H^+]$. Although more complex, this method produces an accurate description of acid-base abnormalities, and often provides clearer pathophysiological explanations of clinically observed acid-base phenomena than traditional methods [6].

Bedside blood gas interpretation

Attempts to compare the different methods of systematic interpretation of arterial blood gases have failed to demonstrate the clear superiority of any one system. The Boston rules approach (including the use of the anion gap) has been shown to be mathematically similar to the BE method and the Stewart physicochemical method [7,8]. When applied in experimental and clinical settings, the ability of traditional and the Stewart systems to predict the outcome of acid-base alterations is also similar [9]. Although the Stewart remains attractive because it provides explanatory information that appears to more precisely explain observed pathophysiological changes, it is currently infrequently used at the bedside. Whether it apparently superior explanatory value will

Box 72.2 Common Causes of Primary Respiratory Acid-base Disorders—Acidosis

Decreased elimination of carbon dioxide

Central respiratory depression

- **Drug**: sedatives, opioids.
- Obesity hypoventilation syndrome.
- **Intracerebral lesions**: infarct, haemorrhage, tumour.

Neuromuscular diseases

- High spinal cord lesions.
- Guillain–Barré syndrome, myasthenia gravis.
- **Neuromuscular toxins**: organophosphates, snake venom.

Lung or chest wall defects

- Obstructive and restrictive lung diseases.
- **Dead space ventilation**: pulmonary embolism, lung hypoperfusion.
- Acute respiratory distress syndrome, pulmonary oedema.
- Pneumothorax, haemothorax.
- **Chest trauma**: flail chest, contusion, haemothorax.

Airway disorders

- Obstructive sleep apnoea.
- **Upper airway obstruction**: laryngospasm, angioedema.

Over-production of carbon dioxide

- Excessive bicarbonate infusion.
- Hypermetabolism (malignant hyperthermia, thyroid storm, seizure).

Increased inspired carbon dioxide

Anaesthetic circuit malfunction/↑ deadspace with rebreathing of CO_2.

Box 72.3 Causes of Primary Respiratory Acid-base Disorders—Alkalosis

Central respiratory centre stimulation

- Head injury.
- Cerebral vascular accident.
- Anxiety-hyperventilation syndrome.
- Pain, fear, stress.
- Pregnancy.
- Sepsis.
- **Drugs**: medroxyprogesterone, catacholaemines, salicylate intoxication.

Hypoxaemia-induced hyperventilation

- Low inspired partial pressure of oxygen.
- Impairment of diffusion across blood-gas membrane.
- Ventilation perfusion inequality.
- Intracardiac shunt.
- Low mixed venous oxygen saturation.

Iatrogenic hyperventilation

Excessive controlled mechanical ventilation.

ultimately translate into superior clinical bedside utility remains to be seen [10].

To summarize, all systematic approaches to the diagnosis of acid-base disorders involve three critical steps. The first is a thorough clinical assessment based on history, examination and initial investigations. This should lead to a clinical decision as to what is the most likely acid-base disorder, and what the possible differential diagnoses are. Mixed disorders are often difficult to recognize, and history and examination alone are usually insufficient to make a firm diagnosis. The second step is to perform a systematic evaluation of the arterial blood gas (Box 72.1), including an analysis of the anion gap, and the last is to synthesize all available information and finalize the diagnosis. For the purposes of respiratory monitoring, a diagnosis of respiratory acidosis or alkalosis should lead to the search for associated clinical causes and the implementation of appropriate interventions (Boxes 72.2 and 72.3). Although the detailed diagnosis of metabolic disorders is beyond the scope of this chapter, recognition of the presence of a metabolic acidosis or alkalosis, and its influence on compensatory respiratory responses is important to recognize.

References

1. Mellemgaard K. (1966). The alveolar-arterial oxygen difference: its size and components in normal man. *Acta Physiologica Scandinavica*, **67**, 10–20.
2. Kellum JA. (2000). Determinants of blood pH in health and disease. *Critical Care*, **4**, 6–14.
3. Severinghaus JW. (1993). Siggaard-Andersen and the 'Great Trans-Atlantic Acid-Base Debate'. *Scandinavian Journal of Clinical Laboratory Investigation*, **214** (Suppl.), 99–104.
4. Severinghaus JW and Astrup PB. (1985). History of blood gas analysis. Part II. pH and acid-base balance measurements. *Journal of Clinical Monitoring*, **1**, 259–77.
5. Stewart PA. (1978). Independent and dependent variables of acid-base control. *Respiratory Physiology*, **33**, 9–26.
6. Kellum JA. (2005). Clinical review: reunification of acid-base physiology. *Critical Care*, **9**, 500–7.
7. Kurtz I, Kraut J, Ornekian V, and Nguyen MK. (2008). Acid-base analysis: a critique of the Stewart and bicarbonate-centered approaches. *American Journal of Physiology—Renal Physiology*, **294**, F1009–31.
8. Matousek S, Handy J, and Rees SE. (2011). Acid-base chemistry of plasma: consolidation of the traditional and modern approaches from a mathematical and clinical perspective. *Journal of Clinical Monitoring and Computing*, **25**, 57–70.
9. Gattinoni L, Carlesso E, Maiocchi G, Polli F, and Cadringher P. (2009). Dilutional acidosis: where do the protons come from? *Intensive Care Medicine*, **35**, 2033–43.
10. Kellum JA. (2007). Disorders of acid-base balance. *Critical Care Medicine*, **35**, 2630–6.

CHAPTER 73

Pulse oximetry and capnography in the ICU

Richard Lee

Key points

- Both pulse oximetry and capnography are essential monitors in the intensive care unit (ICU), particularly during intubation, ventilation, and transport.
- Equivalent continuous information is not otherwise available.
- It is important to understand the principles of measurement and limitations, for safe use and error detection.
- End tidal carbon dioxide ($P_{ET}CO_{2)}$ and oxygen saturation should be regularly checked against $PaCO_2$ and co-oximeter SO_2 obtained from the blood gas machine.
- The P_ECO_2 trace informs endotracheal tube placement, ventilation, and blood flow to the lungs.

Introduction

Pulse oximetry and capnography provide continuous, rapidly obtained, non-invasive, reasonably accurate information. In 1991 the Society of Critical Care Medicine listed both as necessary monitoring for patients on respiratory support [1].

Pulse oximetry

Pulse oximeters are used ubiquitously, in emergency departments, intensive care units (ICUs), operating rooms, during patient transport, in outpatient departments, and in increasingly in general practice. As for many monitors there is no evidence of patient outcome benefit from their use [2], but there is for detecting hypoxaemia and influencing management.

General principles

Oximetry has been performed in vitro since the 1930s by spectrophotometry. The absorption of known wavelengths of light, based on Beer's Law (absorbance is proportional to the chromophore concentration), and Lambert's Law (absorbance is proportional to the thickness of the absorbing layer), and the differing absorption of light by the Hb species are used to measure their concentrations.

Co-Oximetry in modern blood gas machines uses multiple wavelengths of light, passed through a transparent cuvette containing the blood specimen, haemolysed by ultrasound to make a suspension. The light path distances and cuvette wall thickness are known. Non-invasive clinical oximetry had been inhibited by quantifying the variable light absorption and thickness of skin, subcutaneous tissue and venous blood until the 1970s when an eight-wavelength ear oximeter for clinical use was available, but it was expensive, bulky, and required heating of the skin. In 1974, Aoyagi described the principle of pulse oximetry [3]. He noticed a pulsatile variation in the tissue optical density caused by arterial pulsation and realized that if the optical density of the pulsatile component was measured at two appropriate wavelengths a ratio could be obtained, which related closely to arterial SaO_2.The development of compact light emitting diodes (LEDs) and microprocessors led to easy application, and rapid machine response. The first commercial pulse oximeter was marketed in 1983.

The pulse oximeter probe is applied to a part of the body, where pulsatile arterial blood flow is sensed. Probes may be disposable or reusable, and are designed to be applied to finger, forehead, nose, ear, or toe. They are calibrated for transmitted or reflected light, and should not be dismantled or used other than in accordance with the manufacturer's instructions.

The probe consists of two LEDs—one emits 660nm (red, R) and the other 940 nm (infrared, IR) light, chosen for maximum separation in absorbance characteristics of deoxyhaemoglobin (deoxyHb) and oxyhaemoglobin (oxyHb)—and a photodiode, which detects the intensity of the light—reflected or transmitted. The LEDs strobe at 720 Hz, sequentially (R, IR, and both OFF to provide a reference), cycling at 30 cycles/sec. The transmitted or reflected signal is digitalized, the difference between systolic and diastolic measured to give a pulsatile component (ac) and non-pulsatile component (dc), therefore allowing for quantification of absorption due to tissue, venous blood, nail, and polish. A ratio of ratios, *R*, is then obtained [(ac R/ac IR)/(dc IR/dc R)], simplified to *R* = ac 660.dc 660/ac 940. dc 940. *R* is empirically calibrated against look up tables of *R* versus known SaO_2 [4]. The tables are obtained using co-oximetry and having normal young volunteers breathe hypoxic mixtures to produce saturations in the range 70–100% SaO_2.

Pulse oximeters usually also calculate heart rate and provide visual measures of signal quality.

The monitor may calculate SpO_2 25–30 times per second, but averages SpO_2 over 3–12 seconds to allow artefact rejection, and update the screen every 1–2 seconds, depending on fast or slow mode, and the manufacturer.

A delay of around 1–2 minutes occurs after application of a finger probe before achieving a measurement, and a sudden reduction in FIO_2 produces a fall in SpO_2 with a lag of 10 seconds for ear probes and 50 seconds for finger probes [4].

Terminology

Oximetry is the measurement of oxyHb in blood as a percentage of Hb species. Because of the use of only two wavelengths of light the only species of Hb targeted in pulse oximetry are oxyHb and deoxyHb. Co-oximeters using multiple wavelengths of light (commonly 128) may report functional saturation (SO_2, the ratio: oxyHb/(oxyHb + deoxyHb)) and fractional saturation (FO_2Hb, the ratio oxyHb/tHb including dyshaemoglobins) and report methaemoglobin (MetHb) and carboxyhaemoglobin (COHb)). The terminology is often misused and misunderstood [5].

Accuracy

The pulse oximeter reading generally achieves a mean bias of ±2% in normal volunteers in the SO_2 range of 80–100%, although the International Standard requires ±4%. There are large variations in bias and error between machines, manufacturers, clinical situations, sexes, and saturation levels [6] and it is suggested that a pulse oximeter SO_2 of 94% is necessary to ensure a co-oximeter SO_2 of 90% from a simultaneous arterial blood gas [7]. Bias increases as Hb and SO_2 fall.

Errors

There are many potential sources of error [8]. Pulse oximeters require a detectable pulse and perform poorly in poor perfusion states. They are insensitive to large changes in PaO_2 in the high PaO_2 range and increasing bias occurs at low PaO_2. They are calibrated using co-oximetry, which is also prone to errors [9].

Errors can be described as 'safe' (under-read or fail to read, leading to false alarms) or 'unsafe' errors (over-read, leading to false security) due to the following factors.

Patient factors

- **Abnormal Hb** [10]:
  - Pulse oximeters read HbCO as mostly HbO_2, over-read SO_2 1% for every 1% of COHb in blood.
  - MetHb absorbs both wavelengths tending to an R of 1, forces SpO_2 towards 85% as MetHb rises.
  - Fetal Hb absorbs similarly to adult Hb, produces no clinically significant error.
- **Dyes**: methylene blue and indocyanine green absorb red light, artificially lower SpO_2.
- **Other light absorbents**: bilirubin does not interfere with oximetry.
- **Nail varnish**: blue, black, green, beige, purple, and white polish artificially lower SpO_2. Racial pigment does not significantly affect the measurement; difficulty with signal may be overcome by using the nail bed, less pigmented.
- **Pulsatile veins** (tricuspid regurgitation, venous congestion) lower SpO_2.
- **Non-pulsatile flow** on cardiopulmonary bypass decreases signal to noise ratio, measurement difficult.
- Anaemia increases bias at low SO_2.

Equipment factors

- Delay due to averaging and blood flow to peripheral tissues.
- Flooding of external light may force a value of 85% or trigger alarm.
- Penumbra or optical shunting around the tissue will produce false readings, countered by the 'LED OFF' period as a reference in the machine algorithm.
- Movement artefact may trigger an alarm or variable errors. Seizures and helicopter vibration are reported to not interfere.
- Fluorescent light falsely lowers SpO_2, but is countered by the LED OFF period as reference in the machine algorithm.
- **Radio-frequency interference**:
  - MRI use requires a link to the patient with fibre optic cables, may produce a falsely low SpO_2.
  - Cautery artificially decreases SpO_2 with older machines, interferes with heart rate estimation.

Advances have occurred in new software and hardware for movement artefact rejection, e.g. signal extraction technology (SET), Fourier artefact suppression (FAST) and Oxismart technology [11]. Multiple wavelength pulse oximeters are available to measure other haemoglobin species, but inherent limitations of the techniques confound the accuracy [12].

Capnography and end-tidal CO_2 monitoring

Most national intensive care organizations recommend that capnography be used for all sedated or intubated patients, and failure to use or misinterpret the readings is regarded as a gap in care [13].

Technology

Methods available to measure CO_2 in the gas phase include IR absorption, mass spectrometry, Raman scattering, and photo-acoustic spectroscopy. IR absorption is the commonly used technique in ICU because of cost and rapid response. The Beer and Lambert Laws are applied to measurement in a calibrated cuvette either positioned within the ventilator circuit with an adaptor (mainstream) or remote from the circuit with gas aspirated via a thin tube to the analyser (sidestream). As absorption is dependent on the number of particles of targeted substance in the gas mixture, it is a partial pressure detector. End tidal carbon dioxide partial pressure ($PETCO_2$) measurement requires rapid response for clinically useful breath-by-breath analysis.

IR gas analysers use the principle that all gases with two or more dissimilar atoms in the molecule absorb IR radiation. CO_2 is absorbed in the band 4.3 μm, oxygen does not absorb IR, but anaesthetic gases (e.g. nitrous oxide in the 4.5 μm band) and water will.

Collision broadening is the phenomenon where the presence of a second gas (e.g. N_2, N_2O, C_3H_6) widens the absorption spectrum of the other gas so that absorption is increased. This is usually countered by a standard offset.

Features of mainstream sensors

- Better capnograph.
- More rapid response.
- No gas aspirated from the airway.
- Heavier, bulkier, and more cumbersome in the circuit.
- Expensive electronic consumables, which are prone to damage.
- Measuring window heated to 40°C and needs to be kept clean.
- Periodic calibration.

Features of sidestream systems

- Cheaper consumables.
- Practical in non-intubated patients.
- Prone to distorted capnogram.
- Sampling rates 50–500 mL/min may interfere with ventilation in small patients.
- Slow response distorts capnogram.
- Fast aspiration falsely lowers $P_{ET}CO_2$.
- Sampling tube occlusion may occur due to airway secretions or water.
- Need fluid trap and filter.

Information revealed

The presence of a continued CO_2 trace indicates the intra-airway position of the endotracheal tube (ETT) following intubation. The trace acts as a disconnection alarm and apnoea detector, and may detect respiratory change (V/Q mismatch, bronchospasm, etc.), effectiveness and prognosis of cardiopulmonary resuscitation (CPR), and air embolism [14]. This continuous non-invasive information decreases need for arterial blood gas estimation (ABGE) as $P_{ET}CO_2$ provides a useful surrogate of $PaCO_2$ in patients with normal lung function and trend in patients with COPD.

Four phases are visible on the P_ECO_2 time trace (Fig. 73.1):

- **I** represents the expiration of carbon dioxide free gas from anatomical dead space, upper airway to bronchi.
- **II** represents mixed gas from airways and alveoli.
- **III** represents the alveolar plateau of gas from alveoli, rising slightly due to variable mixing and time constants. The peak value represents $P_{ET}CO_2$
- 0 sharp descent is due to the absence of carbon dioxide in inspired gas.
- Two angles are observed (A and B), which may be increased by lung pathology (V/Q mismatch, asthma) and rebreathing (from incompetent valves, low fresh gas flow), respectively.

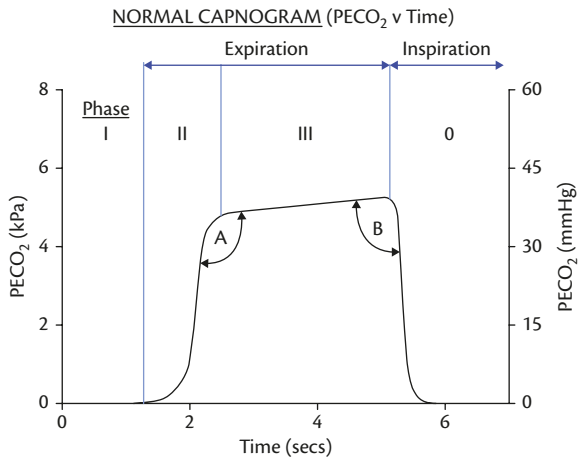


Fig. 73.1 Normal capnogram. Partial pressure of expired carbon dioxide (P_ECO_2) graphed against time in seconds, from time 0 at the start of expiration (for phases and angles, see in Information Revealed).

$P_{ET}CO_2$ approximates P_ACO_2 and, hence, $PaCO_2$.

$$PaCO_2 = k.\,VCO_2/AV, \qquad \text{[eqn 1]}$$

where AV or alveolar ventilation = (TV – VD) × RR, k is a constant, VCO_2 is CO_2 production, AV is alveolar ventilation, TV is tidal volume, VD is dead space volume, and RR is respiratory rate.

Therefore, a change in an accurately recorded $P_{ET}CO_2$ suggests a change in CO_2 production, minute ventilation, or dead space ventilation.

CO_2 production

- Increased by fever, parenteral nutrition, malignant hyperthermia, thyrotoxicosis, tourniquet release, bicarbonate infusion.
- Decreased by hypothermia, sedation.

Minute ventilation

- Increased by hyperventilation.
- Decreased by hypoventilation.

Dead space ventilation

- Increased by shock, cardiac arrest, air embolism, pulmonary embolism, V/Q mismatch.
- Decreased by effective CPR.
- The gap between $P_{ET}CO_2$ and $PaCO_2$ is usually < 5 mmHg (0.67 kPa), but may be >15 mmHg (1.99 kPa) in ARDS and is dependent on ventilation mode, dead space, and cardiac output. **Alveolar dead space can be estimated as 1– ($P_{ET}CO_2$: $PaCO_2$).**

Errors

Most errors relate to technical problems of calibration, blocked sensor window or blocked sampling tube, or delay in achieving a trace. High sampling flow rate with a sidestream sensor will produce a falsely low $P_{ET}CO_2$. Capnography provides information, which requires pattern recognition, interpretation, comparison with normal, and clinical decision-making, which are all major clinical sources of error. An absent trace after intubation in cardiac arrest may be falsely attributed to ineffective CPR and low cardiac output, but a flattened trace should at least be seen. In event of oesophageal intubation after ingestion of carbonated drinks may give an initial CO_2 trace, falling after several breaths.

Common abnormal patterns

- **Absent PCO_2 trace**: oesophageal intubation, disconnection, apnoea, total airway obstruction, cardiac arrest without CPR.
- **Elevated Phase 1**: rebreathing, incompetent circuit valves, exhausted CO_2 absorber during anaesthesia, low fresh gas flow, slow sidestream sampling rate.
- **Decreased Phase II slope**: slow sidestream sampling rate, kinked or blocked ETT, expiratory obstruction (e.g. asthma or chronic obstructive pulmonary disease (COPD)).
- **Absent Phase III plateau:** in COPD, bronchospasm, acute respiratory distress syndrome (ARDS).
- **Elevated $P_{ET}CO_2$**: hypoventilation, malignant hyperthermia (MH), CO_2 insufflated at laparoscopy, bicarbonate administration, release tourniquet.
- **Decreased $P_{ET}CO_2$**: hyperventilation, hypothermia, low cardiac output (CO), pulmonary embolus (PE) [15].

References

1. Society of Critical Care Medicine (1991). Guidelines For Standards of Care for Patients with Acute Respiratory Failure on Mechanical Ventilatory Support. *Critical Care Medicine*, **19**(2), 275–8.
2. Pedersen T, Hovhannisyan K, and Moller AM (2010). Pulse oximetry for perioperative monitoring (Review). *The Cochrane Library*, Issue 12.
3. Severinghaus JW. (2007). Takuo Aoyagi: discovery of pulse oximetry. *Anesthesia and Analgesia*, **105**, S1–4.
4. Tremper KK and Barker SJ (1989). Pulse oximetry. *Anaesthesiology*, **70**, 98–108.
5. Toffaletti J and Zijlstra WG. (2007). Misconceptions in reporting oxygen saturation. *Anesthesia and Analgesia*, **105**, S5–9.
6. Feiner J, Severinghaus JW, and Bickler PE (2007). Dark skin decreases the accuracy of pulse oximeters at low oxygen saturation: the effects of oximeter probe type and gender. *Anesthesia and Analgesia*, **105**, S18–23.
7. Van de Louw A, Cracco C, Cerf C, et al. (2001). Accuracy of pulse oximetry in the intensive care unit. *Intensive Care Medicine*, **27**, 1606–13.
8. Milner QJW and Matthews GR. (2012). An assessment of the accuracy of pulse oximeters. *Anaesthesia*, **67**, 396–401.
9. Gehring H, Duembgen L, Peterlein M, HagelBerg S, and Dibbelt L (2007). Hemoximetry as the 'gold standard'? Error assessment based on differences among identical blood gas analyser devices of five manufacturers. *Anesthesia and Analgesia*, **105**, S24–30.
11. Giuliano K and Higgins TL. (2005). New-generation pulse oximetry in the care of critically ill patients. *American Journal of Critical Care*, **14**(1), 26–37.
10. Barker SJ and Badal JJ. (2008). The measurement of dyshaemoglobins and total haemoglobin by pulse oximetry. *Current Opinion in Anesthesiology*, **21**, 805–10.
12. Shamir M Y, Avramovich A, and Smaka T (2012). The current status of continuous non-invasive measurement of total, oxy, and methaemoglobin concentration. *Anesthesia and Analgesia*, **114**, 972–8.
13. Editorial (2009). Airway incidents in critical care, the NPSA, medical training and capnography. *Anaesthesia*, **64**, 351–7.
14. Soubani AO. (2001). Non-invasive monitoring of oxygen and carbon dioxide. *American Journal of Emergency Medicine*, **19**(2), 141–6.
15. Sivarajan VB and Bohn D. (2011). Monitoring of standard hemodynamic parameters: Heart rate, systemic blood pressure, atrial pressure, pulse oximetry, and end-tidal CO_2. *Pediatric Critical Care Medicine*, **12**(4), S2–11.

CHAPTER 74

Respiratory system compliance and resistance in the critically ill

Ricardo Luiz Cordioli and Laurent Brochard

Key points

- Correct understanding of the relationship between pressure, volume, and flow is a basic requirement for correctly setting a ventilator.
- The lungs and chest wall both participate to global respiratory mechanics. In some situations, such as obesity or ARDS, the chest wall could explain a large part of the low compliance of the respiratory system.
- Resistance represents the ratio between the pressure dissipated by the friction of gas and the mean gas flow.
- Compliance denotes the capacity of the pulmonary system to expand and is calculated as ratio between volume and pressure.
- Intrinsic positive end expiratory pressure (PEEP) can be present with short expiratory time, high respiratory rate, or expiratory flow limitation in airway obstructive disease.

Introduction

Acute respiratory failure is a common situation in patients admitted to intensive care units (ICU) and, in the most severe forms, mechanical ventilation (MV) is a life-saving support. MV can also be harmful and lead to ventilation-associated lung injury (VALI) [1]. VALI occurs mainly when pressures (**barotrauma**) and volumes (**volutrauma**) are not adapted to the specific respiratory conditions of the patient, which can be assessed by measurement of respiratory mechanics.

Impairment in pulmonary function is, in general, accompanied by changes in respiratory mechanics, especially during acute exacerbations of chronic obstructive pulmonary disease (COPD), asthma, or the acute respiratory distress syndrome (ARDS), situations that are associated with large changes in resistance (R) and compliance (C) of the respiratory system. An assessment of the respiratory mechanics is therefore necessary for correctly adapting the ventilatory settings. Monitoring the magnitude of these changes with time is also important because of their direct relationship with severity of disease. It can help defining prognosis and response to treatment [2,3].

In order to ventilate the patient appropriately, clinicians need to understand the relationship between pressure (P), volume (V), and flow ($\dot{V}$). To appreciate the risks associated with MV, one also needs to understand the partition between lungs and chest wall in terms of respiratory mechanics.

Equation of motion of the respiratory system

To move air in and out the thorax, energy must be dissipated mostly against elastic (F_{EL}) and resistive (F_R) forces. A simple equation of motion describes the forces in the respiratory system (F_{RS}):

$$F_{RS} = F_{EL} + F_R \qquad \text{[eqn 1]}$$

Any pressure applied is either stored as elastic pressure (P_{EL}) or dissipated as resistive pressure (P_{RES}). In some circumstances, another force can participate, the inertial force (F_{IN}). Inertia can usually be neglected in the respiratory system, with rare exceptions such as coughing or high-frequency ventilation.

Elastance (E) relates P to V, and resistance relates P to ($\dot{V}$), so the equation of motion can be modified to explain how the pressure at the airway opening (P_{AW}) can be partitioned into a resistive and an elastic pressure component:

$$P_{AW(t)} = P_0 + E\left(V\right)_{(t)} + R(\dot{V})_{(t)} \qquad \text{[eqn 2]}$$

where $_{(t)}$ is a given time, P_0 is the starting pressure in the respiratory system, and P_0 represents the total positive end expiratory pressure ($PEEP_T$).

Methods of measurement

In passively mechanically-ventilated patients, it is easier to measure pulmonary mechanics during constant flow, volume-controlled ventilation (VCV) than during pressure-controlled ventilation (PCV). In an actively-breathing patient under MV, the total pressure is the sum of P_{AW} and of the muscular pressure. Because the patient's spontaneous breathing activity is usually not directly monitored, this greatly limits the ability to make these measurements at the bedside.

One simple, but essential manoeuvre involves stopping flow by occlusion at the end of the insufflation phase, allowing measurement of the plateau pressure (P_{PLAT}), which represents the alveolar pressure at end-inspiration (P_{ALV}), as shown on Fig. 74.1.

Usually, P, V and $\dot{V}$ are directly measured by the ventilator; V is calculated as the integral of inspiratory flow tracing over time. There are several technological limitations with the calculation of V [4].

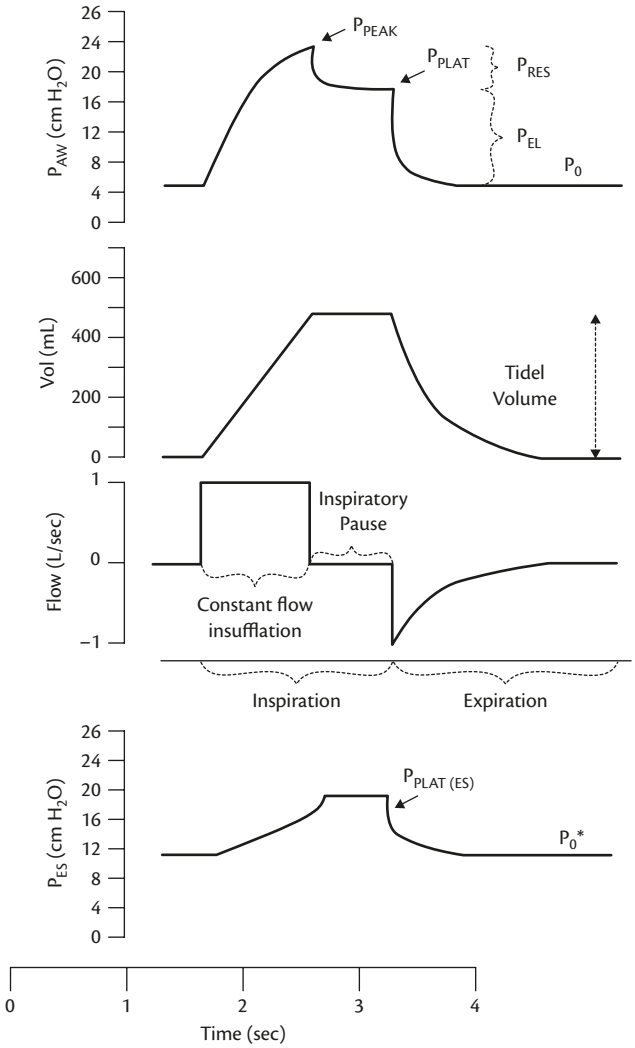


Fig. 74.1 Ventilator screen image representing changes in airway pressure (P_{AW}), flow, volume, and oesophageal pressure (P_{ES}) versus time; P_{PEAK} inspiratory peak pressure, P_{PLAT} plateau airway pressure, $P_{PLAT(ES)}$ plateau oesophageal pressure, P_0 total PEEP at the airway pressure waveform, P_{0*} total PEEP at the oesophageal pressure waveform, V_T tidal volume.

Resistance and flow

Definition

Resistance (R) represents the ratio between the pressure dissipated and the mean gas flow ($\dot{V}$). The resistance of the respiratory system (R_{RS}) is a purely dynamic force caused by the movement of molecules and the friction between them, and against the tracheobronchial tree and the endotracheal tube (ETT), and, to a smaller extent, to the resistance to parenchyma deformation.

Measurement

In a situation of constant flow, R_{RS} can be calculated as:

$$R_{RS} = \frac{P_{PEAK} - P_{PLAT}}{\dot{V}} \rightarrow P_{PEAK} - P_{PLAT} = P_{RES} = R_{RS} \times \dot{V} \quad \text{[eqn 3]}$$

Because flow is constant, one can approximate that this value of R_{RS} is constant during the whole insufflation. Such an assumption cannot be made if ($\dot{V}$) is not constant during insufflation, such as during PCV. The resistive pressure (P_{RES}) reflects the energy lost to overcome F_R, which is usually mainly situated in the upper or proximal airways, including the ETT. As a consequence, P_{RES} disappears before reaching the deep lung and is not present in alveoli.

P_{RES} gives insight about the conducting airways and tells the clinician which part of P_{AW} is not transmitted to the alveoli and does not contribute to a risk of VALI. P_{RES} is, by definition, dependent on flow. R_{RS} can also increase with flow when it changes from laminar to partially or fully turbulent. The pressure and flow relationship is curvilinear as it is the case in endotracheal tubes [5]. In other words, small changes in flow can induce large changes in P_{RES}.

There are many other methods to calculate resistance, but the end-inspiratory occlusion method described here is the simplest.

Flow

In the lung, flow can change from purely laminar with little friction, to fully turbulent with instabilities, large frictional forces and high pressure dissipation. In ETT and in upper airways flow is mostly turbulent, whereas laminar flow predominates in the more distant and small airways.

According to Hagen–Poiseuille's Law during laminar flow, R is directly related to airway length (L), gas viscosity (η) and inversely proportional to tube radius to the fourth power:

$$R_{RS} = \frac{8\eta L}{\prod r^4} \quad \text{[eqn 4]}$$

where Π is a mathematical constant.

Clinical implications

To avoid excessive F_R and, subsequently energy loss, an adequately-sized ETT is important. In severe obstructive lung disease a mixture of helium and oxygen has a decreased density, reducing the resistance of the airway [6]. In a healthy individual adult under MV using a square flow set at 60 L/min (or 1 L/sec), R_{RS} is usually less than 10 cmH_2O/L/sec and rarely exceeds 15 cmH_2O/L/sec. During acute exacerbation of COPD or asthma, R_{RS} can increase up to 20 cmH_2O/L/sec or 40 cmH_2O/L/sec in the most severe forms of bronchospasm. During MV, a sudden augmentation in P_{PEAK} without an increase in P_{PLAT} indicates an abrupt increase in P_{RES} and in R_{RS}; the most common reasons like tube kinking, mucus clotting in the airway or bronchospasm can be readily identified and treated after visualizing the increase of P_{RES} on the P_{AW} curve.

Resistance is a dynamic force, acting only when flow is present. During constant flow VCV the same amount of P_{RES} is present during the whole insufflation. During PCV, the major part of P_{RES} is dissipated at the beginning of the breath due to the decelerating flow pattern. Because flow is decelerating, P_{RES} progressively decreases along insufflation and P_{PEAK} becomes close to P_{PLAT}. P_{PEAK} equals P_{PLAT} only when flow has reached zero at the end of insufflation. So in many instances, P_{PEAK} during PCV remains higher than the true P_{PLAT}.

Flow–volume curves

The effects of airway resistance can be visualized on dynamic flow–volume curves (during inspiration and expiration). Analysis of this curve may be useful for identifying different clinical situations (Fig. 74.2) [7].

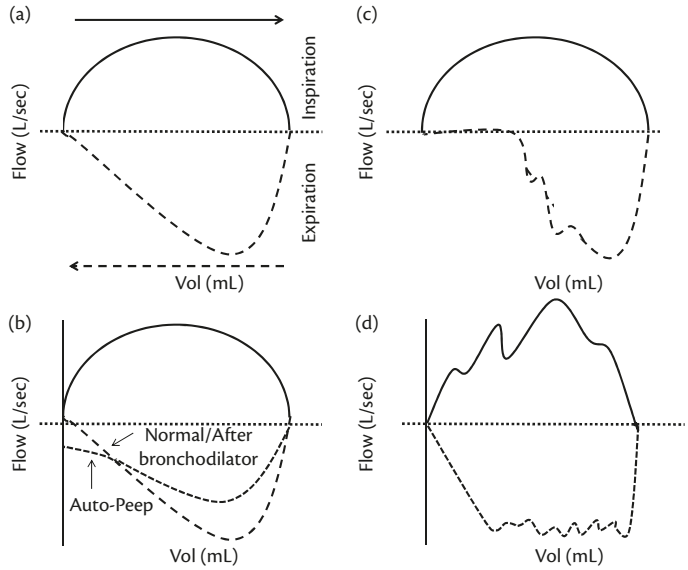


Fig. 74.2 Flow volume curves in different situations. (a) Normal patient; (b) COPD patient with dynamic hyperinflation and auto-PEEP, and after bronchodilator treatment; (c) sudden interruption of exhalation flow representing an important gas leak from the patient (bronchopleural fistulae) or from the ventilator circuit; (d) a saw-tooth pattern is observed in both inspiratory and expiratory limbs and indicate presence of secretions in the airways.

Elastance (E) and compliance (C)

Definition

The elastance of the respiratory system (E_{RS}) reflects the capacity of the pulmonary system to return to its resting position and measure the recoil pressure over a given volume. Since E = 1/C, the compliance of the respiratory system (C_{RS}) denotes the capacity of the pulmonary system to expand. Traditionally, C_{RS} has been used to assess the severity of ARDS [8,9].

Measurement

Compliance (C) can be defined as the change in volume (ΔV) per unit of change in applied pressure (ΔP):

$$C = \Delta V / \Delta P \qquad \text{[eqn 5]}$$

When applying an end-inspiratory occlusion or pause, there is no movement of gas (i.e. no resistive pressure) and the elastic properties can be calculated by these static (or quasi-static) measurements. The static compliance of the respiratory system ($C_{STAT(RS)}$) can be calculated as:

$$C_{STAT(RS)} = \frac{V_T}{P_{PLAT} - P_0} \qquad \text{[eqn 6]}$$

During MV, P_0 is the total PEEP, which is the sum of extrinsic positive end expiratory pressure ($PEEP_E$) set on the ventilator and intrinsic PEEP above it ($PEEP_I$ or auto-PEEP). The latter can be present during short expiratory times (e.g., inverted I/E ratio ventilation), high respiratory rate with fixed inspiratory time, or in expiratory flow limitation (COPD, asthma, cardiogenic pulmonary oedema, ARDS) where alveoli have prolonged and delayed emptying due to their mechanical characteristics or collapse of the small airways, trapping residual gas inside the alveoli. It can be measured with an occlusion manoeuvre at the end of the expiratory phase under controlled MV (Fig. 74.3). $PEEP_I$ and $PEEP_E$ must be taken into account when measuring P_0 with eqn 2. C_{RS} and the equation of motion should be written as:

$$C_{(RS)} = \frac{V_T}{P_{PLAT} - \left(PEEP_E + PEEP_I\right)} \qquad \text{[eqn 7]}$$

$$P_{RS(t)} = \frac{1}{C}\left(V\right)_{(t)} + R(\dot{V})_{(t)} + PEEP_E + PEEP_I \qquad \text{[eqn 8]}$$

Pressure–volume curve

C_{RS} can vary with lung volume. It is analysed over the whole lung volume by plotting static pressure values over a large volume ranges, e.g. from functional residual capacity (FRC) to total lung capacity (TLC), with construction of a pressure–volume (P/V) curve [10–12] (Fig. 74.4). The slope of this curve represents the C_{RS} and is not constant over lung volume. The patient must be passive for accurate results, though paralysis is not always mandatory [13].

The P/V curve of the respiratory system depends on both compliance of the chest wall (C_{CW}) and the lung (C_L). The latter depends primarily on the aerated lung volume available to ventilation.

Information from the shape and the different values of the P/V curve can be extrapolated to the clinical condition of a mechanically ventilated patient [11]. The first part of the P/V curve (starting from FRC) in patients with ARDS often has a relatively flat shape with a low C_{RS} due to a collapsed lung. In this phase, a larger change in P_{AW} is necessary to produce a small change in volume. In the second part, part of the lung has been reopened and/or is reopening, and C_{RS} becomes higher with a more linear curve. It indicates a region where the work of breathing is lower. Finally, the upper section of the P/V curve shows a lower C_{RS} reflecting that the lung has been reopened and possibly overdistended [14].

The lower inflection point (LIP) and upper inflection point (UIP) represent a separation of the different parts. Schematically in ARDS, the LIP represents the beginning of substantial recruitment,

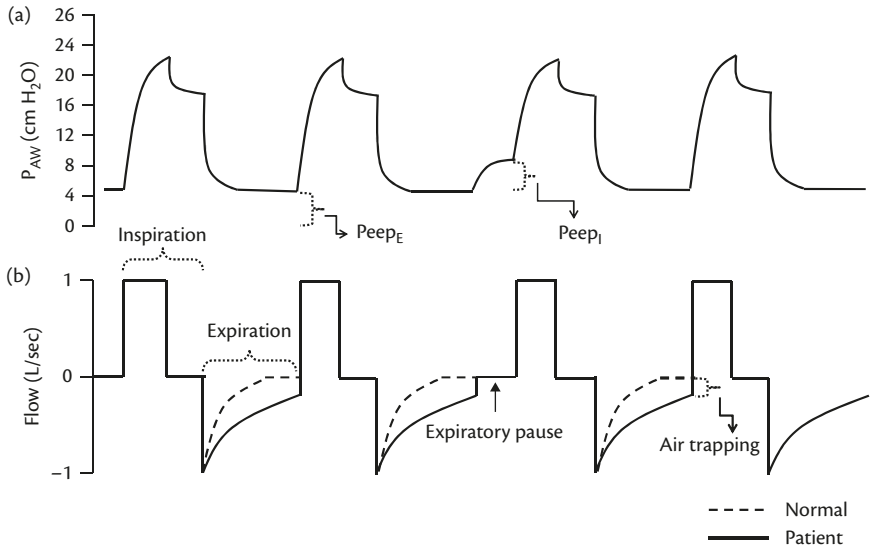


Fig. 74.3 The occurrence of intrinsic PEEP can be observed on the screen of the ventilator from a patient with obstructive lung disease. (a) Airway pressure waveform with an expiratory pause showing the existence of $PEEP_I$ (or auto-PEEP). (b) Flow curve demonstrating the failure to exhale all gas during the expiratory time and, consequently, formation of gas trapping.

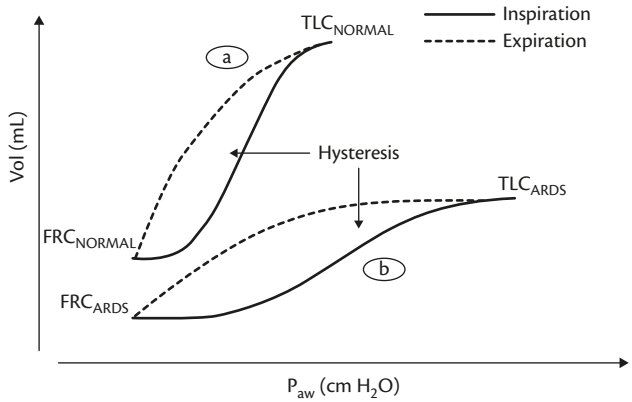


Fig. 74.4 Pressure–volume curves (P/V) and its hysteresis. (a) P/V curve from a normal patient. (b) P/V curve from an ARDS patient.
FRC, functional residual capacity; TLC, total lung capacity.

while the majority of recruitment has already occurred at the UIP. In reality, alveolar recruitment occurs all over the curve [15].

The P/V curve can also be drawn during the expiratory phase of ventilation, better reflecting the closing pressures and more useful when setting PEEP, but being more complex to analyse.

The different slopes of the P/V curve between inspiration and expiration generate an area called hysteresis. P/V curve with a large hysteresis could represent a potential for alveolar recruitment, especially at the early stage of ARDS [11].

Partition of the respiratory system elastance/compliance

The E_{RS} represents the sum of the effects of the lung (E_L) and of the chest wall elastance (E_{CW}):

$$E_{RS} = E_L + E_{CW} \quad \text{[eqn 9]}$$

Usually, the chest wall has a modest influence and more than 80% of the pressure is generated by the lungs. In several situations (e.g. obesity, highly oedematous patients, large pleural effusions, increased intra-abdominal pressure, ARDS) the differentiation of the sources of elastance is important. If E_{CW} is high compared with E_L, then a large part of the elastic pressure will be used to distend the chest wall and much less than the total P_{AW} to expand and distend the lung. Interpretation of the P_{AW} in terms of risk of VALI then differs.

The pleural pressure (P_{PL}) has to be estimated to calculate C_{CW}, and in critical practice this is done using oesophageal catheters with a balloon that measure oesophageal pressure (P_{ES}) (Figs 74.1 and 74.5) [16]. P_{ES} is a very useful substitute in determining P_{PL}, although there are some controversies about its absolute value. The C_{CW} can be calculated with the following equation:

$$C_{STAT(CW)} = \frac{V_T}{P_{PLAT(ES)} - P_0} \quad \text{[eqn 10]}$$

$P_{PLAT(ES)}$ is the end-inspiratory plateau pressure and P_0 the starting pressure both measured on the oesophageal pressure.

Transpulmonary pressure is the difference between P_{AW} and $P_{ES} = P_L$. It represents the force really distending the lung parenchyma. Elastance or compliance of the lung can then be easily obtained as:

$$C_{STAT(L)} = \frac{V_T}{P_{PLAT(L)} - P_{0(L)}} \quad \text{[eqn 11]}$$

Clinical implications

The normal $C_{STAT(RS)}$ in a patient depends first on the size of the lung and, therefore, of the height of the patient (and age for children). Volumes are preferentially expressed in mL/kg of predicted body weight reflecting the height rather than the current weight of the patient [17].

Because compliance has a direct relationship with the lung volume available for ventilation, loss of lung volume (e.g. during atelectasis, pneumonia or pulmonary oedema) will cause a proportional drop in compliance. The concept of 'baby lung', introduced in

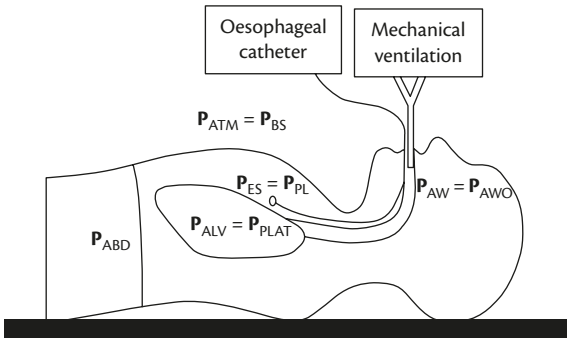


Fig. 74.5 The main different pressures involved in pulmonary mechanics. P_{ABD}, intra-abdominal pressure; P_{ATM}, atmospheric pressure; P_{ALV}, alveolar pressure; P_{AW}, airway pressure; P_{AWO}, opening airway pressure; P_{BS}, body surface pressure; P_{ES}, oesophageal pressure; P_{PL}, pleural pressure; P_{PLAT}, plateau pressure. Transpulmonary pressure (P_L) is the difference between P_{AW} and P_{ES}.

the middle of 1980s showed that, in most ARDS patients, the normally aerated tissue represents only a small proportion of the whole lung, explaining why $C_{STAT(RS)}$ is low, and C_{RS} is proportional to the size of the 'baby lung' (amount of normally aerated tissue) [18]. FRC, representing the amount of lung aerated at end expiration, is much smaller in ARDS patients than in patients with normal lungs [19]. In other words, C and E changes do reflect the amount of aerated lung volume available, which indirectly reflects the severity of the ARDS process in the whole lung. It is an important indication of the volume that can be safely delivered to the remaining lung and the risks of ventilation in terms of VALI.

In mechanically-ventilated adults in the supine position, $C_{STAT(RS)}$ is frequently lower than in erect healthy subjects, often in a range of 40–70 mL/cmH_2O. When it becomes lower than 25 mL/cmH_2O, like in severe ARDS patients, the work of breathing can be 4–6-fold increased, and the total energy dissipated becomes much greater.

The specific elastance is the ratio of elastance to FRC. The concept of specific lung elastance reflects the ratio between the transpulmonary pressure (stress) and the change in lung volume relative to its resting volume during respiration (strain). Specific lung elastance was shown to be constant among patients with ARDS and healthy subjects [20], suggesting that the measurement of FRC could be used to evaluate the change in transpulmonary pressure induced by tidal volume. Therefore, monitoring these parameters could potentially be used to better set MV and avoid VALI [3].

Conclusion

Understanding the relationship between P, V, and $\dot{V}$ as well as the concepts of R and C makes understanding of ventilation much easier, as well as the interpretation of the changes of pressure and flow traces on the ventilator screen. This knowledge helps the clinician to decide for the best treatment option.

References

1. Dreyfuss D and Saumon G. (1998). From ventilator-induced lung injury to multiple organ dysfunction? *Intensive Care Medicine*, **24**, 102–4.
2. Henderson WR and Sheel AW. (2012). Pulmonary mechanics during mechanical ventilation. *Respiratory Physiology & Neurobiology*, **180**, 162–72.
3. Brochard L, Martin GS, Blanch L, et al. (2012). Clinical review: respiratory monitoring in the ICU—a consensus of 16. *Critical Care*, **16**, 219.
4. Lyazidi A, Thille AW, Carteaux G, Galia F, Brochard L, and Richard JC. (2010). Bench test evaluation of volume delivered by modern ICU ventilators during volume-controlled ventilation. *Intensive Care Medicine*, **36**, 2074–80.
5. Bock KR, Silver P, Rom M, and Sagy M. (2000). Reduction in tracheal lumen due to endotracheal intubation and its calculated clinical significance. *Chest*, **118**, 468–72.
6. Diehl JL, Mercat A, Guerot E, et al. (2003). Helium/oxygen mixture reduces the work of breathing at the end of the weaning process in patients with severe chronic obstructive pulmonary disease. *Critical Care Medicine*, **31**, 1415–20.
7. Jubran A and Tobin MJ. (1994). Use of flow-volume curves in detecting secretions in ventilator-dependent patients. *American Journal of Respiratory and Critical Care Medicine*, **150**, 766–9.
8. Gattinoni L, Pesenti A, Caspani ML, et al. (1984). The role of total static lung compliance in the management of severe ARDS unresponsive to conventional treatment. *Intensive Care Medicine*, **10**, 121–6.
9. Murray J, Matthay M, Luce J, and Flick M. (1988). An expanded definition of the adult respiratory distress syndrome. *American Reviews of Respiratory Diseases*, **138**, 720–3.
10. Jonson B, Richard J-C, Straus C, Mancebo J, Lemaire F, and Brochard L. (1999). Pressure–volume curves and compliance in acute lung injury. Evidence of recruitment above the lower inflection point. *American Journal of Respiratory and Critical Care Medicine*, **159**, 1172–8.
11. Matamis D, Lemaire F, Harf A, Brun-Buisson C, Ansquer JC, and Atlan G. (1984). Total respiratory pressure-volume curves in the adult respiratory distress syndrome. *Chest*, **86**, 58–66.
12. Ranieri MV, Giuliani R, Fiore T, Dambrosio M, and Milic-Emili J. (1994). Volume–pressure curve of the respiratory system predicts effects of PEEP in ARDS: 'Occlusion' versus 'Constant flow' technique. *American Journal of Respiratory and Critical Care Medicine*, **149**, 19–27.
13. Decailliot F, Demoule A, Maggiore SM, Jonson B, Duvaldestin P, and Brochard L. (2006). Pressure–volume curves with and without muscle paralysis in acute respiratory distress syndrome. *Intensive Care Medicine*, **32**, 1322–8.
14. Maggiore S, Richard J, and Brochard L. (2003). What has been learnt from P/V curves in patients with acute lung injury/acute respiratory distress syndrome. *European Respiratory Journal*, **42**, 22s–6s.
15. Crotti S, Mascheroni D, Caironi P, et al. (2001). Recruitment and derecruitment during acute respiratory failure. A clinical study. *American Journal of Respiratory and Critical Care Medicine*, **164**, 131–40.
16. Akoumianaki E, Maggiore SM, Valenza F, et al. PLUG Working Group. (2014). The application of esophageal pressure measurement in patients with respiratory failure. *American Journal of Respiratory and Critical Care Medicine*. **189**, 520–31.
17. Network ARDS. (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *New England Journal of Medicine*, **342**, 1301–8.
18. Gattinoni L and Pesenti A. (2005). The concept of 'baby lung'. *Intensive Care Medicine*, **31**, 776–84.
19. Dellamonica J, Lerolle N, Sargentini C, et al. (2011). PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment. *Intensive Care Medicine*, **37**, 1595–604.
20. Chiumello D, Carlesso E, Cadringher P, et al. (2008). Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **178**, 346–55.

CHAPTER 75

Gas exchange principles in the critically ill

Peter D. Wagner

Key points

- Gas exchange is a process of molecular movement governed by the unifying principle of mass conservation applied equally to both gas uptake and elimination.
- Pulmonary gas exchange in the critically-ill patient is almost always impaired with multiple causes both internal and external to the lung.
- In a normal subject breathing sea level air at rest, the $\dot{V}A / \dot{Q}$ ratio of the lung as a whole is around 1 because total alveolar ventilation and pulmonary blood flow are about the same. In the critically ill, inequality can be very severe.
- The $\dot{V}A / \dot{Q}$ ratio uniquely determines PaO_2 and $PaCO_2$ in a given lung region, since all lung regions are subject to the same boundary conditions and O_2-Hb and CO_2 dissociation curves.
- Hypoxaemia and hypercapnia are caused by $\dot{V}A / \dot{Q}$ inequality, inspiratory hypoxia, hypoventilation, diffusion limitation, shunt, or extrapulmonary factors.

Introduction

This chapter discusses the several reasons for, and mechanisms of, abnormal gas exchange in critically-ill patients in intensive care units (ICUs). The principles underlying gas exchange have been well known since the 1950s when Rahn and Fenn [1], and Riley [2–4] and colleagues developed quantitative approaches to its understanding. While these principles apply equally to normal subjects and patients with lung disease, nowhere is their application and understanding both more difficult and also more important than in the ICU. It is well known that patients in the ICU usually endure severe lung disease, no matter what the cause of their illness, and that supportive interventions to improve gas exchange carry their own, sometimes severe, risks of further lung damage.

What follows applies only under steady-state conditions—that is, conditions in which concentrations of gases (such as O_2 and CO_2) are constant in time for at least several minutes. Rapid changes in cardiopulmonary structure or function frequently occur in the ICU, and then the steady state is disturbed, with O_2 and CO_2 concentrations rapidly changing, and the use of steady-state concepts will be in error.

Basic principle: mass conservation

Gas exchange is a process of molecular movement governed by the unifying principle of mass conservation, both when movement is by convection (ventilation and blood flow) and by diffusion (gas transfer across the alveolar-capillary blood gas barrier). It applies equally to gas uptake (e.g. O_2) and elimination (e.g. CO_2).

To best understand this, one applies conservation of mass equations, similar for O_2 and CO_2, so that illustrating the case using O_2 is here sufficient. Conservation of mass decrees that all the inhaled O_2 not exhaled on the next breath (eqn 1) is transferred into the pulmonary capillary blood (eqn 2). This transfer rate is the O_2 uptake, $\dot{V}O_2$:

$$\dot{V}O_2 = \dot{V}A[FIO_2 - FAO_2] \quad \text{[eqn 1]}$$

$$\dot{V}O_2 = \dot{Q}[CaO_2 - CvO_2] \quad \text{[eqn 2]}$$

Taking eqns 1 and 2, and rearranging gives:

$$\dot{V}A / \dot{Q} = [CaO_2 - CvO_2] / [FIO_2 - FAO_2] \quad \text{[eqn 3]}$$

$\dot{V}A$ is alveolar ventilation and $\dot{Q}$ total pulmonary blood flow; CaO_2 and CvO_2 are systemic and pulmonary arterial O_2 concentrations, respectively; FIO_2 and FAO_2 are inspired and alveolar O_2 concentrations respectively. A minor approximation appears above—inspired and expired gas volumes are taken to be the same, which is true to within about 1%.

This equation is written for the whole lung, so that CaO_2 is mixed arterial blood $[O_2]$, while FAO_2 is mixed alveolar gas O_2 fractional concentration. It applies equally to small homogeneous regions in the lung (i.e. approximately, the acinus [5], but the terminology differs:

$$\dot{V}A / \dot{Q} = [Cc'O_2 - CvO_2] / [FIO_2 - FAO_2] \quad \text{[eqn 4]}$$

where 'c', or 'end-capillary', represents $[O_2]$ in the pulmonary venule draining the homogeneous region, and FAO_2 is now the alveolar $[O_2]$ in the same region.

Eqn (4) shows that three factors determine gas exchange:

- The region's $\dot{V}A / \dot{Q}$ ratio.
- The 'boundary conditions', i.e. O_2 composition of inspired gas (FIO_2) and pulmonary arterial blood (CvO_2).
- The characteristics of the O_2-Hb dissociation curve.

The latter is involved because $Cc'O_2$ and FAO_2 are directly linked through that curve. Since by Dalton's law of partial pressures $PO_2 = FO_2 * [PB - PH_2O]$, the alveolar PO_2 (PaO_2) is also defined. Thus, there is only a single value of PaO_2 that satisfies eqn 4 for

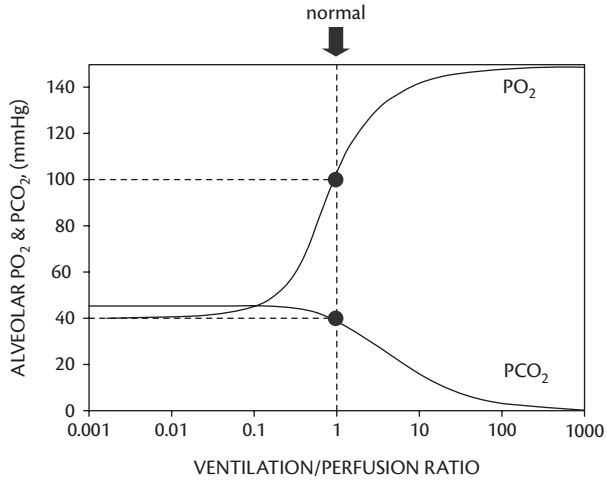


Fig. 75.1 Semi-logarithmic plot of alveolar gas PO_2 and PCO_2 as a function of the ventilation/perfusion ratio.

any set of the three groups of variables listed immediately previously. This is shown in Fig. 75.1, where the boundary conditions and O_2Hb dissociation curve are held constant (using normal values), while the $\dot{V}A / \dot{Q}$ ratio is systematically varied from zero to infinity. Fig. 75.1 also shows the results for CO_2, based on identical considerations and normal values. Eqn 4 is called the ventilation/perfusion ($\dot{V}A / \dot{Q}$) eqn for O_2. For CO_2, it is in essence identical, but because CO_2 is eliminated while O_2 is taken up, the quantities appear in reverse order to avoid negative signs:

$$\dot{V}A/\dot{Q} = [CvCO_2 - Cc'CO_2] / [FACO_2 - FICO_2] \quad \text{[eqn 5]}$$

It is also useful to write the analog of eqn 1 for CO_2, giving:

$$\dot{V}CO_2 = \dot{V}A * FACO_2 - \dot{V}I * FICO_2 \quad \text{[eqn 6]}$$

This is useful, because, disregarding inspired [CO_2] as negligible, the ratio of eqn 6 to eqn 1, gives:

$$\dot{V}CO_2 / \dot{V}O_2 = (\dot{V}A * [FACO_2]) / (\dot{V}A * [FIO_2 - FAO_2]) \quad \text{[eqn 7]}$$

or,

$$\dot{V}CO_2 / \dot{V}O_2 = R = (PACO_2) / [PIO_2 - PAO_2] \quad \text{[eqn 8]}$$

because F (fractional alveolar gas concentration) and P (alveolar partial pressure) are proportional. $\dot{V}A$ cancels out of the equation; R is the respiratory exchange ratio (the ratio of CO_2 produced to O_2 consumed). Re-arranging gives:

$$PAO_2 = PIO_2 - PACO_2 / R \quad \text{[eqn 9]}$$

This is the simple form of the alveolar gas equation. It suffices for clinical use, but if one wishes to account for $\dot{V}I$ and $\dot{V}A$ being slightly different, it becomes:

$$PAO_2 = PIO_2 - (PACO_2/R) + (PACO_2 * FIO_2 * (1-R)/R) \quad \text{[eqn 10]}$$

The alveolar gas equation defines the PaO_2 if we know $PaCO_2$, PIO_2, and R. It applies to the lung as a whole or to a small homogenous region, just like the ventilation/perfusion equation.

The most important outcome is understanding that the $\dot{V}A / \dot{Q}$ ratio uniquely determines PaO_2 and $PaCO_2$ in a given lung region (since all lung regions are subject to the same boundary conditions and O_2-Hb and CO_2 dissociation curves); see Fig. 75.1.

Ventilation/perfusion matching and gas exchange

If all lung regions had the same $\dot{V}A / \dot{Q}$ ratio, they would all have the same PaO_2 and $PaCO_2$. In a normal subject breathing sea level air at rest, the $\dot{V}A / \dot{Q}$ ratio of the lung as a whole is around 1 because total alveolar ventilation and pulmonary blood flow are about the same at 5–6 L/min. PaO_2 is ~100 mmHg, while $PaCO_2$ is ~40 mmHg (Fig. 75.1). Because all regions reach diffusion equilibrium of O_2 exchange across the blood–gas barrier at rest in health [6], end capillary PO_2 and PCO_2 would equal their alveolar counterparts in each region, and thus the systemic arterial blood would also have a PO_2 of 100 mmHg and PCO_2 of 40 mmHg. However, if regional $\dot{V}A / \dot{Q}$ ratio was lower than average. Fig. 75.1 shows PaO_2 is reduced and $PaCO_2$ increased in that region. Symmetrically, in a high $\dot{V}A / \dot{Q}$ region, PaO_2 will rise, and $PACO_2$ fall.

Using Fig. 75.1, we may consider what we call $\dot{V}A / \dot{Q}$ inequality, when not all regions have the same values of $\dot{V}A / \dot{Q}$. In the critically ill, inequality can be very severe. A simple 'two-compartment' model suffices to illustrate the principles, lung is usually far more complex. The top panel (Fig. 75.2A) shows the two-compartment model in the homogeneous state, with both ventilation ($\dot{V}A$) and blood flow ($\dot{Q}$) equally distributed. With total ventilation and perfusion each set to 6 L/min, the $\dot{V}A / \dot{Q}$ ratio is 1.0 in each compartment. From Fig. 75.1, PaO_2 is 104 mmHg and $PACO_2$ 39 mmHg in each compartment. Mixed exhaled gas will also have these partial pressures, as will the mixed pulmonary venous blood returning to the left heart, and then systemic arterial PO_2.

If the left airway is now largely partially obstructed (by mucus, bronchoconstriction, airway wall thickening, aspirated foreign object, tumour, etc.) as in the lower panel, Fig. 75.2B, $\dot{V}A$ of the obstructed compartment will be reduced (here by 90%) to 0.3 L/min. Because we wish to model only the effects of $\dot{V}A / \dot{Q}$ inequality, total ventilation, and blood flow are unchanged. Thus, the right-hand compartment now receives more ventilation than normal, here 5.7 L/min. There is, thus, one compartment with low $\dot{V}A / \dot{Q}$ ratio (0.1) and one with high $\dot{V}A / \dot{Q}$ ratio (1.9), but the total ventilation and blood flow remain normal. From Fig. 75.1, the alveolar (and end capillary) PO_2 are 45 (low $\dot{V}A / \dot{Q}$ unit) and 122 mmHg (high $\dot{V}A / \dot{Q}$ unit). PO_2 in mixed exhaled gas (PE) is the ventilation-weighted average of the two PaO_2 values. Ventilation weighting is required to ensure conservation of mass.

$$PE = [(0.3 * 45) + (5.7 * 122)] / 6.0 = 118\,\text{mmHg} \quad \text{[eqn 11]}$$

This calculation should strictly use concentration, rather than partial pressure. However, partial pressure can be used because Dalton's Law states that partial pressure and concentration are proportional.

This is 14 mmHg higher than in the homogeneous lung (Fig. 75.2A). Inspired PO_2 is about 150 mmHg and thus the inspired-exhaled PO_2 difference in the homogeneous state is 150 – 104 = 46 mmHg and after airway obstruction is 150 – 118 = 32 mmHg. If mixed exhaled gas has a higher PO_2, more O_2 is

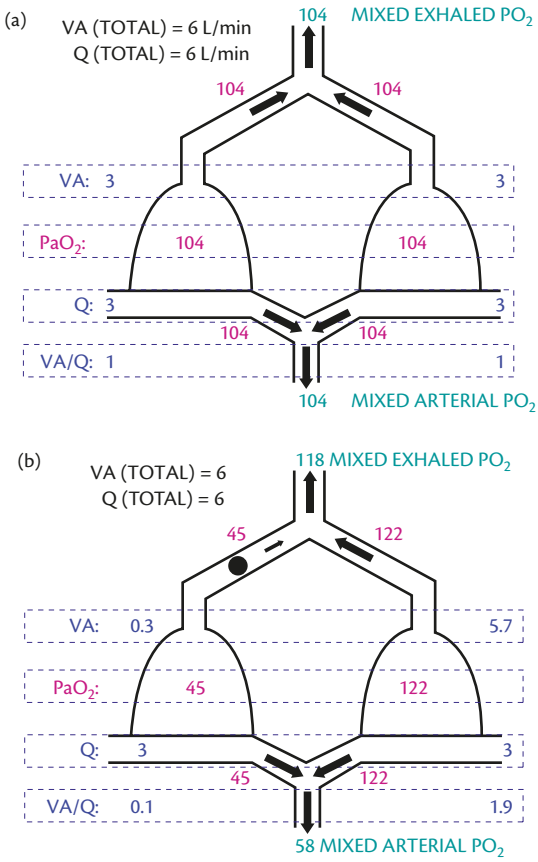


Fig. 75.2 (a) A two-compartment model of the lungs, with equally distributed ventilation and blood flow, resulting in a homogeneous lung. (b) A two-compartment model of the lungs with ventilation reduced by 90% on the left side (see text for description).

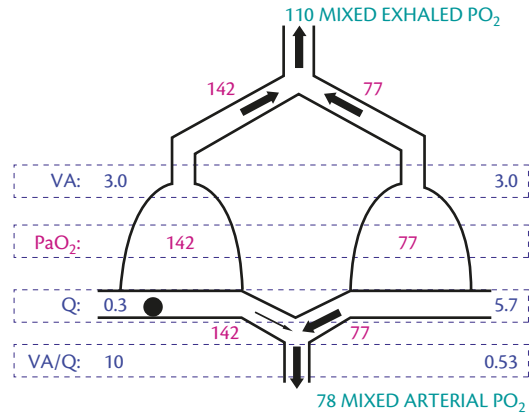


Fig. 75.3 A two-compartment model of the lungs with blood flow reduced by 90% on the left side (see text for description).

exhaled and therefore less is transferred into the blood: $\dot{V}O_2$ has fallen to 32/46 (i.e. ~70%) of that in the homogeneous lung.

PO_2 in the mixed pulmonary venous blood is calculated from the perfusion-weighted average of the two O_2 concentration values, using the O_2-Hb dissociation curve to compute the corresponding PO_2. This PO_2 is only 58 mmHg.

For CO_2, the numbers are quite different, but the outcome is qualitatively identical, but opposite: CO_2 elimination is reduced, but only by ~13%, and arterial PCO_2 rises, but by less than 1 mmHg. Indeed, the exchange of all gases is impaired by $\dot{V}A / \dot{Q}$ inequality and is manifest by a fall in arterial blood values for all gases taken up (e.g. O_2) and a rise in arterial blood values for all gases being eliminated (e.g. CO_2).

In this example, the effects are greater for O_2 than for CO_2. The same analysis obstructing the pulmonary artery of the left compartment (and restoring equal ventilation distribution) is shown in Fig. 75.3. Here, everything else is identical to that in Fig. 75.2B. The resulting compartmental ratios of $\dot{V}A / \dot{Q}$ are 10.0 and 0.53. As in the airway obstruction model, the two compartments have a below-average (right) and above-average (left) $\dot{V}A / \dot{Q}$ ratio. Reading off Fig. 75.1, PaO_2 are 142 and 77 mmHg, respectively. Mixed exhaled PO_2 is 110 mmHg (weighted mean of 142 and 77), while arterial PO_2 is 78 mmHg. $\dot{V}o_2$ is reduced, to (150–110)/(150–104), or 87% of control, while $\dot{V}co_2$ falls to 75% of control and arterial PCO_2 increases by 2 mmHg.

Thus, the two models—airway and vascular obstruction—both show impaired overall gas transfer, hypoxaemia, and hypercapnia, but airway obstruction affects O_2 transfer more than it affects CO_2, while with vascular obstruction, CO_2 transfer is more affected.

The causes of hypoxaemia and hypercapnia

There are six possible physiological causes of hypoxaemia and hypercapnia:

- $\dot{V}A / \dot{Q}$ inequality.
- Inspiratory hypoxia.
- Hypoventilation.
- Diffusion limitation.
- Shunt.
- Extra-pulmonary factors related to metabolic rate and cardiac output.

$\dot{V}/\dot{Q}$ inequality

Very important in critically-ill patients, inequality is defined as a range of $\dot{V}A / \dot{Q}$ ratios throughout the lung. In some regions, the $\dot{V}A / \dot{Q}$ ratio is low, in others normal, and in others high. This impairs overall O_2 uptake and CO_2 elimination (until compensated by increased O_2 extraction, ventilation, or cardiac output), and causes hypoxaemia and hypercapnia.

There are many reasons for $\dot{V}A / \dot{Q}$ inequality in ICU patients. They result from the pathological processes in the lung—infection, inflammation, fluid accumulation, vascular obstruction, tissue breakdown, and effects of ventilator management and other therapies. Importantly, these processes are never uniformly distributed throughout the lung. They are conveniently discussed by site of origin—airways, alveoli, blood vessels, and pleura. What follows is not exhaustive, but addresses the majority of mechanisms of inequality.

In the airways, bronchial wall thickening, mucus secretions, alveolar debris (cells, bacteria, inhaled particles, fluid) moved up the airways by ciliary function, bronchial smooth muscle contraction, and diminished parenchymal radial traction on the airway wall (the latter especially with pre-existing COPD) will each act to

reduce airway lumen size, (partially) obstructing the airway, and increasing airflow resistance. Because some regions will be more obstructed than others, more affected regions become underventilated, and a low regional $\dot{V}_A / \dot{Q}$ ratio will usually develop. With overall lung ventilation maintained, less affected regions (taking the air originally designated for the obstructed regions) are over-ventilated, raising the $\dot{V}_A / \dot{Q}$ ratio above normal, and causing hyperinflation and risk of barotrauma.

In affected alveoli, cellular debris, oedema fluid, and bacterial fragments will (partly) displace the air, diminishing their ventilation (even if the airways are normal). Alveoli completely filled with such material will not be ventilated at all, resulting in shunt. Collapsed alveoli will not receive ventilation, also resulting in shunt. Impaired surfactant activity often occurs, reducing compliance and promoting atelectasis. Interstitial oedema will also reduce compliance, and, with airways factors mentioned in the preceding paragraph, reduce regional ventilation.

Thus, a large number of specific processes all acting to impair regional ventilation may be present in the lungs of critically-ill patients, creating regions of low $\dot{V}_A / \dot{Q}$ ratio, $\dot{V}_A / \dot{Q}$ inequality and hypoxaemia. At the same time, over-ventilation of less affected regions occurs. As pathological processes continue, partial airway obstruction may become complete, converting what was $\dot{V}_A / \dot{Q}$ inequality into shunt.

Pulmonary vascular pathology may also cause $\dot{V}_A / \dot{Q}$ inequality and hypoxaemia. In the ICU, one cause is pulmonary thromboembolism. It may be classical emboli from thrombosed veins in extra-pulmonary regions of the body or local thrombosis in damaged pulmonary vessels. The resulting (partial) vascular obstruction diverts blood flow to less affected lung regions. In this manner, the affected regions develop high $\dot{V}_A / \dot{Q}$ ratios due to loss of perfusion, while the unaffected regions become over-perfused, so their $\dot{V}_A / \dot{Q}$ ratio falls.

High $\dot{V}_A / \dot{Q}$ regions may develop from mechanical ventilation with high airway pressures. This may overventilate and hyperinflate the most normal, compliant alveoli, stretching alveolar walls, compressing alveolar capillaries [7], increasing vascular resistance, reducing their perfusion and increasing the $\dot{V}_A / \dot{Q}$ ratio. At first sight, this may not seem problematic (a high $\dot{V}_A / \dot{Q}$ ratio corresponds to a high PO_2 and low PCO_2, Fig. 75.1). However, there are three major concerns:

- Risk of barotrauma from the hyperinflation.
- Poorly perfused alveoli are not effective for gas exchange, because little O_2 can be added to the blood or CO_2 removed.
- The ventilation delivered to these alveoli causes the perfused alveoli that undertake most of the gas exchange to become under-ventilated and CO_2 retention may develop.

Pleural processes that may affect gas exchange include pneumothorax and effusion, both of which promote atelectasis (and thus shunt), or pleural thickening that restricts lung inflation.

To summarize, many mechanisms may co-exist in ICU patients to produce $\dot{V}_A / \dot{Q}$ inequality. Those that primarily affect the airways, alveoli, and pleura lead mostly to regions of reduced $\dot{V}_A / \dot{Q}$ ratio, while those that primarily affect the vasculature result in regions of high $\dot{V}_A / \dot{Q}$ ratio. These different locations of effect may then result in different arterial PO_2/PCO_2 pictures, as expressed in Figs 75.2 and 75.3, gas exchange is always impaired.

Inspiratory hypoxia

Reduced inspired PO_2 (e.g. ascent to altitude, plane flight) causes arterial hypoxaemia, but in the ICU, this should not occur and will not be discussed.

Hypoventilation

Insufficient ventilation to the lungs as a whole will cause arterial PO_2 to fall and PCO_2 to rise. Fig. 75.4 (representing eqns 1 and 6) shows how sensitive PO_2 and PCO_2 are to changes in ventilation, especially when reduced. Unless by therapeutic design, overall hypoventilation is not commonly seen in ICU patients.

Diffusion limitation

An assumption of the preceding analysis has been that diffusion of O_2 and CO_2 between alveolar gas and capillary blood is complete within the transit time of a red cell through the lung capillaries, such that alveolar and end-capillary PO_2 are equal (and similarly for PCO_2). In critically-ill patients in the ICU, this assumption is known to be reasonable.

Shunt

Shunt is defined as blood flowing from the right side to the left side of the heart without any alveolar gas contact, thus affording no O_2 uptake or CO_2 elimination. Shunt pathways include direct communications between the ventricles or atria of the heart, and blood passing through completely unventilated lung regions. Common causes include atelectasis, alveolar filling with fluid or exudate, and pneumothorax. Shunting is common and often substantial in the ICU. Uncommonly, dilated pulmonary vessels may carry blood that fails to (fully) oxygenate, even when adjacent alveoli are ventilated. This may happen in chronic liver disease [8], and in infants/children suffering bronchopulmonary dysplasia.

Extrapulmonary factors

For a given metabolic rate ($\dot{V}o_2$), reduction in cardiac output will necessitate greater tissue O_2 extraction to maintain adequate O_2 supply. If cardiac output falls (in relation to $\dot{V}o_2$), PO_2 of the venous blood returning to the lungs also falls. Similarly, high cardiac output (in relation to $\dot{V}o_2$) will result in an elevated venous PO_2. As

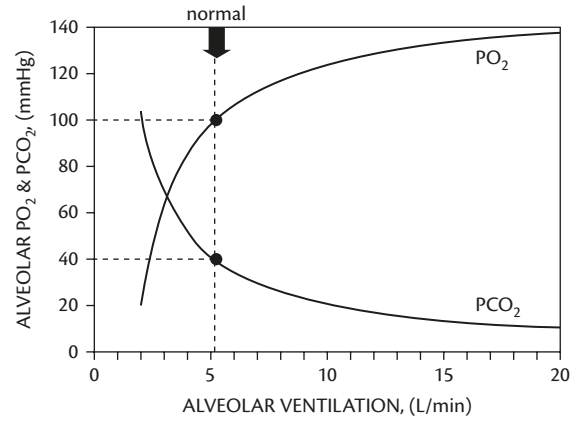


Fig. 75.4 Alveolar PO_2 and PCO_2 as a function of alveolar ventilation in a homogeneous lung. Vertical dashed line represent a normal ventilation, black dots represent the interception with PO_2 and PCO_2 curves, and vertical dashed lines indicates the corresponding pressure values on the ordinate axis.

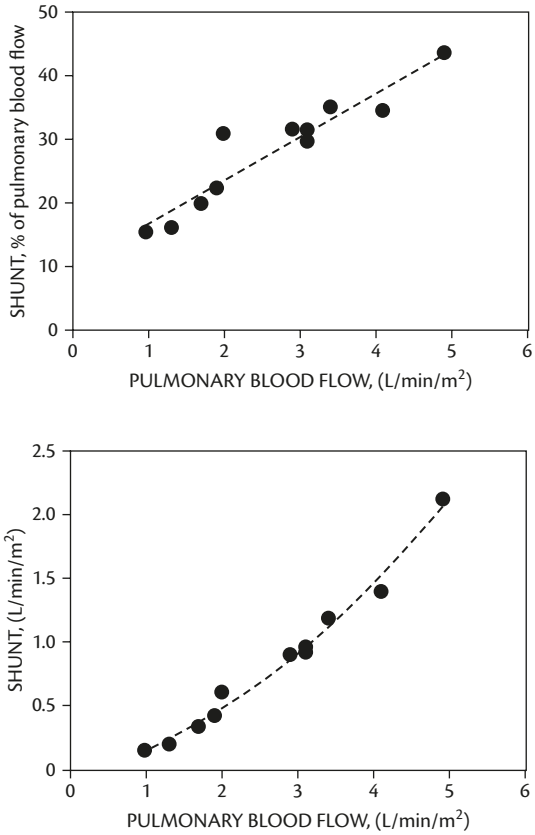


Fig. 75.5 Change in shunt fraction and flow in one ICU patient [9]. Reproduced with permission of the authors. Lemaire F, Harf A, Teisseire BP, 'Oxygen exchange across the acutely injured lung'. In: Zapol WM, Falke KJ (eds), *Acute Respiratory Failure*, New York: Dekker; 1985, p. 521–52.

the ventilation/perfusion equation shows (eqn. 4), the boundary conditions (composition of pulmonary arterial blood and inspired gas) affect the values of PO_2 and PCO_2 independently of the $\dot{V}_A / \dot{Q}$ ratio. As venous PO_2 falls, alveolar, and end-capillary PO_2 will fall at a given $\dot{V}_A / \dot{Q}$ ratio, and vice versa. In this way, extrapulmonary factors (cardiac output and $\dot{V}o_2$ especially) will affect arterial PO_2, in addition to all the preceding potential causes of hypoxaemia. Reduction in blood [Hb] has the same effect as reduction in cardiac output—greater fractional extraction of O_2 and lower venous PO_2.

The message is that when changes in metabolism, cardiac function, and/or [Hb] occur, changes in arterial oxygenation are expected that have nothing to do with lung health. Recognizing this is paramount in providing the best therapeutic response. For example, thinking a sudden fall in arterial PO_2 is due to new alveolar oedema or collapse when it is due to cardiac dysfunction may lead to poor clinical decisions.

In closing, two special cases of the role of extrapulmonary factors deserve mention—the first is dependence of shunt on total pulmonary blood flow. In patients with shunt, a change in cardiac output changes not just venous PO_2 as discussed, but also the volumetric flow distribution between the shunt channels and the rest of the lung. The reason remains unclear, but may have to do with differing degrees of hypoxic pulmonary vasoconstriction in the shunt vessels compared to the rest of the lungs. Fig. 75.5 shows an extraordinary example of this effect [9]. The implication is clear—increasing blood flow through a damaged lung has the potential of worsening the shunt, which will oppose any beneficial effect of higher blood flow on the venous PO_2.

The second example occurs when high positive airway pressure are used. This impedes venous return to the heart and cardiac output falls. As a result, even if higher airway pressure successfully re-inflates collapsed alveoli and reduces shunt, the expected benefit in arterial PO_2 may not occur, or may be lessened, because the reduced cardiac output lowers venous PO_2.

References

1. Rahn H and Fenn WO. (1955). *A graphical analysis of the respiratory gas exchange*. Washington, DC: American Physiological Society.
2. Riley RL and Cournand A. (1951). Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: theory. *Journal of Applied Physiology*, **4**, 77–101.
3. Riley RL, Cournand A, and Donald KW. (1951). Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: methods. *Journal of Applied Physiology*, **4**, 102–20.
4. Riley RL and Houston CS. (1951) Composition of alveolar air and volume of pulmonary ventilation during long exposure to high altitude. *Journal of Applied Physiology*, **3**, 526–34.
5. Young IH, Mazzone RW, and Wagner PD. (1980). Identification of functional lung unit in the dog by graded vascular embolization. *Journal of Applied Physiology*, **49**(1), 132–41.
6. Wagner PD and West JB. (1972). Effects of diffusion impairment on O2 and CO_2 time courses in pulmonary capillaries. *Journal of Applied Physiology*, **33**(1), 62–71.
7. West JB and Dollery CT. (1964). Distribution of blood flow in isolated lung: relation to vascular and alveolar pressures. *Journal of Applied Physiology*, **19**, 713–24.
8. Rodriguez-Roisin R and Krowka MJ. (2008). Hepatopulmonary syndrome—A liver-induced lung vascular disorder. *New England Journal of Medicine*, **358**(22), 2378–87.
9. Lemaire F, Harf A, and Teisseire BP. (1985). Oxygen exchange across the acutely injured lung. In: Zapol WM, Falke KJ (eds) *Acute respiratory failure*, pp. 521–2. New York: Dekker.

CHAPTER 76

Gas exchange assessment in the critically ill

Peter D. Wagner

Key points

- The cornerstone of insightful monitoring is directly sampled systemic arterial blood, but there are both more and less complex and invasive methods.
- Pulse oximetry is the least invasive measure, but limitations include poor signal and inability to track substantial change in PO_2 at higher SaO_2 (flat O_2-Hb curve).
- The PaO_2/FIO_2 ratio is used in the ICU so measurements at different FIO_2 can be compared, although it is not completely independent of FIO_2 in the critically ill.
- The alveolar-arterial PO_2 difference corrects the alveolar PO_2 for values of $PaCO_2$ different than 40 mmHg. It becomes less useful as FIO_2 is increased if $\dot{V}A/\dot{Q}$ inequality is the main problem.
- Using oximeter-tipped catheters placed in the pulmonary artery, mixed venous saturation is continuously available. A high arteriovenous difference implies high O_2 demand in relation to supply, and vice versa but correct interpretation depends on $\dot{V}o_2$ and cardiac output.

Introduction

Since most patients admitted to the intensive care unit (ICU) have damaged lungs, monitoring of gas exchange is critical to informed management. Monitoring can be descriptive (how abnormal is gas exchange?) and mechanistic (how may gas exchange reveal pathophysiological insights?)

The cornerstone of insightful monitoring is directly sampled systemic arterial blood, but there are both more and less complex and invasive methods. Usually, the more complex and invasive, the greater will be the insights gained, and vice versa. The key is to balance the complexities against the information content to select an approach that is sufficiently useful yet not overly complex.

Pulse oximetry

The simplest, least invasive approach is pulse oximetry, which measures arterial O_2 saturation (SaO_2). With immediate, continuous, low cost, non-invasive response requiring no specialty training, it is widely used to good advantage. The clinical range of use is mostly 85–100%. If SaO_2 is <85–90%, direct arterial blood sampling and urgent therapeutic responses are usually required.

Oximetry does not measure arterial PCO_2/pH and usually does not reveal mechanistic information. Moreover, as the O_2-Hb dissociation curve shifts when pH, temperature, and PCO_2 change, a given saturation may correspond to different PO_2 values.

Two major limits to pulse oximetry are:

Inadequate signal: most oximeters are lightly clamped on a finger. They are easily dislodged and require adequate digital perfusion.

The shape of the O_2-Hb dissociation curve: when arterial PO_2 lies on the flat part of the O_2-Hb curve (SaO_2 > ~95%), large changes in PO_2 may occur from significant changes in lung function without measureable differences in SaO_2.

Since the standard deviation of SaO_2 is ~2%, a true SaO_2 of 97% (normal) may read 95%, while a true value of 93% (abnormal) may also read 95%. It is thus problematic to know whether such a value represents poor lung function or random variation from normal.

Additionally, when saturation falls below ~70%, many oximeters will indicate an even lower (i.e. erroneous) value. This should not happen in the ICU, because saturations this low imply life-threateningly poor lung function, requiring placement of an arterial catheter to directly sample arterial blood.

Arterial blood gas sampling

Arterial blood sampling, via in-dwelling catheter or needle puncture, is the current backbone of ICU gas exchange assessment. Unlike oximetry, sampling is discrete, not continuous (continuously recording in-dwelling electrodes are under development). Sample volume can be less than 200 μL, enabling paediatric use. Analysis (blood gas analyser) takes only 1–2 minutes, and yields PO_2, pH, PCO_2, SaO_2 [Hb], lactate, bicarbonate, and base excess, thus evaluating acid–base state and gas exchange.

Precautions in arterial blood sampling

Several important precautions are necessary to avoid errors:

- The sample must be taken and kept without exposure to air until measured.
- The sample syringe must be free of air (bubbles). These distort the results and should be immediately expelled from the syringe.
- The syringe must be pre-heparinized to prevent clotting, which obstructs analysers and causes malfunction. Use just enough heparin to prevent coagulation without diluting the sample.
- The sample should be analysed immediately. If delay is unavoidable, keep it iced to reduce white blood cell metabolism, which will

reduce PO_2 and raise PCO_2. This is especially important when PO_2 is high, since PO_2 may otherwise fall 10–20 mmHg/min.

- Aggressively rotate the sample until the moment of analysis to avoid red cell settling causing errors in [Hb] and haematocrit.
- Document patient temperature, to understand temperature-induced shifts in the O_2-Hb dissociation curve, and to correct of PO_2, PCO_2 and pH back to body temperature (clinical analysers usually run at 37°C). Suppose a patient's temperature is 39°C. As the sample cools to 37°C in the analyser, the number of O_2 molecules per unit volume cannot change (no air contact). Thus, SaO_2 is not affected by cooling. However, the O_2-Hb curve shifts leftward, and so PO_2 falls. We usually need PO_2 at body temperature, and so temperature-correct the value accordingly, about 6% per degree Centigrade. Thus, a PO_2 of 80 mmHg would become ~90 mmHg expressed when the patient's temperature was 39°C. Directional changes are similar for PCO_2 and blood [H^+], yielding a higher PCO_2 and lower pH than indicated by the analyser. The opposite is true when the patient is below 37°C. Most analysers temperature-correct automatically.
- Document inspired [O_2] at sampling. A PO_2 of 90 mmHg, breathing room air, is interpreted very differently from the same PO_2 measured during 100% O_2 breathing.

Interpretation of blood gas variables

First, ask only how different PO_2, PCO_2, pH, SaO_2, and [Hb]/haematocrit are from normal. Two things are required—expected normal values, and analyser measurement error, to establish the 95% confidence limits (roughly, mean ± 2 SD). If the values lie outside those limits, there is at least a 95% chance that the data are abnormal. When FIO_2 is elevated, (common in the ICU), normal alveolar PO_2 expected at any FIO_2 can be estimated from the alveolar gas equation:

$$\text{Expected alveolar } PO_2 = FIO_2 * (PB - PH_2o) - PACO_2/R \quad \text{[eqn 1]}$$

FIO_2 is inspired O_2 fraction, PB is barometric pressure; PH_2O is saturated water vapour pressure (47 mmHg at 37°C); $PaCO_2$ is arterial PCO_2 and R is respiratory exchange ratio, usually assumed to be 0.8.

In sea level room air, normal alveolar PO_2 is about 100 mmHg. On 100% O_2, it rises to ~660 mmHg. The relationship is essentially linear in between. Normal arterial PO_2 should be a few mmHg lower than alveolar.

Clinical analysers commonly have a coefficient of variation for PO_2 of ~5% (thus if PO_2 = 100 mmHg, 95% confidence limits are 90–110 mmHg). If PO_2 is 500 mmHg, 95% confidence range is ~450–550 mmHg.

PCO_2 usually shows less variance; if PCO_2 = 40 mmHg, 95% confidence limits should be 38–42 mmHg, while when pH = 7.40, 95% confidence limits should be 7.38–7.42. However, ignoring the above sampling precautions will increase uncertainty.

Arterial blood gas variables can answer more than whether the results are normal or not. Well-established equations and relationships exist for quantifying gas exchange disturbances to estimate the extent of lung damage, and responses to interventions and therapies.

PaO_2/FIO_2 ratio

This simple and popular ratio [1] is used in the ICU so measurements at different FIO_2 can be compared. Since arterial PO_2 in health rises linearly with FIO_2, PaO_2/FIO_2 is somewhat constant as FIO_2 changes. This attractive concept has limitations: Fig. 76.1 shows the PaO_2 (upper panel) and PaO_2/FIO_2 ratio (lower panel) over the FIO_2 range from room air to 100% O_2 in several computational models [2] of varying gas exchange abnormality, labelled A through G.

Curve A (open squares) represents the normal lung. PaO_2 rises linearly (upper panel) and PaO_2/FIO_2 is very high and is essentially constant. However, even here, PaO_2/FIO_2 is not totally independent of FIO_2—small changes must not be over-interpreted.

Curves B, C, and D represent lungs with increasing heterogeneity of ventilation with respect to blood flow ($\dot{V}A/\dot{Q}$ inequality), quantified by the term SDQ (in effect, the standard deviation of the $\dot{V}A/\dot{Q}$ distribution). The normal range is 0.3–0.6 [3]. SDQ = 1.0 represents moderate inequality as in stable chronic lung disease; SDQ = 2.0 corresponds to a very ill ICU patient. In B, C, and D, there is zero shunt. PaO_2/FIO_2 increases considerably and non-linearly with increasing FIO_2 despite a constant amount of $\dot{V}A/\dot{Q}$ inequality. Both PaO_2/FIO_2 itself and its change with FIO_2 depend on the amount of $\dot{V}A/\dot{Q}$ inequality and the FIO_2, making PaO_2/FIO_2 somewhat difficult to interpret.

Curves E, F, and G represent lungs without $\dot{V}A/\dot{Q}$ inequality, but with shunting of 10, 20, and 30%, respectively. The behaviour

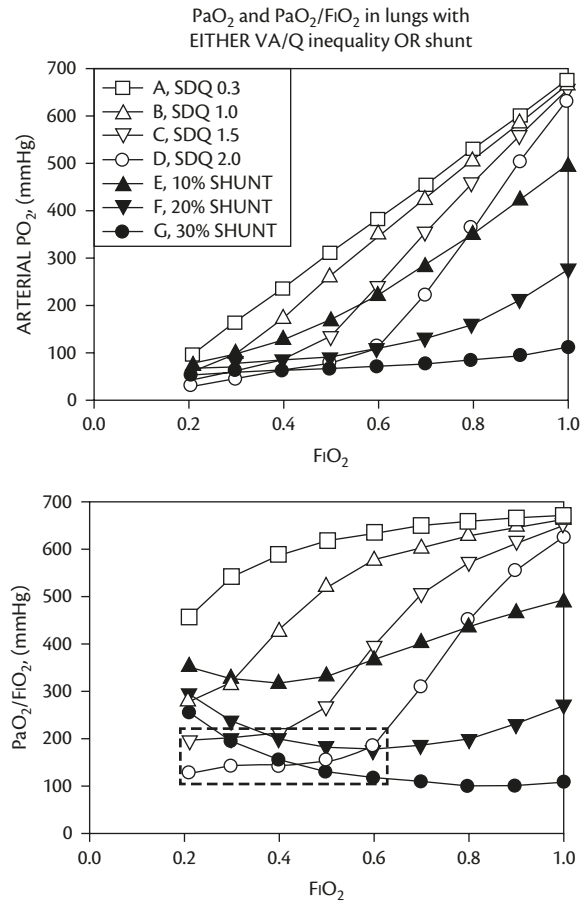


Fig. 76.1 PaO_2 and PaO_2/FIO_2 ratio change with inspired O_2 concentration between room air and 100% O_2 in normal lungs (A), in lungs with moderate to severe $\dot{V}A/\dot{Q}$ inequality (B–D) and in lungs with varying amounts of shunt (E–G) (see text for description).

of PaO_2/FIO_2 as FIO_2 is different again—the ratio first falls as FIO_2 increases, before modestly rising as FIO_2 approaches 1. Especially important is the region encompassed by the dashed-line box: over a wide FIO_2 range (room air to 0.6), PaO_2/FIO_2 is largely independent of FIO_2, but lungs with moderate to severe $\dot{V}A/\dot{Q}$ inequality and lungs with 20–30% shunt are, in practice, unable to be distinguished.

When $FIO_2 = 1$, no matter the severity of $\dot{V}A/\dot{Q}$ inequality, PaO_2/FIO_2 is very high while with shunt, the ratio falls progressively as shunt increases. Fig. 76.1 also suggests that it may be useful to assess PaO_2/FIO_2 at two different values of FIO_2. Its behaviour as FIO_2 changes allows more insight into the gas exchange defect.

The alveolar-arterial PO_2 difference: A-aPO_2

The alveolar gas equation allows calculation of alveolar PO_2, and subtracting arterial PO_2 from this yields the A-aPO_2. The advantage of A-aPO_2 is that it corrects the alveolar PO_2 for values of $PaCO_2$ different than 40 mmHg. Thus, if a patient with normal lungs, breathing room air, hypoventilates and $PaCO_2$ rises to 80 mmHg, alveolar PO_2 is 50 mmHg ($PaO_2 = 150 - 80/0.8 = 50$). If arterial PO_2 were 48 mmHg, A-a$PO_2 = 50 - 48 = 2$ (normal). This shows that the hypoxaemia is fully explained by hypoventilation, which is not evident from looking at PaO_2 alone. Had arterial PO_2 been 40 mmHg, A-aPO_2 would have been 10 mmHg, and this would have suggested the presence of significant additional gas exchange defect from shunt or $\dot{V}A/\dot{Q}$ inequality (or both).

While very useful in patients breathing room air, A-aPO_2 becomes less useful as FIO_2 is increased if $\dot{V}A/\dot{Q}$ inequality is the main problem. This is because at high FIO_2, A-aPO_2 falls, approaching zero on 100% O_2, no matter how severe the $\dot{V}A/\dot{Q}$ mismatch is. However, if A-aPO_2 on 100% O_2 is elevated, the reason has to be a shunt, and A-aPO_2 is very useful.

In between room air and 100% O_2, A-aPO_2 will change with FIO_2 in a manner specific to the nature and extent of the gas exchange disturbance, as shown in Fig. 76.2, which uses the same data as Fig. 76.1. With $\dot{V}A/\dot{Q}$ inequality (open symbols), A-aPO_2 first rises as FIO_2 is increased, and then falls, to nearly zero when 100% O_2 is breathed. The maximal A-aPO_2 and the FIO_2 at which it occurs depends on the severity of the inequality as shown. This behaviour is explained by the shape of the O_2-Hb dissociation curve.

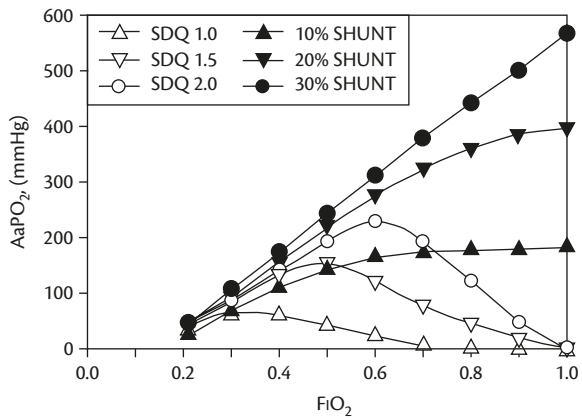


Fig. 76.2 Alveolar-arterial PO_2 difference in the same six lung models of $\dot{V}_A/\dot{Q}$ inequality and shunt as shown in Fig. 76.1.

However, when the problem is shunt, A-aPO_2 rises steadily with FIO_2 as shown.

There is an important cautionary note—Figs 76.1 and 76.2 reflect constancy of the main determining variables as FIO_2 is altered. Thus, the extent of $\dot{V}A/\dot{Q}$ heterogeneity and/or shunt, together with tidal volume and respiratory frequency, cardiac output, metabolic rate, [Hb], acid–base state, and temperature are all presumed to remain fixed. If any of these change over time, or from changing FIO_2, the data shown in these figures must change. Absorption atelectasis, release of hypoxic pulmonary vasoconstriction, and changes in cardiac output may all occur as FIO_2 is raised. Any of these may change shunt and $\dot{V}A/\dot{Q}$ inequality.

Physiological shunt: $\dot{Q}s/\dot{Q}T$

Since the 1950s [4–6], a further, simple, analysis of blood gas data has proven useful. The calculation of physiological shunt, or '$\dot{Q}s/\dot{Q}T$'. $\dot{Q}$ denotes blood flow, s denotes shunt and T denotes total. It reflects the shunt equation, based on mass conservation, applied to a lung imagined as two compartments, one having zero ventilation. The second compartment performs all gas exchange. The shunt equation is:

$$\dot{Q}T \times CaO_2 = \dot{Q}S \times CvO_2 + (\dot{Q}T - \dot{Q}S) \times Cc'O_2 \qquad \text{[eqn 2]}$$

$\dot{Q}T$ is total pulmonary blood flow and $\dot{Q}S$ is blood flow through the shunt compartment, which transmits blood unchanged (with mixed venous O_2 concentration) to the pulmonary veins. CaO_2 is systemic arterial O_2 concentration, CvO_2 is O_2 concentration in mixed venous (pulmonary arterial) blood, and $Cc'O_2$ is end-capillary O_2 concentration of the second, ventilated compartment. $Cc'O_2$ is computed from the O_2-Hb dissociation curve based on the alveolar PO_2 from the alveolar gas equation. The equation states that arterial O_2 concentration is the perfusion-weighted average of O_2 concentrations in the two compartments. After rearrangement:

$$\dot{Q}s/\dot{Q}T = [Cc'O_2 - CaO_2]/[Cc'O_2 - CvO_2] \qquad \text{[eqn 3]}$$

The equation can be used at any FIO_2. However at $FIO_2 < 1.0$, $\dot{Q}s/\dot{Q}T$ is termed 'venous admixture' or 'physiological shunt', while when $FIO_2 = 1.0$, it is regarded as 'true shunt'. This is because at $FIO_2 < 1.0$, $\dot{V}A/\dot{Q}$ inequality will contribute to $\dot{Q}s/\dot{Q}T$, while at $FIO_2 = 1.0$, $\dot{V}A/\dot{Q}$ inequality ceases to contribute and $\dot{Q}s/\dot{Q}T$ does, in fact, represent only shunt (see Figs 76.1 and 76.2).

Fig. 76.3 shows $\dot{Q}s/\dot{Q}T$ for the same data as in Figs 76.1 and 76.2. When the lung really does consist of two functional compartments—normal and shunt, as may happen in localized consolidation or atelectasis—the $\dot{Q}S/\dot{Q}T$ model accurately depicts the extent of shunt across the whole FIO_2 range. However, when there is $\dot{V}A/\dot{Q}$ inequality, rather than shunt, $\dot{Q}s/\dot{Q}T$ can be very high at low FIO_2, but eventually falls to zero on 100% O_2. Thus, the shunt equation will underestimate the true extent of $\dot{V}A/\dot{Q}$ inequality at FIO_2 above room air and may over-estimate true shunt at $FIO_2 < 1.0$.

To use the equation, CaO_2 is calculated from arterial PO_2, saturation, and [Hb], and $Cc'O_2$ is correspondingly computed from alveolar PO_2. The weakness is in CvO_2. To measure this directly requires a pulmonary artery catheter, which is often unavailable.

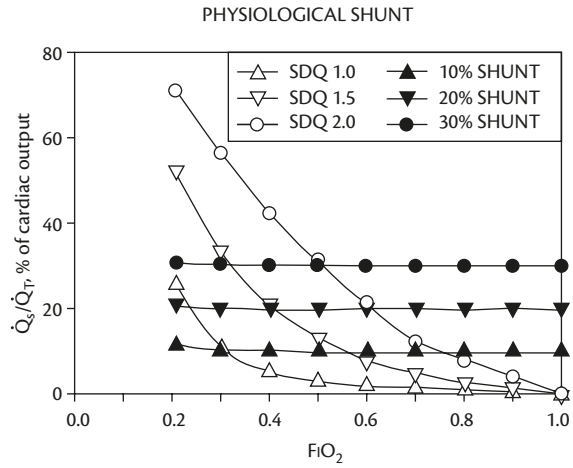


Fig. 76.3 Physiological shunt ($\dot{Q}s/\dot{Q}T$) in the same six disease models as shown in Figs 76.1 and 76.2.

Alternatively, CvO_2 can be calculated from metabolic rate ($\dot{V}o_2$) and cardiac output ($\dot{Q}T$) using the Fick principle:

$$\dot{V}O_2 = \dot{Q}T \times [CaO_2 - CvO_2] \quad \text{[eqn 4]}$$

Rearranging,

$$CvO_2 = CaO_2 - \dot{V}O_2 / \dot{Q}T, \quad \text{[eqn 5]}$$

which can be combined with eqn 3 to yield:

$$\dot{Q}s / \dot{Q}T = [Cc'O_2 - CaO_2] / [Cc'O_2 - CaO_2 + \dot{V}O_2 / \dot{Q}T] \quad \text{[eqn 6]}$$

However, if $\dot{Q}T$ and / or $\dot{V}o_2$ are not known, and must be assumed, application of the shunt equation can be considerably in error as Fig. 76.4 shows. The top panel shows how arterial PO_2 would actually vary as cardiac output (and thus CvO_2) varies for a lung with a fixed shunt that was 20% of the cardiac output, the patient always breathing 100% O_2. The fall in PaO_2 when cardiac output is low is due to the associated fall in mixed venous PO_2 required to meet the unchanged metabolic needs of the tissues, and vice versa when cardiac output is elevated. The lower panel shows the shunt calculated from the arterial PO_2 values in the upper panel if the venous O_2 concentration was assumed constant at the value actually seen when cardiac output was 6 L/min. Only at that cardiac output will the correct shunt value (20%) be obtained (dashed lines). As cardiac output drops, the calculated shunt is erroneously high; when cardiac output is elevated, the shunt is underestimated. The errors may be considerable.

Mixed venous O_2 saturation/PO_2

The preceding illustrates the risk of assuming mixed venous oxygenation when computing the shunt and a rationale for knowing the correct value. Another reason for estimating mixed venous PO_2 and/or saturation is to better understand the relationship between O_2 supply and demand. Using oximeter-tipped catheters placed in the pulmonary artery, mixed venous saturation is continuously available, and arterial saturation is also usually available. Thus, with [Hb], the arteriovenous O_2 concentration difference, CaO_2—CvO_2, becomes available. From the Fick principle in eqn 5, the arteriovenous difference is numerically equal to the ratio $\dot{V}o_2 / \dot{Q}T$, which is the ratio of whole-body O_2 demand ($\dot{V}o_2$) to supply ($\dot{Q}T$). A high arteriovenous difference implies high O_2 demand in relation to supply, and vice versa, which may be clinically useful information. This concept is, however, complicated by a major uncertainty. Suppose $\dot{V}o_2 / \dot{Q}T$ is high. Does that mean that demand is elevated or that supply is reduced? Measuring only the ratio cannot tell. We need the absolute value of either $\dot{V}o_2$ or $\dot{Q}T$ to resolve this. This is important because inappropriate therapy might otherwise be applied.

Physiological dead space, VD/VT

Just as for shunt, a two-compartment approach can estimate how much 'dead space' would have to exist to explain the mixed expired PCO_2 value. The concept is again to imagine the lungs as one normal compartment performing all gas exchange, and a second that is ventilated, but completely unperfused, and not participating in gas exchange (hence, the name 'dead space' for the ventilation associated with it). Again, we use mass conservation, applied to CO_2, as follows:

$$\dot{V}E \times PECO_2 = \dot{V}A \times PACO_2 + VD \times PICO_2 \quad \text{[eqn 7]}$$

Where $\dot{V}E$ is total minute ventilation (tidal volume ($\dot{V}T$) times breathing frequency), $\dot{V}A$ is ventilation of the normal compartment and VD is ventilation of the unperfused compartment. Note that $\dot{V}E = \dot{V}A + VD$. $PECO_2$ is the PCO_2 in the mixed exhaled gas. $PaCO_2$ is the alveolar PCO_2 of the normal compartment, and $PICO_2$ is the inspired PCO_2, since that must be the alveolar PCO_2 of the unperfused compartment. Replacing $\dot{V}A$ by $\dot{V}A - VD$, and rearranging eqn 7 yields:

$$VD / VT = [PACO_2 - PECO_2] / PACO_2 \quad \text{[eqn 8]}$$

If, as is commonly done, we substitute $PaCO_2$ (arterial PCO_2) for $PACO_2$, because the latter is actually very difficult to measure, we end up with:

$$VD / VT = [PACO_2 - PECO_2] / PACO_2 \quad \text{[eqn 9]}$$

VD/VT is the fraction of the total ventilation passing to the unperfused compartment (without gas exchange), and thus 'wasted'. It is a composite of three kinds of dead space: one is normal, and is the contribution from the conducting airway volume (from mouth to the last terminal bronchiole), called the anatomic dead space. The second is the tubing volume, if any, between a ventilated patient and the valve of the ventilator or fork in the ventilator tubing that separates inspired from expired gas. This includes the endotracheal or tracheostomy tube volume. The third is the 'alveolar dead space', which is a virtual volume of gas ventilating hypothetical alveoli that are completely unperfused. It is normally zero. Application of eqn 9 captures all three kinds inseparably as a single value, and what then has to be done is to subtract the first two kinds of dead space to arrive at the alveolar dead space, which is usually the number of interest. Tubing volume is calculated from its length and diameter. Anatomic dead space, rarely measured, is often taken as 1ml per pound (2 mL/kg), of lean body weight. It will be a little less if the pharynx is bypassed by an endotracheal or tracheostomy tube.

It is important to distinguish absolute dead space from percentage dead space. The latter is most frequently reported and, while useful, is affected directly by the tidal volume. A dead space of 200 mL with

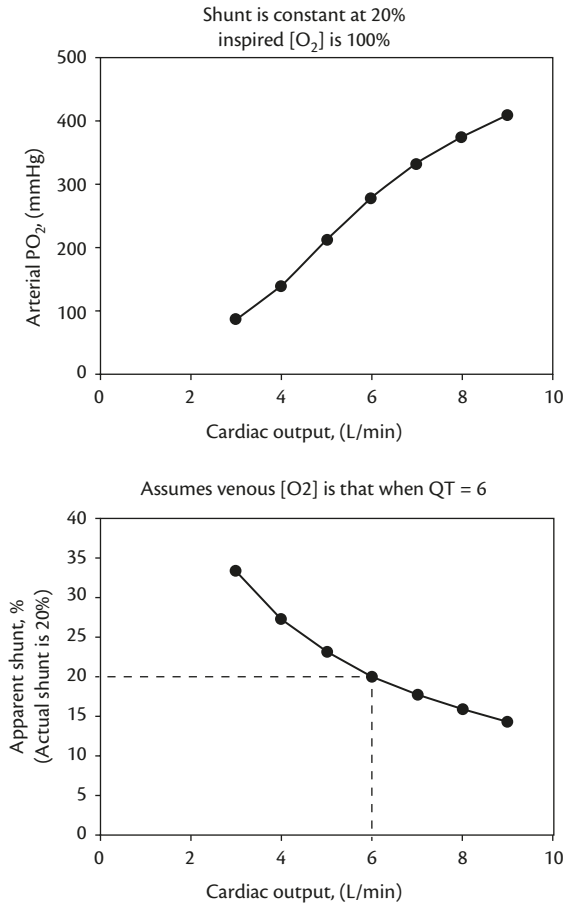


Fig. 76.4 (Upper panel) Arterial PO_2 (PaO_2) change with a fixed shunt (using an example of 20%) as cardiac output varies between 3 and 9 L/min, all other factors constant. As cardiac output falls, so too does mixed venous [O_2], which in turn explains why PaO_2 is lower. PaO_2 may be as low as 100 mmHg or as high as 400 mmHg, depending on cardiac output. (Lower panel) Figure shows how assuming a standard arteriovenous [O_2] difference (equal to that when cardiac output is 6 L/min using the same example) can cause large errors in shunt computed from the shunt equation. Only when cardiac output is 6 L/min will the equation return the correct value. There is two-fold range in apparent shunt.

500 mL tidal volume, yields 40% V_D/V_T, while the same dead space in a 1-L tidal volume reduces V_D/V_T to 20%. Therefore, reporting of alveolar dead space should also use absolute volume. In a normal lung, alveolar dead space (i.e. total, less anatomic, ventilator tubing volume) is essentially zero, but in lung disease with $\dot{V}_A / \dot{Q}$ inequality it can be substantial. In the cases presented in Figs 76.1–76.3, alveolar dead space is 17% when SDQ = 1.0, 35% when SDQ = 1.5, and 52% when SDQ = 2.0.

The popular perception is that only areas of above-normal $\dot{V}_A / \dot{Q}$ ratio contribute to alveolar dead space. However, areas of low $\dot{V}_A / \dot{Q}$ ratio and even shunt contribute to V_D/V_T when arterial PCO_2 is used as in eqn 9 because such areas not only depress arterial PO_2, they elevate arterial PCO_2.

Conclusion

In conclusion, several longstanding approaches to gas exchange allow quantification of gas exchange disturbances in the ICU. Perhaps the key point is that, for all, assumptions are made that may critically affect their interpretation and lead to erroneous therapeutic decisions. This discussion is intended to illustrate those important assumptions and thereby mitigate their consequences.

References

1. Villar J, Perez-Mendez L, Blanco J, et al. (2013). A universal definition of ARDS: the PaO2/FiO2 ratio under a standard ventilatory setting—a prospective, multicenter validation study. *Intensive Care Medicine*, **39**, 583–92.
2. West JB. (1969). Ventilation/perfusion inequality and overall gas exchange in computer models of the lung. *Respiration Physiology*, **7**, 88–110.
3. Wagner PD, Hedenstierna G, and Bylin G. (1987). Ventilation-perfusion inequality in chronic asthma. *American Reviews of Respiratory Diseases*, **136**, 605–12.
4. Riley RL and Cournand A. (1951). Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: theory. *Journal of Applied Physiology*, **4**, 77–101.
5. Riley RL, Cournand A, and Donald KW. (1951). Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: methods. *Journal of Applied Physiology*, **4**, 102–20.
6. Riley RL and Houston CS. (1951). Composition of alveolar air and volume of pulmonary ventilation during long exposure to high altitude. *Journal of Applied Physiology*, **3**, 526–34.

CHAPTER 77

Respiratory muscle function in the critically ill

Theodoros Vassilakopoulos and Charis Roussos

Key points

- The main inspiratory muscle is the diaphragm.
- Hyperinflation places the diaphragm at a great mechanical disadvantage, decreasing its force generating capacity.
- The ability to take one breath depends on the balance between the load faced by the inspiratory muscles and their neuromuscular competence, whereas the ability to breathe over time (endurance) depends on the balance between energy supplies to the inspiratory muscles and their energy demands.
- In response to acute increases in load, the inspiratory muscles develop fatigue, inflammation, and injury. In response to unloading by the use of mechanical ventilation they develop atrophy and dysfunction.
- Respiratory muscle function can be tested using the maximum static inspiratory and expiratory mouth pressures, and sniff pressure. Diaphragm function can be tested by measuring the transdiaphragmatic pressures, and the twitch pressures developed upon electrical or magnetic stimulation of the phrenic nerve.

Functional anatomy

The intercostal muscles

The intercostal muscles are two thin layers of muscle fibres occupying each of the intercostal spaces, the external being superficial to the internal [1]. The muscle fibres of the two layers run approximately at right angles to each other: The **external intercostals** extend from the tubercles of the ribs dorsally to the costochondral junctions ventrally, and their fibres are orientated obliquely, downward and forward, from the rib above to the rib below [1]. The **internal intercostals** begin posteriorly, as the posterior intercostal membrane on the inner aspect of the external intercostal muscles. From approximately the angle of the rib, the internal intercostal muscles run obliquely, upward and forward from the superior border of the rib and costal cartilage below to the floor of the subcostal groove of the rib and the edge of the costal cartilage above, ending at the sternocostal junctions [1]. All the intercostal muscles are innervated by the intercostal nerve [1].

The external intercostal muscles have an inspiratory action on the rib cage, whereas the internal intercostal muscles are expiratory, with the exemption of the parasternal intercostals, which are inspiratory [1].

The diaphragm

The floor of the thoracic cavity is closed by a thin musculotendinous sheet, the diaphragm, the most important inspiratory muscle, accounting for approximately 70% of minute ventilation in normal subjects [1]. The diaphragmatic fibres radiate from the central tendon to insert peripherally into skeletal structures. The diaphragm has two main components based on its point of origin—the crural (vertebral) part and the costal (sternocostal) part. The crural part arises from the crura (strong, tapering tendons attached vertically to the anterolateral aspects of the bodies, and intervertebral disks of the first three lumbar vertebrae on the right and two on the left) and the three aponeurotic arcuate ligaments. The costal part of the diaphragm arises from the xiphoid process, and the lower end of the sternum and the costal cartilages of the lower six ribs. These costal fibres run cranially so that they are directly apposed to the inner aspect of lower rib cage, creating a **zone of apposition** [1].

The shape of the relaxed diaphragm at the end of a normal expiration is that of two domes joined by a saddle that runs from the sternum to the anterior surface of the spinal column. The motor and proprioceptive innervation of the diaphragm is from the phrenic nerves. When tension develops within the diaphragmatic muscle fibres, a caudally-orientated force is applied on the central tendon and the dome of the diaphragm descends; this descent has two effects. First, it expands the thoracic cavity along its craniocaudal axis and, consequently, the pleural pressure falls. Secondly, it produces a caudal displacement of the abdominal visceral contents and an increase in the abdominal pressure that in turn results in an outward motion of the ventral abdominal wall. Moreover, when the diaphragm contracts, a cranially-orientated force is applied by the costal diaphragmatic fibres to the upper margins of the lower six ribs that has the effect of lifting and rotating them outward (insertional force) [1]. The actions mediated by the changes in pleural and abdominal pressures are more complex. If the diaphragm was the only muscle acting on the rib cage, it would have two opposing effects when it contracts [1]. On the upper rib cage, it causes a decrease in the anteroposterior diameter, and this expiratory action is primarily because of the fall in pleural pressure. On the lower rib cage, it causes an expansion. This inspiratory action on the lower rib cage is caused by the concomitant action of two different forces, the 'insertional' force already described and the 'appositional' force, whereby the increase in abdominal pressure expands the lower rib cage at the zone of apposition.

The abdominal muscles

The abdominal expiratory muscles constitute the ventrolateral wall of the abdomen (i.e. the rectus abdominis ventrally, and the external oblique, internal oblique, and transverses abdominis laterally). They are innervated by the lower six thoracic nerves and the first lumbar nerve [1]. As they contract, they pull the abdominal wall inward, thus increasing the intra-abdominal pressure. This causes the relaxed diaphragm to move cranially into the thoracic cavity, increasing the pleural pressure and decreasing lung volume. Expiration is usually passive, but can become active when minute ventilation has to be increased (e.g. during exercise) or during respiratory distress. Expiratory muscle action is also essential during cough.

Physiology: the ability to breathe—the load/capacity balance

For a human to take a spontaneous breath, the inspiratory muscles must generate sufficient force to overcome the elastance of the lungs and chest wall (lung and chest wall elastic loads), as well as the airway and tissue resistance (resistive load). This requires an adequate output of the centres controlling the muscles, anatomic and functional nerve integrity, unimpaired neuromuscular transmission, an intact chest wall, and adequate muscle strength [2,3]. This can be schematically represented by considering the ability to take a breath as a balance between inspiratory load and neuromuscular competence (Fig. 77.1a). Under normal conditions, this system is polarized in favour of neuromuscular competence (i.e. there are reserves that permit considerable increases in load). However, for a human to breathe spontaneously, the inspiratory muscles should be able to sustain the aforementioned load over time, as well as adjust the minute ventilation in such a way that there is adequate gas exchange. The ability of the respiratory muscles to sustain this load without the appearance of fatigue is called endurance, and is determined by the balance between energy supplies and energy demands (Fig. 77.1b).

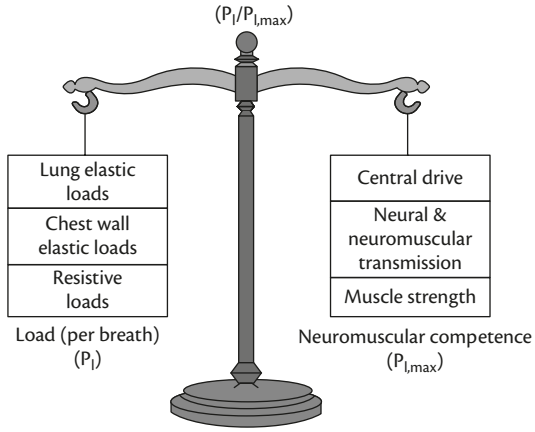


Fig. 77.1a Balance between inspiratory load and neuromuscular competence. The ability to take a spontaneous breath is determined by the balance between the load imposed on the respiratory system (pressure developed by the inspiratory muscles; P_I) and the neuromuscular competence of the ventilatory pump (maximum inspiratory pressure; $P_{I,max}$). Normally, this balance weighs in favour of competence, permitting significant increases in load. However, if the competence is, for whatever reason, reduced below a critical point (e.g. drug overdose, myasthenia gravis), the balance may then weigh in favour of load, rendering the ventilatory pump insufficient to inflate the lungs and chest wall.
Reproduced with permission of the European Respiratory Society ©. *Eur Respir J* November 1, 1996 **9**, 2383–400; doi: 10.1183/09031936.96.09112383.

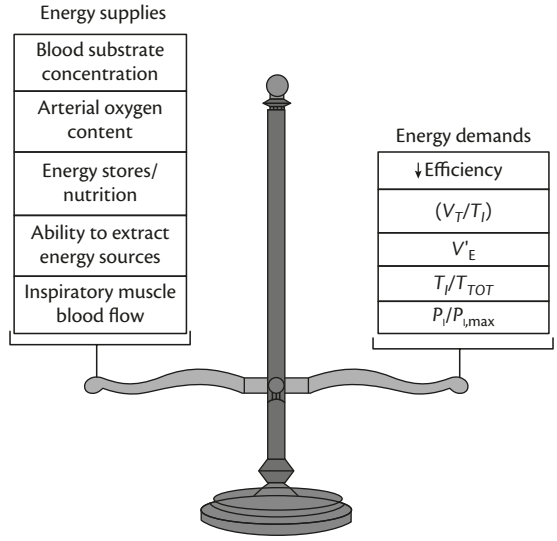


Fig. 77.1b Balance between energy supplies and energy demands. Respiratory muscle endurance is determined by the balance between energy supplies and demands. Normally, the supplies meet the demands, and a large reserve exists. Whenever this balance weighs in favour of demands, the respiratory muscles ultimately become fatigued, leading to inability to sustain spontaneous breathing. V_T/T_I, Mean inspiratory flow (tidal volume/inspiratory time); T_I/T_{TOT}, duty cycle (fraction of inspiration to total breathing cycle duration); $P_I/P_{I,max}$, inspiratory pressure/maximum inspiratory pressure ratio; V'_E, minute ventilation.
Reproduced with permission of the European Respiratory Society ©. *Eur Respir J* November 1, 1996 **9**, 2383–400; doi: 10.1183/09031936.96.09112383.

Energy supplies depend on the inspiratory muscle blood flow, the blood substrate (fuel) concentration, and arterial oxygen content, the muscle's ability to extract and use energy sources, and the muscle's energy stores [2,3]. Under normal circumstances, energy supplies are adequate to meet the demand, and a large recruitable reserve exists (see Fig. 77.1b). Energy demands increase proportionally with the mean pressure developed by the inspiratory muscles per breath (P_I) expressed as a fraction of maximum pressure that the respiratory muscles can voluntarily develop ($P_I/P_{I,max}$), the minute ventilation (V_E), the inspiratory duty cycle (T_I/T_{TOT}), and the mean inspiratory flow rate (V_T/T_I) and are inversely related to the efficiency of the muscles [2,3]. Fatigue develops when the mean rate of energy demands exceeds the mean rate of energy supply (i.e. when the balance is polarized in favour of demands) [2,3].

The product of T_I/T_{TOT} and the mean transdiaphragmatic pressure expressed as a fraction of maximal ($P_{di}/P_{di,max}$) defines a useful 'tension-time index' (TTI_{di}) that is related to the endurance time (i.e. the time that the diaphragm can sustain the load imposed on it). Whenever TTI_{di} is smaller than the critical value of 0.15, the load can be sustained indefinitely; but when TTI_{di} exceeds the critical zone of 0.15–0.18, the load can be sustained only for a limited time period—in other words, the endurance time. This was found to be inversely related to TTI_{di} [2,3]. The TTI concept is assumed to be applicable not only to the diaphragm, but also to the respiratory muscles as a whole:

$$TTI = P_I / P_{I,max} \times T_I / T_{TOT} \qquad \text{[eqn 1]}$$

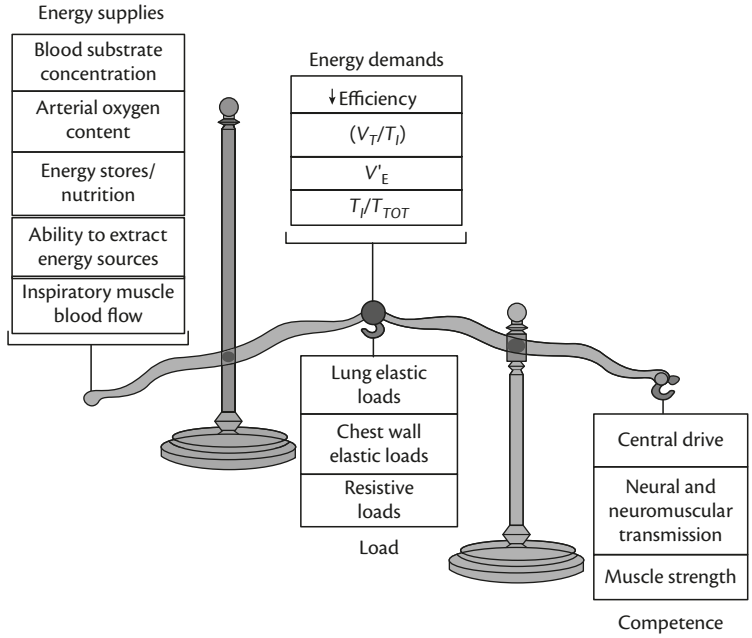


Fig. 77.1c System of two balances—load and competence, energy supplies and demands. The system of two balances, incorporating the various determinants of load, competence, energy supplies, and demands is represented schematically. The $P_I/P_{I,max}$, one of the determinants of energy demands (see Fig. 77.1a) is replaced by its equivalent—the balance between load and neuromuscular competence (see Fig. 77.1b). In fact, this is the reason the two balances are linked. When the central hinge of the system moves upward or is at least at the horizontal level, a balance exists between ventilatory needs and neurorespiratory capacity, and spontaneous ventilation can be sustained. In healthy persons, the hinge moves far upward, creating a large reserve.

Reproduced with permission of the European Respiratory Society ©. *Eur Respir J* November 1, 1996 **9**, 2383–400; doi: 10.1183/09031936.96.09112383.

Because endurance is determined by the balance between energy supply and demand, TTI of the inspiratory muscles has to be in accordance with the energy balance view [2,3]. In fact, as Fig. 77.1b demonstrates, $P_I/P_{I,max}$ and T_I/T_{TOT}, which constitute the TTI, are among the determinants of energy demands. An increase in either that will increase the TTI value, will also increase the demands, but what determines the ratio $P_I/P_{I,max}$? The numerator, the mean inspiratory pressure developed per breath, is determined by the elastic and resistive loads imposed on the inspiratory muscles. The denominator, the maximum inspiratory pressure, is determined by the neuromuscular competence (i.e. the maximum inspiratory muscle activation that can be voluntarily achieved). It follows, then, that the value of $P_I/P_{I,max}$ is determined by the balance between load and competence (see Fig. 77.1a). However, $P_I/P_{I,max}$ is also one of the determinants of energy demands (see Fig. 77.1b; therefore, the two balances (i.e. between load and competence, and energy supply and demand) are in essence linked, creating a system (Fig. 77.1c). Schematically, when the central hinge of the system moves upward, or is at least at the horizontal level, spontaneous ventilation can be sustained indefinitely. The ability of a subject to breathe spontaneously depends on the fine interplay of many different factors. Normally, this interplay moves the central hinge far upward and creates a great ventilatory reserve for the healthy individual. When the central hinge of the system, for whatever reason, moves downward, spontaneous ventilation cannot be sustained, and ventilatory failure ensues [2,3].

Hyperinflation

Hyperinflation (frequently observed in obstructive airway diseases) compromises the force-generating capacity of the diaphragm for a variety of reasons [2]: First, the respiratory muscles, like other skeletal muscles, obey the length–tension relationship. At any given level of activation, changes in muscle fibre length alter tension development. This is because the force-tension developed by a muscle depends on the interaction between actin and myosin fibrils (i.e. the number of myosin heads attaching and thus pulling the actin fibrils closer within each sarcomere). The optimal fibre length (Lo) where tension is maximal, is the length at which all myosin heads attach and pull the actin fibrils. Below this length (as with hyperinflation, which shortens the diaphragm), actin-myosin interaction becomes suboptimal, and tension development declines. Second, as lung volume increases, the zone of apposition of the diaphragm decreases in size, and a larger fraction of the rib cage becomes exposed to pleural pressure. Hence, the diaphragm's inspiratory action on the rib cage diminishes. Third, the resultant flattening of the diaphragm increases its radius of curvature (R_{di}) and, according to Laplace's law, $P_{di} = 2T_{di}/R_{di}$, diminishes its pressure-generating capacity (P_{di}) for the same tension development (T_{di}).

Respiratory muscle responses to changes in load

Acute responses to increased load

Respiratory muscle fatigue

Fatigue is defined as the loss of capacity to develop force and/or velocity in response to a load that is reversible by rest [4,5]. Fatigue should be distinguished from weakness, in which reduced force generation is fixed and not reversed by rest. Theoretically, the site of fatigue may be located anywhere in the long chain of events involved

in voluntary muscle contraction leading from the brain to the contractile machinery. A widely-used convention is to classify fatigue as central, peripheral high-frequency, or peripheral low-frequency.

Central fatigue is present when a maximal voluntary contraction generates less force than does maximal electrical stimulation [4,5].

Peripheral fatigue refers to failure at the neuromuscular junction or distal to this structure and is present when muscle force output falls in response to direct electrical stimulation [4,5]. This type of fatigue may occur because of failure of impulse propagation across the neuromuscular junction, the sarcolemma, or the T-tubules (transmission fatigue), impaired excitation–contraction coupling, or failure of the contractile apparatus of the muscle fibres. Peripheral fatigue can be further classified into **high-frequency** and **low-frequency**, on the basis of the shape of the muscle force-frequency curve. High-frequency fatigue results in depression of the forces generated by a muscle in response to high-frequency electrical stimulation (50–100 Hz), whereas low-frequency fatigue results in depression of force generation in response to low-frequency stimuli (1–20 Hz) [4,5]. **High-frequency fatigue** is attributed to transmission fatigue. Normal subjects breathing against high-intensity inspiratory resistive loads develop high-frequency fatigue, which resolves very quickly after cessation of the strenuous diaphragmatic contractions.

When the loss of force is not accompanied by a parallel decline in the electrical activity impaired excitation-contraction coupling is thought to be responsible. This type of fatigue is characterized by a selective loss of force at low frequencies of stimulation (low-frequency fatigue) and is long-lasting, taking several hours to recover [4,5].

Inflammation and injury

Strenuous diaphragmatic contractions (induced by resistive breathing, which accompanies many disease states such as chronic obstructive pulmonary disease (COPD) and asthma) initiate an up-regulation of cytokines within the diaphragm [6]. Prolonged, strenuous resistive breathing results in diaphragmatic ultrastructural injury (such as sarcomere disruption, necrotic fibres, flocculent degeneration, and influx of inflammatory cells) in both animals and humans. The mechanisms involved are not definitely established, but may involve intradiaphragmatic cytokine induction, adhesion molecule up-regulation, calpain activation, and reactive oxygen species formation [6].

Respiratory muscle response to inactivity and unloading

Respiratory muscles also adapt when they become inactive, as happens during denervation or when a mechanical ventilator undertakes their role as force generator to create the driving pressure permitting airflow into the lungs. Inactivity and unloading of the diaphragm caused by mechanical ventilation is harmful, resulting in decreased diaphragmatic force-generating capacity, diaphragmatic atrophy, and diaphragmatic injury, which are described by the term **ventilator-induced diaphragmatic dysfunction (VIDD)** [7]. The mechanisms are not fully explained, but muscle atrophy, oxidative stress, and structural injury contribute to various extents in the development of VIDD [7].

Testing respiratory muscle function

Maximal static mouth pressures

Measurement of the maximum static inspiratory ($P_{I,max}$) or expiratory ($P_{E,max}$) pressure that a subject can generate at the mouth is a simple way to estimate inspiratory and expiratory muscle strength [3,5]. These are measured at the side port of a mouthpiece that is occluded at the distal end. A small leak is incorporated to prevent glottic closure and buccal muscle use during inspiratory or expiratory manoeuvres [5]. The pressure must be maintained for at least 1.5 seconds, so that the maximum pressure sustained for 1 second can be recorded [5]. The pressure measured during these manoeuvres (P_{mo}) reflects the pressure developed by the respiratory muscles (P_{mus}), plus the passive elastic recoil pressure of the respiratory system including the lung and chest wall (P_{rs}). At functional residual capacity, P_{rs} is 0 so that P_{mo} represents P_{mus}. Normal values are available for adults, children, and the elderly. The tests are easy to perform, yet exhibit significant between- and within-subject variability, as well as learning effect. Nevertheless, a $P_{I,max}$ of –80 cmH_2O usually excludes clinically important inspiratory muscle weakness. In critically ill patients who cannot cooperate $P_{I,max}$ can be measured as the airway pressure developed after a prolonged (20 seconds) occlusion of the airway

Transdiaphragmatic pressure

When inspiratory muscle weakness is confirmed, the next diagnostic step is to unravel whether this is due to diaphragmatic weakness. This is accomplished by the measurement of maximum transdiaphragmatic pressure ($P_{di,max}$) [3,5]. $P_{di,max}$ is the difference between gastric pressure (reflecting abdominal pressure) and oesophageal pressure (reflecting intrapleural pressure) on a maximum inspiratory effort after the insertion of appropriate balloon catheters in the oesophagus and the stomach, respectively.

Sniff pressure

A sniff is a short, sharp voluntary inspiratory manoeuvre performed through one or both unoccluded nostrils [5]. It achieves rapid, fully coordinated recruitment of the diaphragm and other inspiratory muscles. The nose acts as a Starling resistor, so that nasal flow is low and largely independent of the driving pressure that is the oesophageal pressure. P_{di} measured during a sniff ($P_{di,sn,max}$) reflects diaphragm strength, and P_{es} reflects the integrated pressure of the inspiratory muscles on the lungs. Pressures measured in the mouth, nasopharynx, or one nostril give a clinically useful approximation to oesophageal pressure during sniffs without the need to insert oesophageal balloons, especially in the absence of significant obstructive airway disease. There is a wide range of normal values, reflecting the wide range of normal muscle strength in different individuals. In clinical practice, $P_{di,sn,max}$ values greater than 100 cmH_2O in males and 80 cmH_2O in females are unlikely to be associated with clinically significant diaphragm weakness. Values of maximal sniff oesophageal or nasal pressure numerically greater than 70 cmH_2O (males) or 60 cmH_2O (females) are also unlikely to be associated with significant inspiratory muscle weakness.

Electrophysiological testing

Electrophysiological testing helps determining whether weakness is due to muscle, nerve, or neuromuscular transmission impairment. This requires the measurement of P_{di} in response to bilateral supramaximal phrenic nerve electrical or magnetic stimulation, with concurrent recording of the elicited electromyogram of the diaphragm with either surface or oesophageal electrodes [3,5].

References

1. Vassilakopoulos T, Zakynthinos S, and Roussos C. (1998). Muscle function: basic concepts. In: Marini JJ and Slutsky A. (ed.) *Physiologic Basis of Ventilator Support*, pp. 103–52. New York, NY: Marcel Dekker.
2. Vassilakopoulos T, Zakynthinos S, and Roussos C. (1996). Respiratory muscles and weaning failure. *European Respiratory Journal*, **9**, 2383–400.
3. Vassilakopoulos T and Roussos C. (2006). Neuromuscular respiratory failure. In: Albert R, Slutsky A, Ranieri M, Takala J, and Torres A. (eds) *Clinical Critical Care Medicine*, pp. 275–82. St. Louis, MO: Mosby.
4. Roussos C and Zakynthinos S. (1996). Fatigue of the respiratory muscles. *Intensive Care Medicine*, **22**, 134–55.
5. ATS/ERS (2002). Statement on respiratory muscle testing. *American Journal of Respiratory and Critical Care Medicine*, **166**, 518–624.
6. Vassilakopoulos T, Roussos C, and Zakynthinos S. (2004). The immune response to resistive breathing. *European Respiratory Journal*, **24**, 1033–43.
7. Vassilakopoulos T. (2008). Ventilator-induced diaphragmatic dysfunction: the clinical relevance of animal models. *Intensive Care Medicine*, **34**, 7–16.

CHAPTER 78

Imaging the respiratory system in the critically ill

Lawrence R. Goodman

Key points

- Routine radiographs are not cost effective in the ICU setting.
- Most published guidelines agree that radiographs are worthwhile after insertion of tubes or catheters, and in patients receiving mechanical ventilation. Otherwise, they are required only for change in the patient's clinical status.
- Picture archiving and communication systems utilize digital imaging technology. They provide superior quality images, rapid image availability at multiple sites, and fewer repeat examinations, reducing both cost and patient radiation.
- Disadvantages of picture archiving and communication systems include expensive equipment and personnel required to keep them functioning.
- The majority of chest X-ray abnormalities in the ICU are best understood by paying careful attention to the initial appearance of the X-ray in relation to the patient's onset of symptoms and the progression of abnormalities over the next few days.

Introduction

In the 1960s and 1970s when intensive care units (ICUs) were novel, both clinicians and radiologists relied on the routine daily portable radiograph for patient care. As both groups gained sophistication in dealing with these critically-ill patients, and their various tubes and monitoring apparatus, many began to question the need for daily radiographs. Yet daily radiographs persist in many hospitals today despite rising concerns about radiation exposure (especially in patients under 40) and the rising costs of health care. There have been numerous studies looking at differences in outcome between daily and on-demand radiographs. Despite the wide differences in study design, patient mixes, and countries of origin, the results all point in the same direction [1–9]. Changing to on-demand radiographs decreases utilization by approximately 25–35% without measurable difference in outcome parameters (ICU or hospital mortality, length of stay, duration of mechanical ventilation, delay in addressing major unsuspected problems, etc.). Two recent meta-analyses [10,11] have confirmed these findings.

Although routine radiographs may not be rewarding, there are many scenarios where daily images are beneficial. The American College of Radiology has recently revised their guidelines for portable radiographs. Many of the recommendations are based on the articles discussed [1–11] with the ACR citing additional references where appropriate. Specifically, the ACR guidelines discuss four broad categories of clinical scenarios and present justification for their recommendations. Numerical ratings were also applied (less than 3 usually not appropriate, 4–6 may be appropriate, greater than 7 usually appropriate). These recommendations are for portable radiographs only, which produce a relatively low level of radiation (less than 0.1 mSv) [12].

- Admission or transfer to the ICU—recommendation: new patients should have an admission radiograph (rating = 7).
- Stable patients with no change in their clinical status. There is little justification in routine daily radiographs. Recommendation: radiographs should be ordered for change in clinical status only (rating = 3).
- Insertion or tube or catheter
  - Endotracheal tube—between 12–15% tubes are misplaced and malpositioning is seldom detected clinically. Recommendation: chest x-ray should be obtained immediately after intubation (rating = 9).
  - Following intravenous catheter insertion—the overall pneumothorax rate is approximately 10%. In addition, chest x-rays frequently show malpositioned catheters with subclavian vein catheters twice as likely to be malpositioned compared with jugular venous catheters. Recommendation: radiograph after central venous catheter insertion (rating = 9). Follow-up only for suspected complications only.
  - Swan-Ganz catheters—malpositioned catheters are frequent (greater than 20%) while pneumothorax is unusual (2%). Recommendation: radiograph after insertion. Once pneumothorax is excluded and proper position demonstrated, repeat for clinical indications only (rating = 9).
  - Nasogastric tube—significant malposition is uncommon (less than 1%). Recommendation: chest x-ray after initial insertion and before first feeding (rating = 9). Follow-up not required for stable position.
- Chest tube
  - At the time of initial insertion approximately 10% of chest tubes are not in "ideal" position. Many of these "malpositions" are clinically unimportant. Recommendation: chest x-ray on insertion to evaluate position, success of treatment, and complications related to intubation (rating = 9). Routine follow-up not required.

Table 78.1 Intensivist consensus on need for chest X-ray for support and monitoring catheters

Item	CXR after	(Yes)	Item	CXR after	(Yes)
1	Endotracheal intubation	✓*	12	Non-invasive ventilation with PaO_2/FIO_2 ratio of ≤200 mmHg	✓
2	Tracheostomy	✓	17	In-dwelling chest tube	✓
3	Subclavian central venous catheter	✓*	19	Invasive mechanical ventilation for ARDS	✓*
4	Internal jugular central venous catheter	✓*	20	Invasive mechanical ventilation for haemodynamic pulmonary oedema	✓
5	Pulmonary artery catheter	✓*	11	In-dwelling endotracheal tube	?
6	Transvenous pacing lead	✓*	13	Non-invasive ventilation with PaO_2/FIO_2 ratio of >200 mmHg	?
9	Ballasted NG tube	✓*	15	In-dwelling pulmonary artery catheter	?
10	Chest tube	✓*	18	In-dwelling temporary transvenous pacing lead	?
7	NG tube for enteral nutrition	?	14	NG tube for enteral feeding	0
8	Non-feeding NG tube	0	16	Superior vena cava system catheter	0

*Attitude widely accepted.

?Perhaps.

0, not indicated.

Data from Hejblum G, et al., 'A web-based Delphi study on the indications of chest radiographs for patients in ICUs', *Chest*, 2008, **133**(5), pp. 1107–12.

- Chest tube removal—pneumothorax complicates a small percentage of extubations and they are usually clinically apparent. There is seldom need for reinsertion of the tube. Recommendation: repeat chest x-ray for clinical indications only (rating = 5).

Another approach can be found in a survey of 190 intensivists from 34 ICUs (using the Delphi method) on the value of routine radiographs in 29 ICU scenarios (10 new medical devices, 10 existing medical devices and nine clinical situations) [13,14]. The clinicians' recommendations were similar to the radiologists' recommendations. A routine radiograph was considered appropriate after any tube insertion, except a nasogastric (NG) tube for reasons other than nutrition. There was strong, but not universal support for daily X-rays for patients with ARDS or oedema receiving mechanical ventilation, chest tubes, and for patients receiving non-invasive ventilation with a PaO_2/FiO_2 ratio <200 mmHg (Table 78.1).

In four clinical scenarios, there was support for daily radiographs in patients with haemodynamic instability and ventilated, invasive ventilation for status asthmaticus, mechanical ventilation for respiratory failure in the immunocompromised, and non-invasive ventilation for respiratory failure in the immunocompromised (Table 78.2).

In an accompanying editorial, Lessnau [15] correctly pointed out that within each group of catheter insertions and monitoring, there are subgroups where commonly requested radiographs may not be necessary (e.g. following uncomplicated bronchoscopically-guided percutaneous tracheostomy, etc.). He also pointed out that, in some countries such as the USA, there are conflicting financial incentives. If the hospital bills for the radiograph, demand-only X-rays will decrease revenues. If the radiograph is part of a global fee, then there is an incentive to decrease daily films. In 1998, Graham et al. [5] estimated that radiology expenses were 3.5% of overall inpatient costs. At their 1000 bed hospital in 1 year, over 69,000 portable films were obtained at a mean charge of $114.00 per examination; the portable radiograph bill was $8,000,000. In 100 patients after thoracic surgery, they estimated that over 80% of radiographs could have been eliminated, saving $286,000 ($725/patient).

Do on-demand radiographs impact ordering of higher level imaging, such as computed tomography (CT) and ultrasound (US)? Kröner et al. [16] demonstrated in two consecutive five-month periods that the number of X-rays per patient per day dropped from 1.1 to 0.6 with the elimination of routine radiographs. Length of stay and mortality rates were unchanged. During the on-demand period, the number of CTs ordered did not increase, although there

Table 78.2 Intensivist consensus on need for daily chest X-rays for specific clinical scenarios

Item	Patient with	(Yes)
22	Invasive mechanical ventilation for haemodynamic instability	✓
23	Invasive mechanical ventilation for status asthmaticus	✓*
24	Immunocompromised: invasive mechanical ventilation for acute respiratory failure	✓
25	Immunocompromised: non-invasive ventilation for acute respiratory failure	✓
21	Non-invasive ventilation for haemodynamic pulmonary oedema	?
26	Invasive mechanical ventilation for acute-on-chronic respiratory failure	?
27	Non-invasive ventilation for acute-on-chronic respiratory failure	?
28	Invasive mechanical ventilation for neurological or toxic coma, nl. respiratory function	?
29	CXR before extubation	0

*Attitude widely accepted.

?Perhaps.

0, negative.

Data from Hejblum G, et al., 'A web-based Delphi study on the indications of chest radiographs for patients in ICUs', *Chest*, 2008, **133**(5), pp. 1107–12.

was a slight increase in the number of USs. In both periods, 38% of CTs or USs resulted in a change of therapy.

Digital imaging, picture archiving, and communication systems

At major hospitals centres, digital receptors of various kinds have replaced the traditional film screen cassette, and picture archiving, and communication systems (PACS) have replaced the traditional view box. Although the initial investment is steep (but decreasing) the advantages appear overwhelming [17,18].

- Digital images are available within minutes for evaluation in radiology and the ICU. Monitors on newer portable equipment provide almost instantaneous bedside viewing for image quality and for STAT diagnosis.
- Manipulation of the digital image contrast, magnification, and varied processing algorithms enhance diagnosis (e.g. pneumothorax, catheter placement, retro cardiac disease, etc.) and diminish the number of repeats, saving money and patient radiation.
- Serial digital portable radiographs and other studies (CT, US) are easier to compare on monitors. This is critical in understanding short- and long-term trends of disease. Images can be viewed in multiple locations simultaneously.
- Digital storage eliminates lost films, and images are easily transportable (disc or electronically) to other facilities.

There are, of course, disadvantages:

- The initial cost is expensive, sophisticated IT support is required, and robust back-up systems are required.
- If not properly monitored, patient radiation can increase using digital receptors.
- Communication between radiology and the ICU often decreases.

Hains et al. [18] reviewed the 1990s literature and argued that digital imaging was a qualified success. Over the last two decades, digital imaging plates and monitors have improved, and PACS functionality, reliability, and storage capacity have improved dramatically as prices drop [17,18].

Typical ICU imaging cases

A complete review of diagnostic imaging in the ICU is beyond the scope of this chapter. Eight imaging problems frequently seen in the ICU follow. Many believe 'all portables look alike'. Although this is true to some extent, there are many clues to arriving at a more specific diagnosis or a limited list of possibilities. Perhaps the most helpful approach is by considering the time of onset of the imaging findings relative to the patient's disease or status, and the speed of progression. For example, lung contusion is usually worse within the first day, but fades within a day or two. Aspiration of acid contents is usually visible within a few hours, gets worse for a day or two, and then subsides. Heart failure can appear rapidly and disappear just as rapidly with treatment, while ARDS usually appears 1–3 days after a major insult, worsens over a few days, then plateaus, often for prolonged periods of time. Atelectasis, which is the most frequent chest X-ray abnormality in the ICU, is almost universal after surgery, whereas similar appearing consolidation from hospital acquired pneumonia usually do not appear until many days after admission [3,19].

Case 1

A patient presents with shortness of breath and dry cough over a few hours. The focal density in the right costophrenic angle (Fig. 78.1a) is non-specific, but does suggest a pulmonary infarction (Hampton's hump). CT verifies infarction due to acute pulmonary embolism (PE) in the anterior basal segment (Fig. 78.1b—arrow). Although a Hampton's Hump or wedge-shaped pleural densities are highly suggestive of a PE, they are only seen in a minority of PE patients.

Case 2

A patient presents with dyspnoea after cervical spine fracture repair. A chest X-ray (Fig. 78.2a) shows patchy extensive bibasilar infiltrates, cardiomegaly, normal vessels and endotracheal tube within 2 cm of the carina. CT shows patchy infiltrates confined to the lower lobes, worse medially than laterally (Fig. 78.2b). This is the typical X-ray appearance of aspiration pneumonitis in a post-operative patient. The posterior basal segments of the lower lobe are most frequently involved. The only likely differential diagnosis would be extensive post-operative atelectasis.

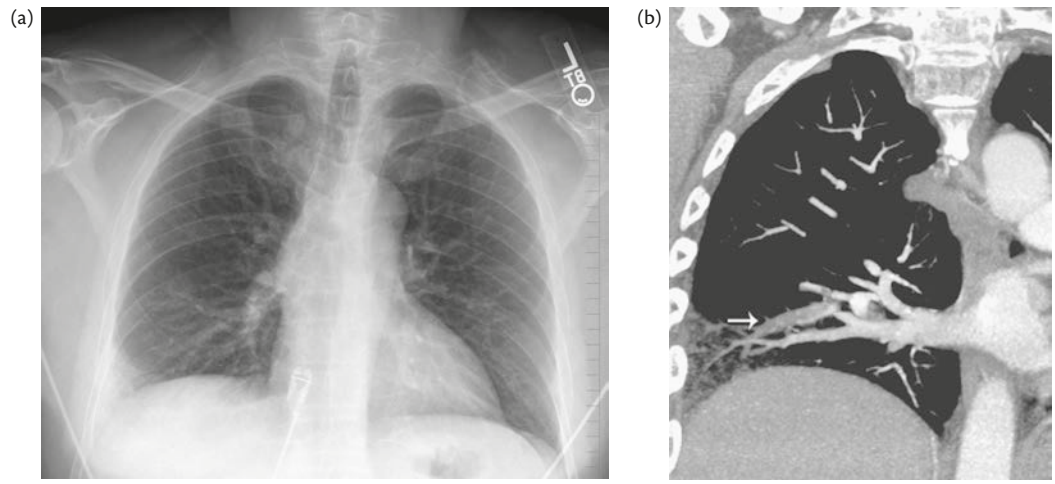


Fig. 78.1 Case 1. (a) X-ray; (b) CT scan.

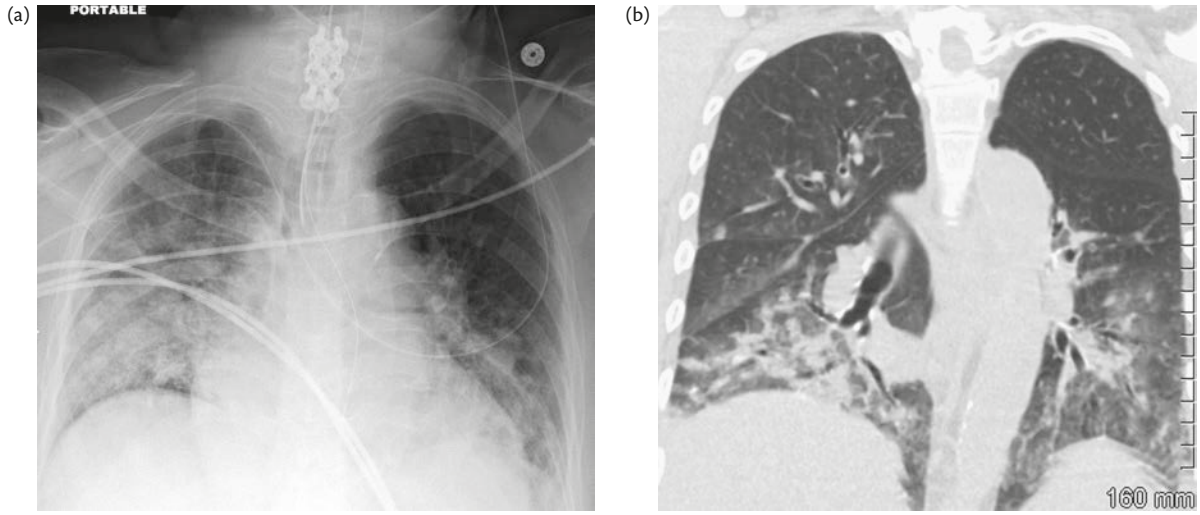


Fig. 78.2 Case 2. (a) X-ray; (b) CT scan.

Case 3

An elderly ICU patient with mild respiratory distress has a chest X-ray to rule out pulmonary embolism (Fig. 78.3a). The X-ray shows borderline enlarged heart, with large indistinct pulmonary arteries, mild peribronchial cuffing, and Kerley lines. CT shows Kerley lines laterally(arrows). The pulmonary artery is bigger than the adjacent bronchus and there is perivascular oedema (Fig. 78.3b circled). The radiographic findings of congestive heart failure (CHF) are well known. One would not order CT to diagnose CHF, but not infrequently, CT done for other reasons (e.g. PE or ARDS) reveals subtle CHF.

Case 4

A middle-aged male has a chest X-ray one day after cervical spine surgery for trauma (Fig. 78.4a). The trachea (ETT) and oesophagus (NG tube) are deviated to the left (arrow) of the spine rods. CT (Fig. 78.4b) shows seroma/haematoma deviating the trachea, the oesophagus, and the jugular vein to the left and the carotid artery to the right (surgically confirmed haematoma).

Case 5

A patient has respiratory distress one day after pancreatic surgery. A chest X-ray (Fig. 78.5a) shows total collapse of the right middle, right lower, and left lower lobes—the superior margin of the density on the right is the minor fissure. Both the right heart border and the right diaphragm are not visible (silhouette sign). Likewise, the left diaphragm is not visible. There are air bronchograms indicating patent airway (arrows). Absent air bronchograms indicate mucus plugging (Fig. 78.5b).

Case 6

A patient has fever of unknown origin several days after abdominal surgery. A chest X-ray shows vague focal densities throughout both lungs (Fig. 78.6a). CT Shows focal areas of consolidation varying from nodules to nodular cavities to focal parenchymal infiltrates (Fig. 78.6b). With septic emboli, the initial chest X-rays are often negative or vaguely positive. CT is virtually diagnostic early on with nodules, cavities and infiltrates in different stages of development.

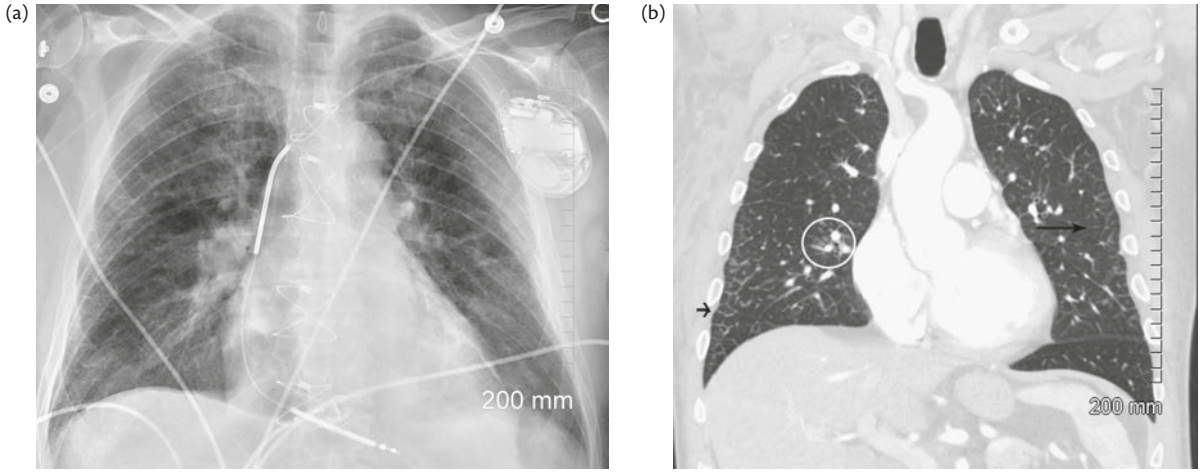


Fig. 78.3 Case 3. (a) X-ray; (b) CT scan.

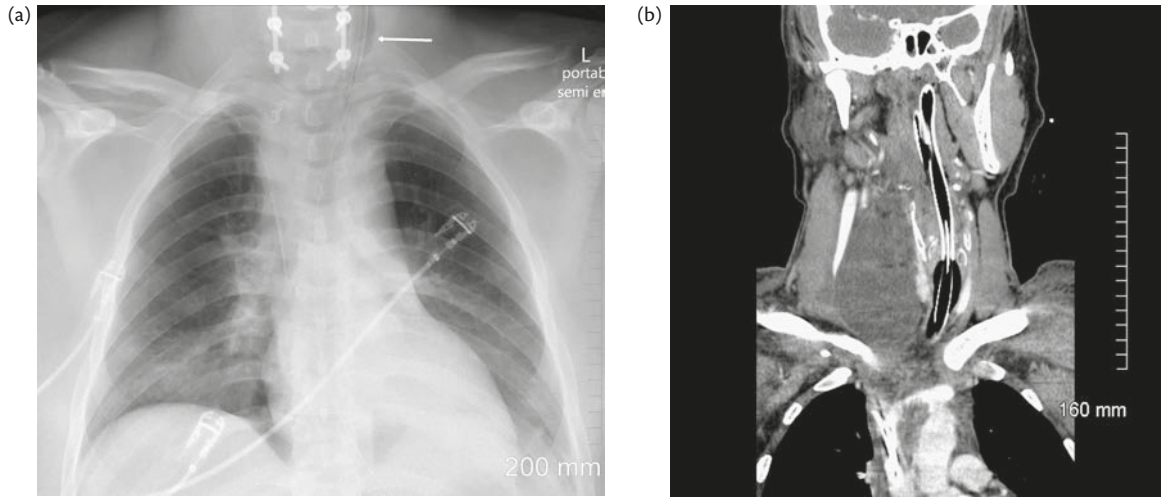


Fig. 78.4 Case 4. (a) X-ray; (b) CT scan.

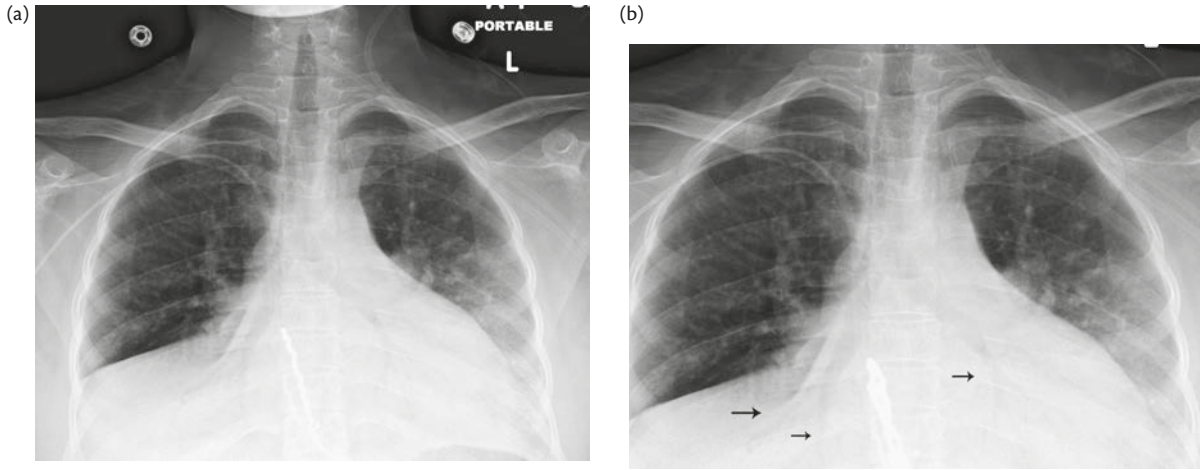


Fig. 78.5 Case 5. (a) X-ray; (b) X-ray (arrows show air bronchograms indicating patent airways).

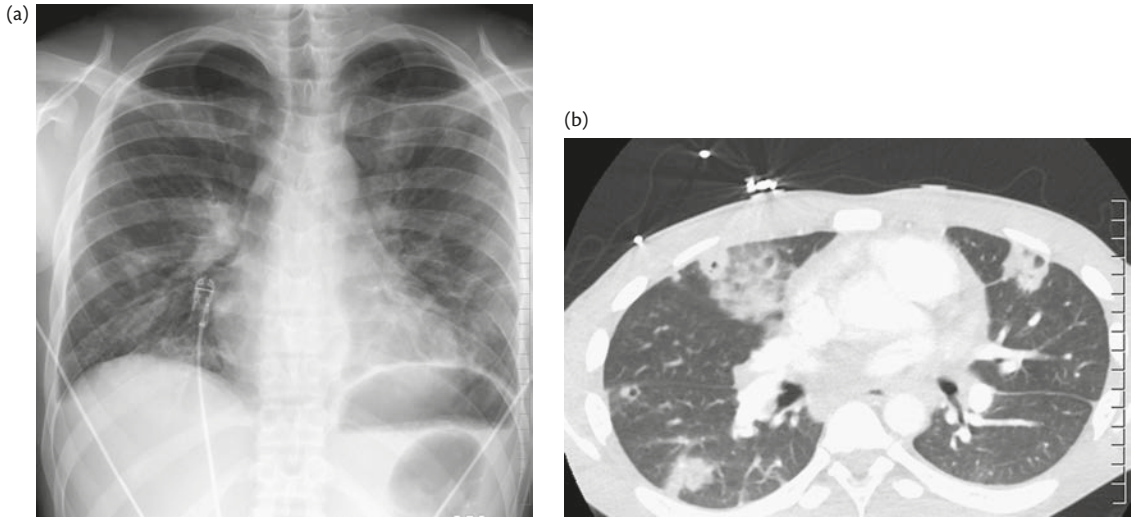


Fig. 78.6 Case 6. (a) X-ray; (b) CT scan.

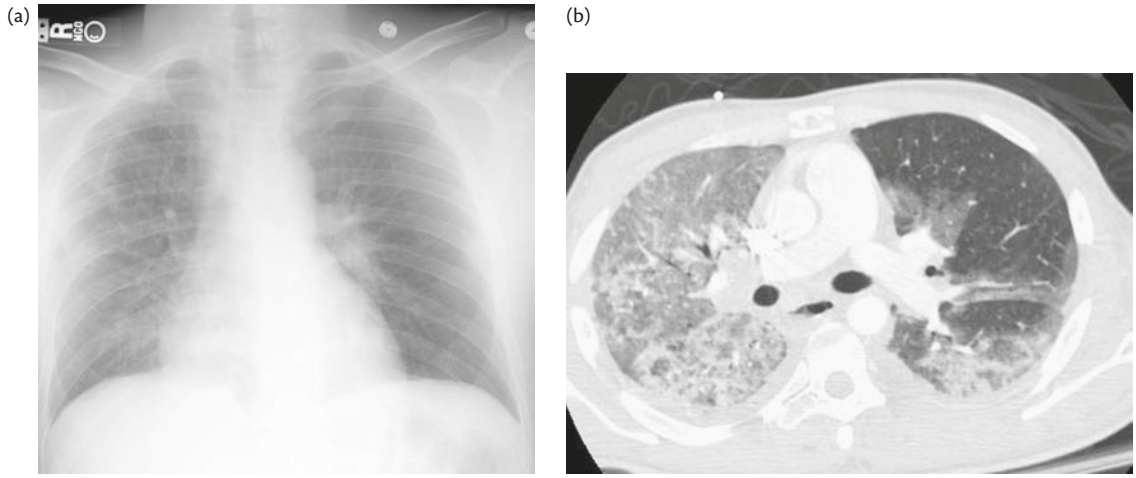


Fig. 78.7 Case 7. (a) X-ray; (b) CT scan.

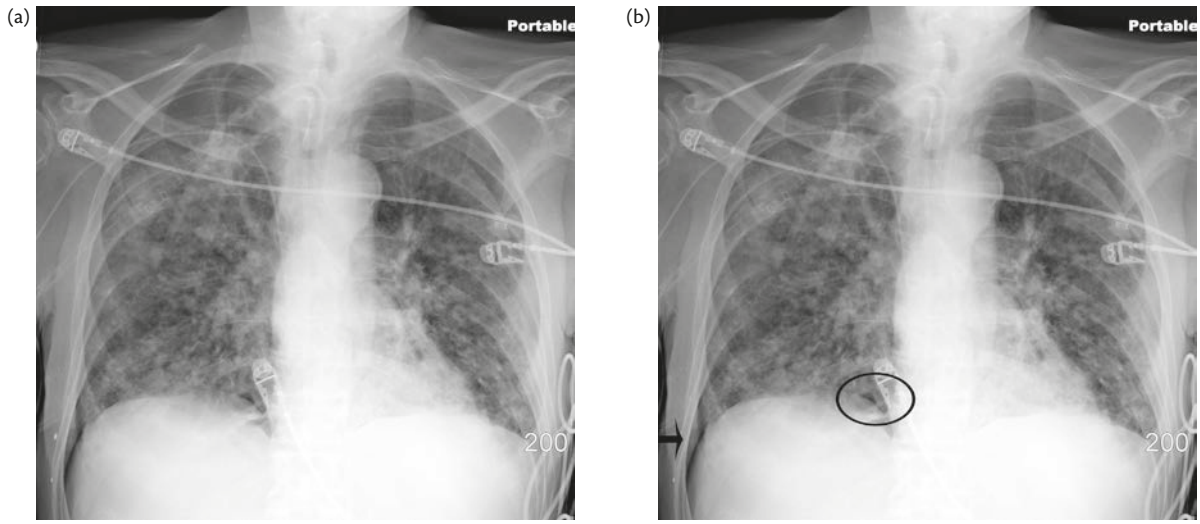


Fig. 78.8 Case 8. (a) X-ray; (b) X-ray (circle shows small amount of air medially along the diaphragm).

Case 7

A patient has shortness of breath several days after caecal perforation. A chest X-ray shows vague interstitial thickening, right greater than left (Fig. 78.7a). The pulmonary vessels and heart are not enlarged. A CT, done for possible PE, shows bilateral asymmetrical ground glass opacification, not gravity dependent (Fig. 78.7b). The pulmonary vessels are not distended and there are no Kerley lines. In this case, the oedema became symmetrical within 24 hours. Otherwise, this is the typical X-ray and CT appearance of ARDS as opposed to CHF.

Case 8

An elderly man in the ICU for 2 weeks with respiratory distress after a perforated appendix has a chest X-ray (Fig. 78.8a). This is a case of established ARDS with diffuse symmetrical patchy infiltrates changing little from day-to-day. The heart and vessels are normal. There is a lucency in the right costophrenic angle (deep sulcus sign). This indicates air in the pleural space collecting anteriorly and laterally (arrow). The deep sulcus sign is not infallible and a confirmatory upright or decubitus film is required for confirmation. A small amount of air is also seen medially along the diaphragm (Fig. 78.8b circle).

References

1. Bekemeyer WB, Crapo RO, Calhoon S, Cannon CY, and Clayton PD. (1985). Efficacy of chest radiography in a respiratory intensive care unit. A prospective study. *Chest*, **88**(5), 691–96.
2. Clec'h C, Simon P, Hamdi A, et al. (2008). Are daily routine chest radiographs useful in critically ill, mechanically ventilated patients? A randomized study. *Intensive Care Medicine*, **34**(2), 264–70.
3. Goodman LG and Putman CE. (1992). *Critical Care Imaging*. Philadelphia, PA: W.B. Saunders Company.
4. Graat ME, Kröner A, Spronk PE, et al. (2007). Elimination of daily routine chest radiographs in a mixed medical-surgical intensive care unit. *Intensive Care Medicine*, **33**(4), 639–44.
5. Graham RJ, Meziane MA, Rice TW, et al. (1998). Postoperative portable chest radiographs: Optimum use in thoracic surgery. *Journal of Thoracic and Cardiovascular Surgery*, **115**(1), 45–52.
6. Hendrikse KA, Gratama JWC., ten Hove W, Rommes JH, Schultz MJ, and Spronk PE. (2007). Low value of routine chest radiographs in a mixed medical-surgical ICU. *Chest*, **132**(3), 823–8.

7. Henschke G, Paternack GS, Schroeder S, Hart KK, and Herman PG. (1983). Bedside chest radiography: diagnostic efficacy. *Radiology*, **149**, 23–6.
8. Janower M, Jennas-Nocera Z, and Mukai J. (1984). Utility and efficacy of portable chest radiographs. *American Journal of Roentgenology*, **142**(2), 265–7.
9. Leong CS, Cascade PN, Kazerooni EA, Bolling SF, and Deeb GM. (2000). Bedside chest radiography as part of a postcardiac surgery critical care pathway: a means of decreasing utilization without adverse clinical impact. Critical Care Medicine, **28**(2), 383–8.
10. Ganapathy A, Adhikari NK, Spiegelman J, and Scales DC. (2012). Routine chest X-rays in intensive care units: a systematic review and meta-analysis. *Critical Care*, **16**(2), R68.
11. Oba Y and Zaza T. (2010). Abandoning daily routine chest radiography in the intensive care unit: meta-analysis1. *Radiology*, **255**(2), 386–95.
12. American College of Radiology. (2011). The American College of Radiology Appropriateness Criteria for Routine Chest Radiographs in ICU patients. Available at: www.ACR.org
13. Hejblum G, Chalumeau-Lemoine L, Ioos V, et al. (2009). Comparison of routine and on-demand prescription of chest radiographs in mechanically ventilated adults: a multicentre, cluster-randomised, two-period crossover study. *Lancet*, **374**(9702), 1687–93.
14. Hejblum G, Ioos V, Vibert J-F, et al. (2008). A web-based Delphi study on the indications of chest radiographs for patients in ICUs. *Chest*, **133**(5), 1107–12.
15. Lessnau K-D. (2008). From Delphi to knowledge and comfort. *Chest*, **133**(5), 1060–2.
16. Kröner A, Binnekade JM, Graat ME, et al. (2008). On-demand rather than daily-routine chest radiography prescription may change neither the number nor the impact of chest computed tomography and ultrasound studies in a multidisciplinary intensive care unit. *Anesthesiology*, **108**(1), 40–5.
17. Tan SL and Lewis RA. (2010). Picture archiving and communication systems: a multicentre survey of users experience and satisfaction. European Journal of Radiology, **75**(3), 406–10.
18. Hains IM, Georgiou A, and Westbrook JI. (2012). The impact of PACS on clinician work practices in the intensive care unit: a systematic review of the literature. *Journal of the American Medical Informatics Association*, **19**(4), 506–13.
19. Goodman LR and Putman C. (1992). *Intensive Care Radiology: Imaging of the Critically Ill. Critical Care Imaging*, 3rd edn. Philadelphia, PA: WB Saunders.

PART 4.3

Upper airway obstruction

CHAPTER 79

Upper airway obstruction in the critically ill

Edmond Cohen

Key points

- Partial upper airway obstruction (UAO) may progress to complete obstruction.
- UAO should be managed by personnel trained to manage airway crises using a supraglottic device, by performing tracheal intubation and, if necessary, by establishing a surgical airway.
- Do not burn any bridges! Sedatives, neuromuscular blocking drugs or airway manipulation may precipitate complete airway obstruction.
- Airway management devices must be immediately available **before attempting** any airway manipulation.
- UAO that develops gradually may not be obvious in a patient at rest. Sudden clinical deterioration is unpredictable. Noisy breathing is better than silence and no breathing.

Presentation

In a conscious patient, upper airway obstruction (UAO) may present as respiratory distress, stridor, dyspnoea, altered voice, cyanosis, cough, decreased or absent breath sounds, wheezing, the hand-to-the-throat choking sign in the case of a foreign body, facial swelling, and distended neck veins. Respiratory depression must be avoided to prevent cardiac arrest and anoxic brain injury. Partial airway obstruction may be mild, as in snoring or nasal congestion, or may be more severe, perhaps requiring the use of airway adjuncts. Complete UAO is usually managed by prompt intubation, but in some situations a surgical airway is life-saving [1].

Causes of upper airway obstruction

Although obstruction can occur at any level of the upper respiratory tract, laryngeal obstruction is especially important because the glottis is the narrowest portion of the upper airway (UA) [2]. UAO may be anatomical or functional, and may develop acutely or subacutely (Box 79.1).

The presence of stridor is ominous. Stridor is a noisy inspiration caused by turbulent gas flow in the UA and is common during airway obstruction [3]. Stridor indicates a serious airway emergency because it can progress rapidly to complete UAO. It is important to establish the aetiology of stridor and determine whether the obstruction can be safely treated by positive pressure mask ventilation or requires tracheal intubation.

Upper airway obstruction during anaesthesia

The induction of general anaesthesia is accompanied by a decrease in UA muscle tone and possibly even airway collapse. UAO may occur depending on the airway's calibre and shape, extraluminal tissue pressure and airway wall compliance [4]. Light sedation offers some protection against obstruction by maintaining muscle tone, whereas deep sedation is associated with muscle relaxation and lack of arousability, which may result in UAO. During anaesthesia, airway maintenance requires active intervention either by mask ventilation or tracheal intubation until the patient regains the ability to spontaneously maintain a patent airway.

Common causes of UAO during anaesthesia include:

- **Laryngospasm** following tracheal extubation due to an irritable airway (common among smokers). Initial treatment is positive pressure ventilation, but sometimes a small dose of succinylcholine (~20 mg iv) may be necessary to break the laryngospasm.
- **Residual neuromuscular block** despite the administration of reversal agents. Patients with impaired renal function require special attention because of their decreased ability to clear drugs.
- **Residual opioid medications** can cause respiratory depression and UAO in the post-anaesthesia care unit (PACU).

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) patients are at increased risk of developing UAO. Factors that act to narrow the airway and predispose to OSA are similar to those that predispose to UAO under anaesthesia [5]. These include increasing age, male gender distribution of body fat, obesity, increased neck circumference (>17 inches), macroglossia, retrognathia, and maxillary constriction [6]. Loud snoring suggests the presence of a narrow floppy airway that causes recurrent episodes of partial or complete UAO, apnoea, and hypoxaemic episodes during sleep [7].

With sleep, sedation or anaesthesia, upper airway collapsibility increases as a result of a reduction in pharyngeal dilator muscle activation, loss of the stimulatory effect of wakefulness, reduction in respiratory drive, and depression of negative pressure reflexes. In normal individuals without anatomic compromise, the upper airway is robust and patency is not significantly compromised. However, in individuals with anatomically vulnerable airways, these changes can precipitate partial or complete upper airway obstruction [8].

Box 79.1 Common causes of UAO in adult patients

Tumour

- Vocal cord tumours.
- Vocal cord paralysis.
- Laryngeal or pharyngeal tumours.
- Tracheal stenosis from intratracheal tumours.
- Tracheal stenosis from compression by extrinsic tumours.

Iatrogenic causes

- Tracheal stenosis following prolonged intubation.
- Tracheal stenosis post-tracheostomy or cricothyrotomy.
- Obstructive sleep apnoea.
- Foreign bodies.
- Tracheomalacia (functional).

Traumatic causes

- Airway burn.
- Acute laryngeal injury (post-thyroidectomy).
- Head and neck trauma.
- Haemorrhage (post-thyroidectomy)

Infections

- Retropharyngeal abscess.
- Tonsillar hypertrophy.
- Ludwig's angina.
- Epiglottitis.

Many OSA patients use a continuous positive airway pressure (CPAP) machine to maintain airway patency during sleep. CPAP titrated to the patient's need should be readily available for use in the peri-operative period. The American Society of Anesthesiologists (ASA) has published guidelines for the identification and management of patients with OSA [8].

Obesity

Obese patients often have a 'bull neck', macroglossia, and/or redundant folds of pharyngeal tissue, rendering them difficult-to-intubate and at increased risk of developing UAO. Mask ventilation may be challenging because of difficulty in maintaining a patent airway, decreased chest wall compliance, decreased FRC, and a high risk of aspiration. If tracheal intubation is not planned, a supraglottic airway device can be effective. If tracheal intubation is planned, adequate pre-oxygenation, and rapid sequence induction with cricoid pressure is recommended. If there is any concern about securing the airway safely, an awake fibre optic intubation is recommended.

Airway polyps

Polyps may occur anywhere in the upper airway and lead to partial or complete UAO. Vocal cord granulomas and polyps may result from traumatic intubation, vocal cord irritation from tracheal tube movement, or from lubricants. Patients with laryngeal papillomatosis may require frequent laser treatments to eradicate the papillomas.

Thyroid goitre

A large thyroid goitre can compress the trachea and, over time, cause tracheomalacia. A retrosternal goitre may exert pressure on the trachea causing partial airway obstruction. The CT scan should be reviewed preoperatively to assess the extent of any tracheal obstruction. If compression is severe, mask ventilation is challenging in these patients, who may progress to complete UAO. If the lesion is anterior to the trachea, the airway obstruction can worsen when the patient is placed supine for induction of general anaesthesia. In such cases, an awake fibre optic intubation would probably be best for the patient's safety. A potential complication of thyroidectomy is uni- or bi-lateral recurrent laryngeal nerve injury, which can result in uni- or bi-lateral vocal cord paralysis. Careful evaluation of the airway (vocal cord movement) following tracheal extubation is therefore crucial [9]. Finally, UAO may result from post-thyroidectomy bleeding in the PACU. If this is suspected, immediate re-opening of the surgical incision to relieve the extrinsic tracheal pressure can be life-saving.

Mediastinal masses

When a patient presents with an anterior mediastinal mass, careful evaluation of the degree of tracheal compression is critical. Some cases are associated with superior vena cava obstruction syndrome. Difficulty breathing when supine or pulmonary function tests showing an obstructive pattern, is cause for concern. Close interaction with the surgeon and review of the CT scan are essential when planning management. Anaesthesia is needed primarily for diagnostic biopsies, staging of neoplasms, and (occasionally) for relief of acute airway obstruction [10]. Use of short-acting agents, small doses of opioids, and adequate post-operative pain management should allow the patient to be tracheally extubated when fully awake. Maintaining spontaneous ventilation is preferable. A rigid bronchoscope should be immediately available in case complete airway obstruction develops. Turning the patient to the lateral position decreases pressure on the airway. If the tracheal obstruction is severe, a tracheal stent placed under sedation can provide some protection prior to the induction of general anaesthesia.

Epiglottitis

Epiglottitis can occur in adults, but is less symptomatic than in children because the adult airway is larger [11]. Management is challenging because the swollen epiglottis can act as a valve mechanism and obstruct the airway. For any surgical intervention, awake fibre optic intubation is the safest approach. These patients should not be paralysed prior to securing the airway because that would only exacerbate the degree of UAO.

Damage from endotracheal intubation

Acquired subglottic stenosis is a complication of long-term tracheal intubation. Tracheal tube complications are usually due to incorrect size, over-inflated cuff, traumatic or multiple intubations,

and movement of the tube due to inadequate analgesia and sedation. Cooper and Grillo [12] studied tracheal stenosis at the cuff site and found that the main cause was the pressure exerted by the cuff. Cuff pressures >30 mmHg (> 4 kPa) cause mucosal ischaemia by exceeding mucosal capillary perfusion pressure. The ischaemic area can develop chondritis and granulation tissue, then heal by fibrosis, leading to progressive tracheal stenosis. Most cases of post-extubation stridor resolve with appropriate medical interventions, such as racemic epinephrine or corticosteroids. Fibre optic bronchoscopy may reveal the formation of soft granulation tissue that can often be treated by the use of the CO_2 laser. In clinical practice, if a patient fails extubation for 2 weeks, an elective tracheostomy should be performed to avoid the development of tracheal stenosis.

Acquired vocal-cord paralysis or dysfunction

Vocal cord paralysis may be uni- or bi-lateral. The most common cause is damage to the recurrent laryngeal nerve (RLN) leading to transient or permanent cord paralysis. Damage to the RLN can result from a laryngeal, thyroid, or Pancoast tumour and from neck or mediastinal surgery. On spontaneous inspiration, the flaccid vocal cord becomes adducted across the midline, creating inspiratory airflow obstruction. UAO may result from vocal cord adduction during inspiration. It presents as acute attacks of dyspnoea, stridor or wheeze, and complaints about tightness at the neck. Tracheomalacia, in contrast, presents as airway obstruction during exhalation because of lack of support from the tracheal rings. Tracheomalacia is a condition in which there has been a weakening of the cartilaginous structures of the trachea [13]. Typical causes are rheumatic (polychondritis), infectious, secondary to external beam radiation, and secondary to trauma or surgery. In all these cases of UAO, the best treatment is to apply gentle positive pressure ventilation with a face mask. This may temporarily overcome the obstruction until a more definitive solution can be established.

Clinical evaluation of UAO

Airway resistance varies inversely with the fourth power of the radius at the point of UAO, and small changes in the underlying pathology may dramatically worsen respiratory airflow. Based on the patient's history and physical examination, it is useful to separate patients with potential UAO into those with severe symptoms and impending respiratory failure who require immediate intervention, from those with a more gradual course and less severe symptoms.

Plain X-ray and CT scan

Plain neck and chest films are useful screening tests that identify tracheal deviation, extrinsic compression, or presence of a foreign body. Computed tomography (CT) can be important in investigating UAO in a patient who is haemodynamically stable or in one who is unstable, but whose airway has already been secured. A CT scan focused on the airway evaluates the entire airway with thinner 'cuts'. If thicker cuts are used, one can underestimate, or miss the site of stenosis or obstruction. High-resolution CT of the neck and chest helps identify intrinsic and extrinsic tumours, vascular structures, and foreign bodies, as well as provides information on the degree and extent of airway compromise in UAO [14]. The risks and benefits of transporting such a patient to the radiology suite for examination must be carefully considered and a person qualified in airway management should accompany the patient.

Pulmonary function testing

Spirometry is useful in patients with gradual onset and mild symptoms of UAO. Flow-volume loops may identify the location and functional severity of the obstruction. Spirometry has no role in the management of a patient with acute respiratory distress [15]. The flow-volume loop shows an obstructive pattern. The flow-volume loop in a patient with fixed UAO shows flattening of the inspiratory and the expiratory phases. The test is performed with the patient upright and is repeated in the supine position to assess the degree of tracheal compression from an intrathoracic mass. The main purpose is to evaluate is the degree of airflow obstruction. It is an effort-dependent test and, therefore, requires the patient's cooperation.

Rigid and flexible bronchoscopy with direct visualization

Bronchoscopy is the primary procedure in the diagnostic work-up of tracheal stenosis and is key in defining the characteristic features, extent, and location of the stenosis. Bronchoscopy is performed with the patient awake and breathing spontaneously following adequate airway topicalization. A rigid bronchoscope should be available for emergency use to secure the airway by carefully passing it through the stenotic segment. Flexible bronchoscopy is useful to establish the diagnosis and deliver treatments including laser therapy, electrocautery, electrosurgery, balloon dilatation, and metal stenting once the airway has been secured and the patient stabilized [16]. Light sedation may be used. Dexmedetomidine infusion is useful because respiratory drive is maintained. Performing a fibre optic bronchoscopy in a conscious patient enables examination of vocal cord function and determination if RLN damage is present. It also permits the evaluation of dynamic airway collapse with respiration.

Management

In all cases of UAO, a rapid evaluation considering age group, history, physical examination, and clinical circumstances helps determine the site, cause, and the severity of the obstruction, and the urgency for establishing an airway. An actual or potential obstruction that impairs ventilation must be immediately addressed. If obstruction is near-complete, mask ventilation or a supraglottic airway device (e.g. laryngeal mask airway (LMA)) may alleviate the obstruction, otherwise prompt tracheal intubation may be life-saving. Management of UAO can be pharmacological or interventional (i.e. supraglottic device, tracheal tube, or a surgical airway).

Pharmacological management

Racemic epinephrine

Racemic epinephrine is used in patients with partial UAO who are conscious and breathe spontaneously. Racemic epinephrine administered by nebulizer is effective by inducing vasoconstriction, which

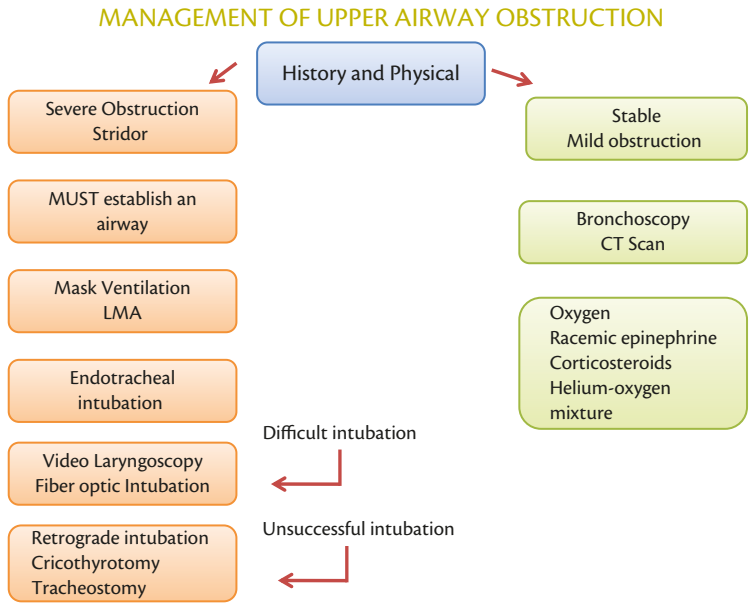


Fig. 79.1 Clinical approach to upper airway obstruction.

decreases mucosal oedema. Racemic epinephrine is also used to treat laryngeal oedema following extubation. The typical case is a patient, breathing easily for the first 2–3 hours, followed by the gradual progression of dyspnoea, inspiratory stridor, and increased respiratory effort. In this situation, racemic epinephrine can be used as a temporizing measure until the acute swelling and inflammation subside. These patients should be carefully monitored in the ICU until there is confirmation that the UAO has resolved, or at least greatly improved.

Corticosteroids

Corticosteroids, such as dexamethasone are used to treat UAO because of their effect in reducing airway oedema. Corticosteroids given at the time of tracheal extubation decrease capillary dilatation and permeability, oedema formation, and inflammatory cell infiltration. Randomized trials have confirmed the efficacy of corticosteroids in the treatment of croup, decreasing the need for intubation and hospital stay. Although the prophylactic use of steroids for post-extubation laryngeal oedema is widely accepted, one placebo-controlled, double-blind, multicentre study reported that dexamethasone does not prevent laryngeal oedema after tracheal extubation, regardless of duration of intubation [17].

Heliox

The low density of a helium–oxygen (heliox) gas mixture decreases the work of breathing by decreasing airway resistance to turbulent gas flow across the obstruction. Heliox has been useful in the treatment of post-extubation laryngeal oedema, tracheal stenosis or extrinsic compression, status asthmaticus, and angioedema [18]. Benefit is temporary because the obstruction remains until relieved. To be effective, the helium–oxygen ratio must be at least 70:30%, which limits its use in patients who cannot tolerate a low FIO_2.

Tracheal intubation and tracheostomy

In most cases of UAO, the airway can be established with tracheal intubation. If the airway is difficult, many video laryngoscopes are commercially available to facilitate the intubation, otherwise fibrescopic intubation may be necessary. If an airway cannot be established, a surgical airway via cricothyrotomy, tracheostomy, or retrograde intubation should be performed. The method of intervention should be individualized for each patient. The intervention chosen will depend on the aetiology of UAO and the urgency with which the airway must be secured.

The surgical airway-securing procedures require special expertise. Comparison of emergent versus elective tracheostomy reveals a two-fold complication rate in the former due to time spent isolating the trachea as a result of bleeding.

Laser therapy

Carbon dioxide or neodymium-doped yttrium-aluminium-garnet (Nd:YAG) laser therapy is used to treat intraluminal tracheobronchial lesions once the UAO has been stabilized and an airway secured. Although the onset of airway compromise is usually gradual, some patients remain asymptomatic despite airways that are only 2–3 mm in diameter. These patients only develop dyspnoea on exercise or when complete obstruction results from mucus, bleeding, inflammation, or swelling. It is easy to underestimate the risk of progression to a complete UAO. Laser therapy can be used to excise tracheal webs, treat benign obstructive lesions, or as palliative therapy for malignant tracheobronchial lesions [19].

Tracheal dilatation and stenting

Stents are usually placed following dilatation and maintain airway patency in patients with tracheal obstruction from benign or malignant conditions. A stent supports the airway wall against collapse or external compression, and impedes extension of tumour into the airway lumen. Rigid bronchoscopy is used to place a silicone stent or a flexible bronchoscope to deploy a metal stent. They are used either in the preparation for a more definitive resection procedure or palliative to alleviate the tracheal compression. If an intraluminal tumour is significant enough to cause UAO, it can be managed with laser therapy, photodynamic therapy, brachytherapy, or electrocautery.

The management of UAO is summarized in Fig. 79.1. Whatever the aetiology, a patient with UAO must be carefully monitored in an intensive care unit for impending respiratory failure [20].

References

1. Hagberg C, Georgi R, Krier C, et al. (2005). Complications of managing the airway. *Best Practice & Research Clinical Anaesthesiology*, **19**, 641–59.
2. Dickison AE. (1987). The normal and abnormal pediatric upper airway. Recognition and management of obstruction. *Clinical Chest Medicine*, **5**, 83–96.
3. Renz V, Hern J, Tostevin P, Hung T, and Wyatt M. (2000). Functional laryngeal dyskinesia: an important cause of stridor. *Journal of Laryngology & Otology*, **114**, 790–2.
4. Eastwood PR, Szollosi I, Platt PR, et al. (2002). Collapsibility of the upper airway during anesthesia with isoflurane. *Anesthesiology*, **97**, 786–93.
5. Malhotra A, Huang Y, Fogel R, et al. (2006). Aging influences on pharyngeal anatomy and physiology: the predisposition to pharyngeal collapse. *American Journal of Medicine*, **119**, 9–14.
6. Young T, Peppard PE, and Taheri S. (2005). Excess weight and sleep disordered breathing. *Journal of Applied Physiology*, **99**, 1592–9.
7. Hillman DR, Platt PR, and Eastwood RP. (2010). Anesthesia, sleep, and upper airway collapsibility. *Anesthesiology Clinics*, **28**(3), 443–55.
8. Gross JB, Bachenberg KL, and Benumof JL. (2006). American Society of Anesthesiologists Task Force on perioperative management of patients with obstructive sleep apnea: practice guidelines for the perioperative management of patients with obstructive sleep apnea. *Anesthesiology*, **104**, 1081–91.
9. Graham, GW, Unger, BP, and Coursin DB. (2000). Perioperative management of selected endocrine disorders. *International Anesthesiology Clinics*, **38**(4), pp. 31–67.
10. Conacher ID. (2003). Anaesthesia and tracheobronchial stenting for central airway obstruction in adults. *British Journal of Anaesthesia*, **90**, 367–74.
11. Ames WA, Ward VM, Tranter RM, and Street M. (2000). Adult epiglottitis: an under-recognized, life-threatening condition. *British Journal of Anaesthesia*, **85**, 795–7.
12. Cooper JD and Grillo HC. (1969). The evolution of tracheal injury due to ventilatory assistance through cuffed tubes: a pathologic study. *Annals of Surgery*, **169**, 334–48.
13. Cansiz H, Yener M, Tahamiler R, et al. (2008). Preoperative detection and management of tracheomalacia in advanced laryngotracheal stenosis. *B-ENT* **4**, 163–7.
14. Boiselle PM and Ernst A.(2002). Recent advances in central airway imaging. *Chest*, **121**, 1651–60.
15. Culver BH. (2004). Pulmonary function and exercise testing. In: Albert RK, Spiro SG, and Jett JR (eds) *Clinical Respiratory Medicine*, 2nd edn, pp. 117–28. Philadelphia, PA: Elsevier Saunders.
16. Shapshay SM and, Valdez TA. (2001). Bronchoscopic management of benign stenosis. *Chest Surgery Clinics of North America*, **11**, 749–68.
17. Klassen TP, Craig WR, Moher D, et al. (1998). Nebulized budesonide and oral dexamethasone for treatment of croup: a randomized controlled trial. *Journal of the American Medical Association*, **279**,7 1629–32.
18. Boorstein JM, Boorstein SM, Humphries GN, et al. (1989). Using helium–oxygen mixtures in the emergency management of acute upper airway obstruction. *Annals of Emergency Medicine*, **18**, 688–90.
19. Bolliger CT, Sutedja TG, Strausz J, et al. (2006). Therapeutic bronchoscopy with immediate effect: laser, electrocautery, argon plasma coagulation and stents [comment]. *European Respiratory Journal*, **27**, 1258–71.
20. Wood DE, Liu YH, Vallieres E, et al. (2003). Airway stenting for malignant and benign tracheobronchial stenosis. *Annals of Thoracic Surgery*, **76**, 167–74.

PART 4.4

Airway access

CHAPTER 80

Standard intubation in the ICU

Sebastian G. Russo and Michael Quintel

Key points

- Preparation and planning are essential for tracheal intubation in the intensive care unit (ICU).
- During standard intubation in the ICU administration of neuromuscular blocking agents should be part of the routine.
- In case of an unexpected difficult airway, the number of intubation attempts should be limited to two and an alternative approach to maintain oxygenation and ventilation, such as extraglottic airway (EGA) devices, needs to be chosen.
- Whenever ventilator support is required, the use of capnography is mandatory to evaluate ventilation and to confirm clear airways.
- The intubating laryngeal mask airway (ILMA) is a useful back-up tool for both ventilation and intubation if tracheal tube placement fails.

Introduction

Airway access or control of the airways to maintain vital oxygenation and ventilation can be assured by different measures—face mask ventilation (FMV), extraglottic airway devices (EGA), endotracheal (ET) tubes, as well as tracheal access via a cricothyrotomy or tracheostomy. This chapter argues with the standard ET placement.

Tracheal intubation in the ICU

Wherever patients require some kind of oxygen administration, the establishment and maintenance of clear airways is the most important task for the caregiver, as without sufficient oxygen supply all other measures remain useless.

For elective conditions direct laryngoscopy is associated with a reassuring high percentage of good views on the laryngeal structures (Cormack & Lehane Score of 1 and 2), as well high success rate for tracheal intubation [1]. However, for the intensive care unit (ICU), several authors have indicated that airway management and tracheal tube placement while in the ICU is remarkably more challenging compared with the operating theatre [2,3]. Heuer et al. reported an incidence of difficult intubation of up to 25%, even if performed by anaesthesiologist [4].

Additionally, intensive care patients are critical ill, have reduced respiratory and haemodynamic capacities, and the circumstances and motives for tracheal intubation are awkward (Box 80.1). Thus, the time until desaturation is significantly shorter and the effects of insufficient oxygenation are more damaging. This is also mirrored by the results presented in the fourth National Audit Project in UK [5]. The outcome of failures during airway management in the ICU were particular adverse, with a high percentage of death or brain damage. Therefore, similar to the prehospital setting, even standard ET placement in the ICU should always considered to be significantly more difficult compared with elective airway management in the operation theatre (see Table 80.1).

Cook et al. have identified several factors contributing to unsuccessful airway management—poor identification of patients at risk, incomplete planning, inadequate provision of skilled staff and equipment, delayed recognition of events, and failed rescue due to lack of or failure of interpretation of capnography. Remarkable, even experienced anaesthetists tend to underestimate the level of complexity, while overestimating their own skills [4]. Therefore, it seems to be useful to define a standard procedure for tracheal intubation in the intensive care unit.

Standard intubation

Preparation

Prior to commencement, it is the health care provider's responsibility to check for the completeness and functionality of the equipment (see Box 80.2). It is essential that the entire equipment is **on scene** and not just **somewhere** in the ICU. Perfect access to the patient is crucial before attempting tracheal intubation. Therefore, whenever possible the strategic and logistical conditions should be optimized.

Whenever possible pre-oxygenation should be performed prior to the induction of anaesthesia. As shown by McGowan and Skinner a tight facemask seal is essential to apply high inspiratory oxygen concentrations [6]. In obese patients or in patients with decreased functional residual capacity, pre-oxygenation in the semi-recumbent position, as well as application of a positive end-expiratory pressure (PEEP) increases the interval to desaturation during apnoea significantly. Furthermore, non-invasive ventilation has been shown to be helpful in increasing the efficiency

Box 80.1 Circumstances for oro-tracheal tube placement in the intensive care unit

- Usually emergency indication to intubate.
- Keeping the patient on spontaneous breathing is usually not an option.
- Extraglottic airway devices as a long-term option most likely not appropriate.

Table 80.1 Reasons why to consider standard oro-tracheal tube placement in the intensive care unit to be difficult

Patient	Logistic
Secretions, blood, oedema	Difficult access to the head
Lung injury with reduced pulmonary reserves	Limited airway management devices
Concomitant haemodynamic instability	Potentially absent of capnography
	Limited access to further expertise

of pre-oxygenation and represents an elegant method of increasing patient safety in the ICU setting [7].

Induction of anaesthesia

In contrast to the most prevalent opinion that length of ICU stay or the fluid balance might influence the occurrence of a difficult intubation, Heuer et al. have shown that some of the main factors contributing to poor intubation conditions are an insufficient depth of anaesthesia and the lack of administration of neuromuscular blocking agents (NMBA) [4]. These observations mirror various publications regarding prehospital trauma care indicating that administration of neuromuscular blocking agents significantly increases the likelihood of successful tracheal intubation [8]. Therefore, if the indication for ET placement is given and the decision is made, adequate depth of anaesthesia and full neuromuscular blockade should be ensured.

As depolarizing NMBA are usually not indicated in the ICU setting, because of its fast onset, rocuronium seems to be the most appropriate NMBA. With sugammadex the effect of rocuronium can be reversed. However, the disposal of sugammadex should not lead to a false sense of security. Several authors have questioned whether the administration of sugammadex can save patients' lives in the case of an unexpected 'cannot ventilation–cannot intubate' scenario [9]. The time from decision making, to finding and preparation of the adequate dosage until full reversal of the neuromuscular block will probably be longer than the apnoeic tolerance of a critical-ill patient. Additionally, return of spontaneous ventilation will be impaired because of the previous administration of narcotics and, furthermore, will usually not resolve a 'cannot ventilation–cannot intubation' scenario [10,11].

Having said that, induction of anaesthesia for the standard intubation—considering no expected difficulties due to patient's anatomy of the upper airways—in the ICU should, nevertheless, always be performed as a rapid sequence induction. In detail, NMBA should be administered without checking the possibility of ventilation by face mask. There are several reasons for this recommendation:

- Once narcotics and anaesthetics have been administered recovery from anaesthesia to re-establish sufficient spontaneous ventilation is usually not an option if tracheal tube placement unexpectedly fails in a 'cannot ventilate–cannot intubation' situation.
- NMBA facilitate face mask ventilation and laryngoscopy, as well as placement of an EGA; especially if anaesthesia is light.
- Finally, the decision for a more defensive pathway needs to be made **prior** to induction **not during**.

As shown by Mort, more than two repeated attempts to intubate the patients tracheally are associated with significant-worth outcomes, such as hypoxaemia, regurgitation, aspiration, oesophageal intubation, and cardiac depression [12]. Therefore, it is crucial to limit the number of intubation attempts and consider alternative strategies for oxygenation and ventilation, e.g. EGA or face mask ventilation. While face mask ventilation will most likely serve only as a short time-bridge until other measures have been taken or prepared (such as videolaryngoscopy (VL), intubating laryngeal mask airway (LMA), or flexible fibre optic), an EGA may help also for a several hours to ventilate and oxygenate the patient.

Independently, whether ventilation is maintained by FMV, use of an EGA, or by tracheal tube placement, capnography is mandatory in all circumstances to confirm ventilation and correct placement of any airway device.

Box 80.2 Standard equipment for tracheal tube placement on the ICU

- Face mask and bag.
- Oropharyngeal tube.
- Functional suction.
- Functional laryngoscope (check light **prior** to induce anaesthesia).
- Adequately-sized tracheal tube (with a stylet if needed) + an additional tracheal tube one size smaller.
- Syringe to inflate the cuff.
- Capnography.
- Fixation.
- EGA device as back-up.

Strategies to increase time to desaturation

Apnoic oxygenation is usually known as a minimal oxygenation by placing the facemask tightly on the patients face with simultaneous application of a high oxygen flow. However, an open airway is a conceptual requirement of apnoeic oxygenation.

Ramachandran et al. [13] have performed a study in the operating theatre, including obese patients in the semi-recumbent position increasing significantly the time to desaturation simply by applying 5 L of oxygen via nasal probe during laryngoscopy (Table 80.2). Despite the lack of similar studies in the ICU setting, this concept seems to be very useful due to its simplicity, as well as because nasal probes are widely available. Therefore, it might by sensible to apply oxygen via nasal probes during laryngoscopy in order to prolong the time to desaturation or reduce the degree of desaturation, especially in patients with severe respiratory dysfunction.

Extraglottic airway devices

Since the first description of the classic LMA in 1983 [14], many other types of EGA became available. While EGA have their

Table 80.2 Effect of apnoeic oxygenation with 5 L of oxygen via a nasal probe during direct laryngoscopy

	Control group without O_2	Study group with O_2
Time to SpO_2 < 95%, min	3.5 (1.3)	5.3 (1.0)
Lowest SpO_2	88 (9)	94 (4)
Time to resaturate, min	1.6 (1.5)	0.7 (0.4)

Data from Ramachandran SK et al., 'Apneic oxygenation during prolonged laryngoscopy in obese patients: a randomized, controlled trial of nasal oxygen administration', *Journal of Clinical Anesthesia*, 2002, **22**(3), pp. 164–8. PubMed PMID: 20400000.

undisputed value during routine as well as emergency care, the use and distribution of EGA one the ICU seems to be limited.

Difficult laryngoscopy does usually not impair the insertion of an EGA. Therefore, EGA, as extensively shown for the OR and prehospital emergency medicine, are very valuable tools to secure patients' airways in case of an unexpected failure to intubate in the ICU. As the learning curves to gain adequate competency are steeper for EGA compared with intubation via direct laryngoscopy, they may be especially useful if expertise in advanced airway management is limited.

Available data for the use of EGA in the ICU refer mainly to LMA. Several case reports describe the use of LMAs in the ICU in cases of failed intubations [15]. Furthermore, so called 'second generation' devices contain an integrated drainage channel to passively or actively drain fluids from the gastrointestinal tract. Despite the lack of scientific evidence, it can be assumed that these features further reduce the risk of regurgitation. Additionally, as ventilation via a correctly-placed EGA reduces the risk of gastric air insufflation compared with FMV, EGA may serve to provisionally establish clear airways for oxygenation and ventilation.

Blind intubation via EGA is usually not associated with promising success rates. However, intubation via an EGA can be aided fibre optically, possibly with the help of an purpose-designed exchange catheter (Aintree Catheter, Cook Critical Care, Bloomington, IN, USA) [16].

One exception is the intubating laryngeal mask airway (ILMA, Teleflex Medical Europe Ltd, Ireland). It allows ventilation of the patients' lungs, as well as blind intubation with a very high success rate [17]. Furthermore, for novice users, both ventilation and intubation have proven to be more successful with the ILMA compared with FMV and intubation via direct laryngoscopy [18]. In case of failed blind intubation attempts, tracheal tube placement can easily be performed using a flexible fibre optic. As the airway tube of the ILMA is large, a tracheal tube can be advanced via a fibre optic once the trachea has been identified. Therefore, the ILMA might be a valuable back-up tool when planning tracheal intubation in the ICU.

Videolaryngoscopy

Currently, standard ET placement usually means the use of direct laryngoscopy. In 1998, the logical combination with a Macintosh blade, the video intubation laryngoscope, was introduced as a new concept for dealing with routine cases, as well as difficult intubations and was the subject of extensive scientific studies. The rapid spread of video laryngoscopy began at the latest with the introduction of the GlideScope® videolaryngoscope (GS-VL, Verthon Medical, Canada) in 2003.

The uncontested preserves of video laryngoscopy are:

- Training and supervising intubation by laryngoscopy.
- Laryngoscopic intubation in cases of an unexpectedly difficult airway in adults and children.
- Assessment and documentation of special constellations and pathological conditions of supraglottic airways and documentation of the tube position in the glottis.

VL systems have shown to improve the view of the laryngeal structures. The view of the glottis is consistently better using a VL system than with direct laryngoscopy. A study by Nouruzi-Sedeh et al., with providers not experienced in airway management, showed that patients were successfully intubated more often and faster with the GS-VL than by direct laryngoscopy [19]. Furthermore, the learning curve for VL seems to be steeper than for direct laryngoscopy, although the data obtained in model-based studies should be regarded with some reservations [20].

Granted, VL is not the Holy Grail for ET placement that will resolve all difficult airway scenarios, and it is self-evident that training and expertise are warranted with the use of VL. However, VL seems to be effective as a back-up device in the case of failed direct laryngoscopy, as well as the first choice tool for health care providers with less skilled in direct laryngoscopy. Furthermore, it can be speculated whether, parallel to the evolution in the OR and the pre-hospital setting, VL will replace direct laryngoscopy in the ICU in the future.

Without going into too much detail about different VL systems and concepts, at this stage it is difficult to predict whether strongly angulated VLs with a mandatory **indirect** view on the glottis (e.g. GlideScope) or VLs with Macintosh-like blades (e.g. CMac®, K. Storz GmbH, Tuttlingen, Germany), including the option of both indirect and direct laryngoscopy, will be the advantageous in the ICU setting.

Conclusion

Standard tracheal intubation in the ICU is more challenging compared with standard intubation in the OR. Therefore, planning and preparation are crucial. In order to facilitate laryngoscopy and tracheal tube placement, adequate anaesthesia, including full neuromuscular blockade should be part of the routine. EGA devices represent useful options in cases of unexpected failed intubation. However, wherever and whenever airway management is attempted, the use of capnography to confirm ventilation is mandatory. In the future, VL might become the standard procedure for tracheal intubation in the ICU.

References

1. Rose DK and Cohen MM. (1994). The airway: problems and predictions in 18,500 patients. *Canadian Journal of Anaesthesia*, **41**(5 Pt 1), 372–83.
2. Jaber S, Amraoui J, Lefrant JY, et al. (2006). Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Critical Care Medicine*, **34**(9), 2355–61.
3. Griesdale DE, Bosma TL, Kurth T, Isac G, and Chittock DR. (2008). Complications of endotracheal intubation in the critically ill. *Intensive Care Medicine*, **34**(10), 1835–42.

4. Heuer JF, Barwing TA, Barwing J, et al. (2012). Incidence of difficult intubation in intensive care patients: analysis of contributing factors. *Anaesthesia and Intensive Care*, **40**(1), 120–7.
5. Cook TM, Woodall N, Harper J, and Benger J (2011). Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. *British Journal of Anaesthesia*, **106**(5), 632–42.
6. McGowan P and Skinner A. (1995). Preoxygenation—the importance of a good face mask seal. *British Journal of Anaesthesia*, **75**(6), 777–8.
7. Cullen A and Ferguson A.(2012). Perioperative management of the severely obese patient: a selective pathophysiological review. *Canadian Journal of Anaesthesia*, **59**(10), 974–96.
8. Bulger EM, Copass MK, Sabath DR, Maier RV, and Jurkovich GJ. (2005). The use of neuromuscular blocking agents to facilitate prehospital intubation does not impair outcome after traumatic brain injury. *Journal of Trauma*, **58**(4), 718–23; discussion 723–4.
9. Bisschops MM, Holleman C, and Huitink JM. (2010). Can sugammadex save a patient in a simulated 'cannot intubate, cannot ventilate' situation? *Anaesthesia*, **65**(9), 936–41.
10. Curtis R, Lomax S, and Patel B. (2012). Use of sugammadex in a 'can't intubate, can't ventilate' situation. *British Journal of Anaesthesia*, **108**(4), 612–14.
11. Kyle BC, Gaylard D, and Riley RH. (2012). A persistent 'can't intubate, can't oxygenate' crisis despite rocuronium reversal with sugammadex. *Anaesthesia and Intensive Care*, **40**(2), 344–6.
12. Mort TC. (2004). Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. *Anesthesia and Analgesia*, **99**(2), 607–13.
13. Ramachandran SK, Cosnowski A, Shanks A, and Turner CR. (2010). Apneic oxygenation during prolonged laryngoscopy in obese patients: a randomized, controlled trial of nasal oxygen administration. *Journal of Clinical Anesthesia*, **22**(3), 164–8.
14. Brain AI. (1983). The laryngeal mask—a new concept in airway management. *British Journal of Anaesthesia*, **55**(8), 801–5.
15. Keller C, Brimacombe J, Lirk P, and Puhringer F. (2004). Failed obstetric tracheal intubation and postoperative respiratory support with the ProSeal laryngeal mask airway. *Anesthesia and Analgesia*, **98**(5), 1467–70.
16. Russo SG, Moerer O, Nickel EA, Goetze B, Timmermann A, and Quintel M. (2010). Extraglottische Atemwegshilfen auf der Intensivstation. [Extraglottic airway devices in the intensive care unit.] *Der Anaesthesist*, **59**(6), 555–63.
17. Ferson DZ, Rosenblatt WH, Johansen MJ, Osborn I, and Ovassapian A. (2001). Use of the intubating LMA-Fastrach in 254 patients with difficult-to-manage airways. *Anesthesiology*, **95**(5), 1175–81.
18. Timmermann A, Russo SG, Crozier TA, et al. (2007). Novices ventilate and intubate quicker and safer via intubating laryngeal mask than by conventional bag-mask ventilation and laryngoscopy. *Anesthesiology*, **107**(4), 570–6.
19. Nouruzi-Sedeh P, Schumann M, and Groeben H. (2009). Laryngoscopy via Macintosh blade versus GlideScope: success rate and time for endotracheal intubation in untrained medical personnel. *Anesthesiology*, **110**(1), 32–7.
20. Nasim S, Maharaj CH, Malik MA, J OD, Higgins BD, and Laffey JG. (2009). Comparison of the Glidescope and Pentax AWS laryngoscopes to the Macintosh laryngoscope for use by advanced paramedics in easy and simulated difficult intubation. *BMC Emergency Medicine*, **9**, 9.

CHAPTER 81

The difficult intubation in the ICU

Michael Frass

Key points

- Endotracheal intubation may sometimes be problematic in ICU (unprepared patients, emergency situations) and non-invasive alternative airway management may be necessary.
- In case of difficult mask ventilation (inability to maintain pulse oximetry oxygen saturation > 50% at FiO_2 = 100%) proper action must be planned.
- The oesophageal tracheal Combitube® and EasyTube™ may be valid alternatives.
- Laryngeal mask has proved of value in cardiopulmonary resuscitation.
- Modification of a laryngeal mask such as Fastrach® has been recommended as a rescue device for emergency airway management.

Airway access

Airway management in the ICU differs from conventional controlled setting, such as general anaesthesia in the operating room (OR). Due to adequate patient preparation and positioning in the OR, endotracheal intubation is mostly easy to perform. However, in the intensive care setting, endotracheal intubation is often difficult or impossible because patients are not prepared and intubation is immediately necessary without sufficient time for putting together technical and pharmaceutical equipment.

In the following, non-invasive alternate airway management with special respect on the recommendations of the 'Task Force on Managing the Difficult Airway' of the American Society of Anesthesiologists (i.e. ASA algorithm) is described [1].

Non-invasive airway management

Non-invasive ventilation (NIV) allows patients to speak and cough [2] and may reduce complications related to intubation. Indications for use of NIV are patients with diagnosis of chronic obstructive lung disease or cardiac failure, since weaning from respirator and cannula in these patients is often very difficult.

NIV can be performed via face mask covering mouth and nose, where a mask is pressed against the patient's face with the help of an elastic band. Ventilation is provided by either continuous positive airway pressure (CPAP, i.e. continuous flow), pressure support ventilation (PSV) or volume—or pressure-cycled systems (e.g. bi-level positive airway pressure (BiPAP). New devices include eyes into the mask and are better tolerated since pressure on the root of the nose can be circumvented.

NIV can also be performed via a helmet consisting of a cylindrical transparent part surrounding the patient's head sealed by an elastic ring around the patient's neck. The advantages of the helmet are that the patient enjoys a free view through the transparent helmet and may use glasses. Furthermore, additional openings allow nursing of the patient's face. Special designs of the helmet provide field of view and minimum level of noise.

In the intensive care unit (ICU), patients with hypoxia and deteriorated cardiopulmonary function may experience adverse events after shorter periods of lack of response to ventilation or intubation. Therefore, emergency tracheal intubation in critically-ill patients may be associated with a significant frequency of major complications. Opposite to routine intubation in the operating room, airway management in intensive care patients may be extremely difficult. Immediate need for intubation and ventilation in situations, such as acute respiratory failure, shock, or cardiopulmonary arrest could make securing of airways and adequate ventilation difficult.

In this situation, the intensivist should consider mask ventilation, when general anaesthesia is induced before securing the airway and whether there are any inadvertent obstacles making awake conventional endotracheal or fibre optic intubation difficult. Furthermore, to prevent adverse effects of unsuccessful intubation, a plan B should be ready.

Difficult mask ventilation (DMV) is defined as the inability of a trained anaesthetist to maintain the arterial oxygen saturation beyond 90% by help of a face mask and use of 100% inspired oxygen, when the preventilation oxygen saturation level was within the normal range [3].

Opposite to previous assumptions, difficulties in laryngoscopy and/or intubation may occur in routine patients in the OR. While minor complications making a second intubation attempt necessary occur in up to 8% of patients, grade 3 laryngoscopy requiring multiple attempts at conventional intubation occurs in 1–4% among all patients. In 0.05–0.35% of routine anaesthesia cases intubate may fail due to grade 3 or 4 laryngoscopic views. A cannot ventilate–cannot intubate situation may occur in approximately 2 out of 10,000 cases.

Alternative airways

Oesophageal-tracheal double lumen airways: combitube® and easytube™

The oesophageal tracheal combitube (ETC) has designed as a double-lumen airway with a 'pharyngeal' and an 'endotracheal' lumen where the lumens are separated by a partition. At the proximal end, the ETC is surrounded by a large oropharyngeal balloon, at the distal end by a conventional cuff (Covidien, Mansfield, MA,

USA). As an advantage, the ETC can be inserted blindly without help of a laryngoscope and works equally well in oesophageal or tracheal position. The ETC is inserted as deeply until the printed ring marks are positioned at the level of the upper teeth. Then, the oropharyngeal balloon is inflated with 85 (37F) or 100 mL (41F) of air sealing the oral and nasal cavities, while the distal cuff is inflated with 5 to 12 (37F) or 15 mL of air (41F) sealing either oesophagus or trachea. In about 97% the ETC enters the oesophagus after blind insertion. Therefore, test ventilation is recommended via the longer 'pharyngeal' blue lumen No. 1 (i.e. supraglottic ventilation). Confirmation of the tube's position may be done by auscultation of breath sounds in the absence of gastric inflation, and by capnography and/or oesophageal detection method. If the ETC has blindly entered the trachea (3% of blind insertions), ventilation is performed via the shorter transparent lumen No. 2, and ventilation is done like via a conventional endotracheal tube (ETT). Two different sizes of the ETC are available: a small adult model (37 Fr, Combitube® SA) for use in patients with a height ranging from 120 to 200 cm and a 41 Fr model for use in taller patients.

The ETC has been studied and used under emergency conditions, as well as during routine anaesthesia. To become familiar with the ETC, it is recommended to train during elective surgery before using the airway in emergency situations. When used routinely, the ETC could be inserted using a (video-) laryngoscope to minimize the risk of pharyngeal injury. Contraindications for use of the ETC are oesophageal pathologies, ingestion of caustic substances and central airway pathologies.

A major advantage of the Combitube® is its unequalled safety to prevent aspiration of gastric contents and the applicability of high airway pressures. The ETC can be left in place for up to 8 hours; replacement by an ETT can be performed either by tracheostomy or by cricothyrotomy with the ETC in place (since the trachea is not occupied in most cases), by direct laryngoscopy after deflation of the oropharyngeal balloon, or by fibre optics.

Recently, the EasyTube™ has been designed (Well Lead, Guangzhou, China). Its appearance is similar to the Combitube®, however, provides several advantages.

The 'pharyngeal' lumen of the EasyTube™ ends just below the oropharyngeal balloon. Therefore, the 'tracheo-oesophageal' lumen is thinner than that of the Combitube®, which carries the two lumens down to the end. Since the distal single lumen of the EasyTube™ is significantly thinner, the potential danger of mucosal damage is minimized. Another advantage is that the oropharyngeal balloon is latex free. The device comes in two sizes: the 28 F EasyTube™ ('paediatric size') is available for patients with a height ranging from 90 to 130 cm; the 41 F EasyTube™ is designed for patients taller than 130 cm. A small fibrescope may be passed via the so-called 'pharyngeal' lumen, since it is open at the distal end. This feature allows inspection of the trachea and possible replacement of the EasyTube™ using a guide wire. Furthermore, a larger suction catheter can be passed via both lumens (14 F suction catheter in the 41 F EasyTube™).

Laryngeal mask airway

The laryngeal mask airway (LMA) (LMA North America, San Diego, CA, USA) has been developed in parallel to the Combitube®. It was accepted rapidly and is used extensively during general anaesthesia. The LMA is used for different reasons—as a routine ventilatory airway as an alternative to conventional endotracheal airway or as help for tracheal intubation. The initial intention for use of the LMA was to replace the conventional face mask in the operating room in Great Britain. Tidal volumes were higher and problems associated with airway management (difficulties in maintaining the airway or maintaining SpO_2 > 95%) less frequently encountered during LMA use when compared with conventional regular face mask.

The use of the LMA as the immediate airway in cardiopulmonary resuscitation has been discussed controversially. Murray et al. performed a two-phase observational study of the effect of paramedic training for LMA insertion using a mannequin and the success rate in the prehospital setting. All paramedics successfully completed classroom mannequin training. Two-hundred-and-eight paramedics (100%) successfully completed training. The mean number of attempts was 1, and only four (2.1%) paramedics required a second attempt with a mannequin. The paramedics' perception of ease of use comparing the LMA with a bag valve mask (BVM) was evenly distributed across the three descriptors: 70 (39%) scored the LMA as easier to use, 57 (31%) as more difficult, and 54 (30%) stated there would be no difference. Of the 291 arrests during the study period, insertion of the LMA was attempted in 283 (97.3%) and was successful in 199 (70%) patients. The LMA became dislodged in 5 (2.5%) cases and was removed in 12 (6%) to clear vomit from the airway. The overall success rate was 182 (64%). The incidence of regurgitation prior to attempted insertion of the LMA was 28% (79 patients). Success rates did not vary significantly with the incidence of vomiting prior to insertion ($p = 0.11$). The majority of the paramedics evaluated LMA insertion as 'Very easy' 49/220 (22.3%) or 'Easy' 87/220 (39.6%). Paramedic evaluation of ease of use varied with success ($p = 0.001$). This study reports a 100% training success rate with a mannequin, and a 64% success with LMA insertion and ventilation in the field by paramedics among adult out-of-hospital non-traumatic cardiac arrest patients.

The potential value of the LMA was assessed in a multicentre study when the LMA inserted by ward nurses during cardiopulmonary resuscitation as a method of airway management before of the advanced life support team with tracheal intubation capability arrived. One-hundred-and-thirty nurses were trained, and 164 cases of cardiac arrest were studied. The LMA was inserted at the first attempt in 71% and at the second attempt in 26% of cases. Satisfactory chest expansion occurred in 86% of cases. The mean interval between cardiac arrest and LMA insertion was 2.4 min. Regurgitation of gastric contents occurred before airway insertion in 20 cases (12%), and during insertion in three cases (2%).

Early LMA insertion should be considered in patients suffering from supraglottic pathologies and unfavourable anatomy for face mask ventilation and/or tracheal intubation. Drawbacks of the LMA include the lack of access to the patient's central airways, risk of aspiration, limited applicability of positive airway pressures due to the often inadequate seal, and the need for training. Moreover, the LMA is a supraglottic ventilatory device and is thereby unable to establish adequate gas exchange in patients with central airway obstruction.

Several modifications of the LMA have been designed, e.g. the intubating LMA (Fastrach™, the Laryngeal Mask Company, Ltd.). The so-called Fastrach differs from conventional LMAs by having a wider, shorter stainless steel tube, a handle to steady the device, and an epiglottic elevating bar (a moveable flap fixed

to the upper rim of the mask). The Fastrach™ allows passage of endotracheal tubes up to an inner diameter (ID) of 8.5 mm providing blind or fibre optic intubation using the correctly placed Fastrach as a conduit. Success rates for blind Fastrach™ intubation in the 75 to >90% range have been shown by several investigators.

The Fastrach™

This has been recommended as a rescue device for emergency airway management. Ferson et al. used the Fastrach™ in 254 patients with different types of difficult airways. Insertions of the LMA-Fastrach™ were accomplished in three attempts or fewer in all patients. The overall success rates for blind and fibre optically-guided intubations through the LMA-Fastrach™ were 96.5 and 100.0%, respectively. Oesophageal perforation has occurred after repeated 'blind' intubation attempts with the LMA-Fastrach™ in an elderly patient. Therefore, the specially designed silicone-tube with rounded bevel should be used for blind Fastrach™ intubation, because success rates exceed those encountered with standard reinforced tubes. Muscle relaxation may help to increase success rates for blind Fastrach™ intubation.

LMA and LMA-Fastrach™ versus Combitube®

Sealing capacities and protection against regurgitation of gastric contents of LMA/Fastrach™ are inferior to those of the ETC, e.g. average leak fractions of the LMA are in the range 20–25% during positive pressure ventilation with airway pressures ranging from 20 to 30 cmH_2O. The special design of the ETC allows the use of high peak airway pressures and permits PEEP ventilation, thereby enabling higher tidal ventilation and maintenance of adequate gas exchange, even in patients suffering from severe underlying pulmonary pathology (e.g. aspiration of gastric contents). In contrast to the ETC, blind, or fibre optic intubation is possible through the LMA lumen (using conventional ETTs up to an ID of 6.5 mm) and especially through the Fastrach™ (up to 8.5 mm). With the currently available ETC model, no blind or fibre optic access to the patient airway is necessary. Krafft et al. modified the standard ETC model and created a larger ventilation hole, which can be used for fibre optic intubation or tracheal toilette. However, the redesigned model is currently not available and it is uncertain whether it will be produced in the near future.

References

1. Benumof JL. (1991). Management of the difficult adult airway. With special emphasis on awake tracheal intubation. *Anesthesiology*, **75**, 1087–110.
2. Mehta S and Hill NS. (2001). Noninvasive ventilation. *American Journal of Respiratory and Critical Care Medicine*, **163**, 540–77.
3. American Society of Anesthesiologists Task Force on Management of the Difficult Airway. (2003). Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*, **98**, 1269–77.

CHAPTER 82

The surgical airway in the ICU

Danja S. Groves and Charles G. Durbin Jr

Key points

- Cricothyrotomy is an emergency surgical airway used to save a life when all attempts at securing a patent airway fail and arrest is eminent.
- Compared with translaryngeal intubation, tracheostomy improves patient comfort, and leads to shorter length of intensive care unit (ICU) and hospital stay.
- Tracheostomy relieves upper airway obstruction, protects the larynx and upper airway from damage, allows access to the lower airway for secretion removal, and provides a stable airway for patients requiring prolonged mechanical ventilation or oxygenation support.
- Timing of tracheostomy remains controversial and should be individualized; however, early tracheostomy (within 7 days) seems to be beneficial in certain patient populations (head injury, medically critically ill).
- Bedside techniques are safe and efficient, allowing timely tracheostomy with low morbidity.

Introduction

Surgical airways are discussed in this section, and include emergency cricothyroidotomy and elective tracheostomy. Emergency cricothyroidotomy is reserved for that urgent situation when spontaneous ventilation is inadequate, manual ventilation unsuccessful, and translaryngeal intubation fails. It is a life-saving intervention, which can be rapidly performed with acceptable risk, using few surgical tools or a special device. While a 'slash' cricothyroidotomy may be performed with only a scalpel and tube, a specially-designed kit with a tube, dilator, and guide wire is more efficient and safer in inexperienced hands. Another approach to a lost airway is transtracheal needle ventilation, which will help to prevent lethal hypoxaemia, while achieving a secure airway by other means. The remainder of this chapter will discuss elective tracheostomy in intensive care unit (ICU) patients. Unlike the emergency surgical airway, this is a carefully considered, surgical approach to prolonged airway management. Some authors suggest a tracheostomy may be performed through the less vascular cricothyroid membrane, but most recommend placement at lower tracheal rings to reduce the chance of permanent laryngeal damage that can result from loss of the cricoid cartilage.

Of the purported advantages of tracheostomy, only improved patient comfort, early discharge from an ICU, and shorter length of ICU and hospital stay have any supporting data. There is a belief that patients are safer following tracheostomy, but even this basic assumption is unsupported by science. Evolution of percutaneous techniques are rapidly reducing the need for surgical tracheostomy. Timing of tracheostomy remains controversial.

Elective tracheostomy

Elective tracheostomy is performed in as many as 10% of patients requiring more than 7 days of mechanical ventilation. Prolonged respiratory failure is the most frequent indication for tracheostomy followed by decreased level of consciousness, poor airway protective reflexes, and severe alterations in physiology. The safety of tracheostomy techniques has improved and most are now performed at the patient's bedside. There are two basic ways to perform tracheostomy—'open' or 'surgical' tracheostomy in which a formal neck incision is made, tissue planes are identified and incised, blood vessels ligated or cauterized, and a tracheal stoma surgically created and stabilized, or by percutaneous dilation, where the trachea is entered with a needle, and then a guide wire used to direct stoma creation and tube placement using tapered dilating devices.

Elective tracheostomy is used to relieve upper airway obstruction due to:

- Tumour, surgery, trauma, foreign body, or infection.
- Protect the larynx and upper airway from damage.
- Allow access to the lower airway for suctioning and secretion removal.
- Provide a stable airway for patients requiring prolonged mechanical ventilation or oxygenation support.

Although there are anecdotal reports using tracheostomy for emergency relief of airway obstruction, cricothyroidotomy remains the recommended approach when manual ventilation and intubation attempts have failed, and complete cessation of gas exchange occurs [1].

Benefits of early elective tracheostomy?

Protection of the larynx and the upper airway from prolonged intubation is an important reason to perform a tracheostomy, and to consider early provision of this airway. Many anatomical structures are at risk from translaryngeal intubation. Vocal cord oedema and damage, laryngeal mucosal erosions, laryngeal scaring and stenosis, and recurrent laryngeal nerve damage can lead to permanent disability. The potential for recovery or successful surgical repair of many of these injuries is less with continued, prolonged intubation. Direct laryngeal examination demonstrates marked airway changes within several days of translaryngeal intubation. Usually, these early changes are reversible and there is gradual improvement in

airway examination after the tube is removed from the larynx [2]. Prediction of progression with continued translaryngeal intubation is poor, but the consequences of injury are severe.

Improved patient comfort

Patients experience discomfort with persistent translaryngeal intubation and are more comfortable following tracheostomy [3]. Improved patient comfort and less requirements for sedation have been reported in several studies following placement of a tracheostomy. In a follow-up study of patients who were randomized to remain intubated translaryngeally for a prolonged period or receive an early tracheostomy, Blot et al. reported that oral comfort scores, mouth cleanliness, perception of change in body image, feelings of safety, and overall comfort were lower in the prolonged translaryngeal intubation group compared with those who were randomized to early tracheostomy [4]. Thirteen patients in this study who survived to hospital discharge, and had undergone both translaryngeal intubation and tracheostomy reported tracheostomy as the most comfortable airway of the two. Patient comfort alone may be enough to justify tracheostomy, rather than continuing with prolonged translaryngeal intubation if the risks of the two approaches are comparable. Other suggested advantages of elective tracheostomy and their strength of evidence are listed in Table 81.1.

Facilitated ventilator weaning and shorter length of stay

Elective tracheostomy may shorten duration of mechanical ventilation due to reduced work of breathing, the need for less sedation and analgesia, or because once a secure airway is in place clinician weaning behaviour changes [5]. A single prospective trial in surgical/trauma patients who were unable to pass a spontaneous breathing trial after 72 hours of mechanical ventilation, were randomly divided to continue translaryngeal intubation or proceed with immediate tracheostomy, demonstrated more rapid weaning following tracheostomy [6]. Several meta-analyses of randomized trials comparing earlier versus later tracheostomy confirmed that weaning is more rapid with early tracheostomy [7]. Earlier transition of a patient from the ICU remains a major demonstrable effect of tracheostomy, thus accruing fewer ICU and hospital days. However, this transition to a lower level care area may not be without risk.

Elective tracheostomy and patient safety

The presumed safety of having a tracheostomy in a patient managed outside an ICU or special care unit has come under scrutiny. In a prospective observational cohort study, Martinez et al. reported that patients discharged to the ward with a tracheostomy in place experienced three times the mortality of those who had received a tracheostomy, but who were decannulated prior to discharge to the ward [8]. Multivariate analysis identified three highly significant factors associated with increased ward mortality:

- Lack of decannulation at ICU discharge.
- Body mass index > 30kg/m^2
- Tenacious sputum at ICU discharge.

The last two would appear to be easier to manage with a tracheostomy, but most of the deaths on the ward were due to unexpected cardiorespiratory arrests, usually in the early morning hours when staffing may be compromised. Failure of monitoring of patients and of early treatment of airway problems may have played a part in the increased mortality in this group. Other groups have reported similar findings in less well-designed trials, while some have not identified having a tracheostomy at ward discharge a risk for increased mortality when corrected for other risk factors.

Others have noticed the additional risks of having a tracheostomy compared with standard translaryngeal intubation even when residing in an ICU environment. In 2000, Kapadia et al. reported airway accidents in 5046 patients intubated for 9289 days during a 4-year period. Of the 36 airway accidents, 26 occurred in the 5043 endotracheally-intubated patients—none were severe and no deaths occurred. Ten tracheostomy-related accidents occurred in 79 patients; six were severe and one resulted in death. Thus, even when monitored in an ICU, airway accidents associated with

Table 81.1 Suggested benefits of performing a tracheostomy in patients requiring prolonged intubation

Benefit	Quality of literature showing benefit
Improved patient comfort	Uncontrolled reports, clinical opinion
Less need for sedation	Several RCTs
Lower work of breathing	Theoretical analysis, one small study
Improved patient safety	Clinical belief, but minimal data, some contradictory (see text for details)
Improved oral hygiene	Clinical observation
Oral intake more likely	Opinion only
Earlier ability to speak	Uncontrolled reports
Better long-term laryngeal function	Large uncontrolled reports
Faster weaning from mechanical ventilation	One RCT
Lower risk of ventilator associated pneumonia	Controversial, data support for both sides
Lower mortality	One RCT supports, many do not; however, large RCT supports mortality not higher with tracheostomy
Shorter ICU and hospital stay	Several meta-analyses

RCT, randomized controlled trial.

tracheostomy tubes occurred more frequently and resulted in higher mortality (10%) than in patients with conventional endotracheal tubes [10].

No fewer lung infections with elective tracheostomy

Since micro-aspiration of oral secretions through the stented larynx, past the endotracheal tube cuff is believed to contribute to development of infection; it was hoped that incidence of ventilator-associated pneumonia (VAP) would decrease with early tracheostomy. If there is an influence on the incidence or course of VAP from tracheostomy, it is small. In addition to the meta-analysis by Griffiths et al. mentioned previously, a recent review and meta-analysis of early versus later tracheostomy by Durbin et al. confirmed the observation of minimal effect on the incidence of VAP [9]. The fact that most patients are intubated through the larynx prior to tracheostomy will contaminate any study attempting evaluate elective tracheostomy and VAP association.

Timing of elective tracheostomy

Tracheostomy is indicated when the need for endotracheal intubation is or is projected to be prolonged. In older guidelines, tracheostomy was recommended after 21 days; more recently, it has been suggested that tracheostomy be considered within 2–10 days of intubation and a projected need for 14 days of intubation. In patients with severe multi-trauma and/or head injury with low Glasgow Coma Scores, elective tracheostomy at the earliest convenient time, often within 3–4 days of intubation, appears to afford some benefits [10]. An argument against early tracheostomy in patients with neurological abnormalities has been advanced by King et al. [11]. In their review, it appears that poor mental status alone is insufficient to require prolonged intubation and thus tracheostomy. They noted cough effectiveness, secretion quantity, and secretion viscosity all impact on the success of extubation in this group (and other patients) as well.

While it is clear that delaying extubation is associated with increased morbidity, and length of stay, the medical literature also demonstrates harm from extubation failure. Over 55 studies, involving more than 30,000 patients, suggest that the overall rate of extubation failure is approximately 12% (range 2–25%) [12]. One study from a medical ICU found that re-intubation resulted in an average 12 additional days of mechanical ventilation, 21 ICU days, 30 hospital days, and an increased need for tracheostomy and post-acute care hospitalization [13]. While patients requiring re-intubation tend to be sicker, multivariate analyses have shown that premorbid health status, severity of illness, and complications directly associated with re-intubation do not explain the increased mortality associated with extubation failure [14]. A direct correlation between increasing time to re-intubation and mortality has led some authors to suggest that clinical deterioration prior to reinstitution of mechanical ventilatory support is responsible for the increased mortality associated with extubation failure [15]. It has been suggested that careful monitoring and rapid intervention for respiratory failure developing following extubation may prevent this excessive mortality. However, this hypothesis has not yet been tested.

Unlike other reports, a study by Rumbak et al. demonstrated a remarkable mortality benefit of early tracheostomy in medical patients, with 32% mortality with early tracheostomy group and over 61% in the late group [16]. This trial was performed in three institutions and included severely-ill patients (APACHE score > 25) randomized to a percutaneous tracheostomy at 48 hours, or at 14 days or later. Low tidal volume ventilation, a ventilator-weaning protocol, and daily spontaneous breathing trials were used in all patients. In addition to mortality benefit of early tracheostomy, infections, and other complications were more common in the late tracheostomy group.

A recent large trial (909 patients) of early (<4 days) versus late tracheotomy (>10 days) demonstrated no survival benefit in the early group, but 44% of the late group either died or were weaned before receiving a tracheostomy [17].

Techniques of elective tracheostomy

Since Ciaglia first described his use of a guide wire and serial dilation technique for percutaneous tracheostomy in 1985, the popularity of this technique over the open technique has grown dramatically. Comparisons between surgical and percutaneous tracheostomy suggest more (but generally less severe) early complications during percutaneous placement, but fewer late problems. These are summarized in several papers by Durbin [18,19]. Initially, percutaneous dilatory tracheostomy was reserved for patients with few risk factors and favourable neck anatomy. With growing experience, the indications for percutaneous dilatory tracheostomy have been expanded and the patient exceptions that mandate a surgical tracheostomy have decreased. In the case of morbid obesity and moderate coagulopathy, percutaneous dilatory tracheostomy may afford better survival with fewer complications [20].

There are several variants on the percutaneous dilatory tracheostomy. A wire-guided sharp, cutting forceps developed by Griggs et al. gained early popularity, but is reported to have more acute problems, including bleeding and possibly decannulation tracheal risks. To improve safety, performance of percutaneous dilatory tracheostomy, use of bronchoscopic visualization during any technique, has been advocated. Creating the stoma with a single, long-tapered dilator, instead of using serial dilators has reduced procedural time and exposure of the team to the patient's blood. A common, but usually insignificant complication is fracture of a tracheal ring. To reduce the likelihood of fracturing a tracheal ring during the forced dilation, Fantoni developed a method of passing the dilator from inside the trachea to the outside using a specially designed tracheostomy tube and a rigid bronchoscope. The complexity of this method has limited its dissemination. Another approach to reduce tracheal trauma has been developed using a screw-like device to gently separate the trachea rings (PercuTwist®), however, ring fractures still occur.

Ultrasonography of the neck identifies underlying anatomy with more precision than palpation. Tracheal rings are easily appreciated, and an overlying large vessel or thyroid gland can be seen and avoided during the procedure. With adequate experience it may be possible to correctly identify the entry point, but confirmation of correct entry and tube placement is best achieved with direct visualization using a fibre optic bronchoscope.

A variant on the dilator technique of tracheostomy placement begins by first creating a small surgical incision, using blunt dissection, and a gloved finger to palpate the trachea. The fingertip is used to identify the cricoid ring and tracheal rings. Operators using this

technique often dispense with the fibre optic bronchoscope, relying on tactile identification of correct position for needle entry.

Whatever technique is chosen, there are major advantages to performing the procedure in the ICU. Unstable patients experience less deterioration in vital signs and avoid the risks of travel to the operating room. Multiple caregivers, already familiar with the patient, can monitor and care for the patient if the procedure is performed in the unit. Charges for the procedure are usually less when performed in the ICU, but actual costs are difficult to calculate, and payments are unrelated to charges or costs. Occasionally, a bedside procedure fails or a problem arises that would benefit from having operating room resources, such as high intensity lights or electrocautery. Whether to move a patient to the operating room if a surgical tracheostomy is needed—or to perform it in the ICU and bring required the equipment—is an institutional decision. Excellent results have been reported with all of the percutaneous dilatory, as well as surgical techniques performed in either the operating room or at the bedside. Local policy and resources guide the decision of where to perform a tracheostomy.

Complications

The overall rate of complications associated with tracheostomy is low. Reported complications range from pneumothorax, subcutaneous emphysema, haemorrhage, stomal infections, granulation tissue, tracheal stenosis, tracheomalacia, and to (rarely) death. These complications have to be weighed against the identified risks of long-term translaryngeal intubation, including oedema, inflammation, ulcerations, granulomas, arytenoid injury, and laryngeal or tracheal stenosis, fibrosis, or necrosis.

Contraindications

Absolute contraindications for tracheostomy, such as soft tissue infections or anatomic aberrations of the neck, are rare. Severe respiratory failure with refractory hypoxaemia and/or hypercapnia may be considered as relative contraindications requiring delay. Haematological and coagulation disorders may be considered as contraindications for tracheostomy, although percutaneous tracheostomy has been safely performed in patients with severe thrombocytopenia and other coagulation abnormalities.

References

1. American Society of Anesthesiologists Task Force on Management of the Difficult Airway. (2003). Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*, **98**(5), 1269–77.
2. McWhorter AJ. (2003). Tracheotomy: timing and techniques. Current Opinion in Otolaryngology, & Head and Neck Surgery, **11**(6), 473–9.
3. Nieszkowska A, Combes A, Luyt CE, et al. (2005). Impact of tracheotomy on sedative administration, sedation level, and comfort of mechanically ventilated intensive care unit patients. *Critical Care Medicine*, **33**(11), 2527–33.
4. Blot F, Similowski T, Trouillet JL, et al. (2008). Early tracheotomy versus prolonged endotracheal intubation in unselected severely ill ICU patients. *Intensive Care Medicine*, **34**(10), 1779–87.
5. Jaeger JM, Littlewood KA, and Durbin CG, Jr. (2002). The role of tracheostomy in weaning from mechanical ventilation. *Respiratory Care*, **47**(4), 469–80; discussion 81–2.
6. Boynton JH, Hawkins K, Eastridge BJ, and O'Keefe GE. (2004). Tracheostomy timing and the duration of weaning in patients with acute respiratory failure. *Critical Care*, **8**(4), R261–7.
7. Griffiths J, Barber VS, Morgan L, and Young JD. (2005). Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. *British Medical Journal*, **330**(7502), 1243.
8. Martinez GH, Fernandez R, Casado MS, et al. (2009). Tracheostomy tube in place at intensive care unit discharge is associated with increased ward mortality. *Respiratory Care*, **54**(12), 1644–52.
9. Durbin CG, Jr, Perkins MP, and Moores LK. (2010). Should tracheostomy be performed as early as 72 hours in patients requiring prolonged mechanical ventilation? *Respiratory Care*, **55**(1), 76–87.
10. Holevar M, Dunham JC, Brautigan R, et al. (2009). Practice management guidelines for timing of tracheostomy: the EAST Practice Management Guidelines Work Group. *Journal of Trauma*, **67**(4), 870–4.
11. King CS, Moores LK, and Epstein SK. (2010). Should patients be able to follow commands prior to extubation? *Respiratory Care*, **55**(1), 56–65.
12. Epstein SK. (2002). Decision to extubate. *Intensive Care Medicine*, **28**(5), 535–46.
13. Epstein SK, Ciubotaru RL, and Wong JB. (1997). Effect of failed extubation on the outcome of mechanical ventilation. *Chest*, **112**(1), 186–92.
14. Epstein SK. (2006). Preventing postextubation respiratory failure. *Critical Care Medicine*, **34**(5), 1547–8.
15. Epstein SK and Ciubotaru RL. (1998). Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. *American Journal of Respiratory and Critical Care Medicine*, **158**(2), 489–93.
16. Rumbak MJ, Newton M, Truncale T, Schwartz SW, Adams JW, and Hazard PB. (2004). A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. *Critical Care Medicine*, **32**(8), 1689–94.
17. Young D, Harrison DA, Cuthbertson BH, Rowan K, and TracMan C. (2013). Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial. *Journal of the American Medical Association*, **309**(20), 2121–9.
18. Durbin CG, Jr. (2010). Tracheostomy: why, when, and how? *Respiratory Care*, **55**(8), 1056–68.
19. Durbin CG, Jr. (2005). Early complications of tracheostomy. *Respiratory Care*, **50**(4), 511–15.
20. Groves DS and Durbin CG, Jr. (2007). Tracheostomy in the critically ill: indications, timing and techniques. *Current Opinions in Critical Care*, **13**(1), 90–7.

PART 4.5

Acute respiratory failure

CHAPTER 83

Dyspnoea in the critically ill

Paolo Tarsia

Key points

- Dyspnoea is a common clinical finding in patients with respiratory, cardiovascular, neuromuscular, and neoplastic diseases. It may also be present in healthy obese and/or deconditioned subjects.
- Dyspnoea is thought to derive from the conscious awareness of a mismatch between outgoing motor command to the respiratory system and afferent information on the ventilatory response to the command.
- At least three qualitatively distinct sensations of breathing discomfort have been recognized—air hunger, effort of breathing, and chest tightness.
- Dyspnoea quantification measures should be employed to better assess dyspnoea and evaluate response to treatment.
- Both pharmacological and non-pharmacological treatment options are available for dyspnoea relief. In refractory dyspnoea, interventions aimed at reducing the affective component of breathlessness that do not necessarily modulate symptom intensity may be of use.

Introduction

In healthy conditions, the human respiratory system is built in such a way that, lungs, airways, and respiratory muscles adequately satisfy the ventilatory demands imposed by the entire organism, even during vigorous exercise conditions. However, a number of common clinical conditions are associated with dyspnoea. Dyspnoea may be defined as a subjective experience of discomfort associated with breathing. An American Thoracic Society Statement on dyspnoea recognizes that 'the experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioural responses' [1]. Being a subjective experience, each individual perceives, interprets, and reacts differently to the sensation of dyspnoea depending on circumstances, previous experiences, values, and beliefs. Dyspnoea and pain share both neurological pathways and perceptive behaviours. Both consist of sensory (intensity) and affective (unpleasantness) dimensions. The sensation of dyspnoea is not unique to respiratory diseases, but may be also be experienced in cardiovascular, neuromuscular, and malignant diseases. Furthermore, dyspnoea may be present in healthy individuals who are obese and/or deconditioned.

Dyspnoea is common in the acute setting, affecting up to 50% of patients requiring hospital admission or 25% of patients seeking ambulatory assistance [2]. Chronic shortness of breath is reported in over 90% of advanced chronic obstructive pulmonary disease (COPD) patients and > 60% of patients with advanced heart disease [3]. Among the general population mild-to-moderate dyspnoea may be observed in roughly 15% of adults aged over 40 years, and roughly 30% of adults aged over 70 years [4].

Pathophysiology

Breathing discomfort arises as a result of complex interactions between signals relayed from the upper airways, the chest wall, the lungs, and the central nervous system. Integration of this information with higher brain centres provides further processing. The final aspects of the sensation of dyspnoea are influenced by contextual, environmental, behavioural, and cognitive factors.

Chemoreceptors

Blood variations in pH, $PaCO_2$ and PaO_2 are sensed by central chemoreceptors in the medulla and peripheral chemoreceptors in the carotid and aortic bodies. The effect of $PaCO_2$ is primarily mediated through chemoreceptor changes in hydrogen ion (and thus pH). Increased chemoreceptor activation results in afferent information reaching respiratory motor centres, triggering their activity. In healthy subjects, hypercapnia and severe hypoxaemia cause breathlessness. Studies in quadriplegics with spinal cord transaction indicate that hypercapnia elicits a reflex increase of respiratory centre motor output. Resulting dyspnoea is therefore an expression of involuntary reflex respiratory activity, rather than increased voluntary respiratory muscle activity [5]. Patients with congenital central hypoventilation syndrome lack a ventilator response to CO_2. These subjects do not feel breathless during CO_2 rebreathing or protracted breath hold.

Chest wall receptors

Mechanoreceptors in the joints, tendons, and muscle spindles of the chest sense muscle tension and contraction, and send afferent signals to the somatosensory cortex in the brain. This information contributes to proprioception and kinaesthesia. The central areas receiving information from chest wall afferents may have a role in gating the intensity of the dyspnoea sensation. Vibrations of the chest wall in phase with respiration (vibration of inspiratory muscles during inspiration and expiratory muscles during expiration) attenuate breathlessness, whereas out-of-phase vibrations worsen dyspnoea [6]. Thus, chest wall mechanoreceptors may have an important modifying effect on dyspnoea, rather than playing an essential role in generating the perception of dyspnoea per se.

Airway vagal receptors

Receptors present in the airways and the lung relay afferent information via vagus nerve fibres. These include cold receptors, slow-adapting stretch receptors (SARs) and rapidly-adapting stretch receptors (RARs), and C-fibre receptors. Stimulation of cold receptors in the upper airways relieves dyspnoea, as evidenced by sources of cool air directed onto the face [7]. SARs are present in the smooth muscle cells of the large airways. Stimulation of these receptors is also associated with reduced sensation of dyspnoea. RARs react rapidly to sustained inflation or deflation of the lungs, and may be associated with dyspnoea sensation in conditions such as pneumothorax and asthma. Stretch receptors are mainly involved in pulmonary stretch and cough reflexes, modulating airway calibre and ventilator pattern. Their activation permits awareness of the level of ventilation and dilation of the lungs, thus contributing to the overall sensation of dyspnoea. Juxta-pulmonary capillary receptors (J receptors) are localized close to alveolar capillaries and respond to increases in interstitial fluid. Pulmonary C-fibres are located in the lung parenchyma, whereas bronchial C-fibre receptors are located in the airways. Stimulation of these receptors with a number of agents (e.g. capsaicin) induces respiratory sensations such as cough, but not breathlessness in humans. In contrast, adenosine activation of C-fibre receptors is dyspnogenic [8].

Central processing of dyspnoea

Afferent information from chemoreceptors, airway and chest sensors reach the nucleus tractus solitarius (NTS) in the medulla. The NTS is a key site where all peripheral afferent signals are processed prior to presentation to higher centres. Information from the NTS is first projected to the thalamus. The thalamus relays information to areas of the limbic system, such as the insula, the amygdala, and the anterior and posterior insular cortex. These cortical structures are also involved in the perception of other sensations, such as pain, nausea, hunger, and thirst. It is possible that common areas of the brain process the unpleasant perception of different sensations. The anterior insular cortex is thought to play a central role in the conscious awareness of dyspnoea, rather than just processing information. Patients with lesions of the insular cortex present reduced perception of dyspnoea and pain [9].

Corollary discharge

When the brainstem and the motor cortex send outgoing efferent commands to the ventilator muscles, a neurological copy of this information is sent to the sensory cortex. This exchange between the motor and sensory cortex is known as corollary discharge. Corollary discharge is thought to be the mechanism through which conscious awareness of the effort of breathing occurs.

Therefore, afferent information from chemoreceptor and peripheral receptors shapes the motor neural output to the respiratory system. A copy of this information is relayed to the sensory cortex. If afferent feedback to the sensory cortex indicates that the neural motor output does not produce the expected results in terms of airflow or ventilation, a sensation of dyspnoea is generated [10]. It is assumed that the cortical centres possess a pre-existing memory of expected respiratory response to given intensity of motor commands, and that a mismatch between afferent/efferent information and pre-existing memory determines the intensity of dyspnoea. Respiratory disruption leads to distressing emotions, thus eliciting behavioural adaptations.

Qualitatively distinct sensations of dyspnoea

Dyspnoea is not a single sensation. Using patient questionnaires, at least three qualitatively distinct sensations have been employed to describe discomfort in breathing. These are:

- Air hunger.
- Increased effort or work of breathing.
- Chest tightness.

These different sensations are, at least in part, associated with diverse pathophysiological mechanisms.

The sensation termed as 'air hunger' may be defined by patients as unsatisfied inspiration, needing more air, not getting enough air, an unpleasant urge to breath, etc. Air hunger has been shown to be associated with the stimulation of chemoreceptors, such as by hypoxia, hypercapnia, or acidosis, which results in increased spontaneous respiratory drive. Information regarding this increased spontaneous respiratory motor drive activity of the brainstem is conveyed to the cerebral cortex as corollary discharge. When this is not matched by an adequate ventilator response, individuals perceive air hunger. This seldom happens in healthy individuals, except at strenuous exercise levels. Conversely, in cardiac or respiratory conditions, the capacity to provide the additional ventilation required by the increased motor drive activity is limited. This creates an imbalance between the motor drive to breathe, as sensed by corollary discharge, and afferent feedback from mechanoreceptors on the ventilatory response of the respiratory system. The intensity of the sensation of air hunger may be regulated by inhibitory activity from mechanoreceptors. In fact, pulmonary stretch receptor and chest wall afferent information is capable of relieving the sensation of air hunger through signalling the level of current ventilation. Therefore, the perceived severity of the sensation of air hunger is the result of a balance between medullary respiratory motor discharge and simultaneous mechanosensor feedback. Air hunger is not specific to any particular disease or stimulus.

A sense of increased effort of breathing has also been termed as 'difficult breathing', 'breathing takes a lot of work', or 'breathing takes effort'. Chest wall volume variations during breathing activate respiratory muscle afferent information that projects to the cerebral cortex. During normal breathing or exercise in healthy subjects, unless physiological capacity to match ventilation to metabolic demand is surpassed, afferent mechanoreceptor feedback signals that breathing is appropriate to the prevailing respiratory drive. In clinical conditions that impair respiratory muscle performance through abnormal mechanical loads (COPD, asthma, or interstitial lung disease) or when respiratory muscles are weakened (neuromuscular diseases), increased work of breathing generates greater muscle afferent cortical projections that induce motor cortical increase in voluntary breathing drive. Corollary discharge from cortical motor centres to cortical sensory centres increases awareness of cortical motor command and thus contributes to generating the work/effort dyspnoea sensation. Therefore, whereas air hunger is the result of perceived increased **spontaneous** brainstem ventilatory drive through chemoreceptor stimulation, work/effort is the result or perceived increased **voluntary** cortical motor centre activity associated with increased work of breathing.

A sensation of 'chest tightness' is often experienced by asthmatic patients during episodes of acute bronchoconstriction and may alternatively be described as 'chest is constricted' or 'chest is tight'. This sensation may be prevalent during the early phases of

an asthma attack. With increasing severity of bronchoconstriction, hyperinflation may ensue, giving rise to a work/effort sensation. In fact, patients describe that the feeling of chest tightness rapidly responds to albuterol administration [11], whereas the work/effort sensation is best alleviated by mechanical ventilation. It has been suggested that chest tightness develops through stimulation from pulmonary receptor afferents, such as C-fibres or RARs, which respond to bronchoconstriction. Blocking such afferent information relieves the sensation of tightness.

Quantification of dyspnoea

Measurement of dyspnoea is essential in order to assess it adequately and monitor response to treatment. Dyspnoea assessment may be carried out thorough different scales, questionnaires or exercise tests. It must be recognized that different tools measure different aspects of breathlessness. For example, some tools address the intensity of dyspnoea, others the unpleasantness associated with breathlessness, whereas others investigate the impact on dyspnoea on performing tasks or on quality of life. It is important to understand whether a patient is reporting 'how much' or 'how bad' the symptom is. Rating may be influenced by the condition giving rise to the dyspnoeic symptom: healthy adults under laboratory conditions are more prone to report dyspnoea intensity, whereas a COPD patient may give ratings dominated by unpleasantness.

Measures of intensity include the Borg scale, and the visual analogue scale. So far, measures of the affective component have been relatively little used in the context of dyspnoea compared with other sensations such as pain. However, there is evidence that intensity and affective dimensions of breathlessness can meaningfully be distinguished during laboratory challenges [12], and may be thus usefully employed in clinical practice.

Measures of the impact of dyspnoea on functional ability or quality of life encompass both one- and multidimensional rating scales. Examples of the former include the Medical Research Council (MRC) five-point scale that asks the patient to indicate the level of activity that evokes dyspnoea, ranging from strenuous exercise to resting conditions. Multidimensional ratings include the Saint George Respiratory Questionnaire (SGRQ), a 76-item questionnaire involving three areas—symptoms, activity, and impact on daily life.

Dyspnoea management

Management of both acute and chronic forms of dyspnoea should be targeted to optimizing medical treatment of the underlying condition. However, in many cases, maximal medical treatment is ineffective in controlling breathlessness and the symptom persists. This requires the adoption of measures that impact on the symptom per se. Strategies in controlling dyspnoea should not focus uniquely on decreasing dyspnoea intensity. Patients may favourably profit from interventions that decrease the unpleasantness associated with breathlessness without necessarily affecting the intensity component of the symptom. Consequently, both pharmacological and non-pharmacological coping strategies may be of use in bedside clinical management.

Opioids

Administration of opioids relieves dyspnoea in a number of different clinical conditions such as COPD, interstitial lung diseases, cancer, and heart failure. Opioids may attenuate breathlessness via different mechanisms. On the one hand, opioids are respiratory depressants that blunt the central processing of neural signalling related to breathing status and result in decreased motor respiratory command and ventilatory drive. On the other hand, these drugs also alter perceptual sensitivity, thus decreasing patient perception of breathlessness. Therefore, these agents affect both the 'intensity', and the 'unpleasantness' associated with dyspnoea. The side effects of opioids include altered mental status, hypercapnic respiratory failure, constipation, nausea, and vomiting. Opioid administration is still underused in conditions such as COPD, possibly due to clinician fear of precipitating respiratory acidosis. Nonetheless, a systematic review [13] indicated that opioids are associated with a significant 16% improvement in dyspnoea intensity, and a randomized control trial supports the notion that opioids are both effective and safe in patients with refractory dyspnoea [14]. Although opioid receptors are present on sensory nerves in the airways, current evidence does not support the use of nebulized morphine in relieving dyspnoea [13].

Anxiolytic agents

Similarly to opioids, anxiolytic agents may exert a two-fold positive effect in breathless patients by depressing hypoxic—or hypercapnic-induced increases in respiratory drive and dampening emotional responses to dyspnoea. Nonetheless, clinical trials have failed to indicate consistent superiority over placebo for various benzodiazepine derivatives [15], indicating that these drugs should not be routinely employed in the management of dyspnoea. Their use may be considered in individual patients, particularly when anxiety components are critical symptom determinants.

Oxygen therapy

In hypoxic patients, oxygen administration decreases peripheral chemoreceptor activity, thereby causing a reduction in hypoxic ventilatory drive, and thus relieving dyspnoea. Conversely, oxygen use in non-hypoxaemic advanced-stage respiratory and cardiac patients has not been convincingly demonstrated to be of benefit as a symptom reliever, and should not be routinely employed.

Other pharmacological approaches

Novel treatment approaches are currently being evaluated in the management of dyspnoea. Nebulized furosemide decreases breathlessness in healthy volunteers, possibly through the mediation of vagal efferents [16]. Retrosternal block with injection of 35–50 mL of lidocaine 1% attenuates dyspnoea, either through changes in afferent information from chest wall and respiratory muscles, or by direct inhibitory effects on cholinergic airway pathways [17].

Non-pharmacological approaches

Pulmonary rehabilitation in patients with chronic lung diseases is associated with reduced exertional dyspnoea and improves exercise tolerance. The benefit likely derives from multiple mechanisms, including improved physical conditioning, pacing of activities, and desensitization to respiratory distress. Chest wall vibration in COPD patients relieves dyspnoea at rest, but not during exercise [6], probably through the activation of muscle spindles in the intercostals muscles causing modified respiratory sensations. Dyspnoeic patients report that movement of cool air through a fan is associated with symptom relief. Cold

air on the face attenuates dyspnoea in healthy individuals [7], and preliminary data indicate some activity in clinical practice [18]. Neuromuscular electrical muscle stimulation over 4–6 weeks attenuates dyspnoea in COPD patients, and may be of particular use in patients who are unable to exercise [19]. A number of additional techniques have been insufficiently tested as dyspnoea-relief modalities, such as acupuncture, yoga, or relaxation, self-efficacy dyspnoea management, cognitive-behavioural psychotherapy, and educational counselling, and are currently not recommended for routine use [20].

References

1. American Thoracic Society. (1999). Dyspnea: mechanism, assessment, and management. A consensus statement. *American Journal of Respiratory and Critical Care Medicine*, **159**, 321–40.
2. Kroenke K, Arrington ME, and Mangelsdorff AD. (1990). The prevalence of symptoms in medical outpatients and the adequacy of therapy. *Archives of Internal Medicine*, **150**, 1685–9.
3. Bausewein C, Farquhar M, Booth S, Gysels M, and Higginson IJ. (2007). Measurement of breathlessness in advanced disease: a systematic review. *Respiratory Medicine*, **101**, 399–410.
4. Bowden J, To T, Abermethy A, and Currow D. (2011). Predictors of chronic breathlessness: a large population study. *BMC Public Health*, **11**, 33.
5. Banzett RB, Lansing RW, Reid MB, Adams L, and Brown R. (1989). 'Air hunger' arising from increased PCO_2 in mechanically ventilated quadriplegics. Respiratory Physiology, **76**, 53–67.
6. Sibuya M, Yamada M, Kanamaru A, et al. (1994) Effect of chest wall vibration on dyspnea in patients with chronic respiratory disease. *American Journal of Respiratory and Critical Care Medicine*, **149**, 1235–40.
7. Schwartzstein R, Lahive MK, Pope A, Weinberger SE, and Weiss JW. (1987). Cold facial stimulation reduces breathlessness induced in normal subjects. *American Review of Respiratory Disease*, **136**, 58–61.
8. Burki NK, Dale WJ, and Lee L-Y. (2005). Intravenous adenosine and dyspnea in humans. *Journal of Applied Physiology*, **98**, 180–5.
9. Schon D, Rosenkranz M, Regelsberg J, et al. (2008). Reduced perception of dyspnea and pain after right insular cortex lesions. *American Journal of Respiratory and Critical Care Medicine*, **178**, 1173–9.
10. Burki NK and Lee L-Y. (2010). Mechanisms of dyspnea. *Chest*, **138**, 1196–201.
11. Moy ML, Lantin ML, Harver A, and Schwartzstein RM. (1998). Language of dyspnea in assessment of patients with acute asthma treated with nebulized albuterol. *American Journal of Respiratory and Critical Care Medicine*, **158**,749–53.
12. Wan L, Van Diest I, De Peuter S, et al. (2009). Repeated breathlessness experiences induced by hypercapnia: differential effects on intensity and unpleasantness. *Chest*, **135**, 455–61.
13. Jennings AL, Davies AN, Higgins JP, Gibbs JS, and Broadley KE. (2002). A systematic review of the use of opioids in the management of dyspnea. *Thorax*, **57**, 939–44.
14. Abernethy AP, Currow DC, Frith P, Fazekas BS, Mc Hugh A, and Bui C. (2003). Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnea. *British Medical Journal*, **327**, 523–8.
15. Man GC, Hsu K, and Sproule BJ. (1986). Effect of alprazolam on exercise and dyspnea in patients with chronic obstructive pulmonary disease. *Chest*, **90**, 832–6.
16. Moosavi SH, Binks AP, Lansing RW, Topulos GP, Banzett RB, and Schwartzstein RM. (2007). Effect of inhaled furosemide on air hunger induced in healthy humans. *Respiratory Physiology and Neurobiology*, **156**, 1–8.
17. Barak M, Isserles S, and Katz Y. (2005). Retrosternal block use in the treatment of dyspnoea. *Anaesthesia and Intensive Care*, **33**, 531–3.
18. Galbraith S, Fagan P, Perkins P, Lynch A, and Booth S. (2010). Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. *Journal of Pain Symptom Management*, **39**, 831–8.
19. Vivodtzev I, Pepin JL, Voltero G, et al. (2006). Improvement in quadriceps strength and dyspnea in severely deconditioned and malnourished COPD. *Chest*, **129**, 1540–9.
20. Marciniuk DD, Goodridge D, Hernandez P, et al. (2011). Canadian Thoracic Society COPD Committee Dyspnea Expert Working Group. Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline. *Canadian Respiratory Journal*, **18**(2), 69–78.

CHAPTER 84

Pulmonary mechanical dysfunction in the critically ill

Umberto Lucangelo and Massimo Ferluga

Key points

- Modern ventilators display real time curves, which can help the physician to understand the interactions between the patient and the ventilator.
- In patients undergoing mechanical ventilation, measurements of respiratory mechanics can be performed at the bedside in dynamic or static conditions.
- In flow-limited chronic obstructive pulmonary disease (COPD) patients, the expiration is interrupted by the next breath and, therefore, the end-expiration volume remains trapped into the alveoli. This phenomenon is called **dynamic hyperinflation** and also depends on the tidal volume, the expiratory time, the resistance and the compliance of the respiratory system.
- Patient–ventilator synchrony represents a main goal in the management of the mechanically-ventilated patient. The correct interpretation of the waveforms provided by the monitor can help the physician to set properly the ventilator.
- The variables that should be monitored during mechanical ventilation are airway pressure, flow, tidal volume, and minute ventilation, whereas positive end-expiratory pressure (PEEP) and mean airway pressure gain significance in acute respiratory distress syndrome.

Introduction

Modern ventilators employed in intensive care units (ICUs) display in real time and breath by breath flow ($\dot{V}$), volume (V), and pressure (P_{aw}) curves, both as a function of time and as a loop. Data obtained from curve analysis can help the physician to understand the interactions between the patient and the ventilator. The right interpretation of information provided from modern ventilators allows real time monitoring of the actual needs of the patient, ensuring a custom ventilatory support and reducing the risk of complications that can increase the mortality and prolong the ICU length of stay. In patients undergoing mechanical ventilation, measurements of respiratory mechanics can be performed at the bedside in dynamic (no flow interruption) or static (occlusion techniques) conditions. From these, it's also possible to derive the values of pulmonary compliance and airway resistance [1].

Dynamic conditions

In dynamic conditions, without flow interruption, the values of resistance (R_{rs}) and compliance (C_{rs}) of the respiratory system are obtained by inserting in the equation of motion, the values of airway pressure (P_{aw}), flow, and volume, provided by the ventilator time after time, and applying a multiple linear regression (least square fitting, LSF) [2]. This allows the derivation of the mean values of compliance and resistance of the respiratory system using the numerical values derived from repeated statistical operations performed on a single breath. If there is a limitation of expiratory flow, such as in chronic obstructive pulmonary disease (COPD) patients, it is appropriate to restrict the analysis at the inspiratory phase alone, since it was shown that this condition significantly undermines the accuracy of the measurements of resistance and compliance, compared with traditional (end-inspiratory occlusion). Since in volume-controlled ventilation (VCV) the flow remains constant during the whole inspiratory tract, the pressure–time curve can be considered as a pressure–volume or elastance curve. From the analysis of his shape it is possible to recognize hyperinflation of the lung, which can lead to barotrauma, and the alveolar recruitment phenomenon—both requires an adjustment of the ventilatory parameters [3].

Static conditions

Instead, in static conditions, the monitoring is provide by the multiple occlusion technique and requires a square flow waveform. If a pause is inserted at the end of the inspiratory phase, it can be possible to distinguish, analysing the pressure–time curve of the ventilator, the drop in pressure due to the resistive forces from that due to the elastic component of the respiratory system. The pressure–time curve takes a characteristic shape, with an end-inspiratory peak (P_{peak}) followed by a rapid drop (P_1), which precede a slow decay until the achievement of the plateau pressure (P_{plat}). If the end-inspiratory pause is long enough to permit both lungs to reach equilibrium, the plateau pressure can be assimilated to the alveolar pressure (P_{alv}). The pressure difference between P_{peak} and P_1 depends on the flow and resistance variations of the endotracheal tube and the airways, whereas P_1–P_{plat} depends on the **pendelluft** phenomenon, i.e. the shift of air from alveoli with short time constant to alveoli with fast time constant, and on the visco-elastic properties of the respiratory system (Fig. 84.1). The analysis of the pressure–time curve can give some useful information about the respiratory system: the P_{peak} can rise during bronchospasm episodes or presence of bronchial secretions and if a too small endotracheal tube size is used. A slow achievement of the P_{plat} suggests the presence of a flow limitation disease, whereas the missed reaching of it can tell on leaks of the respiratory circuit [4].

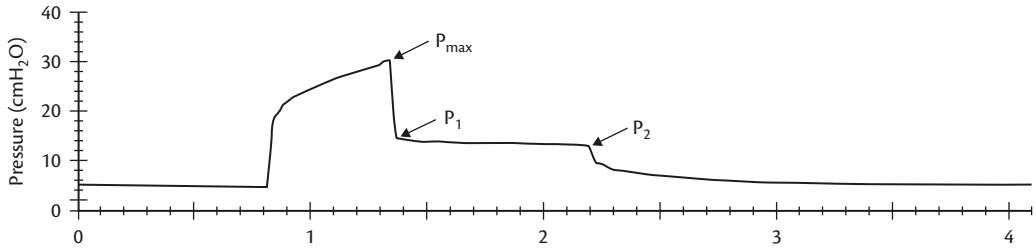


Fig. 84.1 Post-inspiratory and expiratory occlusion is performed. P_{max} is the maximum (peak) airway pressure. P_1 points to the end of the rapid post-occlusion pressure drop. P_2 points to the end of the slope pressure decay plateau.

Dynamic hyperinflation

In physiological conditions, at the end of expiration, the lungs reach the functional residual capacity, but if a flow limitation subsists, i.e. COPD patients, the expiration is interrupted by the next breath and, therefore, the end-expiration volume do not reach the functional residual capacity (FRC) and remain trapped into the alveoli, whereas it can be seen as a continuous expiratory flow. This phenomenon is called **dynamic hyperinflation** (also note as auto-PEEP or $PEEP_i$) and also depends on the tidal volume, the expiratory time, and the resistance and the compliance of the respiratory system [5]. This phenomenon could also present in the absence of conditions limiting the expiratory flow, such as high volume ventilation or an increase in the resistance of the ventilation circuit (i.e. the presence of secretions in the endotracheal tube with narrowing of the lumen) with the consequence that the lungs do not have the time to reach the functional residual capacity, which means that at the end of expiration it is still possible to detect the presence of an expiratory flow, supported by the pressure gradient between the alveoli and the atmosphere.

In paralysed patients or patients who have become well adapted to the ventilator and undergoing mechanical ventilation, it is possible to recognize the existence of dynamic hyperinflation of the lungs observing the flow and pressure curves at the end of expiration (dynamic autoPEEP). Whenever the end-expiratory flow does not reach zero, the respiratory system is considered to be hyperinflated, i.e. the alveolar pressure is greater than the atmospheric pressure or the PEEP applied. The autoPEEP can be also measured by inserting an end-expiratory occlusion, and is called static autoPEEP. This is because the dynamic autoPEEP reflects the instantaneous pressure value of short time constant lung units, while the longer time constant pulmonary units are still being emptied. The occlusion manoeuvre allows the lung units to equilibrate. Furthermore, to avoid underestimation, the value of static compliance should be measured correctly according to the presence of autoPEEP. The increase in volume due to the application of a PEEP or a condition of dynamic hyperinflation can be measured disconnect the patient from the ventilator or prolonging the expiratory time to allow the patient to reach the FRC. Once they reach the equilibrium, the patient is reconnected to the ventilator and it can be seen that the initial volume inspired will be greater than the volume expired. In the absence of extrinsic PEEP, the difference between the volume inspired and expired corresponds to the volume of air trapped in the lungs at the end of expiration. If an extrinsic PEEP is applied, the end-expiration volume observed will be the result of the sum of two components—the PEEP applied and the PEEP due to dynamic hyperinflation.

Patient–ventilator interaction

Patient–ventilator synchrony represents one of the main goals in the management of the mechanically-ventilated patient in the ICU [6]. It has been shown that up to 25% of ventilated patients exhibit problems of interaction with the ventilator and that this may be associated with increased duration of ventilatory support. The correct interpretation of the waveforms provided by the monitor can help the physician to correctly set the ventilator. Two variables determine the breath delivery in a modern positive pressure ventilator—the trigger and the cycling-off variable. The first one determines the start of the mechanical breath and can be pressure- or flow-regulated. With pressure triggering, the ventilator is able to detect the drop in airway pressure generated by the inspiratory effort of the patient—if the effort is effective, i.e. the reduction of pressure is equal to or above the threshold value set by the machine (usually between –0.5 and –1 cmH_2O), the ventilator delivers a breath. The erroneous application of a pressure trigger (e.g. a too high value in relation to the patient's muscle strength) increases the work of breathing and promotes patient–ventilator asynchrony. The consequence of this phenomenon is the need for patient sedation, lengthening the weaning from mechanical ventilation. When the physician reduces the sensitivity of the pressure trigger (i.e. the patient must generate more negative pressure to trigger the ventilator), that inevitably increases the number of ineffective breaths. They appear on the monitor like negative deflections on the pressure curve, which would not be followed by a positive deflection in the volume curve, in other words, the effort of the patient is not followed by the provision of a mechanical breath.

With a flow trigger system, the ventilator provides the ventilation circuit with a constant flow (bias flow), measured continuously at the inlet and at the outlet. When the value of the bias flow in output is lower than that in entry (and in the absence of leak in the system or when that is compensated), it means that the patient has performed an inspiratory effort and the ventilator then provides a breath even before any change of pressure in the system. The flow trigger decrease the inspiratory work, but on the other hand, promotes the phenomenon of self-triggering, i.e. incorrect triggering of breaths due to registration of changes in flow, which are not attributable to a patient's inspiratory effort (e.g. leak in the circuit, water in the circuit, and cardiogenic oscillations). Understanding the mechanisms that regulate the ventilation with flow triggering is crucial during non-invasive ventilation through a helmet or mask. The presence of leak in the system means that the bias flow needs to be set higher in order to avoid the phenomenon of self-triggering and promote patient–ventilator synchrony, ensuring adherence to the treatment.

The cycling-off variable determines how the ventilator terminates the inspiration. Usually, the criterion used in patients without inspiratory effort is time, whereas during assisted ventilation flow or pressure was preferred. When pressure is used, the ventilator opens the expiratory valve and begins the expiration when the airway pressure increases above a predetermined threshold (usually 1–3 cmH_2O), due to expiratory muscle contraction or sudden relaxation of inspiratory muscles. On the contrary, flow cycling-off occurs when inspiratory flow decreases to a preset flow value (usually a percentage of the peak inspiratory flow, 25–50%). Regardless of the type of cycling-off criterion used, the end of mechanical inspiration should coincide with the end of neural inspiration, but this synchrony is as yet not obtainable. In fact, expiratory asynchrony is common in ICU and occurs in two ways—premature or delayed termination of mechanical inspiration. The first one occurs when the exhalation valve is open, while the neural inspiration is still ongoing. The flow wave did not reverse from inspiratory to expiratory due to elastic recoil of the respiratory system, but remained around the zero line, indicating that the inspiratory effort should continue. In addition, if the remaining effort is sufficient to meet the trigger set, it generates another mechanical breath, leading to the phenomenon of so-called double trigger or breath stacking. In other words, the delayed opening of the exhalation valve can be observed on the ventilator when there is a rapid decrease of the inspiratory flow toward the end of mechanical inspiration. It should be noted, that, as mentioned previously, if the premature expiratory effort increases the pressure of the system above a predetermined threshold, the exhalation valve opens, and the expiration can start.

Capnography and CO_2 clearance

The advanced technology combination of airway flow monitoring and mainstream capnography enables a non-invasive breath-by-breath bedside calculation of CO_2 elimination per breath, independent of set ventilatory parameters. Carbon dioxide kinetics depend on three factors—peripheral production, cardiac output, and alveolar ventilation. If catabolism is assumed to be constant, haemodynamic or alveolar ventilation modifications produce typical volumetric capnographic curves. It is generally known that all situations producing a decrease in lung flow (pulmonary embolism and severe haemorrhage) affect the capnographic wave, which decreases in width. This phenomenon is due to the decrease in pulmonary blood flow, alveolar ventilation being equal. In this situation, the shape of phase III on volumetric capnograms (CO_2/V_T curve) does not vary except in width, and VCO_2 elimination decreases. Lung pathologies affect CO_2 washout, altering both convective and diffusive processes, as well as the time, available cross-section, and intra-airway concentration gradient. Bronchial obstruction makes regional alveolar ventilation inhomogeneous, altering the normal V/Q ratio. This determines different readings of CO_2 alveolar pressure that are asynchronously exhaled, changing the shape of the CO_2/V_T curve, with a prevalent increase in the slope of phase III [7].

Recently, a new index, the fraction between alveolar ejection volume and tidal volume (V_{AE}/V_T), was introduced by Lucangelo et al. [7]. Briefly, VCO_2 plotted as a function of expired volume originates a VCO_2/V_T curve (Fig. 84.2). From this curve, the last 50 points of every cycle were back-extrapolated by least-square linear regression analysis representing the ideal lung behaviour. Assuming a fixed amount of dead space contamination of 5% (dead space allowance), a straight line having its maximal value at end-expiration and slope of 0.95 (1-dead space allowance) times that of the ideal line is plotted. Alveolar ejection begins at the intersection between the VCO_2/V_T curve and the linear regression. The volume between this point and end-expiration is V_{AE}, and this is expressed as a fraction of expired tidal volume. Lucangelo et al. [7] demonstrated that V_{AE}/V_T represents a valid prognostic value in acute respiratory distress syndrome patients and is less dependent on haemodynamic variations.

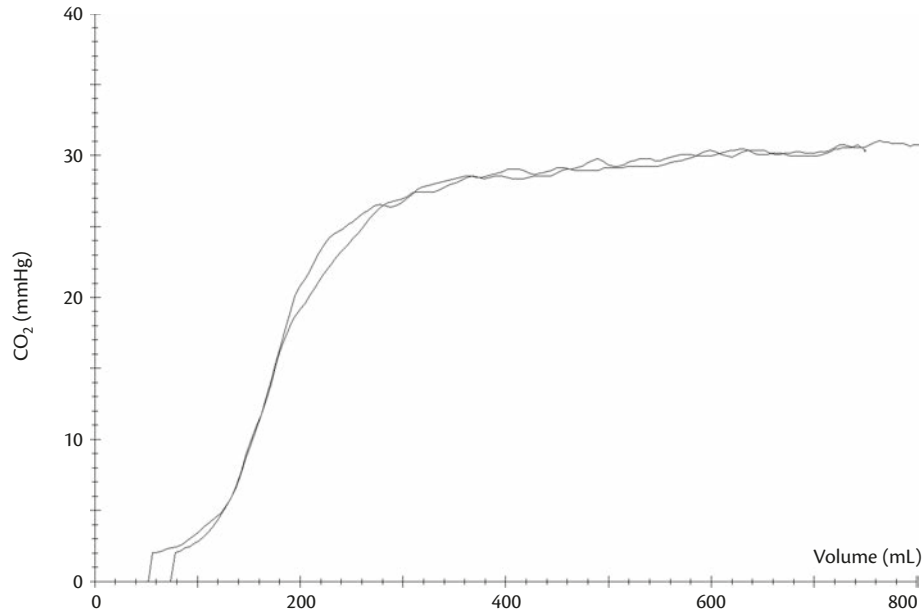


Fig. 84.2 Normal volumetric capnogram.

Conclusion

In conclusion, the only variables of crucial significance to the vast majority of patients are airway pressure, flow, tidal volume, and minute ventilation, which also provides useful data regarding the synchrony of patient–ventilator interactions.

Acknowledgements

The authors would like to thank Lluis Blanch MD, PhD, for intellectual content and revision of the chapter.

References

1. Lucangelo U, Bernabè F, and Blanch L. (2007). Lung mechanics at the bedside: make it simple. *Current Opinions in Critical Care*, **13**, 64–72.
2. Volta CA, Marangoni E, Alvisi V, et al. (2002). Respiratory mechanics by least squares fitting in mechanically ventilated patients: application on flow-limited COPD patients. *Intensive Care Medicine*, **28**, 48–52.
3. Georgopulos D, Prinianankis G, and Kondili E. (2006). Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. *Intensive Care Medicine*, **32**, 34–47.
4. D'Angelo E, Calderini E, Torri G, Robatto F, Bono D, and Milic-Emili J. (1989). Respiratory mechanics in anesthetized paralyzed humans: effects of flow, volume, and time. *Journal of Applied Physiology*, **67**, 2556–64.
5. Blanch L, Bernabè F, and Lucangelo U. (2005). Measurement of air trapping, intrinsic positive end-expiratory pressure, and dynamic hyperinflation in mechanically ventilated patients. *Respiratory Care*, **1**, 110–24.
6. Lucangelo U, Bernabè F, and Blanch L. (2005). Respiratory mechanics derived from signals in the ventilator circuit. *Respiratory Care*, **1**, 55–67.
7. Lucangelo U, Bernabè F, Vatua S, et al. (2008). Prognostic value of different dead space indices in mechanically ventilated patients with acute lung injury and ARDS. *Chest*, **133**, 62–71.

CHAPTER 85

Hypoxaemia in the critically ill

Susannah Leaver and Timothy Evans

Key points

- Hypoxaemia is reduced arterial oxygen tension (usually below 8 kPa). Hypoxia is an inadequate oxygen supply to the tissues.
- Hypoxaemia can result from a ventilation (V)/perfusion (Q) mismatch, anatomical (intrapulmonary, intracardiac) shunt, diffusion limitation, and/or hypoventilation. In clinical practice, a combination of these factors is usually responsible.
- Diagnosis is based on a clinical history and examination, with appropriate blood tests, imaging and physiological tests.
- Management involves securing the airway (if required), correcting hypoxaemia by increasing inspired oxygen concentration (FIO_2) and where necessary instituting respiratory support (mechanical, extracorporeal, non-invasive/invasive).
- The precipitating cause should be identified and treated.

Definition

The term hypoxaemia is defined by a reduction in the partial pressure of oxygen in the blood below 8 kPa/60 mmHg (normal range 10–13.3 kPa/75–100 mmHg). Hypoxia has no precise or quantitative definition, but describes inadequate oxygen supply to the tissues.

Acute respiratory failure (ARF) has conventionally been divided into hypoxaemic (type I) and hypoxaemic/hypercapnic (type II) subgroups. Type I is the principle focus of this chapter. Ventilatory/hypercapnic (type II) respiratory failure is the presence of hypoxaemia with hypercapnia ($PaCO_2$ >6.5 kPa/50 mmHg, normal range 4.5–6.2 kPa/35–45 mmHg). In clinical practice, type II can occur following type I if the underlying cause is not corrected.

Pathophysiology of hypoxaemia

Different causes of hypoxaemia are discussed below as separate entities [1], but in the critically ill a combination of these is usual.

- **Ventilation/perfusion mismatch:** In the perfect lung, each alveolus would be ventilated by a volume of gas equal to that of the blood perfusing it. However, even in normal physiological circumstances ventilation/perfusion (V/Q) mismatch exists. Both V and Q are greater in the anatomically dependent parts of the lung, which vary with posture (i.e. erect supine and prone), although while ventilation diminishes slowly across the relevant gradient (bases to apices when upright) perfusion decreases faster. V/Q mismatch is therefore greater in the lung apices. V/Q mismatch is responsible for the normal alveolar–arterial (A–a) gradient. In the diseased lung, V/Q mismatch increases as both become more heterogeneous resulting in hypoxaemia. If alveoli are ventilated and not perfused, such as occurs following pulmonary thromboembolism, a proportion of ventilation is wasted and behaves as dead space. By contrast, if alveoli are perfused and not ventilated, for example, in pneumonia, oxygenation of the blood is impaired through intrapulmonary shunt. Increased V/Q mismatch increases A–a gradient and is the commonest cause of hypoxaemia.
- Right-to-left shunt occurs when blood bypasses ventilated areas of lung. There are two types:
  - **Anatomical**: alveoli are bypassed, for example, via intracardiac shunts or pulmonary arteriovenous malformations.
  - **Physiological (intra-pulmonary) shunt**: blood passes through non-ventilated areas, for example, when alveoli are collapsed (atelectasis), consolidated (pneumonia), or fluid-filled (pulmonary oedema).
- **Diffusion limitation**: transfer of oxygen across the alveolar-capillary membrane is impaired due to alveolar and/or interstitial inflammation or fibrosis.
- **Hypoventilation**: causing low alveolar oxygen tension (PAO_2). PAO_2 is determined by the rate of oxygen extraction from the blood by the tissues, and is therefore dependent on the metabolic demands of tissues (oxygen consumption); and the supply of oxygen to the alveoli, which reflects alveolar ventilation. Low PAO_2 thereby reduces the rate of diffusion of oxygen from the alveoli to the pulmonary capillaries and hypoxaemia ensues. Carbon dioxide is retained, and arterial and alveolar PCO_2 rise. In accordance with the simplified alveolar gas equation (eqn 1) alveolar oxygen concentration falls further, but will rise if supplementary oxygen is administered.

$$PAO_2 = PIO_2 - \left(PaCO_2 / R\right) \qquad \text{[eqn 1]}$$

where PAO_2 is the alveolar partial pressure of oxygen, PIO_2 is the inspired partial pressure of oxygen, $PaCO_2$ is the arterial tension of carbon dioxide, R is the respiratory quotient.

Other causes of hypoxaemia include decreased inspired oxygen tension, such as occurs at high altitude, decreased mixed venous oxygen saturations (e.g. in anaemia or low cardiac outputs states) and changes in affinity of haemoglobin for oxygen due to a shift in the oxygen dissociation curve.

Diagnosis

History and examination

Hypoxaemia can manifest clinically in a number of ways (Box 85.1). The history and physical examination must be comprehensive as ARF may result from pulmonary or extrapulmonary causes.

Box 85.1 Signs of respiratory distress

- Respiratory rate >25/min or <8/min—the most sensitive indicator.
- Cyanosis.
- Inability to speak full sentences.
- Use of accessory muscles of respiration.
- Sweaty/clammy.
- Tachycardia/arrhythmias.
- Stridor/obstructed airway.
- Inability to lie flat.
- Pulsus paradoxus.
- Restlessness/agitation.
- Reduced conscious level.

Recording observations and calculating a clinical (early warning) score may facilitate recognition of impending or actual hypoxaemia. By contrast, delays adversely affect outcome. ARF is a dynamic process and frequent reassessment is required. A differential diagnosis of acute type I hypoxaemia is displayed in Box 85.2.

Investigations

Blood tests and infection screen

Abnormalities in common haematological and biochemical indices aid diagnosis (raised C-reactive protein indicating infection, raised B-type natri-uretic peptide indicating pulmonary oedema) and the identification of other organ system failures (e.g. acute kidney injury, disseminated intravascular coagulopathy) and/or previously unknown premorbid conditions. Furthermore, anaemia contributes to tissue hypoxaemia and polycythaemia might be secondary to chronic hypoxaemia.

Sepsis is commonly associated with acute respiratory insufficiency and a full infection screen should be sent. In immunosuppressed or immunocompromised patients evidence of fungal infection and tuberculosis should be sought. *Pneumocystis jirovecii* can induce type 1 respiratory failure.

Box 85.2 Differential diagnosis of acute type I hypoxaemia

- Exacerbation COPD/asthma.
- Pulmonary oedema.
- Pulmonary embolism.
- Pneumonia.
- Aspiration.
- Lobar collapse.
- Pneumothorax.
- Pleural effusion.
- Pulmonary contusion (blunt chest trauma).
- ALI/ARDS (pulmonary or extra-pulmonary).

Arterial blood gas

Arterial blood gas measurement quantifies the severity of hypoxaemia, identifies the type of respiratory failure and can provide information regarding metabolic status, haemoglobin, electrolytes, and lactate.

The defining criteria for respiratory failure are most applicable to patients breathing room air. When oxygen supplements are administered, calculating the A–a gradient or PaO_2:FIO_2 ratio is more useful in determining the severity of hypoxaemia.

The alveolar–arterial (A–a) gradient

The A–a gradient is the difference between the amount of oxygen in the alveoli (PAO_2) and the amount of oxygen in the blood (PaO_2) (eqn 2). Therefore:

$$\text{A} - \text{a gradient} = PAO_2 - PaO_2 \qquad \text{[eqn 2]}$$

PaO_2 is measured by arterial blood gas analysis and PAO_2 derived from the alveolar gas equation (eqn 1). Normal A–a gradient is age-dependent and in healthy adults is <3.5 kPa (26 mmHg). Hypoxaemia with a normal A–a gradient is secondary to alveolar hypoventilation (raised $PACO_2$), low PIO_2 or low barometric pressure <760 mmHg, whereas hypoxaemia associated with an elevated A–a gradient is secondary to V/Q mismatch, right–left shunt, a diffusion defect or increased oxygen extraction.

The PaO_2:FIO_2 (P:F) ratio

The ratio of partial pressure of oxygen in the blood to inspired oxygen concentration also defines the severity of hypoxaemia (normal value of > 40 kPa, >300 mmHg). P:F ratio is used to define acute respiratory distress syndrome (ARDS) with mild moderate and severe ARDS defined as values of <40 kPa, <300 mmHg; <26.6 kPa, 200 mmHg, and <13.3 kPa, <100 mmHg, respectively.

Imaging

Chest radiography is mandatory in any patient with respiratory failure and may reveal abnormalities suggestive of pneumonia, lobar collapse, pulmonary oedema, or pneumothorax. Conversely, in asthma or chronic obstructive pulmonary disease (COPD) it might be normal.

Bedside ultrasound is an increasingly recognized useful diagnostic adjunct, which can assist in revealing pleural effusions, and facilitates safe diagnostic aspiration or therapeutic drainage. Removal of fluid can improve hypoxaemia through enhanced ventilation and increased pulmonary compliance. In experienced hands, ultrasound can aid the diagnosis of a pneumothorax when suspected clinically.

Transporting critically-ill patients is not without risk, but thoracic computed tomography (CT) can identify pathologies such as pulmonary emboli, pneumothoraces, small pleural effusions, parenchymal infiltrates, and abscess cavities that are not apparent on plain chest radiography.

Electrocardiogram and echocardiography

Electrocardiogram (ECG) and echocardiography can help to exclude a cardiac cause of hypoxaemia, and differentiate between acute pulmonary oedema and ALI/ARDS, as well as identify right heart strain secondary to massive pulmonary embolism.

Fibre optic bronchoscopy

Fibre optic bronchoscopy can be used for therapeutic reasons such as to alleviate endobronchial obstruction or for diagnostic purposes

to obtain samples for microbiology or cytology, or to identify the source or bleeding in patients with haemoptysis.

Principles of management

Clearly, if the patient is 'in extremis' or in cardiopulmonary arrest the airway breathing circulation disability exposure (ABCDE) algorithm advocated by advanced life support guidelines should be adopted [2].

Once identified, the principles of management of hypoxaemia are:

- Securing the airway if required.
- Correcting hypoxaemia by increasing inspired oxygen.
- Identifying and treating the precipitating cause.
- Control of secretions.
- Instituting respiratory support (invasive/non-invasive) if necessary.

Airway management

In assessing a critically-ill patient ensuring a patent airway and adequate oxygenation takes priority even in the absence of a specific diagnosis. Simple procedures, such as head positioning (head tilt, chin lift, jaw thrust), removal of obstructions, such as vomitus or dentures, and airway adjuncts, such as nasopharyngeal or oropharyngeal airways may be sufficient. However, application of positive pressure using bag-mask supplementation, escalating to non-invasive intermittent positive pressure ventilation (NIV) administered by mask or other interface, or to endotracheal intubation and invasive ventilatory support might be required. Common indications for endotracheal intubation are displayed in Box 85.3.

Box 85.3 Indications for intubation

Inability to protect airway

- Excessive secretions.
- Obtunded patient (GCS <8).

Failure of ventilation

- Airway obstruction.
- During cardiopulmonary or respiratory arrest.
- Hypercapnia with impaired conscious level.
- Respiratory rate <10 breaths/min.

Failure of oxygenation

- Life threatening hypoxaemia.
- PaO_2 <8 kPa or sats <90% despite FiO_2 >0.6 and CPAP.

Anticipated need for ventilation

- Failure of NIV or CPAP.
- Deteriorating parameters despite optimal treatment.
- Exhaustion RR>40 breaths/min.
- In patients with neuromuscular disease (vital capacity <15 mL/ kg (normal 65–75), <1 L or <30% predicted).

Correcting hypoxaemia

Supplementary oxygen is always indicated in patients with acute hypoxaemia and should improve oxygenation in all cases except those with true right to left shunt. Oxygen can be delivered via a number of devices. However, in the initial management of a critically-ill hypoxaemic patient, who does not require immediate intubation, high dose oxygen therapy should be administered via reservoir mask at 10–15 L/min. Following stabilization this can be titrated to achieve arterial oxygen saturations estimated by oximetry of 94–98%, or escalated to supportive ventilation should the patient deteriorate. In patients at risk of hypercapnic respiratory failure controlled oxygen therapy administered via a venturi mask aiming for saturations of 88–92% should be given. Concerns regarding the provocation of hypercapnia through suppression of respiratory drive should not take precedence over the need for oxygenation.

Identify and treat the precipitating cause

Hypoxaemia is the final common pathway of a number of conditions. It may not be possible to identify the cause of the deterioration immediately, in which circumstances general respiratory and haemodynamic support should be applied. However, if the cause is identified immediate specific treatment should be instituted (see Table 85.1).

Control of secretions

Patients with ARF may produce copious secretions, for which physiotherapy and mucolytics can be helpful. Ultimately, if these cannot be controlled, endotracheal intubation can alleviate sputum retention and airway obstruction.

Non-invasive ventilation (NIV)

NIV is the delivery of a mechanically-ventilated breath, either via a portable or standard intensive care unit (ICU) ventilator, through an appropriate interface (e.g. nasal mask, full face mask, or nasal pillows), rather than an endotracheal tube or tracheostomy. The term NIV incorporates systems that deliver bi-level positive pressure ventilation (BiPAP), in which inspiratory and expiratory pressures are set at required levels, and continuous positive airway pressure ventilation (CPAP), where one pressure is maintained throughout inspiration and expiration. The rationale for NIV is to support the patient during respiratory failure, but avoiding the need for intubation and its associated complications. While there is evidence for the benefits of NIV in patients with hypercapnic respiratory failure, especially secondary to COPD, its use in hypoxaemic respiratory failure remains less evident. However, a trial of NIV in patients who do not require immediate endotracheal intubation and who have no contraindications is recommended (Box 85.4), instituted in the high dependency unit or ICU setting, and monitored over a preset time (e.g. 1–2 hours).

Acute pulmonary oedema

NIV improves pulmonary compliance in cardiogenic pulmonary oedema through alveolar recruitment and redistribution of intra-alveolar fluid. A Cochrane review comprising 21 studies found NIV to be safe and effective in reducing hospital mortality, and the need for intubation compared with standard treatment [3]. However, more recent randomized controlled trials showed

Table 85.1 Identification and treatment of common causes of acute hypoxaemia

Condition	Aids to diagnosis	Specific management
Obstructive airways disease	Previous history and lung function. Wheeze on examination. Hyperexpanded chest X-ray.	Nebulised B2 agonists and ipatropium bromide. Steroids. **Consider**: ◆ Theophyllines. ◆ Magnesium. ◆ NIV. ◆ Volatile anaesthetic agents. ◆ Ketamine. ◆ Heliox.
Pneumonia	History of cough and sputum. Signs of sepsis +/– septic shock. Raised inflammatory markers. Consolidation on chest X-ray. Positive microbiology.	Early antibiotic therapy according to local hospital policy. **Control of secretions**: ◆ Mucolytic agents. ◆ Physiotherapy.
Pulmonary oedema	History of cardiac disease. Clinical examination. ECG and chest X-ray. Raised troponin/BNP.	Diuretics. iv nitrates. CPAP. Treat acute coronary syndrome if indicated.
Pneumothorax	Clinical examination: Chest X-ray.	Decompression/intercostal drainage. Oxygen therapy.
ARDS	Presence of risk factors for ARDS. P:F ratio. Chest X-ray and ECHO.	Treat underlying cause. Conservative fluid balance [9]. Low tidal volume ventilation [8].
Pulmonary embolism	History and examination: presence of risk factors. ECG/ECHO. CTPA.	Thrombolysis if massive PE. Anti-coagulation.
Pleural effusion	History and examination. CXR.	Drainage and search for underlying cause.

NIV, Non-invasive ventilation; CPAP, continuous positive airway pressure; ECG, electrocardiogram; BNP, B-type natri-uretic peptide; ECHO, echocardiogram; PE pulmonary embolism; CTPA, CT pulmonary angiogram.

that, despite rapid improvement in physiological parameters and dyspnoea scores, NIV does not confer a mortality benefit [4,5]. Furthermore, in these patients no significant difference in the combined endpoint of death or intubation within 7 days was found between CPAP and BiPAP. Despite this, it is usual to treat hypoxic patients with acute pulmonary oedema who do not require immediate intubation with CPAP as it is easier to implement.

Severe community-acquired pneumonia

If secretions are controlled, NIV can be applied successfully in community-acquired pneumonia (CAP) [6]. In those with successful NIV, ICU stay was shorter and mortality was lower. Variables independently associated with failure of NIV were maximum sepsis-related organ failure assessment (SOFA) score during NIV, worsening infiltrates on chest X-ray at 24 hours, and higher heart rate, lower PaO_2:FIO_2 ratio and bicarbonate after 1 hour of NIV. The increased duration of NIV prior to intubation was associated with increased mortality. Thus, emphasizing the importance of a short trial of NIV with early endotracheal intubation and mechanical ventilation if no improvement is seen after a preset time.

ARDS

While small studies have shown improved oxygenation and reduced intubation rates compared with oxygen therapy alone, the majority of patients with ARDS require ventilation.

Asthma

One small trial in severe asthma found NIV improved rates of hospitalization and simple indices of lung function [7]. However, until larger randomized controlled trials are performed NIV is not routinely recommended in asthmatic patients and should only be considered in an ICU setting.

COPD

The use of NIV in hypercapnic respiratory failure is well established.

Invasive ventilation

In patients unresponsive or unsuitable for other forms of support, endotracheal intubation should be instituted in those with reversible pathology. The decision to intubate is based on clinical grounds, with the assistance of arterial blood gases and the investigations mentioned previously. Indications are outlined in

Box 85.4 Contraindications to NIV

- Life threatening hypoxaemia.
- **Non-respiratory organ failure**: haemodynamic instability.
- Inability to protect airway:
  - Reduced GCS.
  - Excessive/inability to clear secretions.
  - Gastrointestinal (GI) aspiration.
- Undrained pneumothorax.
- Agitation/confusion.
- Vomiting.
- Recent surgery involving:
  - Face.
  - Upper airway.
  - Upper GI tract.
- Facial burns or trauma.

Box 85.3. Ventilation is applied as support to facilitate treatment of the underlying condition while minimizing side effects. The optimal mode depends on the nature of the underlying disease process. Ventilator strategies should include first, titration of PEEP to maximize alveolar recruitment, increase FRC, and minimize intrapulmonary shunt, and secondly, lung protective ventilation using low tidal volumes to minimize alveolar damage secondary to cyclical opening and closing of damaged lung units [8]. These approaches can result in reduced CO_2 clearance and, therefore, a respiratory acidosis. While evidence is lacking regarding the safe level of acidosis, 'permissive hypercapnia' is accepted as long as oxygenation is not compromised. In patients with refractory hypoxaemia, despite conventional ventilation prone positioning, nitric oxide, high frequency oscillation ventilation, and extracorporeal membrane oxygenation can be considered but are beyond the scope of this chapter.

References

1. West JB (ed.) (2000). *Respiratory Physiology The Essentials*, 6th edn. Baltimore, MD: Lippincott Williams & Wilkins.
2. UK RC (ed.) (2011). *Advanced Life Support*, 6th edn. London: Resuscitation Council UK.
3. Vital FM, Saconato H, Ladeira MT, et al. (2008). Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary edema. *Cochrane Database Systematic Reviews*, **3**, CD005351.
4. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, and Nicholl J. (2008). Noninvasive ventilation in acute cardiogenic pulmonary edema. *New England Journal of Medicine*, **359**(2), 142–51.
5. Moritz F, Brousse B, Gellee B, et al. (2007). Continuous positive airway pressure versus bilevel noninvasive ventilation in acute cardiogenic pulmonary edema: a randomized multicenter trial. *Annals of Emergency Medicine*, **50**(6), 666–75.
6. Carrillo A, Gonzalez-Diaz G, Ferrer M, et al. (2012). Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. *Intensive Care Medicine*, **38**(3), 458–66.
7. Soroksky A, Stav D, and Shpirer I. (2003). A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest*, **123**(4), 1018–25.
8. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *New England Journal of Medicine*, **342**(18), 1301–8.
9. Wiedemann HP, Wheeler AP, Bernard GR, et al. (2006). Comparison of two fluid-management strategies in acute lung injury. *New England Journal of Medicine*, **354**(24), 2564–75.

CHAPTER 86

Hypercapnia in the critically ill

John G. Laffey and Brian P. Kavanagh

Key points

- Hypercapnia is a central component of current 'protective' ventilator management.
- Hypercapnia and the associated acidosis, has potentially important biological effects on immune responses, injury, and repair.
- There are distinct patient groups, such as patients with limited intracranial compliance or elevated pulmonary vascular pressures, in which hypercapnia may be poorly tolerated and must be carefully titrated.
- Hypercapnia can suppress the immune response to bacterial infection.
- Hypercapnia is usually well tolerated in health and in the critically ill, with intact survival reported even following exposure to extreme levels.

Causes of hypercapnia

The causes of elevated (or lowered) arterial carbon dioxide tension ($PaCO_2$) reflect the balance of its production, elimination and (rarely) the presence of any CO_2 in the inspired gas:

$$PaCO_2 \propto [(\text{Produced } CO_2 / \text{Eliminated } CO_2) + \text{Inspired } CO_2] \quad \text{[eqn 1]}$$

The key cause of hypercapnia in critical illness is reduced elimination. CO_2 elimination depends on alveolar ventilation ($\dot{V}_A$), i.e. the minute ventilation (tidal volume × respiratory rate) minus the dead space ventilation ($\dot{V}_D$). In severe lung or neurological disease states, a combination of low minute ventilation and/or elevated $\dot{V}_D$, means that the alveolar ventilation—and, hence CO_2 elimination—is reduced. Increased $\dot{V}_D$, e.g. due to a pulmonary embolism, also decreases CO_2 elimination unless minute ventilation is significantly increased.

Inspired CO_2 is usually negligible, but it can be elevated due to circuit misconnection, or with rebreathing circuits if CO_2 absorption fails. Increased CO_2 production is common, but rarely results in hypercapnia except in rare crises, such as malignant hyperthermia or thyroid storm, where production is massively increased. Administration of bicarbonate to buffer H^+ can transiently increase CO_2 production.

Physiological responses to hypercapnia

Physiological buffering

Hypercapnia results in higher concentrations of H^+, by combining with H_2O to form carbonic acid (H_2CO_3), which then dissociates into bicarbonate (HCO_3^-) and H^+. Because acidosis suppresses many cellular functions, physiological strategies maintain intra- and extracellular pH within narrow ranges. First, tissue buffering occurs over minutes to hours via active cell membrane ion transporters that extrude H^+ in exchange for sodium. Secondly, acidaemia inhibits production of organic acids. Finally, the kidney (if function is preserved) generates additional HCO_3^- and, by different mechanisms, directly excretes H^+; such 'renal compensation' occurs over hours to days.

Physiologic effects of $PaCo_2$ versus H^+

While many effects of hypercapnia appear to be mediated by changes in H^+, CO_2 may also have direct effects. CO_2 molecules may react directly with free amine groups, forming carbamate residues that can modify protein structure and function, e.g. the rightward shift of the Hb-O_2 dissociation curve induced by elevated $PaCO_2$ (the Bohr effect). This may explain why at a similar pH, metabolic, and hypercapnic acidosis can have different consequences.

Respiratory physiology

Hypercapnic acidosis has important effects on the pulmonary vasculature, the airways and on control of breathing. Hypercapnic acidosis increases pulmonary vascular resistance and intensifies hypoxic pulmonary vasoconstriction. CO_2 administration improves $\dot{V}/\dot{Q}$ matching (and oxygenation) in healthy volunteers. In ARDS, the increase in venous admixture during permissive hypercapnia probably occurs due to airway closure and atelectasis, rather than from a direct effect of the hypercapnic acidosis [1].

Hypercapnia can directly dilate small airways and, by indirect vagus nerve-mediated mechanisms, constrict larger airways; However, there is little net impact on airway resistance. Finally, hypercapnic acidosis stimulates respiration predominately via central chemoreceptors, which respond to increased H^+ levels in the cerebrospinal fluid. In addition, both hypercapnia and acidosis augment the responses of the peripheral chemoreceptors to hypoxia.

Cardiovascular physiology

The cardiovascular impact of hypercapnic acidosis is complex, with direct effects including diminished vascular and myocardial contractility opposed by the indirect sympatho-adrenal stimulation causing increased preload and heart rate, and decreased afterload. The net effect is an increase in cardiac output.

Hypercapnia enhances tissue oxygen delivery by increasing cardiac output, improving lung $\dot{V}/\dot{Q}$ matching and tissue blood flow. Both hypercapnia and acidosis cause a shift to the right of the Hb-O_2 dissociation curve, augmenting O_2 release at the tissues. In addition, hypercapnic acidosis may slightly elevate haematocrit, incrementally increasing O_2 delivery. At the cellular level,

hypercapnic acidosis may reduce oxygen consumption; thus, in aggregate, hypercapnic acidosis tends to augment O_2 supply and reduce demand.

Central nervous system effects

Hypercapnic acidosis causes cerebral vasodilation, mediated predominantly by local pH altering potassium channels and neuronal nitric oxide synthase, which results in an increase in cerebral blood flow and blood volume. However, when administered over a prolonged period, hypercapnic acidosis becomes buffered and the cerebral vascular tone returns towards normal. Exposure to profound levels of CO_2 (e.g. accidental exposure) causes acute narcosis and coma.

There are significant neuromuscular effects. Short-term exposure may cause reversible impairment in muscle contractility, whereas prolonged hypercapnia (e.g. for weeks) can result in structural alterations including increased slow-twitch (and decreased fast-twitch) fibres.

Mechanisms of action

Immunology and inflammation

Hypercapnia and acidosis modulate diverse components of the host immune system, especially in terms of mediator and cellular responses. Important signalling molecules, such as IL-6, IL-8, TNFα, and IL-1 are suppressed by hypercapnic acidosis. In addition, hypercapnia can inhibit expression of binding molecules, such as selectins and intercellular adhesion molecules.

Hypercapnic acidosis can inhibit NF-κB activation [2], an important early step in inflammatory gene activation; while this may have useful anti-inflammatory effects, it may also impair resolution of injury [2].

Elevated CO_2 may directly alter cellular immune responses, including neutrophil [3] and macrophage recruitment and phagocytosis. Oxidant generation, a critical step in neutrophil and macrophage function, is reduced by hypercapnia (and increased by hypocapnia). Hypercapnia can minimize depletion of (the anti-oxidant) glutathione and directly inhibit xanthine oxidase [4]. However, while free radicals contribute to tissue injury, they are also necessary for bacterial killing. The impact of hypercapnic acidosis on free radical injury may be injury-specific; e.g. hypercapnic acidosis decreases tissue nitration following reperfusion injury [5], but increases it in sepsis [6].

Injury effects: hypercapnia versus acidosis

Most of the protective effects of hypercapnic acidosis are due to acidosis, rather than hypercapnia. In the lung, buffering hypercapnia reduces the protection against injury [5], while in cultured cells it inhibits epithelial wound healing [7]. Metabolic acidosis attenuates reperfusion injury less effectively than hypercapnic acidosis [5]. Some effects of hypercapnia appear to be a function of CO_2 and not pH, such as the worsening injury in prolonged pulmonary sepsis [3], inhibition of the NF-κB pathway and altering development, as demonstrated in *Drosophila* [8].

Organ-specific effects in acute injury (laboratory and clinical)

Acute respiratory failure

The alveolus

Hypercapnia reduces alveolar-capillary permeability [4], but can also inhibit fluid clearance by alveolar epithelial cells whereby CO_2, (but not H^+) activates AMP-activated protein kinase, which promotes endocytosis (and sequestration) of Na/K-ATPase [9]. In addition, hypercapnia inhibits pulmonary epithelial healing by reducing activation of NF-κB, effects more closely associated with elevations in PCO_2 than H^+ [7].

Status asthmaticus

Although the studies of limiting tidal volume predominantly focus on ARDS, the practice was first described in status asthmaticus—the result was greater survival (and less barotrauma) versus historical controls [10].

Ventilator-associated lung injury

The potential for reduced tidal volume (V_T) to lessen mortality in ARDS was first demonstrated by Hickling et al. in two pivotal studies [11,12]. A retrospective analysis of 50 patients with severe ARDS who had limitation of P_{AW} (<30 cmH_2O) resulting in significant hypercapnia, demonstrated mortality was far less than predicted by APACHE II score (16 versus 40%) [11]. A survival advantage was again found in a series of prospectively studied patients, managed with 'permissive hypercapnia' with an actual mortality of 26.4% (versus predicted 53.3%) [12]. These pivotal studies, coining the term 'permissive hypercapnia', are the clinical basis for adoption of protective mechanical ventilation in adults with ARDS.

A retrospective analysis of the largest randomized controlled trial of tidal volume in ARDS [13] suggested that the presence of hypercapnic acidosis was associated with increased survival among patients randomized to higher—but not lower—V_T [14].

Hypercapnic acidosis directly reduces ventilator-induced lung injury in pre-clinical studies (Fig. 86.1) [15], and a key mechanism of this is attenuation of stretch-induced activation of the NF-κB pathway [16].

Gas exchange in ARDS

In patients with ARDS, reduction of V_T, with concomitant permissive hypercapnia, increases both cardiac output and intrapulmonary shunt [1]. The modest decrease in PaO_2 is a result of increased shunt fraction (because of atelectasis caused by low V_T without recruitment), as well as the decrease in alveolar ventilation; these effects are countered by the increased cardiac output and central venous oxygenation.

Pulmonary hypertension

Acute hypercapnic acidosis worsens pulmonary hypertension in patients. However, prolonged experimental hypercapnia can lower pulmonary hypertension and reverse vascular hypertrophy, in part by increasing expression of L-arginase (produces local NO) or inhibiting expression of the vasoconstrictor endothelin [17].

Pulmonary infection

Hypercapnia reduces the severity of lung injury following endotoxin [6], and in the short-term, following experimental *E. coli* inoculation [18]. However, in the longer term (~72 hours) *E. coli* pneumonia, hypercapnic acidosis worsens injury because of neutrophil inhibition (Fig. 86.2) [3]. Mortality in *Drosophilia* infected with different bacteria (*S. aureus, E. fecalius, E. coli*) is increased by the presence of elevated CO_2 (but not by lowered pH), and this is mediated in part by suppression of Rel/NF-κB, an important signalling pathway that is conserved in higher mammals [8].

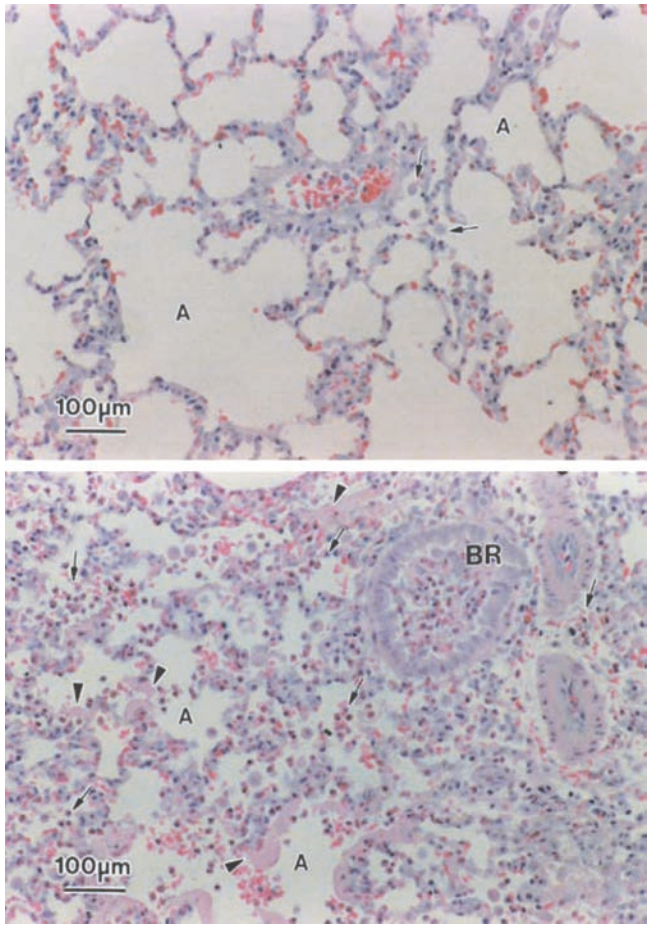


Fig. 86.1 Hypercapnic acidosis attenuates ventilation-induced lung injury. Histological injury is less in the setting of hypercapnic acidosis (PCO_2 80–100 mmHg; Panel a) compared with normocapnia (PCO_2 40 mmHg; Panel b). *Symbols:* Arrow, macrophage; arrowhead, hyaline membrane formation; 'BR', bronchiole. Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Sinclair SE et al., 2002, 'Hypercapnic acidosis is protective in an in vivo model of ventilator-induced lung injury', *American Journal of Respiratory and Critical Care Medicine*, **166**, pp. 403–8. Official journal of the American Thoracic Society.

The circulation in critical illness

Effects on the myocardium

Hypercapnic acidosis protects against experimental myocardial ischaemia-reperfusion injury; in addition, it directly reduces contractility and in vivo infarct size by reducing myocardial calcium loading and increasing coronary vasodilation.

Effects on the vasculature

In experimental abdominal sepsis, hypercapnic acidosis mitigates the onset of shock, with a comparable haemodynamic profile to dobutamine (i.e. augmentation of cardiac output and $\dot{D}O_2$) [9]; this appears to be due to the elevated CO_2 and not acidosis [7]. Finally, hypercapnia augments microcirculation in experimental models, and enhances tissue oxygenation in patients during surgery.

Hypercapnia and brain injury

Perfusion and intracranial pressure

Hypercapnia increases cerebral blood flow, and can raise intracranial pressure and, in the setting of critically raised intracranial pressure (ICP), potentially cause brainstem herniation; at very high levels it causes narcosis and coma.

Brain protection

Several studies have demonstrated protection in experimental brain injury. One study reported that hypercapnic acidosis protected against hypoxic-ischemic injury in the immature rat brain [19], although it is possible that the magnitude of the effect (i.e. the between-group difference) reflected a lowering of the $PaCO_2$ in the control group, rather than an elevation of the CO_2 in the intervention group. Hypercapnia reduces excitatory amino acids (e.g. glutamate) in cerebrospinal fluid, and coupled with inhibition of oxyradicals and neuronal apoptosis, this may contribute to CNS protection.

Renal, hepatic, and splanchnic impact

Acidosis can delay the onset of cell death in anoxic hepatocytes and renal tubules. In the gastrointestinal mucosa, elevated CO_2 preserves oxygenation during experimental haemorrhage; in addition, raised $PaCO_2$ during experimental sepsis lessens depletion of ATP and protects the mucosal permeability barrier. However, patients with ARDS exposed to permissive hypercapnia demonstrated no important alterations in splanchnic circulation.

Tolerance and contraindications

Tolerance to hypercapnia

The potential for full recovery exists following exposure to extreme levels of hypercapnia, sometimes called 'supercarbia'. Several children exposed to high levels (e.g. $PaCO_2$ 150–270 mmHg), as well as one patient with asthma ($PaCO_2$ 293 mmHg, pH 6.77) have been described with no long-term sequelae. However, extremes of hypercapnia are less likely to be well tolerated in the critically ill.

Contraindications

Contraindications are more apparent when the underlying concerns (e.g. pulmonary hypertension, raised ICP, uncontrolled metabolic acidosis) are more severe, when the extent hypercapnic acidosis is greater and its onset more acute.

Management of hypercapnic acidosis

Buffering hypercapnic acidosis

Buffering of the hypercapnic acidosis in patients with ARDS remains a common intervention with uncertain benefit. There are several buffers in clinical use.

Sodium bicarbonate

Buffering hypercapnic acidosis with bicarbonate was undertaken in several ARDS clinical trials, but concerns remain. Bicarbonate causes generation of additional CO_2, which must be excreted in order for pH to be buffered. In permissive hypercapnia, the excretion of CO_2 is limited because a lower V_T is targeted. Bicarbonate has been removed from most routine cardiac arrest algorithms.

Tromethamine

Tromethamine (*tris*-hydroxymethylaminomethane, THAM) readily penetrates cell membranes and buffers pH, while reducing $PaCO_2$. In contrast to bicarbonate, THAM is effective in a closed system. In a study of 12 patients with ARDS, acute hypercapnic

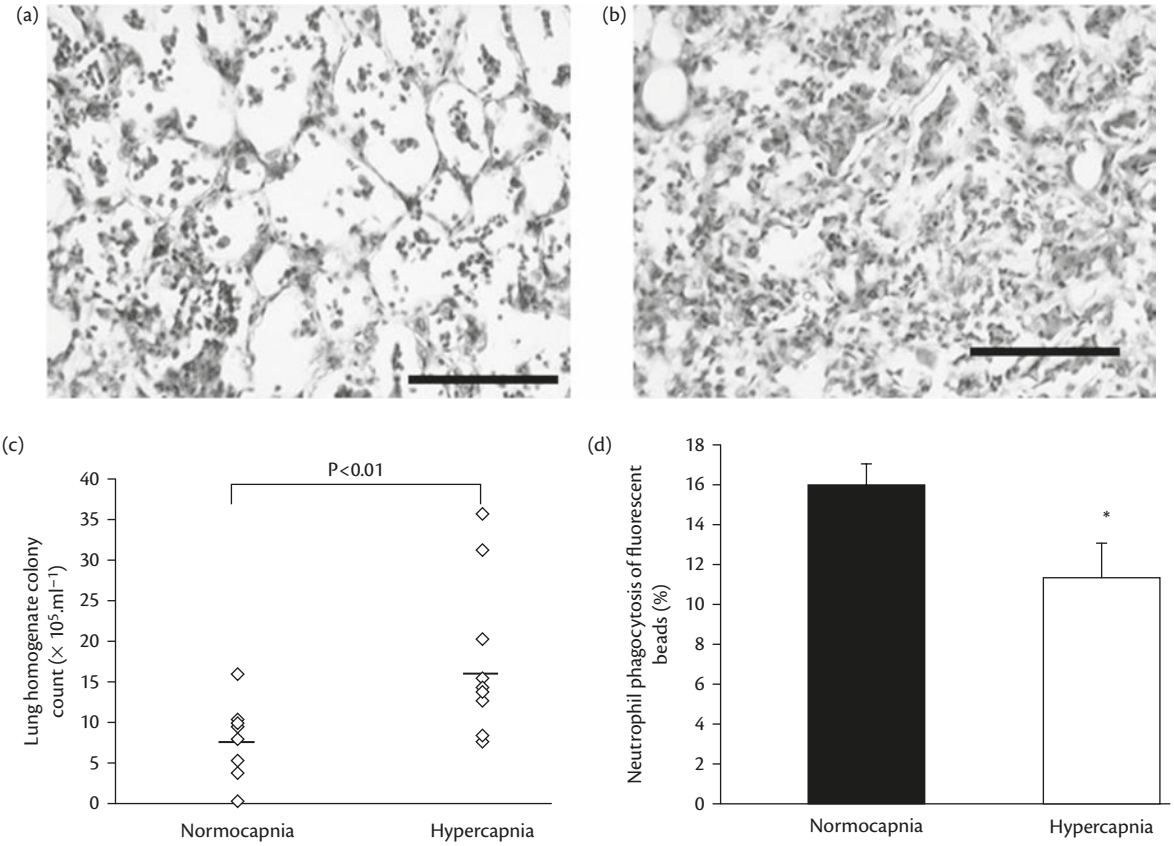


Fig. 86.2 Hypercapnic acidosis worsens lung injury and increases bacterial load in model of prolonged pneumonia. Lung tissue sections at 48 hours after infection with *E. coli* (normocapnia control; Panel a) demonstrated more severe lung injury in the setting of environmental hypercapnia (Panel b; inspired CO_2 5%). The bacterial load was greater following hypercapnia compared with normocapnia (Panel c), and neutrophils from animals exposed to hypercapnia (versus normocapnia) demonstrated reduced capacity to phagocytose fluorescent latex beads (Panel d).

acidosis decreased systemic vascular resistance, myocardial contractility and systemic mean arterial pressure, and increased cardiac output and pulmonary arterial pressure; buffering with THAM lessened these changes [20].

Carbicarb

Carbicarb is an equimolar mixture of sodium carbonate and sodium bicarbonate (Na_2CO_3 0.33 M **with** $NaHCO_3$ 0.33 M). It buffers hypercapnic acidosis without increasing lactate, but has no haemodynamic advantages.

To summarize, no outcome data support buffering hypercapnic acidosis. In the absence of correcting the primary problem, buffering hypercapnic acidosis with bicarbonate is not likely to be of long-term benefit. If the clinician elects to buffer hypercapnic acidosis in individual cases, the immediate rationale should be clear (e.g., to ameliorate potentially deleterious haemodynamic consequences) and the responses measured. THAM and carbicarb may have a role in such clinical situations.

Augmenting CO_2 clearance

Tracheal gas insufflation (TGI)

This approach delivers fresh gas into the trachea so that each inspiration commences with lower concentrations of CO_2 (than would otherwise exist from the terminal stages of the previous exhalation). However, intrinsic PEEP in invariable elevated and the overall safety profile has not been established.

Extracorporeal support

Extracorporeal membrane oxygenation (ECMO) provides oxygenation and CO_2 removal. Extracorporeal CO_2 removal can be achieved using a simpler (pumpless) circuit operating at a lower flow, which removes CO_2 from the blood at a membrane and returns blood *via* a venous cannula.

Conclusion

Permissive hypercapnia means accepting the hypercapnia that results from V_T reduction, and is undertaken to reduce the likelihood of ventilator-associated lung injury. Elevated $PaCO_2$ causes many physiological alterations, which may be neutral, harmful, or potentially beneficial. Nonetheless, high V_T can clearly cause harm and the physician must decide, for each patient individually, the optimal balance between avoiding high V_T and the potential cost of hypercapnia.

References

1. Feihl F, Eckert P, Brimioulle S, et al. (2000). Permissive hypercapnia impairs pulmonary gas exchange in the acute respiratory distress

syndrome. *American Journal of Respiratory and Critical Care Medicine*, **162**, 209–15.
2. O'Toole D, Hassett P, Contreras M, et al. (2009). Hypercapnic acidosis attenuates pulmonary epithelial wound repair by an NF-kappaB dependent mechanism. *Thorax*, **64**, 976–82.
3. O'Croinin DF, Nichol AD, Hopkins N, et al. (2008). Sustained hypercapnic acidosis during pulmonary infection increases bacterial load and worsens lung injury. *Critical Care Medicine*, **36**, 2128–35.
4. Shibata K, Cregg N, Engelberts D, Takeuchi A, Fedorko L, and Kavanagh BP. (1998). Hypercapnic acidosis may attenuate acute lung injury by inhibition of endogenous xanthine oxidase. *American Journal of Respiratory and Critical Care Medicine*, **158**, 1578–84.
5. Higgins BD, Costello J, Contreras M, Hassett P, O'Toole D, and Laffey JG. (2009). Differential effects of buffered hypercapnia versus hypercapnic acidosis on shock and lung injury induced by systemic sepsis. *Anesthesiology*, **111**, 1317–26.
6. Laffey JG, Honan D, Hopkins N, Hyvelin JM, Boylan JF, and McLoughlin P. (2004). Hypercapnic acidosis attenuates endotoxin-induced acute lung injury. *American Journal of Respiratory and Critical Care Medicine*, **169**, 46–56.
7. Costello J, Higgins B, Contreras M, et al. (2009). Hypercapnic acidosis attenuates shock and lung injury in early and prolonged systemic sepsis. Critical Care Medicine, **37**, 2412–20.
8. Helenius IT, Krupinski T, Turnbull DW, et al. (2009). Elevated CO2 suppresses specific Drosophila innate immune responses and resistance to bacterial infection. *Proceedings of the National Academy of Sciences, USA*, **106**, 18710–15.
9. Vadasz I, Dada LA, Briva A, et al. (2008). AMP-activated protein kinase regulates CO2-induced alveolar epithelial dysfunction in rats and human cells by promoting Na,K-ATPase endocytosis. *Journal of Clinical Investigations*, **118**, 752–62.
10. Darioli R and Perret C. (1984). Mechanical controlled hypoventilation in status asthmaticus. *American Reviews of Respiratory Diseases*, **129**, 385–7.
11. Hickling KG, Henderson SJ, and Jackson R. (1990). Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Medicine*, **16**, 372–7.
12. Hickling KG, Walsh J, Henderson S, and Jackson R. (1994). Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Critical Care Medicine*, **22**, 1568–78.
13. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *New England Journal of Medicine*, **342**, 1301–8.
14. Kregenow DA, Rubenfeld GD, Hudson LD, and Swenson ER. (2006). Hypercapnic acidosis and mortality in acute lung injury. *Critical Care Medicine*, **34**, 1–7.
15. Sinclair SE, Kregenow DA, Lamm WJ, Starr IR, Chi EY, and Hlastala MP. (2002). Hypercapnic acidosis is protective in an in vivo model of ventilator-induced lung injury. *American Journal of Respiratory and Critical Care Medicine*, **166**, 403–8.
16. Contreras M, Ansari B, Curley G, et al. (2012). Hypercapnic acidosis attenuates ventilation-induced lung injury by a nuclear factor-kappaB-dependent mechanism. *Critical Care Medicine*, **40**, 2622–30.
17. Kantores C, McNamara PJ, Teixeira L, et al. (2006). Therapeutic hypercapnia prevents chronic hypoxia-induced pulmonary hypertension in the newborn rat. *American Journal of Physiology—Lung Cellular and Molecular Physiology*, **291**, L912–22.
18. Chonghaile MN, Higgins BD, Costello J, and Laffey JG. (2008). Hypercapnic acidosis attenuates lung injury induced by established bacterial pneumonia. *Anesthesiology*, **109**, 837–48.
19. Vannucci RC, Towfighi J, Heitjan DF, and Brucklacher RM. (1995). Carbon dioxide protects the perinatal brain from hypoxic-ischemic damage: an experimental study in the immature rat. *Pediatrics*, **95**, 868–74.
20. Weber T, Tschernich H, Sitzwohl C, et al. (2000). Tromethamine buffer modifies the depressant effect of permissive hypercapnia on myocardial contractility in patients with acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **162**, 1361–5.

CHAPTER 87

Cardiovascular interactions in respiratory failure

Jae Myeong Lee and Michael R. Pinsky

Key points

- Spontaneous ventilation is exercise.
- Acute respiratory failure placed an increased metabolic demand on the cardiovascular system.
- Spontaneous inspiration increases venous return and impedes left ventricular ejection increasing intrathoracic blood volume.
- Positive pressure ventilation decreases venous return and augments left ventricular ejection decreasing intrathoracic blood volume.
- Lung hyperinflation, either by spontaneous ventilation or mechanical ventilation, increases pulmonary vascular resistance and can cause acute cor pulmonale.

Introduction

Acute respiratory failure (ARF) can directly alter cardiovascular function in a number of seemingly unrelated ways. However, many of these effects are predictable from a knowledge of the determinants of cardiovascular function. The respiratory and the cardiovascular systems are not separate, but tightly integrated. The ultimate cardiovascular response to ARF is dependent on the patient's baseline cardiovascular state, the type of respiratory dysfunction present, and the ventilatory pattern and ventilatory support being used.

Hypoxaemia causes increased demand on the cardiovascular system to deliver higher cardiac output (CO) to sustain a constant O_2 delivery. Spontaneous inspiratory efforts during acute bronchospasm and acute lung injury (ALI) induce marked/prominent negative swings in intrathoracic pressures (ITP) as the muscles of inspiration try to increase lung volume against increased airflow resistance or stiff lungs, respectively. Both of which also increase the work of breathing. Both lung under- and hyperinflation will increase pulmonary vascular resistance directly impeding right ventricular (RV) ejection. Lung hyperinflation also limits diastolic filling. Furthermore, spontaneous inspiratory efforts will decrease ITP, increasing venous return and intrathoracic blood volume, whereas positive-pressure ventilation by increasing ITP will have the opposite effect. These specific processes explain all the relevant determinants of heart–lung interaction.

Thus, heart–lung interactions involve four basic concepts:

- Inspiration increases lung volume above the end-expiratory volume.
- Spontaneous inspiration decreases ITP.
- Positive-pressure ventilation increases ITP.
- Spontaneous ventilation is exercise.

Haemodynamic effects of changes in lung volume

Lung inflation alters autonomic tone, pulmonary vascular resistance, and at high lung volumes, compresses the heart in the cardiac fossa. The associated diaphragmatic descent also increases intra-abdominal pressure and compresses the liver increasing hepatic vascular resistance. Each of these processes may predominate in determining the final cardiovascular state. Small tidal volumes (<10 mL/kg) increase heart rate (HR) by vagal (parasympathetic) withdrawal, causing an inspiration-associated cardiac acceleration called **respiratory sinus arrhythmia**. Whereas large tidal volumes (>15 mL/kg) decrease HR, arterial tone, and cardiac contractility by sympathetic withdrawal.

The haemodynamic response to increases in lung volume are mainly mechanical [1]. Lung inflation, independent of changes in ITP, primarily affects cardiac function and CO by altering RV preload and afterload, and left ventricular (LV) preload. First, inspiration induces diaphragmatic descent that increases hepatic outflow resistance, while simultaneously increasing intra-abdominal pressure. Systemic venous return to the heart is a function of the pressure difference between the right atrium and the systemic venous reservoirs and the resistance to venous return. Since a large proportion of the venous blood volume is in the abdomen, increases in intra-abdominal pressure will increase the venous pressure in this vascular space augmenting venous blood flow [2]. However, diaphragmatic descent will compress the liver increasing hepatic outflow resistance thus decreasing flow from the splanchnic venous reservoirs to the right heart. Complicating this further, inspiration will shift venous flow from high resistance splanchnic circuits, which must drain through the liver, to low resistance systemic venous circuits, making flow greater for the same driving pressure. Thus, inspiration may increase, decrease, or not alter venous return depending on which of these factors are predominant. Inspiration will increase venous return in volume overloaded states, whereas in hypovolaemic states and with hepatic cirrhosis, the same inspiratory effect will decrease venous return.

RV output is sensitive to changes in pulmonary outflow resistance. Alveolar collapse occurs in ALI and is associated with increased pulmonary vasomotor tone due to hypoxic

pulmonary vasoconstriction [3]. Alveolar recruitment by restoring end-expiratory lung volume back to functional residual capacity (FRC) and improving oxygenation often decreases hypoxic pulmonary vasoconstriction, thus decreasing RV outflow resistance. Increasing lung volume above FRC in increases RV outflow resistance [4] due to progressive increases in transpulmonary pressure (airway pressure relative to ITP) associated with increasing lung volume. Since the heart and great vessels exist in the thorax, and sense ITP as their surrounding pressure, increases in transpulmonary pressure will induce pulmonary vascular collapse if transpulmonary pressure exceeds pulmonary artery pressure [1]. Thus, hyperinflation increases pulmonary vascular resistance and impedes RV ejection. Using the smallest tidal volumes, least PEEP, and other protective lung ventilation strategies will also improve RV ejection.

LV end-diastolic volume can be altered by ventilatory changes in three ways. First, since the RV and LV outputs are in series, changes in RV preload will eventually alter LV preload. Secondly, by ventricular interdependence changes, RV end-diastolic volume inversely changes LV diastolic compliance [5]. Ventricular interdependence is a major factor in altering LV output during spontaneous ventilation when RV end-diastolic volumes may vary widely from expiration (small volumes) to inspiration (large volumes). Thirdly, increasing lung volume restricts absolute cardiac volume by directly compressing the heart [1]. As the lungs expand, the heart is compressed in the cardiac fossa and absolute bi-ventricular volume is limited in a fashion analogous to cardiac tamponade.

Haemodynamic effects of changes in intrathoracic pressure

The heart within the thorax is a pressure chamber within a pressure chamber. Thus, changes in ITP will affect the pressure gradients for both systemic venous return to the RV and systemic outflow from the LV, independent of the heart itself [1,4]. Increases in ITP, by both increasing Pra and decreasing transmural LV systolic pressure, will reduce these pressure gradients, decreasing intrathoracic blood volume. Whereas decreases in ITP, using the same argument, will augment venous return and impede LV ejection, increasing intrathoracic blood volume. Variations in Pra represent the major factor determining the fluctuation in pressure gradient for systemic venous return during ventilation [2]. Increases in ITP, as seen with positive-pressure ventilation or hyperinflation, by increasing Pra decrease venous return, whereas decreases in ITP, as seen with usual spontaneous inspiration, by decreasing Pra increase venous return.

Spontaneous inspiratory efforts by decreasing ITP both increases lung volume and decreases right atrial pressure accelerating blood flow into the RV [6] and increasing pulmonary blood flow on the subsequent beat. Thus, normal respiration-associated haemodynamic changes maximize ventilation–perfusion temporal matching because inspiration matches increased alveolar capillary flow. However, this venous flow augmentation is limited because if transmural vascular pressure falls below zero the extrathoracic veins collapse at the thoracic inlet, limiting flow [7]. This 'flow-limitation' is useful, because ITP can decrease greatly with obstructive inspiratory efforts. Without this flow-limitation, the RV could overdistend and fail.

Thus, we can see that spontaneous ventilatory efforts performed against a resistive (bronchospasm) or elastic (ALI) load, decrease LV stroke volume via a complex mechanism collectively called pulsus paradoxus that decreases LV end-diastolic volume and LV ejection. Transient intraventricular septal shift into the LV lumen by the dilated right ventricle plus pericardial volume restraint decreases absolute LV end-diastolic volume [1,5]. Furthermore, increases in LV afterload (LV ejection pressure minus ITP) increase LV end-systolic volume [8].

LV afterload is approximated by maximal systolic wall tension, which is proportional to the product of transmural LV pressure and LV volume. Since increasing ITP will mechanically decrease transmural LV pressure, if arterial pressure is constant, increases in ITP will unload the LV, whereas decreases in ITP have the opposite effect [8]. Thus, in ventricular failure due to fluid resuscitation, increases in ITP may increase CO by decreasing LV afterload [8,9].

Sudden increases in ITP increase arterial pressure to an amount equal to the increase in ITP without changing aortic blood flow. If the increase in ITP is sustained, however, then the ITP-induced decrease in systemic venous return will eventually decrease LV output, decreasing arterial pressure. In the steady state, changes in ITP that result in altered CO also alter peripheral vasomotor tone through baroreceptor mechanisms. Baroreceptor reflexes tend to keep arterial pressure and CO constant. Thus, if ITP increases arterial pressure without changing transmural arterial pressure, then the periphery would vasodilate to maintain a constant extrathoracic arterial pressure-flow relation [4]. Since coronary perfusion pressure is not increased by ITP-induced increases in arterial pressure, whereas mechanical constraint from the expanding lungs may obstruct coronary blood flow, coronary hypoperfusion from a combined coronary compression, and a decrease in coronary perfusion pressure is a potential complication of increased ITP.

Although increases in ITP should augment LV ejection by decreasing LV afterload, this effect has limited therapeutic potential, just as all afterload reducing therapies are limited by both the minimal end-systolic volume and the obligatory decrease in venous return. Thus, the potential augmentation of LV ejection by increasing ITP is limited because increasing ITP, by reducing LV ejection pressure, can only decrease end-systolic volume, which is usually already small and cannot decrease much more except in markedly dilated cardiomyopathies. However, the decrease in venous return associated with the increase in ITP can continue to total circulatory arrest.

From the perspective of the ejecting LV, there is no difference between increasing ITP from a basal end-expiratory level and eliminating negative end-inspiratory ITP swings seen in spontaneous ventilation. Removing negative swings in ITP may be more clinically relevant than increasing ITP for many reasons. First, many pulmonary diseases are associated with exaggerated decreases in ITP during inspiration. In restrictive lung disease states, such as interstitial fibrosis or acute hypoxaemic respiratory failure, ITP must decrease greatly to generate a large enough transpulmonary pressure to ventilate the alveoli. Similarly, in obstructive diseases, such as upper airway obstruction or asthma, large decreases in ITP occur owing to increased resistance to inspiratory airflow. Secondly, exaggerated decreases in ITP require increased respiratory efforts that increase the work of breathing, taxing a potentially stressed circulation. Finally, the exaggerated decreases in ITP can only increase venous blood flow increasing intrathoracic blood

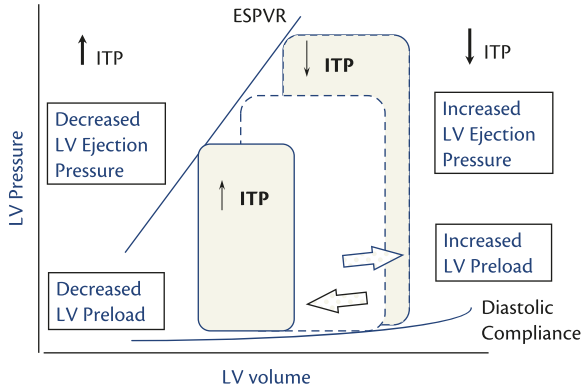


Fig. 87.1 The effect of increasing (dark shading) and decreasing (no shading) intrathoracic pressure (ITP) on the left ventricular (LV) relation with LV contractility is normal. The slope of the LV end-systolic pressure volume relationship (ESPVR) is proportional to contractility. The slope of the diastolic LV pressure-volume relationship defines diastolic compliance.

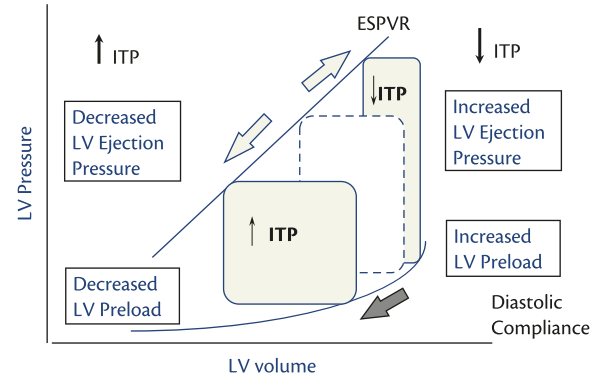


Fig. 87.2 The effect of increasing (dark shading) and decreasing (no shading) intrathoracic pressure (ITP) on the left ventricular (LV) relation in congestive heart failure when LV contractility is reduced and intravascular volume is expanded. The slope of the LV ESPVR is proportional to contractility. The slope of the diastolic LV pressure–volume relationship defines diastolic compliance.

volume. The level to which ITP must decrease to induce venous flow-limitation is different in different circulatory conditions but occurs in most patients below an ITP of –10 cmH_2O [1]. Thus, further decreases in ITP will further increase only LV afterload without increasing venous return. Accordingly, abolishing these markedly negative swings in ITP should disproportionally reduce LV afterload more than venous return (LV preload). These concepts of a differential effect of increasing and decreasing ITP on cardiac function are illustrated for both normal and failing hearts in Figs 87.1 and 87.2 using the LV pressure-volume relationship during one cardiac cycle to interpose venous return (end-diastolic volume) and afterload (end-systolic volume). Using this logic, one would predict that by endotracheal intubation and ventilation in patients requiring markedly negative swings in ITP to breath will abolish the increased LV afterload without impairing systemic venous return. These interactions have important implications in the decision to both institute and withdraw mechanical ventilatory support, as in acute cardiogenic pulmonary oedema.

Ventilation as exercise

Spontaneous ventilatory efforts require muscular activity, consume O_2 and produce CO_2, they represent a metabolic load on the cardiovascular system. Although ventilation normally requires less than 5% of total O_2 delivery to meet its demand, in lung disease states where the work of breathing is increased, such as pulmonary oedema or bronchospasm, the requirements for O_2 may increase to 25% or more of total O_2 delivery [10]. Furthermore, if cardiac output is limited, then spontaneous ventilation may not be possible without additional cardiovascular support. The institution of mechanical ventilation for ventilatory and hypoxaemic respiratory failure may reduce metabolic demand on the stressed cardiovascular system, decrease O_2 consumption, and thus for the same cardiac output, mixed venous oxygen saturation (SvO_2) will increase. In patients with right-to-left intrapulmonary shunts, this increased SvO_2 will increase PaO_2 independent of changes in ventilatory status. Intubation and mechanical ventilation, when adjusted to the metabolic demands of the patient, may dramatically decrease the work of breathing, resulting in increased O_2 delivery to other vital organs.

Functional haemodynamic monitoring

Positive pressure inspiration by increasing ITP passively increases right atrial pressure, venous return transiently decreases. This dynamic flow variation will alter both RV filling and RV output, if the RV is volume responsive and then after a short pulmonary transient time alter LV filling and LV output if the LV is volume responsive. Numerous studies have documented that the associated LV stroke volume variation (SVV) and arterial pulse pressure variation (PPV) will vary in direct proportion to volume responsiveness and can be used for clinical decision making about fluid therapy in ARF [11–13]. A PPV >13% or a SVV >10% on positive-pressure ventilation is highly predictive of volume responsiveness and the accuracy of these variations was excellent in predicting volume responsiveness (PPV 0.94 (receiving operation curve), systolic pressure variation (SPV) 0.86, and SVV 0.84) with PPV significantly better than SPV or SVV ($p < 0.001$) [14].

If chest wall compliance is normal, however, a minimal tidal volume (V_T) of 8 mg/kg is required to cause a large enough swing in ITP to induce theses effects. Since lower V_T ventilation is recommended in the management of patients with ALI, the ITP swings may not be large enough to allow PPV and SVV thresholds to be predictive [9]. Still, many patients with ALI also have increased intra-abdominal pressure owing to fluid resuscitation and ileus [15]. This increased intra-abdominal pressure decreases chest wall compliance, making the ITP swings during positive-pressure ventilation still predictive of volume responsiveness despite low V_T breathing [16,17]. Therefore, PPV or SVV often has a lesser predictive value of identifying volume responsiveness when measured in patients receiving a V_T <8 mL/kg [18,19], but if present signifies volume responsiveness.

References

1. Butler J. (1983). The heart is in 'good hands'. *Circulation*, **67**(6), 1163–8.
2. Fessler HE, Brower R, Wise RA, and Permutt S. (1992). Effects of positive end-expiratory pressure on the canine venous return curve. *American Reviews of Respiratory Diseases*, **146**(1), 4–10.
3. Mitchell JR, Doig CJ, Whitelaw WA, Tyberg JV, and Belenkie I. (2011). Volume loading reduces pulmonary vascular resistance in ventilated animals with acute lung injury: evaluation of RV afterload. *American Journal of Physiology*, **300**(3), R763–70.

4. Pinsky MR, Matuschak GM, and Klain M. (1985). Determinants of cardiac augmentation by elevations in intrathoracic pressure. *Journal of Applied Physiology*, **58**(4), 1189–98.
5. Taylor RR, Corell JW, Sonnenblick EH, and Ross J, Jr. (1987). Dependence of ventricular distensibility on filling of the opposite ventricle. American Journal of Physiology, **213**(3), 711–18.
6. Pinsky MR. (1984). Determinants of pulmonary artery flow variation during respiration. *Journal of Applied Physiology*, **56**(5), 1237–45.
7. Guyton AC, Lindsey AW, Abernathy B, and Richardson T. (1957). Venous return at various right atrial pressures and the normal venous return curve. *American Journal of Physiology*, **189**, 609–15.
8. Buda AJ, Pinsky MR, Ingles NB, Daughters GT, and Alderman EL. (1979). Effect of intrathoracic pressure on left ventricular performance. *New England Journal of Medicine*, **301**(9), 453–9.
9. Renner J, Cavus E, Meybohm P, et al. (2007). Stroke volume variation during hemorrhage and after fluid loading: impact of different tidal volumes. *Acta Anaesthesiologica Scandinavica*, **51**(5), 538–44.
10. Stock MC, David DW, Manning JW, and Rtyan ML. (1999). Lung mechanics and oxygen consumption during spontaneous ventilation and severe heart failure. *Chest*, **102**(1), 279–83.
11. Cannesson M, Le Manach Y, Hofer CK, et al. (2011). Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a 'gray zone' approach. *Anesthesiology*, **115**(2), 231–41.
12. Hofer CK, Muller SM, Furrer L, Klaghofer R, Genoni M, and Zollinger A. (2005). Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting. *Chest*, **128**(2), 848–54.
13. Perel A, Pizov R, and Cotev S. (1987). Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. *Anesthesiology*, **67**(4), 498–502.
14. Marik PE, Cavallazzi R, Vasu T, and Hirani A. (2009). Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Critical Care Medicine*, **37**(9), 2642–7.
15. Krebs J, Pelosi P, Tsagogiorgas C, Alb M, and Luecke T. (2009). Effects of positive end-expiratory pressure on respiratory function and hemodynamics in patients with acute respiratory failure with and without intra-abdominal hypertension: a pilot study. *Critical Care*, **13**(5), R160.
16. Gunn SR, Kim HK, Harrigan P, and Pinsky MR. (2006). Ability of pulse contour and esophageal Doppler to estimate rapid changes in stroke volume. *Intensive Care Medicine*, **32**(10), 1537–46.
17. da Silva Ramos FJ, de Oliveira EM, Park M, Schettino GP, and Azevedo LC. (2011). Heart–lung interactions with different ventilatory settings during acute lung injury and hypovolaemia: an experimental study. *British Journal of Anaesthesia*, **106**(3), 394–402.
18. Vallee F, Richard JCM, Mari A, et al. (2009). Pulse pressure variations adjusted by alveolar driving pressure to assess fluid responsiveness. *Intensive Care Medicine*, **35**(6), 1004–10.
19. Debacker D, Taccone FS, Holsten R, Ibrahimi F, and Vincent JL. (2009). Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology*, **110**(5), 1092–7.

PART 4.6

Ventilatory support

CHAPTER 88

Physiology of positive-pressure ventilation

Göran Hedenstierna and Hans Ulrich Rothen

Key points

- Positive-pressure ventilation (PPV) compared with spontaneous breathing increases airway and alveolar pressures.
- It also distributes ventilation preferentially to non-dependent, possibly less perfused lung regions.
- PPV squeezes blood flow to regions with lower alveolar pressure, possibly less or not at all ventilated regions.
- It impedes venous return to the right heart that may lower cardiac output.
- PPV elevates systemic capillary pressure that promotes vascular leakage, at the same time abdominal lymph drainage may be impeded, all-in-all promoting oedema formation.

Introduction

Ventilatory support can be provided by different techniques, the dominating one being positive pressure ventilation (PPV), with the breath forced into the lungs via the airways by increasing airway pressure. The force applied to the respiratory system (lung and chest wall) is the upper airway pressure (P_{AW}) minus the pressure surrounding the body, normally atmospheric pressure (P_B). This pressure difference can be partitioned into P_{AW} minus pleural pressure (and its substitute, oesophageal pressure, P_{ES}) for expanding the lung and the pressure required to expand the chest wall (ribcage and the diaphragm), P_{ES} minus P_B. In principle, these pressures generate the volume changes also during a spontaneous breath.

Respiratory muscle tone

Although pressure differences over the respiratory system may be similar during spontaneous breathing (SB) and PPV, the effects on the ventilation distribution and lung perfusion are different. In addition, with PPV there is frequently a fall in respiratory muscle tone, either by the deliberate use of muscle relaxants, anaesthetics, or sedatives or by reduced consciousness of the patient. This causes a lowering of the resting lung volume (FRC) [1], which has an additional and substantial effect on respiratory and circulatory mechanics.

With SB, the major respiratory muscle is the diaphragm and when it contracts the dome is flattened and the thoracic cavity will be increased. In the supine position, the tensing of the diaphragm will mainly shorten the dorsal fibres, which are the ones that are most elongated because they have been pushed cranially by the abdominal organs. In addition, the distribution of muscle fibres in the diaphragm may vary with more fibres in the dorsal part studied by Decramer et al. in dogs [2]. Moreover, dependent lung regions (dorsal in supine position) are located on the lower, steeper part and non-dependent regions are located higher up on the upper, flatter part of the pressure–volume curve. An inspiration is assumed to cause similar change in the transpulmonary pressure along the whole pleural space, causing larger volume change for dependent than non-dependent lung regions.

Ventilation distribution

With mechanical ventilation, the distribution of the breath may be different from that by spontaneous breathing. The reason is two-fold. First, the lung volume is reduced because of loss of respiratory muscle tone as discussed in 'Respiratory Muscle Tone', and this promotes airway closure that occurs primarily in more dependent lung regions [3]. The closure prevents at least the initial inspiration to go to the dependent regions, but during the succeeding inflations, the airways may open up so that some ventilation goes to lower lung (dorsal regions in the supine subject). If airways are continuously closed, which is also possible in a healthy lung when breathing at low lung volume, atelectasis will eventually develop because of gas absorption behind the continuously closed airways. The time it takes until collapse occurs depends on the inspired oxygen concentration, from a few minutes with 100% oxygen to a few hours with air [4]. The other reason for a different distribution of the breath is that the diaphragm is no longer acting as an active muscle, but just as a passive membrane separating abdominal content from the thoracic cavity. Since the abdominal pressure increases down from anterior to posterior in the gravitational orientation, more pressure is needed to move the dependent part of the diaphragm and the abdominal content than the non-dependent region of the diaphragm. Volume expansion of the thoracic cavity will thus be facilitated in the upper regions [5].

The smaller lung volume that is frequently seen in the mechanically-ventilated subject increases airway resistance and the difference will be larger between the dependent, narrower, and upper, non-dependent, less narrowed airways [6]. This adds to the shift in ventilation to upper lung regions.

Pulmonary circulation

The pulmonary circulation is a low pressure system and is, therefore, susceptible to increased intrathoracic pressure. The lower the vascular pressure is, the larger is the difference in perfusion

to upper and lower lung units [7]. With increase in vascular pressure as, for example, during physical exercise, perfusion of the lung will be more homogeneous. If alveolar pressure is increased, as during a mechanical breath, it may exceed that of the surrounding capillaries, compressing them so that the alveolus is non-perfused. This is possible, even likely, in the non-dependent lung regions where perfusion pressure is the lowest. Due to hydrostatic forces vascular pressure increases down the lung by approximately 1 cm H_2O (0.7 mmHg) per cm distance so there may be a pressure difference between top and bottom of the lung by 11–12 mmHg. A mechanical breath will thus force the blood flow towards dependent regions, whereas ventilation is forced towards non-dependent regions. The ventilation/perfusion ratio (V/Q) departs from an ideal ratio of 1 to well above 1 ('high V/Q') in non-dependent regions (a dead space like effect) to a ratio well below 1 ('low V/Q') in dependent lung regions causing a shunt-like effect [8] (Fig. 88.1).

The spontaneous breath may more easily recruit collapsed lung tissue in the dependent regions because of larger tidal swing of the diaphragm in the dorsal part than in the mechanically-ventilated subject, where the diaphragm moves more in the non-dependent regions, as mentioned in 'Ventilation Distribution'. A prerequisite for such beneficial effects is that the spontaneous breath is large enough to overcome the forces that keep collapsed alveoli together (e.g. surface tension [9]). This should reduce shunting and improve oxygenation of blood. However, even without recruitment of collapsed lung by the spontaneous breath a beneficial effect can still be seen. This is because the spontaneous breath attracts blood flow to ventilated regions from collapsed areas, whereas the mechanical breath squeezes blood away from the ventilated region to atelectatic and consolidated regions [10,11].

Systemic circulation

PPV may impede return of venous blood to the thorax and the right heart [12]. With high enough pressure, stroke volume and also heart rate can be reduced to zero. A hypovolaemic subject will be more susceptible to a decrease in cardiac output when intrathoracic pressure is elevated as during mechanical ventilation [12].

Impeded venous return raises venous pressure that is causing an increase in systemic capillary pressure with increased capillary leakage and possible oedema formation in peripheral organs. Lymph vessels will take care of an increased capillary leakage and there is also a return of fluid in the distal end of the capillary back to the venous system. However, in the abdomen lymph flow may be impeded because the thoracic duct is the main channel for the abdominal lymph return. It passes through the thorax and with an elevated intrathoracic pressure as during mechanical ventilation, the thoracic duct may be compressed and lymph flow impeded [13]. Thus, there may be a double cause of abdominal oedema formation in the mechanically-ventilated subject—increased capillary leakage and impeded lymph drainage. PPV may also impede

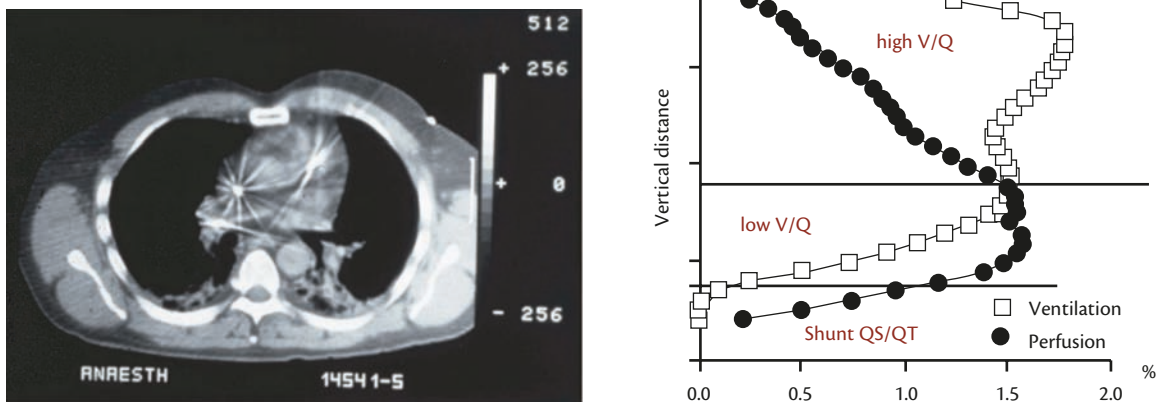


Fig. 88.1 Atelectasis (left panel) and distributions of ventilation and blood flow in an anaesthetized and mechanically-ventilated (ZEEP) subject (right panel). Note the atelectasis and absence of ventilation in the bottom of the lungs, causing shunt (QS), the poor ventilation in a zone above the atelectasis, causing low V/Q, and the preferential ventilation of the upper half of the lung, well in excess of perfusion, causing high V/Q and adding to dead space as measured by CO_2 technique. Compare also with the schematic drawing of ventilation and perfusion distributions in awake, upright man in the insert (upper right).
Data from Tokics L et al., 'V/Q distribution and correlation to atelectasis in anaesthetized paralyzed humans', *Journal of Applied Physiology*, 1996, **81**(4), pp. 1822–33.

drainage of the lung tissue and increase lung fluid. PPV with positive end-expiratory pressure (PEEP), has been shown to impede lung lymph flow [14] and this can be one of several mechanisms behind the fluid accumulation. However, conflicting results have also been reported [15].

How to reduce negative effects of positive pressure ventilation?

What then can be done to counter the negative effects of mechanical ventilation? First, an increase in lung volume by recruitment of the collapsed lung, the application of appropriate PEEP to keep the aerated lung open, and to prevent cyclic airway closure should redirect ventilation to more dependent lung regions. Secondly, maintaining normo- or even hypervolaemia should make the pulmonary circulation less vulnerable to increased airway and alveolar pressures, and result in a better match of ventilation and perfusion. Thirdly, maintenance of any respiratory muscle tone or mimicking spontaneous breaths in addition to the mechanical breaths may improve matching of ventilation and blood flow, facilitate venous return and decrease systemic organ oedema formation (keeping in mind respiratory muscle fatigue and even overexpansion of lung if uncontrolled).

Different forms of positive pressure ventilation

A short note will also be made on different forms of PPV. Different inspiratory flow patterns can be used to fine-tune the ventilator settings, but with limited effects on respiratory function [16]. A combination of slow mechanical respiratory rates, e.g. 8 breaths/min, on top of which the patient can breathe spontaneously (airway pressure release ventilation (APRV), or bi-level positive airway pressure, (BiPAP)) appears also to improve gas exchange [17,18]. Applying a cuirass around the chest enables negative pressure selectively over the thorax. This will be as close to a spontaneous breath as possible and it will cause an improvement of blood flow to the lung [19]. This is different from negative pressure ventilation with a patient in a tank just keeping the head outside the tank. With this technique the whole body is exposed to the same pressure variation and there will be no favourable return of venous blood to the heart.

The spontaneously breathing subject changes both respiration rate and size of the tidal volume, and will intermittently also take deep breaths, which may even mimic a recruitment manoeuvre. In conventional mechanical ventilation, respiratory rate and tidal volume are kept constant with a monotonous ventilatory pattern. If anything, this will promote successive deterioration of surfactant function and also promote alveolar collapse. One can speculate on other negative effects on vascular pressures and perfusion distribution. There are reports showing that the gas exchange is improved if the ventilatory pattern is varying in a random fashion [20].

Conclusion

To summarize, positive pressure ventilation differs from spontaneous breathing by exposing the lung to higher pressures, impairing matching of ventilation and blood flow, and impeding cardiac output. At the same time, PPV may be a life-saving treatment, but not necessarily the optimum technique for ventilatory support.

References

1. Wahba RWM. (1991). Perioperative functional residual capacity. *Canadian Journal of Anaesthesia*, **38**, 384–400.
2. Decramer M, De Troyer A, Kelly S, and Macklem PT (1984). Mechanical arrangement of costal and crural diaphragms in dogs. *Journal of Applied Physiology*, **56**, 1484–90.
3. Milic-Emili J, Torchio R, and D'Angelo E (2007). Closing volume: a reappraisal (1967–2007). *European Journal of Applied Physiology*, **99**, 567–83.
4. Hedenstierna G and Edmark L (2010). Mechanisms of atelectasis in the peri-operative period. *Best Practice & Research, Clinical Anaesthesiology*, **24**, 157–69.
5. Froese AB and Bryan AC (1974). Effects of anesthesia and paralysis on diaphragmatic mechanics in man. *Anesthesiology*, **41**, 242–55.
6. West JB. (1989). Mechanics of breathing. In: West JB (ed.) *Best and Taylor´s Physiological Basis of Medical Practice*, pp. 560–78. Baltimore, MD: Williams and Wilkins.
7. West JB, Dollery CT, and Naimark A (1964). Distribution of blood flow in isolated lung: relation to vasculkar and alveolar pressures. *Journal of Applied Physiology*, **19**, 713–24.
8. Tokics L, Hedenstierna G, Svensson L, et al. (1996). V/Q distribution and correlation to atelectasis in anesthetized paralyzed humans. *Journal of Applied Physiology*, **81**, 1822–33.
9. Rothen HU, Neumann P, Berglund JE, et al (1999). Dynamics of re-expansion of atelectasis during general anaesthesia. *British Journal of Anaesthesia*, **82**, 551–6.
10. Carvalho AR, Spieth PM, Pelosi P, et al. (2009). Pressure support ventilation and biphasic positive airway pressure improve oxygenation by redistribution of pulmonary blood flow. *Anesthesia and Analgesia*, **109**, 856–65.
11. Vimlati L, Kawati R, Hedenstierna G, Larsson A, and Lichtwarck-Aschoff M (2011). Spontaneous breathing improves shunt fraction and oxygenation in comparison with controlled ventilation at a similar amount of lung collapse. *Anesthesia and Analgesia*, **113**, 1089–95.
12. Pinsky MR. (2007). Heart–lung interactions. *Current Opinions in Critical Care*, **13**, 528–31.
13. Lattuada M and Hedenstierna G. (2006). Abdominal lymph flow in an endotoxin sepsis model: Influence of spontaneous breathing and mechanical ventilation. *Critical Care Medicine*, **34**, 2792–8.
14. Frostell C, Blomqvist H, Hedenstierna G, Halbig I, and Pieper R (1987). Thoracic and abdominal lymph drainage in relation to mechanical ventilation and PEEP. *Acta Anaesthesiologica Scandinavica*, **31**, 405–11.
15. García-Delgado M, Touma-Fernández A, Chamorro-Marín V, Ruiz-Aguilar A, Aguilar-Alonso E, and Fernández-Mondéjar E (2010). Alveolar fluid clearance in healthy pigs and influence of positive end-expiratory pressure. *Critical Care*, 14R36.
16. Jansson L and Jonson B (1972). A theoretical study on flow patterns of ventilators. *Scandinavian Journal of Respiratory Diseases*, **53**, 237–46.
17. Putensen C, Zech S, Wrigge H, et al. (2001). Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. *American Journal of Respiratory and Critical Care Medicine*, **164**, 43–9.
18. Wrigge H, Zinserling J, Neumann P, et al. (2003). Spontaneous breathing improves lung aeration in oleic acid-induced lung injury. *Anesthesiology*, **99**, 376–84.
19. Schiavina M, Fabiani A, and Gunella G. (1994). External negative pressure ventilation techniques. *Monaldi Archives for Chest Diseases*, **49**, 516–21.
20. Spieth PM, Carvalho AR, Guldner A, et al. (2011). Pressure support improves oxygenation and lung protection compared to pressure-controlled ventilation and is further improved by random variation of pressure support. *Critical Care Medicine*, **39**, 746–55.

CHAPTER 89

Respiratory support with continuous positive airways pressure

Francesco Mojoli and Antonio Braschi

Key points

- Continuous positive airway pressure (CPAP) is a mode of respiratory assistance in which the patient breaths spontaneously at higher than atmospheric pressure.
- In heart and/or respiratory failure patients, CPAP application can provide favourable haemodynamic and respiratory effects.
- CPAP is indicated in patients with parenchymal respiratory failure, and normal respiratory drive and muscular pump.
- The CPAP apparatus not only keeps the airway pressure positive throughout the respiratory cycle, but also regulates FIO_2, humidity and temperature of inspired gases.
- CPAP may be delivered by different flow generators and interfaces—the final choice depends on patient's disease and compliance, environment, material availability, and clinical practice.

Introduction

Continuous positive airway pressure (CPAP) is the simplest mode of respiratory assistance. A CPAP respiratory device is less sophisticated than a ventilator and is designed to keep the patient's airway pressure at a higher level than atmospheric pressure during the whole respiratory cycle. CPAP also conditions the inspired gas in terms of oxygen concentration (FIO_2), humidity, and temperature. Essentially, ventilation is performed by the patient's own respiratory drive and muscular pump.

Mechanical ventilation (MV) was introduced in clinical practice for patients with respiratory pump failure and healthy lungs (during the epidemic of poliomyelitis in the 1950s) as opposed to CPAP, which is indicated in patients with respiratory failure and a normal drive and muscular pump. CPAP was first employed in the early 1970s to treat acute respiratory distress syndrome (ARDS). However, in 1938, Barach used it for acute cardiogenic pulmonary oedema (ACPE), while others found CPAP useful in military medicine and aeronautics. Nowadays, CPAP is largely used in critically-ill patients with parenchymal respiratory failure in various clinical settings.

Physiological effects of CPAP

The use of CPAP leads to an increase of transpulmonary pressure (P_{TP}). P_{TP} is the pressure that distends the lung parenchyma, and will end up in an increase of lung volume at end expiration, i.e. the functional residual capacity (FRC). When an increase in FRC is due to recruitment of previously collapsed alveoli, lung compliance improves, whereas shunt and low ventilation/perfusion conditions decrease within the lungs [1]. Therefore, CPAP can significantly improve gas exchange and reduce the work of breathing (WOB). On the other hand, when an increase in FRC is due to overdistention of already open alveolar spaces, lung compliance can decrease, whereas dead space (both anatomical and functional) and pulmonary vascular resistance increase [2].

Although CPAP does not directly assist patients' inspiratory efforts, its use often provides favourable effects on spontaneous ventilation. CPAP can decrease every single component of patients' WOB (resistive, elastic, and threshold loads) by improving respiratory mechanics (both airway flow resistance and compliance) [3] and by opposing flow limitation. Progressive collapse of small airways during expiration promotes intrinsic positive end-expiratory pressure ($PEEP_i$), i.e. a pressure gradient between alveoli and proximal airways at the end of expiration. $PEEP_i$ represents a threshold load for the inspiratory muscles, which can be substantially decreased by PEEP and CPAP in chronic obstructive pulmonary disease (COPD) flow-limited patients. In asthmatic patients, PEEP and CPAP use can be detrimental due to pulmonary hyperinflation. Finally, CPAP increases the ability of the expiratory muscles to share the workload with the inspiratory muscles.

CPAP use has some haemodynamic effects, mainly mediated by an increase of intrathoracic pressure secondary to greater elastic recoil of the chest wall and/or lower inspiratory efforts. The corresponding fall in right atrial transmural pressure decreases venous return and preload, especially in hypovolaemic patients, whereas the fall in left ventricle transmural pressure translates into lower afterload, particularly in heart failure patients. Moreover, the CPAP-induced increase in oxygen delivery may result in a better myocardial oxygen supply-demand balance, improving diastolic function, ventricular relaxation, and compliance.

Clinical indications for CPAP

Acute cardiogenic pulmonary oedema

By the early twentieth century, evidence showed the application of a positive pulmonary pressure to a patient experiencing ACPE allowed haemodynamic and respiratory mechanics to improve together with less clinical symptoms of respiratory distress. CPAP has been shown to reduce hospital mortality, endotracheal intubation rate, and ICU length of stay in patients with acute pulmonary oedema [4]. In addition, CPAP can also effectively treat ACPE patients with established respiratory muscle fatigue [5]. Accordingly, hypercapnic ACPE patients had similar recovery times and similar gas exchange responses when treated by CPAP or NIV [6]. Compared with NIV, CPAP is less dependent on the experience of the care team and is a simpler technique. This also makes CPAP useful in the out-of-hospital setting.

Post-operative respiratory failure and post-extubation failure treatment/prevention

CPAP is a widely-used strategy to prevent or to treat post-operative pulmonary complications. Several studies have demonstrated the efficacy of CPAP to reduce atelectasis and improve oxygenation in post-operative settings [7]. The efficacy of CPAP in hypoxaemic patients after abdominal surgery is strictly related to the length of use. Therefore, interfaces that improve patient tolerance and length of treatment, such as the helmet, are preferred [8]. The use of CPAP in obese patients following bariatric surgery is questioned because of concerns that pressurized air may inflate the stomach and proximal intestine, resulting in anastomotic disruption. However, it was recently proved that CPAP can be a safe and effective method for respiratory support in this context, provided it is used as early as possible after extubation [9]. CPAP has been shown to reduce reintubation rate in post-extubation hypoxaemic failure after cardiac surgery [10].

Chest trauma

CPAP should be used in patients with chest wall trauma who remain hypoxic despite adequate regional anaesthesia and high-flow oxygen. Several studies have shown that CPAP resulted in fewer treatment days when compared with immediate intubation followed by intermittent positive pressure ventilation. This improvement is obtained mainly through a decrease of infection rate in non-intubated patients. In view of the risk of pneumothorax, patients with chest trauma who are treated with CPAP or non-invasive ventilation (NIV), especially in presence of multiple rib fractures, should be monitored in the intensive care unit (ICU).

Community-acquired pneumonia

In patients with community-acquired pneumonia (CAP), time is needed for conventional therapy to show its effect; during this period, the maintenance of a satisfactory oxygenation represents the main goal in the management of acute respiratory failure (ARF). CPAP can rapidly improve oxygenation in CAP patients, but the beneficial effects disappear early after its discontinuation. The choice of helmet improves tolerance by allowing expectoration and ameliorating patient–environment interaction, and could be the right choice in patients with pneumonia who may need longer periods of CPAP treatment [11].

Respiratory failure in immunocompromised patients

Any less invasive method able to avoid the use of endotracheal ventilation appears to be particularly useful in immunocompromised patients. CPAP used at an early stage of hypoxaemic ARF is effective in reducing intubation and ICU admission rate, often related to an increased risk of infectious complications and death in these patients [12].

Mild/moderate acute respiratory distress syndrome

In patients with acute lung injury (ALI), applying positive pressure to the airways has been shown to lessen the reduction in functional residual capacity, and to improve respiratory mechanics and gas exchange. However, the efficacy of CPAP to prevent subsequent clinical deterioration and to reduce the need for endotracheal intubation has never been certainly shown. Despite early physiological benefits, CPAP delivered via face mask did not reduce the need for endotracheal intubation among ALI patients, and did not impact the length of hospital stay or hospital mortality [13]. Whether the use of the helmet interface, allowing prolonged administration of high PEEP levels, could improve outcome in patient affected by mild ARDS, has to be definitively demonstrated [12].

COPD exacerbation

The increase in WOB during COPD exacerbations is due to both an increased resistive load and dynamic hyperinflation; $PEEP_i$ imposes an additional inspiratory threshold load, while decreasing the effectiveness of the inspiratory muscle. CPAP can counterbalance $PEEP_i$ without causing further hyperinflation, decreasing inspiratory effort and dyspnoea, while improving the pattern of breathing. Arterial blood gases tend to remain the same or improve slightly, probably due to improvement in breathing pattern at constant minute ventilation, and eventually to decreased WOB. For these reasons, despite the evidence demonstrating NIV effectiveness in COPD exacerbation, also the use of CPAP can be considered, especially in particular settings where NIV is not available.

High-risk fibre optic bronchoscopy

CPAP delivered by full face mask allows better tolerance of fibre optic bronchoscopy compared with oxygen therapy. In hypoxaemic patients undergoing bronchoscopy, CPAP improves oxygenation and reduces the rate of subsequent respiratory failure.

Techniques for CPAP administration

The main goal of CPAP delivering is to maintain pressure in the proximal patient's airways at the same desired level during the whole respiratory circle, together with full control of inhaled gas mixture. This means low difference between set and delivered oxygen fraction, low level of CO_2 rebreathing, temperature, and humidity according to invasive or non-invasive setting. Additional goals are patient's compliance, safety and monitoring, and technique's easiness and cheapness.

CPAP can be delivered by different flow generators and interfaces. The final choice depends on patient's disease and compliance, environment, material availability, and clinical practice.

Continuous flow systems

Continuous flow systems consist of a mixer-flow meter (or two separate flow meters for air and oxygen, or a Venturi system), a heater-humidifier, a pressure stabilizer, a PEEP valve, and a manometer. Oxygen fraction delivered by Venturi systems depends on flow and pressure in the CPAP circuit, and should be monitored at every setting change. Ideally, to maintain constant positive pressure in the patient's airways, a continuous flow at least equal to patient's peak inspiratory flow should be set. Anyway, besides a great gas wasting, very high (50–100 L/min) fresh gas flows have some drawbacks. Gas conditioning can be suboptimal, noise substantially increases, and the effect of even small expiratory circuit resistance is magnified. The increase of pressure during expiration can put a significant brake on the patient's expiratory flow. A large volume (10 L at atmospheric pressure) and highly compliant (500 mL/cmH_2O) balloon provides good pressure stabilization in the CPAP circuit without the need of very high fresh gas flow. Its optimal position is in the inspiratory limb nearest the patient's airways opening. Gas flow lower than 30 L/min favours CO_2 rebreathing, both in an invasive and non-invasive setting.

PEEP valves

Commercially-available PEEP valves, such as water valves, and adjustable or precalibrated spring-loaded valves, are threshold resistors. Ideally, exhaled gas freely flows away through the valve until airway pressure decreases to a preset level, at which time the valve abruptly closes. In practice, these valves are not pure threshold resistors, but offer a small (and variable among different devices) resistance to flow, eventually to be added to the resistive behaviour of the expiratory limb of the circuit, and of the expiratory port of mask and helmet interfaces [14]. This small resistance to flow has significant effects on patient's airways pressure when high flow rates are used. Therefore, when administering CPAP with continuous flow systems, pressure must be monitored with a manometer placed as near as possible patient's airways, to control the effective pressure applied, and detect respiratory oscillations. Excessive pressure oscillations (>3–4 cmH_2O) correspond to significant additional respiratory load for the patient. In this case, the use of a high-volume high-compliance balloon becomes mandatory, an increase of gas flow, and the use of the helmet interface should be considered. Recently, the Boussignac valve has been proposed for non-invasive CPAP delivery [15]. This device consists of a plastic tube open to atmosphere and provided with microchannels in the tube wall. The gas injected into the system accelerates through the microchannels, leading to turbulence, and finally positive pressure, corresponding to a 'virtual' valve at the patient's side of the tube. Generated pressure depends on the flow administered; therefore, CPAP level and oxygen concentration cannot be adjusted separately. Moreover, the Boussignac device is not able to maintain a stable positive pressure value in the case of forced breathing and/or high respiratory rate [16]. Anyway, special features of this device (an 'open' system with small dimensions and easy to use) make it a good choice in particular settings, like pre-hospital treatments [15] and bronchoscopy procedures.

Demand-flow systems

Mechanical ventilators can be used as demand-flow systems to administer CPAP, where the alternate opening of the inspiratory and the expiratory valves should provide the inhalational gas volume required by the patient and allow its exhalation, respectively. When the control systems of the mechanical ventilator assure both fast detection of patient's respiratory activity and a rapid reaction of mechanical valves, pressure oscillation in the airways will be not clinically significant. This was not the case with old generation ventilators—the inspiratory decrease and expiratory increase of pressure were significant, leading to additional work to inhale and braked exhalation. Technological improvements allow new generation ventilators to perform, as well as continuous flow systems, with some differences among models. Additional benefit of ventilator-delivered CPAP is respiratory monitoring and alarming that is necessarily incomplete with continuous flow systems. Higher costs and low availability of both instruments and practice, limit the use of mechanical ventilators to specific settings.

Interfaces

CPAP can be administered by different interfaces: nasal and face masks, nasal pillows and helmets. Nasal devices need cooperation of the patient that has to breathe with a closed mouth to effectively receive CPAP. Among full-face devices, the helmet is more efficient than the mask because of its high internal volume and compliance, making it an additional pressure stabilizer in the CPAP circuit [17]. Moreover, the helmet provides a good tightness by non-traumatic adhesion of the soft collar to the neck of the patient with less discomfort and skin lesions compared with face masks. Because high pressures inside masks—but not inside helmets—increase leaks [18], higher PEEP levels can be administered with helmets. Therefore, acute hypoxaemic patients needing high-level CPAP without interruptions may particularly take advantage from the helmet device [11,12]. CO_2 rebreathing during mask CPAP is limited mainly by leaks, both unintentional and intentional through expiratory ports. Conversely, during helmet CPAP significant CO_2 rebreathing may occurs when the amount of fresh gas flowing through the device is not well matched with patient's CO_2 production. A minimum fresh flow delivery of 30–35 L/min is always mandatory, to be increased to 50 L/min or more in case of higher metabolic requirements. This also means that the use of mechanical ventilators, that provide fresh gas flow equal to patient's minute ventilation, must be avoided for helmet CPAP. Mean inhaled CO_2 can be easily monitored by gas sampling at the outlet port of the helmet [19]; this value should be maintained below 0.5% by adjusting fresh gas flow in order not to increase patient's ventilatory workload.

Comfort data suggest that humidity of inspired gases during CPAP should be at or above 15 mgH_2O/L with temperatures ranging from 25 to 30°C. Heated humidifier can provide this gas conditioning [20].

Acknowledgements

We are indebted to Doctor Ilaria Currò (Section of Anesthesia, Intensive Care and Pain Therapy; Department of Clinical, Surgical, Diagnostic, and Pediatric Sciences; University of Pavia, Italy) and Doctor Marco Pozzi (Anesthesia and Intensive Care Division I; Emergency Department; Fondazione IRCCS Policlinico San Matteo, Pavia, Italy), for assisting with the literature revision, and with Doctor Houman Amirfarzan (Harvard Medical Instructor; V.A. Hospital, Boston, USA), for the language revision.

References

1. Mike Lin, Yun-Fu Yang, Hung-Ting Chiang, et al. (1995). Reappraisal of continuous positive airway pressure therapy in acute cardiogenic pulmonary edema short-term results and long-term follow-up. *Chest*, **107**, 1379–86.
2. Holanda MA, Fortaleza SCB, Alves-de-Almeida M, et al. (2010). Continuous positive airway pressure effects on regional lung aeration in patients with COPD a high-resolution CT scan study. *Chest*, **138**, 305–14.
3. Katz JA and Marks JD. (1985). Inspiratory work with and without continuous positive airway pressure in patients with acute respiratory failure. *Anesthesiology*, **63**, 598–607.
4. Vital FM, Saconato H, Ladeira MT, et al. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary edema. *Cochrane Database Systematic Reviews*, **16**, CD005351.
5. Mojoli F, Monti L, Zanierato M, et al. Respiratory fatigue in patients with acute cardiogenic pulmonary edema. *European Heart Journal Supplements*, **6**(F), F74–F80.
6. Bellone A, Vettorello M, Monari A, et al. (2005). Noninvasive pressure support ventilation vs. continuous positive airway pressure in acute hypercapnic pulmonary edema. *Intensive Care Medicine*, **31**, 807–11.
7. Ferreyra G, Long Y, and Ranieri VM. (2009). Respiratory complications after major surgery. *Current Opinion in Critical Care*, **15**, 342–8.
8. Squadrone V, Coha M, Cerutti E, et al. (2005). Continuous positive airway pressure for treatment of postoperative hypoxemia a randomized controlled trial. *Journal of the American Medical Association*, **293**, 589–95.
9. Neligan PJ, Malhotra G, Fraser M, et al. (2009). Continuous positive airway pressure via the Boussignac system immediately after extubation improves lung function in morbidly obese patients with obstructive sleep apnea undergoing laparoscopic bariatric surgery. *Anesthesiology*, **110**, 878–84.
10. Zarbock A, Mueller E, Netzer S, et al. (2009). Prophylactic nasal continuous positive airway pressure following cardiac surgery protects from postoperative pulmonary complications. *Chest*, **35**, 1252–9.
11. Cosentini R, Brambilla AM, Aliberti S, et al. (2010). Helmet continuous positive airway pressure vs oxygen therapy to improve oxygenation in community-acquired pneumonia. *Chest*, **138**, 114–20.
12. Principi T, Pantanetti S, Catani F, et al. (2004). Noninvasive continuous positive air way pressure delivered by helmet in hematological malignancy patients with hypoxemic acute respiratory failure. *Intensive Care Medicine*, **30**, 147–50.
13. Declaux C, L'Her E, Alberti C, et al. (2000). Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask. *Journal of the American Medical Association*, **284**, 2352–60.
14. Isgrò S, Zanella A, Giani M, et al. (2012). Performance of different PEEP valves and helmet outlets at increasing gas flow rates: a bench top study. *Minerva Anestesiologica*, **78**, 1095–100.
15. Templier F, Dolveck F, Baer M, et al. (2003). 'Boussignac' continuous positive airway pressure system: practical use in a prehospital medical care unit. *European Journal of Emergency Medicine*, **10**, 87–93.
16. Sehlin M, Törnell SS, Öhberg F, et al. (2011). Pneumatic performance of the Boussignac CPAP system in healthy humans. *Respiratory Care*, **56**, 818–26.
17. Chiumello D, Pelosi P, Carlesso E, et al. (2003). Noninvasive positive pressure ventilation delivered by helmet vs. standard face mask. *Intensive Care Medicine*, **29**, 1671–9.
18. Mojoli F, Iotti GA, Currò I, et al. (2013). An optimized set-up for helmet noninvasive ventilation improves pressure support delivery and patient-ventilator interaction. *Intensive Care* Medicine, **39**, 38–44.
19. Mojoli F, Iotti GA, Gerletti M, et al. (2008). Carbon dioxide rebreathing during non-invasive ventilation delivered by helmet: a bench study. *Intensive Care Medicine*, 34, 1454–60.
20. Lellouche F, Maggiore SM, Lyazidi A, et al. (2009). Water content of delivered gases during non-invasive ventilation in healthy subjects. *Intensive Care Medicine*, **35**, 987–95.

CHAPTER 90

Non-invasive positive-pressure ventilation

Giulia Spoletini and Nicholas S. Hill

Key points

- Exacerbations of chronic obstructive pulmonary disease (COPD), cardiogenic pulmonary oedema and acute respiratory failure in immunocompromised patients are the main indications for non-invasive ventilation (level 1 evidence).
- Weaker evidence supports the use of non-invasive ventilation (NIV) in other forms of hypercapnic respiratory failure (acute asthma, cystic fibrosis, obesity–hypoventilation syndrome) and in hypoxaemic respiratory failure (pneumonia, acute respiratory distress syndrome (ARDS), chest trauma).
- Proper selection of patients, considering both indications and contraindication to NIV, plays a key-role in NIV success.
- Trained staff with knowledge and skill in the proper application of NIV is another determinant of success.
- Avoid delays in the initiation of NIV as well as in intubation when NIV fails.

Introduction

Non-invasive ventilation (NIV) is a technique that provides respiratory assistance and avoids airway invasion in patients with certain kinds of acute respiratory failure (ARF). The most common NIV application is non-invasive positive pressure ventilation (NIPPV), which conducts pressurized gas from a positive pressure ventilator to the patient via an external interface strapped over the nose and/or mouth. This technique avoids airway invasion, and can thereby avoid complications related to intubation and invasive mechanical ventilation (INV), especially ventilator-associated pneumonias. Furthermore, it avoids the trauma associated with intubation and usually augments comfort compared with INV, thereby reducing the need for analgesia and sedation. It is suitable for intermittent use, allowing breaks for eating and communicating. It may also reduce morbidity and mortality, and shorten ICU stays or avoid the need for ICU altogether, thus reducing costs. This brief review will focus on current indications for NIV, selection of appropriate patients, and proper application.

Indications with level 1 evidence: NIV is first choice for ventilatory support

Chronic obstructive pulmonary disease

The main indication for NIV in chronic obstructive pulmonary disease (COPD) is an exacerbation with persistent acute or acute on chronic hypercapnic respiratory failure (AHRF) despite initial medical treatment. In these patients, NIV combines positive end expiratory pressure (PEEP) to counterbalance auto-PEEP and pressure support to assist inspiratory muscles, thereby reducing the work of breathing and averting inspiratory muscle fatigue. Compared with standard medical care in COPD patients, NIV more rapidly improves vital signs (especially respiratory rate) and gas exchange, and reduces the need for intubation, complications, length of hospital stay, and mortality [1]. In particular, NIV is strongly recommended in those patients with a $7.25 < pH < 7.35$. With a $pH < 7.25$, NIV could still be successful, but should be managed in an ICU with very close observation in order to intubate without delay if necessary [2,3].

Not only is NIV indicated for moderate to severe COPD exacerbations, but also for COPD patients with respiratory failure in a number of other settings including:

- When associated with pneumonia.
- Post-operative patients, especially after lung resection.
- To facilitate extubation in COPD patients requiring INV initially.
- To avoid extubation failure after a standard extubation.
- In do-not-intubate patients.

Cardiogenic pulmonary oedema

In patients with cardiogenic pulmonary oedema (CPE), CPAP (10–12.5 cmH_2O) compared with standard oxygen supplementation increases intrathoracic pressure and raises functional residual capacity, thus re-expanding alveoli, rapidly improving oxygenation, improving lung compliance, reducing left ventricular afterload, and often increasing cardiac output. These benefits translate into the avoidance of intubation and reduced mortality. In the past decade, a number of studies have compared 'bilevel' ventilation (combining inspiratory pressure support with positive expiratory pressure) with CPAP alone to treat CPE, but have found no differences between the modes in intubation, myocardial infarction and mortality rates [4]. The European Society of Cardiology considers CPAP as first-line treatment of CPE [5], but the Canadian NIV Guideline group considers them equivalent and recommends either CPAP or 'bi-level' ventilation for CPE patients in the absence of shock or need for coronary revascularization [6]. These positive results from in-patients have been replicated in the field where a number of randomized trials have demonstrated that CPAP administered by ambulance crews reduces intubation and mortality rates in CPE patients prior to hospitalization [7].

Immunocompromised patients

INV in immunocompromised patients is associated with infectious and haemorrhagic complications, including septic shock and high mortality rates. NIV can reduce the occurrence of nosocomial infections and septic shock and avoid INV in such patients, thereby improving survival [8]. It should be emphasized, however, that such patients should be started early on NIV, closely monitored in an ICU, and promptly intubated if they continue to deteriorate with worsening oxygenation and haemodynamic instability.

Weaker evidence—NIV is an option

Other forms of hypercapnic respiratory failure

Asthma

Some earlier uncontrolled cohort series have associated improvements in gas exchange and low intubation rates with use of NIV in patients with severe asthma, but no controlled trials have confirmed these benefits. Some of the few randomized trials reported have demonstrated that NIV increases airflow more rapidly than a sham mask [9] or standard oxygen [10] during severe asthma attacks, suggesting a bronchodilator effect of positive pressure. One study also showed a lower hospitalization rate from the ED with NIV [9]. Thus, NIV with close monitoring is an option for severe asthma that does not respond promptly to standard medical treatment, perhaps combined with helium oxygen mixtures and/or continuous bronchodilator nebulization. However, considering that supportive evidence is weak, patients should be monitored closely and promptly intubated if they fail to improve.

Cystic fibrosis

NIV has been used for cystic fibrosis in the chronic or subacute setting as a bridge-to-transplant [11]. It may also serve a role as an adjuvant to secretion clearance techniques. However, few studies have evaluated its use in acute care. It remains an option in the acute setting, but for patients with acute pneumonias and secretion retention, prompt intubation followed by transition to NIV once the patient has stabilized may be the preferred approach.

Obesity-hypoventilation syndrome

Morbid obesity is often associated with chronic hypoventilation, defining the obesity-hypoventilation syndrome (OHS). Episodes of acute on chronic respiratory acidosis occurring in this entity may be treated with NIV, avoiding INV. Some of these patients are initially too ill for NIV, due to altered neurological status, excessive secretions, or decompensated congestive heart failure, but can be transitioned to NIV when stabilized. In one cohort, initiation during acute exacerbations, rather than the chronic state, and cardiovascular morbidities were associated with worse long-term NIV outcomes [12].

Hypoxaemic respiratory failure

ARDS/pneumonia

Pneumonia and ARDS are associated with a substantially higher risk of NIV failure than most other forms of acute respiratory failure, and NIV is not routinely recommended to treat them. Oxygenation needs are high, necessitating higher PEEP levels, which detracts from mask comfort and predisposes to greater mask leak. In addition, the underlying process often progresses, rendering the patient too ill to be safely managed with NIV. Thus, patients with ARDS or pneumonia treated with NIV must be selected with great caution. They must not have multi-organ dysfunction or haemodynamic instability, and must be watched very carefully in an ICU. If their oxygenation does not improve substantially within 1–2 hours of NIV initiation, they should be promptly intubated [13].

Chest trauma

Chest trauma patients may develop hypoxaemic ARF after lung contusion or acute lung injury related to activation of the inflammatory cascade. They may also develop hypercapnic ARF after rib fractures, leading to flail chest. A randomized controlled trial showed avoidance of respiratory muscle fatigue and the need for intubation in severely hypoxemic chest trauma patients [14]. A subsequent meta-analysis [15] showed that NIV not only reduces intubation rate, but also length of ICU stay and mortality, and may be a preferable alternative to INV in these patients.

Do-not-intubate

Many patients with chronic respiratory conditions decide to forego heroic measures and decline intubation. NIV can still help many of these patients, especially those with COPD or CPE who have a reasonably good chance of surviving hospitalization for an acute exacerbation [16]. NIV may also be used for palliative purposes, mainly to relieve dyspnoea in terminal patients, or to extend life long enough for relatives to visit or settle their affairs. However, it is important to make certain that patients and their families who wish for NIV understand such circumstances and establish realistic goals for its use. If these goals are not being met, NIV should be stopped and alternative palliation instituted.

Practical aspects

The success of NIPPV depends not only on the disease underlying NIV, but also on the proper selection of patients, timing, and setting of the treatment.

Selection of patients

All patients in respiratory distress, defined as tachypnoea, use of accessory muscles, hypoxaemia, diagnosed with ARF (pH < 7.35 and PCO_2 > 45 mmHg, or PO_2/FIO_2 < 200), should be considered as soon as possible for NIV. Delay in starting the treatment can increase the risk of complications and NIV failure. Before starting NIV, it is mandatory to determine whether they have contraindications, such as respiratory arrest, septic shock with multiple organ failure, or the inability to fit the mask or to protect the airways, in which case they should be promptly intubated. Some patients have relative contraindications, such as unstable medical conditions, agitation, the presence of excessive secretions, or recent thoracic or upper abdomen surgery, and should be evaluated on a case-by-case basis. In marginal cases at higher risk of NIV failure, a NIV trial of 1–2 hours could be tried and intubation undertaken if there is no improvement [17].

Interface

The choice of a comfortable and properly fitted interface is key to a favourable NIV outcome, since it can improve patients' tolerance and adherence to the treatment, minimize air leaks, and optimize patient–ventilator synchrony. Oro-nasal (or full-face) are generally preferred, since they are associated with less air leaking through the mouth. On the other hand, nasal masks can facilitate speech

and expectoration, and may be better tolerated by claustrophobic patients. The helmet is an alternative interface that consists of a soft clear plastic cylinder that seals over the neck and shoulders, and has been extensively studied, mainly in Italy. It has proven quite effective in delivering CPAP, but requires high air flow to minimize rebreathing, which are quite noisy. When used to deliver pressure support and PEEP, patient–ventilator asynchrony can be a problem with the helmet [18], but a newer, stiffer version may counter this problem.

Ventilator selection

Either ICU ventilators using pressure- or volume-limited modes or portable bi-level ventilators can be used for NIV with equal expectations of success. However 'bi-level' devices designed specifically for delivery of NIV are the most often chosen for hypercapnic ARF, whereas ICU ventilators may be selected more often for hypoxaemic respiratory failure. Many ICU ventilators now have 'NIV' modes that facilitate delivery of NIV, but may require additional adjustments in the face of leaks.

Ventilator settings

Successful NIV requires that sufficient ventilator support is provided in synchrony with the patient's breathing efforts. Thus, proper adjustment of ventilator settings is very important. Usually, the pressure-support (or bi-level) mode starting with lower settings (inspiratory pressure 8–12 cmH_2O, expiratory pressure 4–5 cmH_2O) enhances tolerance for patients. Inspiratory pressure can then be gradually adjusted upward to alleviate persistent respiratory distress, within the patient's limit of tolerance. Expiratory pressure can be increased to improve triggering in the presence of auto-PEEP or to improve oxygenation. Oxygen supplementation is titrated to achieve a desired O_2 saturation (>90–92%). Humidification is not necessary for brief applications (such as for CPE), but helps to avoid mucosal drying and enhances comfort for longer applications [18].

Monitoring

Close monitoring of NIV is important for success, especially during the early adaptation period. The value of frequent checks to optimize mask fit and ventilator settings, and to encourage the patient cannot be overemphasized. Acutely-ill patients should be monitored in an ICU or intermediate care unit until they are more stable. NIV can be administered on regular wards by experienced staff, but only for cooperative patients who are relatively stable and can call for help if needed [19].

All patients undergoing NIV should be monitored at least with:

- Clinical examination of:
  - Dyspnoea.
  - Respiratory and heart rate.
  - Other signs of respiratory distress—abdominal paradox, accessory muscles use, etc.).
  - Mask comfort, fit.
- Gas exchange:
  - Arterial blood gases before initiation, after 1–2 hours of NIV and as needed.
  - Continuous O_2 saturation.
- Blood pressure and EKG.
- Ventilator:
  - Synchrony with patient.
  - Tidal volume (target 6–7 mL/kg ideal body weight).
  - Air leaks from mask and tubing.

Complications

NIPPV is usually a safe and well-tolerated technique. The adverse effect are related to the interface, which can cause skin reddening or ulceration, especially over the nasal bridge, claustrophobia, sinus or nasal pain, and dryness of eyes and mouth due to air leaks. Improbable, but possible complications include pneumothoraces, painful gastric insufflation, and aspiration of gastric contents. Patient agitation interferes with efficacy, but can be ameliorated by sedation.

Predicting outcome

When applied in properly selected patients using optimal techniques by an experienced staff, success rates of NIV, especially for COPD and CPE, are generally over 80%. However, some patients fail, especially if they have diagnoses like pneumonia or cancer. In hypercapnic ARF, APACHE II score > 34, pH < 7.25, respiratory rate > 35, and Glasgow Coma Score ≤ 11 have all been shown to predict NIV failure, especially if they persist for the first 2 hours [17]. In hypoxaemic ARF, having ARDS, pneumonia, or shock are the strongest predictors of failure, but other predictors include older age, high acuity of illness, and lack of improvement in PaO_2/FiO_2 after the first hour of NIV [20].

Conclusion

NIV has been one of the most important developments in the field of mechanical ventilation over the past 20 years and its use is increasing around the world. This increase has been associated with improved outcomes for patients with ARF due to COPD and CPE, and it is being used increasingly in other types of ARF as well. To achieve optimal results, it must be applied in carefully-selected patients, using appropriate techniques implemented by a skilled staff with conscientious monitoring.

References

1. Quon BS, Gan WQ, and Sin DD. (2008). Contemporary management of acute exacerbations of COPD: a systematic review and meta-analysis. *Chest,* **133**(3), 756–66.
2. Plant PK, Owen JL, and Elliot MW. (2000). Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory ward: a multicentre randomized trial. *Lancet*, **355**, 1931–5.
3. Squadrone E, Frigerio P, Fogliati C, et al. (2004). Noninvasive vs invasive ventilation in COPD patients with severe acute respiratory failure deemed to require ventilatory assistance. *Intensive Care Medicine*, **30**, 1303–10.
4. Masip J, Roque M, Sanchez B, et al. (2005). Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. *Journal of the American Medical Association*, **294**(24), 3124–30.
5. The Task Force on Acute Heart Failure of the European Society of Cardiology. (2005). Executive summary of the guidelines on diagnosis and treatment of acute heart failure. *European Heart Journal*, **26**, 384–416.

6. Keenan SP, Sinuff T, Burns KE, et al. (2011). Canadian Critical Care Trials Group. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. *Canadian Medical Association Journal*, **183**(3), E195–214.
7. Ducros L, Logeart D, Vicaut E, et al. (2011). CPAP for acute cardiogenic pulmonary oedema from out-of-hospital to cardiac intensive care unit: a randomized multicenter study. *Intensive Care Medicine*, **37**(9), 1501–9.
8. Hilbert G, Gruson D, Vargas F, et al. (2001). Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *New England Journal of Medicine*, **344**, 481–7.
9. Soroksky A, Stav D, and Shpirer I. (2003). A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest*, **123**, 1018–25.
10. Soma T, Hino M, Kida K, and Kudoh S. (2008). A prospective and randomized study for improvement of acute asthma by non-invasive positive pressure ventilation (NPPV). *Internal Medicine*, **47**(6), 493–501.
11. Noone PG. (2008). Non-invasive ventilation for the treatment of hypercapnic respiratory failure in cystic fibrosis. *Thorax*, **63**, 5–7.
12. Borel JC, Burel B, Tamisier R, et al. (2013). Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. *PloS One*, **8**, e52006.
13. Antonelli M, Conti G, Esquinas A, et al. (2007). A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. *Critical Care Medicine*, **35**(1), 18–25.
14. Hernandez G, Fernandez R, Lopez-Reina P, et al. (2010). Noninvasive ventilation reduces intubation in chest trauma-related hypoxemia. *Chest*, **137**, 74–80.
15. Chiumello D, Coppola S, Froio S, Gregoretti C, and Consonni D.(2013). Noninvasive ventilation in chest trauma: a systematic review and meta-analysis. *Intensive Care Medicine*, **39**, 1171–80.
16. Levy M, Tanios MA, Nelson D, et al. (2004). Outcomes of patients with do-not-intubate orders treated with noninvasive ventilation. *Critical Care Medicine*, **32**, 2002–7.
17. Confalonieri M, Garuti G, Cattaruzza MS, et al. (2005). A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. *European Respiratory Journal*, **25**, 348–55.
18. Nava S, Navalesi P, and Gregoretti C. (2009). Interfaces and humidification for noninvasive mechanical ventilation. *Respiratory Care*, **54**(1), 71–84.
19. Elliott MW, Confalonieri M, and Nava S. (2002). Where to perform noninvasive ventilation? *European Respiratory Journal*, **19**, 1159–66.
20. Antonelli M, Conti G, Moro ML, et al. (2001). Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Medicine*, **27**, 1718–28.

CHAPTER 91

Indications for mechanical ventilation

Neil R. MacIntyre

Key points

- Mechanical ventilation can be life-sustaining, but is associated with significant risk.
- Mechanical ventilation with a guaranteed rate/tidal volume is indicated when the patient's ventilatory control system is unreliable.
- Mechanical ventilation with appropriate muscle unloading is indicated when a mechanical load–metabolic demand imbalance exists.
- Mechanical ventilation with end-expiratory pressure is indicated when alveolar patency is compromised.
- Mechanical ventilation with low level inspiratory pressure is indicated if an artificial airway imposes an uncomfortable muscle load.

Introduction

Mechanical ventilation is the process of using positive pressure devices to provide O_2 and CO_2 transport between the environment and the pulmonary capillary bed. The desired effect of mechanical ventilation is to maintain adequate levels of PO_2 and PCO_2 in arterial blood, while also unloading the inspiratory muscles. At the same time, this process should be done in a manner that avoids injury to the lungs and other organ systems. Ventilator-induced lung injury [1], infection [2], and the need for potentially harmful sedatives/neuromuscular blockers [3], all underscore the need to assure that initiation of mechanical ventilatory support is worth these risks.

The basic components of a mechanical ventilatory support system are:

- An artificial airway (or sometimes a mask) that provides the interface between the mechanical ventilator and the patients airways.
- A source of oxygen enriched positive pressure breaths delivered either in accordance with a set timer or in response to a patient effort.
- The capability to maintain an end expiratory positive pressure.

These features are designed to address the following clinical problems that constitute the 'indications' for providing mechanical ventilatory support:

- The need for providing a reliable number of breaths in patients without an appropriate spontaneous ventilatory controller.
- The need for unloading fatigued or impaired ventilatory muscles that are incapable of providing adequate tidal breaths.
- The need for maintaining alveolar patency in patients with inflamed or flooded lung units.
- The need to support an artificial airway in a patient who cannot maintain and/or protect the natural airway.

In a large survey of over 5000 mechanically-ventilated patients in 361 ICUs worldwide [4], the vast majority required mechanical ventilation because of either acute cardio-pulmonary failure (68%) or acute on chronic cardio-pulmonary failure (13%)—the second and third indications 2 and 3 in the list above. The remainder (the first and fourth indications in the list above) were patients requiring mechanical ventilation for largely neuromuscular issues.

The remainder of this chapter will review the underlying pathophysiology of these indications and clinical signs/thresholds that usually trigger institution of mechanical ventilatory support. There will also be brief discussions on how modern systems are designed to address these indications.

Controller failure

The ventilatory control system is centered in the brain stem and consists of an intrinsic ventilator pattern generator with three types of inputs [5]. One input is a series of afferent nerves from mechanoreceptors in the lung and chest wall. These sense respiratory system stretch, irritants, and ventilatory muscle loads. A second set of inputs arise from central and peripheral chemo receptors sensing pH, PCO_2, and PO_2. A final input involves cortical signals designed to modulate the respiratory pattern for voluntary activities. The purpose of the control system is to provide an adequate level of ventilation to effect CO_2 and O_2 transport, while minimizing the mechanical loads on the ventilatory muscles. The normal resting ventilatory pattern of 10–12 breaths/min, tidal volumes of 5–7 mL/kg, and inspiratory:expiratory timing of 1:2–1:3 is a consequence of this control system strategy [6].

This system can be compromised with any central nervous system (CNS) injury, but especially those that affect brain stem function. In addition to CNS injury, general anaesthesia and a variety of drugs, especially sedatives and opioid analgesics can also affect this function. At its extreme, ventilatory controller failure results in a respiratory arrest. Damage to efferent nerves, primarily the phrenic nerve, will compromise the controller's ability to provide adequate inspiratory muscle stimulation.

Although some CNS injuries can produce inappropriate hyperventilation, the consequence of most diseases/drugs affecting the ventilatory control system is usually inadequate ventilation resulting in a respiratory acidosis (hypercarbic respiratory failure). The pH threshold from a respiratory acidosis that requires intervening with mechanical ventilatory support depends on the clinical situation. In the absence of significant cardiac dysrhythmias, pressor-dependent hypotension, or elevated intracranial pressure, pH values as low as 7.15 (or perhaps lower) have been shown in clinical trials to not cause harm [7]. However, the initiation of mechanical ventilatory support for hypoventilation and respiratory acidosis from CNS causes is usually driven by the clinical judgment that the ventilatory drive is unreliable for maintaining a safe level of ventilation for an extended period.

If mechanical ventilation is required for an impaired ventilatory controller, the mechanical ventilation strategy must assure that an adequate minute ventilation is delivered. This often requires clinician set ventilator breath rates, and either set tidal volumes or pressure targeted feedback mechanisms to assure adequate tidal volumes. Alarm systems that are properly set are critical.

Abnormal ventilatory control systems may also create inappropriate flow demands and breath timing patterns. These can be especially challenging to clinicians trying to minimize sedation while providing assisted breaths that can synchronize with these patient demands [8].

Demand/capability imbalances

The mechanical loads on the ventilatory muscles are primarily those imposed by the minute ventilation demands, airway resistance, and the compliance/elastance of the respiratory system [9]. Minute ventilation demands are driven by metabolic demands (i.e. oxygen consumption (VO_2) and carbon dioxide production (VCO_2)) and the amount of minute ventilation that is wasted (dead space ventilation or VD). Airway resistance is due to both patient airway geometry and the artificial airway properties. Compliance/elastance properties are driven by both parenchymal lung abnormalities, as well as chest wall abnormalities (e.g. tight surgical bandages, abdominal compartment syndrome, anasarca, ascites, and obesity). Imposed loads from the ventilator itself (artificial airway resistance and patient ventilator dys-synchrony) can also exist [10]. The presence of intrinsic positive end expiratory pressure (PEEP) can add to inspiratory muscle loads required to initiate a breath.

The capability of the patient's ventilatory system is composed of the inspiratory muscle's strength and endurance properties. These can be affected by metabolic abnormalities, systemic inflammation, nutritional factors, electrolyte factors, and drugs. The resting position of the diaphragm is particularly important as it is the major muscle of inspiration. If the diaphragm is flattened from lung hyperinflation, bullous disease and/or intrinsic PEEP, inspiratory muscle capabilities are greatly diminished.

Ventilatory muscle failure and resulting inadequate ventilation occurs when the demands outstrip the capabilities (Fig. 91.1). Clinically, this is often manifest initially by rapid-shallow breathing (a muscle 'protective' response driven by the ventilatory control center) [11]. As overloaded muscles continue to work, muscle damage occurs, hypoventilation worsens, and a respiratory acidosis develops (hypercarbic respiratory failure). At its extreme, ventilatory muscle failure produces a respiratory arrest.

Because gas exchange may be adequate in the face of progressive ventilatory muscle overload for a prolonged period, the clinical decision to initiate mechanical ventilatory support for demand/capability imbalances is best driven by mechanical assessments. Importantly, this is not so much by an assessment of mechanical loads (e.g. work of breathing or pressure time product which may be elevated several fold in patients requiring mechanical ventilation), but rather by an assessment of muscle load tolerance. Conceptually, this can be expressed using a transdiaphragmatic pressure referenced to muscle strength to calculate a pressure time index (PTI) (12):

$$PTI = (P_{Dtidal} / P_{D\,max}) \times (T_i / T_{tot}) \qquad \text{[eqn 1]}$$

where P_{Dtidal} is the transdiaphragmatic pressure change during inspiration, P_{Dmax} is the maximal voluntary transdiaphragmatic pressure, and T_i/T_{tot} is the fraction of the ventilator cycle spent in inspiration. A PTI value greater than 0.15 is associated with impending inspiratory muscle failure.

Clinically, load intolerance is associated with diaphoresis, accessory muscle use, abdominal paradox, inability to speak short phrases, and tachycardia [11,13,14]. The decision to institute mechanical ventilation in this setting is usually based on clinical judgment that load intolerance is becoming life threatening. Objective measurements or laboratory values can support the decision to initiate mechanical ventilatory support under these circumstances but these rarely provide definitive information that would override the clinical assessment.

Mechanical ventilation strategies in the setting of demand/capability imbalances focus on both improving muscle capabilities and reducing muscle loads. This involves proper unloading of ventilatory muscles with positive pressure breaths. Support strategies,

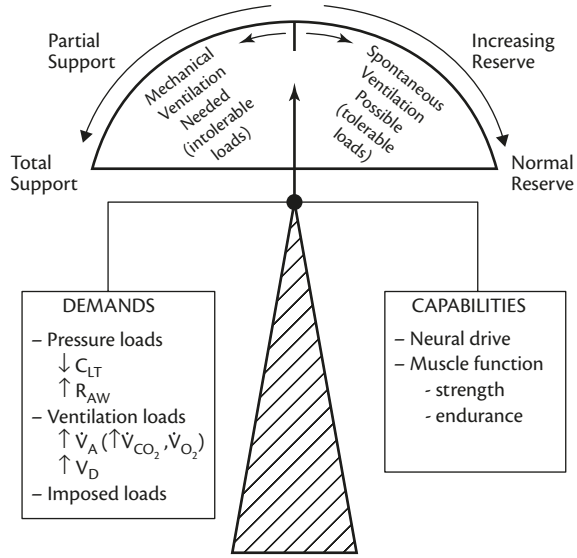


Fig. 91.1 Conceptual relationship between ventilatory muscle demands (left side of balance) and capabilities (right side of balance). As demands overwhelm capabilities, the balance shifts to the left and indications for mechanical ventilatory support increases.

however, must not totally unload ventilatory muscles as this can produce muscle atrophy [15]. In practice, this means a mechanical ventilation strategy focused on patient-triggered assisted modes of ventilation titrated to comfort. This requires skill in assuring appropriate triggering of breaths (including the use of circuit PEEP in the setting of intrinsic PEEP), proper flow synchrony such that ventilator flow matches patient demand, and proper breath cycling to coincide with neural cycling [8,10]. It also requires the proper setting of the respiratory rate and I:E ratio to assure adequate lung emptying is occurring, and intrinsic PEEP is minimized. Importantly, placement of an endotracheal tube is not always required for this support. In patients with load/capability imbalances, but with good airway protection capabilities, non-invasive (mask) ventilation may avoid endotracheal intubation, most notably in the COPD population with an acute exacerbation.

Maintaining alveolar patency

Many lung diseases affecting lung parenchyma can cause alveoli to flood and/or collapse. Inhalation injuries, infections, systemic inflammation (e.g. sepsis, pancreatitis), blunt chest trauma, aspiration, congestive heart failure, and fluid overload all can contribute. The predominant clinical manifestation of loss of alveolar patency is ventilation perfusion mismatching, producing shunts and hypoxaemia (hypoxaemic respiratory failure). If severe enough, the resulting compliance/elastance loads from alveolar instability can also contribute to ventilatory muscles overload and hypercarbic respiratory failure.

Provided that other components of oxygen delivery (i.e. cardiac output and haemoglobin concentration) and tissue oxygen extraction are adequate, arterial PO_2 values above 55 mmHg are generally adequate to assure tissue oxygen delivery. Clinical clues that oxygen delivery is inadequate and in need of therapy include altered mental status, cardiac dysrhythmias, and other organ dysfunction. Objective data suggesting impaired tissue oxygenation includes the development of a metabolic (lactic) acidosis.

Support of patients with compromised alveolar function involves the judicious use of PEEP to stabilize alveoli along with administration of supplemental oxygen [16]. If a tolerable load/capability balance exists (e.g. patients with some forms of cardiogenic pulmonary oedema), continuous positive airway pressure (CPAP), through either a mask or an endotracheal tube, may be all that is required to accomplish this. However, concomitant ventilatory support is often as needed as well. Under these conditions it is important to remember that PEEP is a two-edged sword. While, on one hand, the expiratory pressure can help maintain alveolar patency during exhalation, it will add to the total interthoracic pressure and could increase the risk of overdistention injury, especially when coupled with an excessive tidal volume [16–18]. Balancing PEEP and FIO_2 to provide proper oxygenation in the setting of alveolar injury is clearly a major clinical challenge and, as described elsewhere in this book, various imaging, mechanical, and gas exchange methodologies have been proposed.

Support for an artificial airway

Airway function can be compromised from a variety of different disease states [19]. CNS abnormalities (e.g. CNS injury, tumours, drugs) can result in a failure to maintain appropriate muscle tone for airway patency, and loss of cough and/or other airway defence reflexes. Clinical consequences can include the inability to ventilate due to airway compromise and aspiration of posterior pharyngeal material. Airway function can also be compromised by structural injuries to the pharynx, larynx, and major airways.

Clinically, loss of airway patency is manifest by a high work of breathing, inadequate ventilation, and sometimes stridor. Inadequate airway protection is manifest by weak or absent cough (especially when being suctioned), a need for frequent suctioning (e.g. more than every 2 hours), and clinical aspiration [19].

Although a mask system with constant positive airway pressure can often alleviate airway compromise from some structural abnormalities (e.g. obstructive sleep apnoea), compromised airway function, and/or inability to protect the airway often requires placement of an artificial airway (endotracheal tube or tracheostomy). In a large survey of over 5000 patients receiving mechanical ventilation [4], 89% had an oral tracheal tube, 4% had a nasal tracheal tube, and 4.9% had a facial mask. A tracheostomy was present in 2% of the patients. Interestingly, 85 patients with COPD received non-invasive ventilation (NIV) in this survey of whom 22% subsequently required tracheal intubation. One-hundred-and-forty-eight patients with other forms of respiratory failure received NIV and 36.5% subsequently required tracheal intubation.

Unless a need for positive pressure ventilation is required many patients can tolerate an artificial airway for isolated airway issues reasonably well (especially a tracheostomy). However, endotracheal tubes in particular can impose a significant resistive load on inspiratory muscles, especially if narrow (i.e. less than 7 mm internal diameter) and/or partially occluded with secretions [20]. Endotracheal tubes can also be uncomfortable, and require sedation and/or analgesics to assure tolerance. Under these conditions, some mechanically-ventilatory support may be needed to allow patients to tolerate the artificial airway. Often this is a low level of pressure, targeted ventilation (e.g. inspiratory pressure support of 5–10 cmH_2O) with optional back-up rates and PEEP. Some devices offer an automatic tube or airway compensation feedback mechanism that delivers inspiratory pressure support in a pattern designed to specifically unload the calculated resistance loads of the artificial airway. While theoretically appealing, this feedback capability has not as yet been shown to improve clinical outcomes.

Conclusion

Mechanical ventilation is a commonly-used modality in ICUs worldwide. Conceptually, mechanical ventilation is indicated when the patient's ability to ventilate the lung and/or effect gas transport across the alveolar capillary interface is compromised to a point that harm is imminent. In practice, this means addressing one or more of three fundamental pathophysiological processes—loss of proper ventilatory control, ventilatory muscle demand–capability imbalances, and/or loss of alveolar patency. A fourth general indication involves providing a positive pressure assistance to allow tolerance of an artificial airway in the patient unable to maintain a patent, protected airway.

Although some hard and fast thresholds for initiating mechanical ventilation exist (e.g. respiratory arrest, refractory hypoxaemia, severe acidosis from ventilatory muscle failure, inability to protect the airway), the decision to initiate mechanical ventilation usually involves an integrated assessment of the patient. This assessment should include mental status, airway protection capabilities, ventilatory muscle load tolerance, spontaneous ventilatory pattern,

and signs of organ dysfunction from either acidosis, and/or hypoxaemia. This involves a high level of clinical expertise. Providing mechanical ventilatory assistance can be life sustaining; however, it is associated with significant risk and must be applied only when indications justify the risk.

References

1. Gattinoni L, Protti A, Caironi P, and Carlesso E. (2010). Ventilator-induced lung injury: the anatomical and physiological framework. *Critical Care Medicine*, **38**(10, Suppl.), S539–48.
2. Tejerina E, Frutos-Vivar F, Restrepo MI, et al. (2006). Incidence, risk factors, and outcome of ventilator-associated pneumonia. *Journal of Critical Care*, **21**, 56–65.
3. Girard TD, Kress, JP, Fuchs BD, et al. (2008). Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): a randomized controlled trial. *Lancet*, **371**, 126–34.
4. Esteban A, Anzueto A, Frutos F, et al. (2002). Characteristics and outcomes in adult patients receiving mechanical ventilation. *Journal of the American Medical Association*, **287**(3), 345–55.
5. Ramirez JM, Zuperku EJ, Alheid GF, et al. (2002). Respiratory rhythm generation: converging concepts from in vitro in vivo approaches? *Respiratory Physiology & Neurobiology*, **131**, 43–56.
6. Otis AB, Fenn WO, and Rahn H. (1950). Mechanics of breathing in man. *Journal of Applied Physiology*, **2**(11), 592–607.
7. Hickling KG, Walsh J, Henderson S, and Jackson R. (1994). Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Critical Care Medicine*, **22**, 1568–78.
8. Tobin MJ, Jubran A, and Laghi F. (2001). Patient-ventilator interaction. *American Journal of Respiratory and Critical Care Medicine*, **163**, 1059–63.
9. Marini JJ and Crooke PS. (1993). A general mathematical model for respiratory dynamics relevant to the clinical setting. *American Reviews of Respiratory Diseases*, **147**, 14–24.
10. MacIntyre NR. McConnell R, and Cheng KC. (1997). Applied PEEP reduces the inspiratory load of intrinsic PEEP during pressure support. *Chest*, **1111**, 188–93.
11. Tobin MJ, Chadha TS, Jenouri G, et al. (1983). Breathing patterns 2: diseased subjects. *Chest*, **84**, 286–94.
12. Bellemare, F and Grassino A. (1982). Effect of pressure and timing of contraction on human diaphragm fatigue. *Journal of Applied Physiology*, **53**(5), 1190–5.
13. Pierson DJ. (2002). Indications for mechanical ventilation in adults with acute respiratory failure. *Respiratory Care*, **47**, 249–62.
14. Hudson LD. (1983). Evaluation of the patient with acute respiratory failure. *Respiratory Care*, **28**, 542–52.
15. Petrof BJ, Jaber S, and Matecki S. (2010). Ventilator-induced diaphragmatic dysfunction. *Current Opinion in Critical Care*, **16**, 19–25.
16. MacIntyre NR. (2008). Is there a best way to set positive end expiratory pressure for mechanical ventilatory support in acute lung injury. *Clinical Chest Medicine*, **29**, 233–40.
17. Gattinoni L, Carlesso E, and Cressoni M. (2011). Assessing gas exchange in acute lung injury/acute respiratory distress syndrome: diagnostic techniques and prognostic relevance. *Current Opinion in Critical Care*, **17**, 18–23.
18. Briel M, Meade M, Mercat A, et al. (2010). Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *Journal of the American Medical Association*, **303**, 865–73.
19. Shaker R. (1995). Airway protective mechanisms: current concepts. *Dysphagia*, **10**, 216–27.
20. Shapiro M, Wilson RK, Casar G, et al. (1986). Work of breathing through different sized endotracheal tubes. *Critical Care Medicine*, **14**, 1028–31.

CHAPTER 92

Design and function of mechanical ventilators

Robert L. Chatburn and Eduardo Mireles-Cabodevila

Key points

- A mode of ventilation is a predefined pattern of interaction between the ventilator and the patient.
- There are nearly 300 commercial names for modes of ventilation and no standardized vocabulary nor classification system. There is a great need to distinguish modes based on tags (classifications) instead of names.
- A taxonomy or hierarchical classification system suitable for comparing modes can be based on 10 fundamental concepts described in this chapter.
- The taxonomy based on these concepts allows description of modes in terms of control variable, breath sequence, and targeting schemes.
- Once modes can be classified, their ability to serve the goals of ventilation can be compared and matched appropriately to patient needs. This is analogous to the way drugs are prescribed.

Introduction to ventilator design

A mechanical ventilator is an automatic machine designed to provide all or part of the work required to move gas in and out of the lungs. There is a huge variety of ventilator designs, but no standardized classification system. To understand such a vast subject in such a small chapter requires that we depart from the traditional approach of describing schematics and specific design components (e.g. drive mechanisms, valves, pneumatic circuits, etc.) [1]. Indeed, the internal operations of modern ventilators are largely unknowable and unimportant to most clinicians. What distinguishes ventilators is their range of technological capabilities, expressed mainly by the 'modes of ventilation' they offer. There are nearly 300 commercial names for modes of ventilation and no standardized vocabulary nor classification system. To address this problem, we use a simple taxonomy which is based on the fundamental concepts of pulmonary physiology and ventilator design [2–4]. What follows is a description of this approach. These concepts build on one another to yield a practical taxonomy that may be used to simplify the task of comparing and contrasting the features of ventilators, and ultimately, to select the most appropriate mode for a given clinical situation. This didactic approach is informed by over 30 years of experience teaching mechanical ventilation and the data from an international survey [4]. After describing these 10 concepts, we demonstrate how the resulting taxonomy can be used to guide the selection of modes.

Defining a breath

The most basic function of a ventilator is to deliver a breath. A breath is defined in operational terms using a graph of flow versus time (Fig. 92.1). A breath is defined as one cycle of inspiratory flow followed by a matching expiratory flow, yielding approximately the same volumes. These flows are paired by size, not necessarily by timing. For example, in Airway Pressure Release Ventilation there is a large inspiration (transition from low pressure to high pressure) possibly followed by a few small inspirations and expirations, followed finally by a large expiration (transition from high pressure to low pressure). These inspirations and expirations represent several small spontaneous breaths superimposed on one large mandatory breath. In contrast, during high frequency oscillatory ventilation, small mandatory breaths are superimposed on larger spontaneous breaths.

Ventilators shape the flow waveform using a wide variety of physical systems comprised of a source of high pressure gas (e.g. a compressor), flow control valves, and electronic control systems. A detailed description of these components is beyond the scope of this chapter. However, a generalized schematic of a ventilator is shown in Fig. 92.2. The two most important valves are shown in Fig. 92.3. They are similar in design in that an electronic signal adjusts the position of the actuator such that the orifice diameter changes and thus controls the flow through the valve [5]. They work in synchrony, meaning that during inspiration the output flow control valve opens and the exhalation valve closes, forcing gas into the lungs. During expiration, the output flow control valve closes and the exhalation valve opens, allowing gas to flow from the lungs to the atmosphere. In the case of the output flow control valve, the input source is at high pressure (e.g. 10–20 psi) and the output is adjusted by the targeting scheme software to achieve a desired waveform for either inspiratory flow or inspiratory pressure. In contrast, the exhalation valve operates at patient circuit pressures (<1 psi) and generally controls the end expiratory pressure level, rather than the expiratory flow waveform.

Assisting a breath

The definition of a ventilator implies assistance with the patient's work of breathing. Work is a function of pressure and volume;

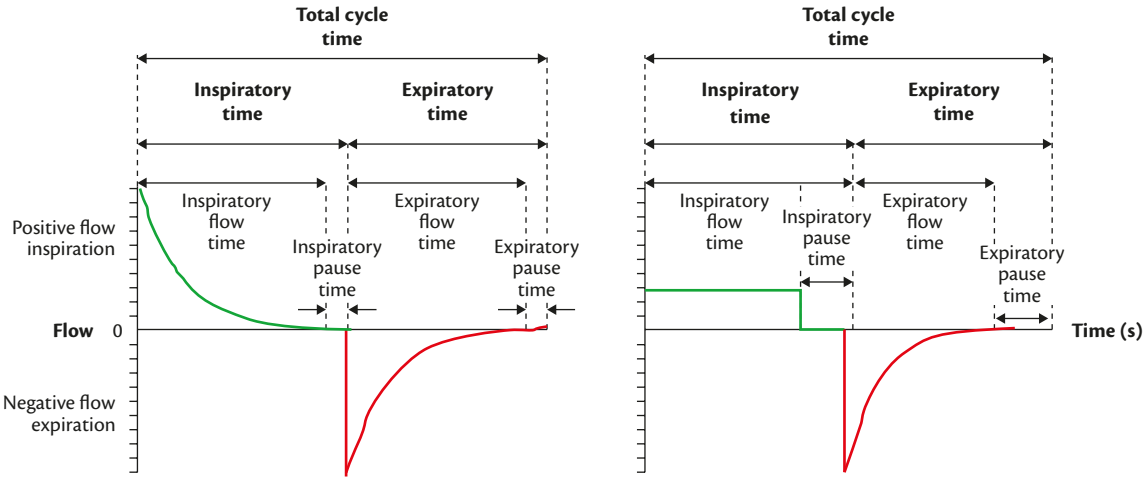


Fig. 92.1 A breath is defined as one cycle of inspiratory flow followed by a matching expiratory flow. (Left) Pressure control ventilation. (Right) Volume control ventilation.

Courtesy of Mandu Press Ltd., Cleveland Heights, Ohio.

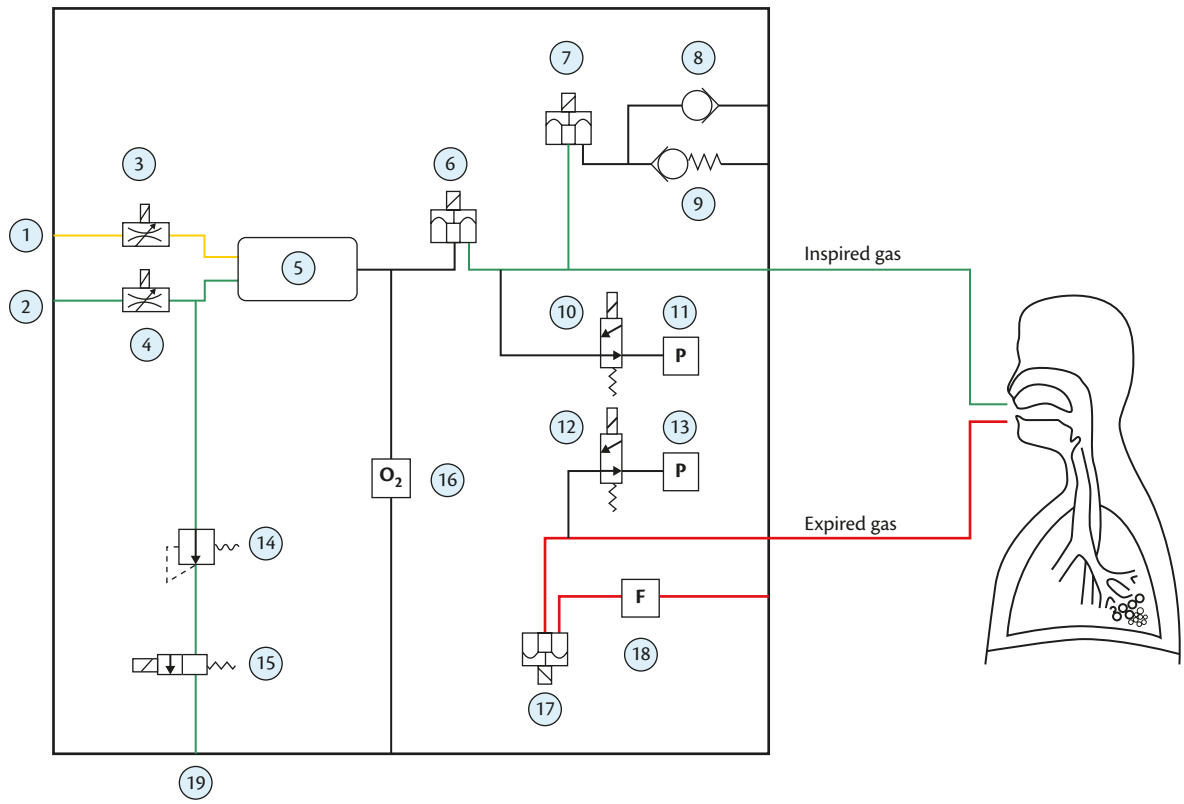


Fig. 92.2 Simplified schematic of a modern intensive care ventilator. High pressure gas enters the ventilator through the gas inlet connections for oxygen and air (1,2). Mixing takes place in a reservoir (5) and is controlled by two valves (3,4). Oxygen content is monitored by an oxygen sensor (16). Inspiratory flow from the reservoir is controlled by a separate inspiratory flow control valve (6). On the inspiratory circuit there is a safety valve (7) and two non-return valves (8,9). In normal operation the safety valve is closed so that inspiratory flow is supplied to the patient's lungs. When the safety valve is open, spontaneous inspiration of atmospheric air is possible through the emergency breathing valve (8). The emergency exhalation valve (9) provides a second channel for expiration when the exhalation valve (17) is blocked. Also on the inspiratory circuit are an inspiratory pressure (P) sensor (11) and a pressure sensor calibration valve (10). The exhalation circuit consists of the exhalation valve (17), expiratory pressure sensor (13) with its calibration valve (12), and an expiratory flow (F) sensor (18). The exhalation valve is a proportional valve and is used to adjust the pressure in the patient circuit. Conversion of mass flow to volume (barometric temperature and pressure saturated, BTPS) requires knowledge of ambient pressure, measured by another pressure sensor. Pressure in the patient circuit is measured with two independent pressure sensors (11,13). Oxygen flow to the nebulizer port (19) is controlled by a pressure regulator (14) and a solenoid valve (15).

Courtesy of Mandu Press Ltd., Cleveland Heights, Ohio.

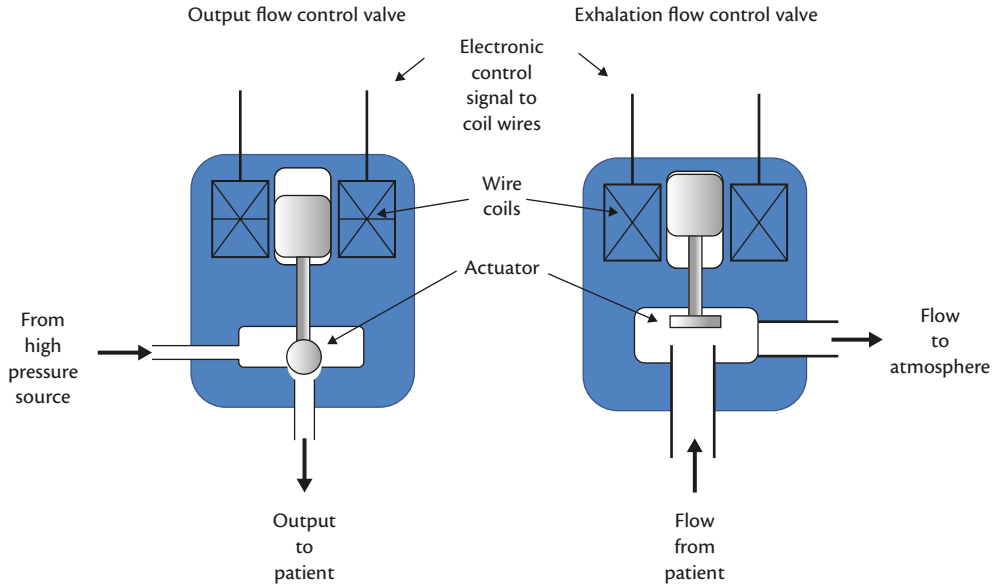


Fig. 92.3 Schematics of output flow control valve and exhalation valve.
Courtesy of Mandu Press Ltd., Cleveland Heights, Ohio.

either the patient's inspiratory muscles or the ventilator generates an increase in the pressure difference across the lungs (which we will refer to simply as inspiratory pressure; a detailed discussion of the subject is provided in a recent textbook [6]) so that their volume increases during inspiration. In terms of ventilator graphic displays, an assisted inspiration can be recognized as one for which airway pressure rises above baseline (positive end expiratory pressure) during inspiratory flow. On the other hand, if airway pressure drops below baseline pressure during inspiration, the patient is doing some work on the ventilator and the breath is 'loaded', rather than assisted. Some loading is unavoidable for several reasons—ventilators cannot control airway pressure perfectly so pressure always drops a little with patient inspiratory effort, some pressure drop may be necessary for triggering a breath, and the presence of electrical/mechanical delays between sensing a patient effort and the start of inspiratory flow [7].

Assistance with volume control versus pressure control

A ventilator provides assistance either by manipulating inspiratory pressure (called **pressure control**) or by manipulating inspiratory flow (called **volume control**). To understand this, we employ a mathematical model of patient-ventilator interaction known as the equation of motion for the respiratory system[8]:

$$P(t) = EV(t) + R\dot{V}(t) \qquad \text{[eqn 1]}$$

where $P(t)$ is inspiratory pressure generated by the ventilator as a function of time (t), E is respiratory-system elastance, $V(t)$ is volume as a function of time, R is respiratory-system resistance, and $\dot{V}(t)$ is flow as a function of time. This is a simplified version that assumes a passive respiratory system; otherwise patient inspiratory effort is represented as muscle pressure, $Pmus(t)$, on the left side of the equation. The equation indicates that the ventilator can either control the left side of the equation (pressure control, implying preset inspiratory pressure, either as a specific target value or in proportion to patient effort) or the right side (volume control, implying preset tidal volume and inspiratory flow). With pressure control, for a given pressure waveform, the inspired volume and flow are functions of elastance, resistance, and time. In contrast, with volume control, for a given flow waveform, inspiratory pressure is a function of elastance, resistance, and time. Idealized waveforms for volume and pressure control are shown in Fig. 92.4.

For completeness, we mention the case where neither pressure nor volume are controlled and the only preset values are inspiratory and expiratory times. This case is called **time control** and while rare, does exist in the modes called High Frequency Oscillatory Ventilation and Intrapulmonary Percussive Ventilation.

Starting and stopping inspiration

To assist a breath, the ventilator must know when to start and stop the inspiratory time (see Fig. 92.1). It does this by monitoring one or more variables and taking action when a preset threshold value is met. Starting inspiration is called **triggering**. Common trigger variables include time, airway pressure or flow change and the electrical signal from the diaphragm. Stopping inspiration is called **cycling**. Common cycle variables are the same as for triggering. The amount that the trigger or cycle variables must change before triggering or cycling occurs is called trigger or cycle **sensitivity**.

Machine versus patient triggering and cycling

Machine triggering or cycling is the initiation or termination of inspiratory flow, independent of the patient determined components of the equation of motion, i.e. *Pmus* (effort), elastance, or resistance. Common examples of machine trigger variables are preset frequency and minimum minute ventilation. Common examples of machine cycling variables are preset inspiratory

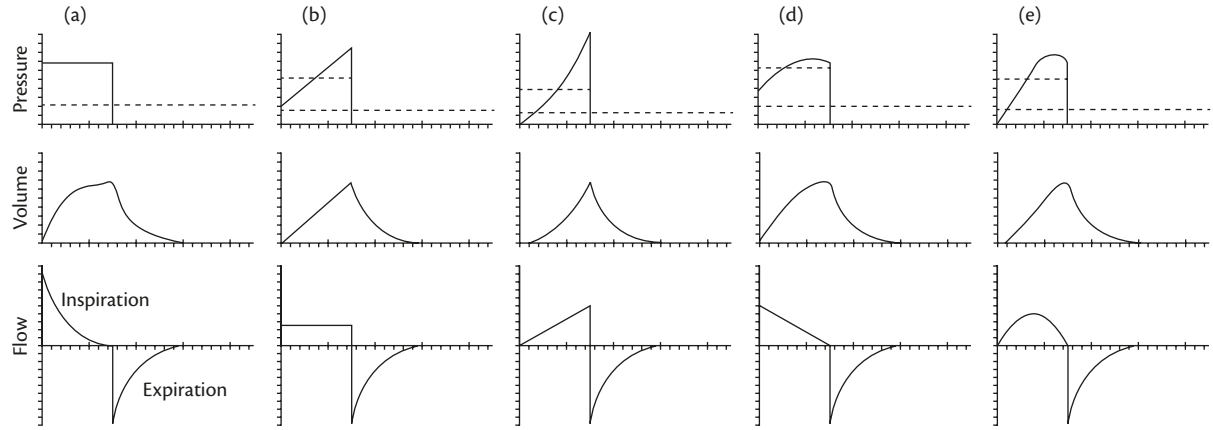


Fig. 92.4 Idealized ventilator output waveforms. (a) Pressure-controlled inspiration with a rectangular pressure waveform. (b) Volume-controlled inspiration with a rectangular flow waveform. (c) Volume-controlled inspiration with an ascending-ramp flow waveform. (d) Volume-controlled inspiration with a descending-ramp flow waveform. (e) Volume-controlled inspiration with a sinusoidal flow waveform. The short dashed lines represent mean inspiratory pressure, and the long dashed lines represent mean pressure for the complete respiratory cycle (i.e. mean airway pressure). Note that mean inspiratory pressure is the same as the pressure limit in (A). These waveforms were created as follows: (1) defining the control waveform using a mathematical equation (e.g. an ascending-ramp flow waveform is specified as flow = constant × time); (2) specifying the tidal volume for flow- and volume-control waveforms; (3) specifying the resistance and compliance; (4) substituting the preceding information into the equation of motion for the respiratory system; and (5) using a computer to solve the equation for the unknown variables and plotting the results against time.

Courtesy of Mandu Press Ltd., Cleveland Heights, Ohio.

time and tidal volume. Patient triggering or cycling is the initiation or termination inspiratory flow based on one of the patient determined components of the equation of motion, i.e. *Pmus*, elastance, or resistance. Common examples of patient trigger variables are airway pressure drop below baseline and inspiratory flow due to patient effort. Common examples of cycling variables are peak inspiratory pressure and percentage of peak inspiratory flow. A detailed description of trigger and cycle variables has been presented elsewhere [9].

Mandatory versus spontaneous breaths

A **spontaneous** breath is one for which the patient **both** initiates and terminates inspiration, independent of machine settings, e.g. inspiratory time. Thus, the patient both triggers and cycles inspiration. If the machine triggers or cycles inspiration, the breath is defined as **mandatory**.

Breath sequences

There are only two classes of breaths—mandatory and spontaneous—which can be combined in only three basic sequences. If every breath is spontaneous, we call the sequence continuous spontaneous ventilation (CSV). If spontaneous breaths may exist between mandatory breaths (whether or not they actually happen) we call the sequence intermittent mandatory ventilation (IMV). Finally, if spontaneous breaths are not permitted between mandatory breaths, we call the sequence continuous mandatory ventilation (CMV).

Ventilatory patterns

Combining the concepts of control variable and breath sequence, we can construct a simple means for classifying modes of ventilation. With two main control variables and three possible breath sequences, there are only five basic ventilatory patterns: volume control continuous mandatory ventilation (VC-CMV), volume control intermittent mandatory ventilation (VC-IMV), pressure control continuous mandatory ventilation (PC-CMV), pressure control intermittent mandatory ventilation (PC-IMV), and pressure control continuous spontaneous ventilation (PC-CSV). Volume control continuous spontaneous ventilation (VC-CSV) is not valid because presetting the tidal volume implies machine cycling, which makes spontaneous breaths impossible.

Again, for completeness we note the rare case of time control intermittent mandatory ventilation (TC-IMV) is a ventilatory pattern that describes High Frequency Oscillatory Ventilation and Intrapulmonary Percussive Ventilation.

Targeting schemes

Ventilatory patterns can be used to sort the large number of mode names into just a few categories. This is very useful for many purposes, but when it becomes necessary to distinguish among modes within the same category, we need to consider the underlying feedback control or targeting schemes used to create the mode. We define a targeting scheme as a model of the relationship between operator inputs and ventilator outputs to achieve a specific ventilatory pattern. Targeting schemes are being developed all the time, but currently, there are only seven that are used for most commercially available ventilators [10]. These targeting schemes are described in Table 92.1.

A taxonomy for modes of ventilation

A **mode of ventilation** may be generally defined a predetermined pattern of interaction between the ventilator and the patient [3]. Referring to a mode using the name coined by the manufacturer has become problematic with the proliferation of new modes. The solution is a hierarchical classification system, a taxonomy that allows us to describe and compare modes at any level of detail. The previous

Table 92.1 Explanation of how targeting schemes transform operator inputs into ventilator outputs

Name	Description	Advantage	Disadvantage	Example mode name	Ventilator	Manufacturer
Set-point	The operator sets all parameters of the pressure waveform (pressure control modes) or volume and flow waveforms (volume control modes)	Simplicity	Changing patient condition may make settings inappropriate	Volume Control Continuous Mandatory Ventilation	Evita Infinity 500	Dräger
Dual	The ventilator can automatically switch between volume control and pressure control during a single inspiration	Can adjust to changing patient condition and assure either a preset tidal volume or peak inspiratory pressure, whichever is deemed most important	May be complicated to set correctly and may need constant readjustment if not automatically controlled by the ventilator	Volume Control	Servo-i	Maquet
Servo	The output of the ventilator (pressure/volume/flow) automatically follows a varying input	Support by the ventilator is proportional to inspiratory effort	Requires estimates of artificial airway and/or respiratory system mechanical properties	Proportional Assist Ventilation Plus	PB 840	Covidien
Adaptive	The ventilator automatically sets target(s) between breaths in response to varying patient conditions	Can maintain stable tidal volume delivery with pressure control for changing lung mechanics or patient inspiratory effort	Automatic adjustment may be inappropriate if algorithm assumptions are violated or they do not match physiology	Pressure Regulated Volume Control	Servo-i	Maquet
Bio-variable	The ventilator automatically adjusts the inspiratory pressure or tidal volume randomly	Simulates the variability observed during normal breathing	Manually set range of variability may be inappropriate to achieve goals	Variable Pressure Support	Evita Infinity 500	Dräger
Optimal	The ventilator automatically adjusts the targets of the ventilatory pattern to either minimize or maximize some overall performance characteristic (e.g. work rate of breathing)	Can adjust to changing lung mechanics or patient inspiratory effort	Automatic adjustment may be inappropriate if algorithm assumptions are violated or they do not match physiology	Adaptive Support Ventilation	G5	Hamilton Medical
Intelligent	Targeting scheme that uses artificial intelligence programs such as fuzzy logic, rule based expert systems, and artificial neural networks	Can adjust to changing lung mechanics or patient inspiratory effort	Automatic adjustment may be inappropriate if algorithm assumptions are violated or they do not match physiology	IntelliVent ASV	G5	Hamilton Medical

Courtesy of Mandu Press Ltd., Cleveland Heights, Ohio.

nine theoretical constructs support a practical taxonomy to achieve these goals [11–16]. The taxonomy has four levels as follows:

1. Control variable (pressure or volume).
   A. Breath sequence (CMV, IMV, or CSV).
      i. Primary breath targeting scheme.
         a. Secondary breath targeting scheme (only for IMV).

In CMV and CSV there is only one type of breath; mandatory for CMV and spontaneous for CSV. We refer to those breaths as primary breaths when specifying their targeting schemes. For IMV we will consider mandatory breaths primary and spontaneous breaths secondary. An example of how this taxonomy can be used to compare the modes of two common intensive care ventilators is shown in Table 92.2. This table illustrates two very important points. First, modes that are essentially the same or very similar are given very

Table 92.2 Classification of mode names on two common intensive care ventilators

Manufacturer	Model	Manufacturer's mode name	Control variable	Breath sequence	Primary breath target scheme	Secondary breath target scheme	Tag
Covidien	840	Volume control plus assist/control	Pressure	CMV	Adaptive	N/A	PC-CMVa
Maquet	Servo i	Pressure-regulated volume control	Pressure	CMV	Adaptive	N/A	PC-CMVa
Covidien	840	Pressure control assist control	Pressure	CMV	Set-point	N/A	PC-CMVs
Maquet	Servo i	Pressure control	Pressure	CMV	Set-point	N/A	PC-CMVs
Covidien	840	Volume support	Pressure	CSV	Adaptive	N/A	PC-CSVa
Maquet	Servo i	Volume support	Pressure	CSV	Adaptive	N/A	PC-CSVa
Covidien	840	Tube compensation	Pressure	CSV	Servo	N/A	PC-CSVr
Covidien	840	Proportional assist ventilation plus	Pressure	CSV	Servo	N/A	PC-CSVr
Maquet	Servo i	Neurally-adjusted ventilatory assist	Pressure	CSV	Servo	N/A	PC-CSVr
Covidien	840	Pressure support	Pressure	CSV	Set-point	N/A	PC-CSVs
Covidien	840	Spontaneous	Pressure	CSV	Set-point	N/A	PC-CSVs
Maquet	Servo i	Pressure support/CPAP	Pressure	CSV	Set-point	N/A	PC-CSVs
Covidien	840	Volume control plus synchronized intermittent mandatory ventilation	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Maquet	Servo i	Synchronized intermittent mandatory ventilation (pressure-regulated volume control)	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Covidien	840	Volume ventilation plus synchronized intermittent mandatory ventilation	Pressure	IMV	Adaptive	Adaptive	PC-IMVa,a
Maquet	Servo i	Automode (pressure-regulated volume control to volume support)	Pressure	IMV	Adaptive	Adaptive	PC-IMVa,a
Covidien	840	Pressure control synchronized intermittent mandatory ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Covidien	840	Bi-level	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Maquet	Servo i	Synchronized intermittent mandatory ventilation (pressure control)	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Maquet	Servo i	Bi-vent	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Maquet	Servo i	Automode (pressure control to pressure support)	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Covidien	840	Volume control assist/control	Volume	CMV	Set-point	N/A	VC-CMVs
Maquet	Servo i	Volume control	Volume	IMV	Dual	Dual	VC-IMVd,d
Maquet	Servo i	Synchronized intermittent mandatory ventilation (volume control)	Volume	IMV	Dual	Set-point	VC-IMVd,s
Maquet	Servo i	Automode (volume control to volume support)	Volume	IMV	Dual	Adaptive	VC-IMVd,a
Covidien	840	Volume control synchronized intermittent mandatory ventilation	Volume	IMV	Set-point	Set-point	VC-IMVs,s

a, adaptive; d, dual; r, servo; s, set-point.

Courtesy of Mandu Press Ltd., Cleveland Heights, Ohio.

different names by manufacturers and, secondly, because of this, modes are most practically compared using their **tags** (taxonomic attribute groupings), rather than by their **names** or ad hoc pseudo-classifications (e.g., VC-CMV is often referred to as 'assist/control' in the adult literature, but it means PC-CMV in the paediatric literature).

Fig. 92.5 provides an algorithm for recognizing the control variable of a mode. Fig. 92.6 shows an algorithm for determining the

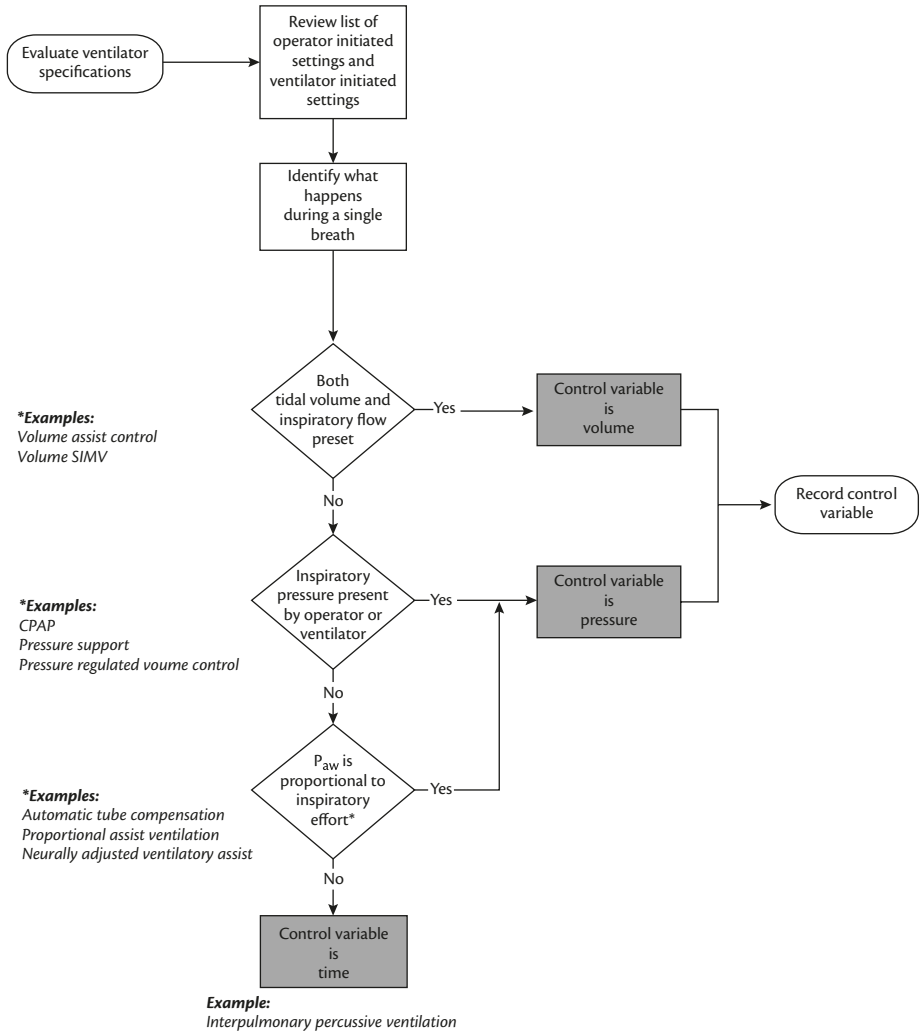


Fig. 92.5 Algorithm for recognizing the control variable of a mode.
P_{aw}, airway pressure.
Courtesy of Mandu Press Ltd., Cleveland Heights, Ohio.

breath sequence. Table 92.1 provides the information necessary for identifying targeting schemes.

Comparing modes

The previous section provides a means for identifying modes. This is useful to clinicians, educators, researchers, and manufacturers alike. However, clinicians are faced with the task of not only identifying modes, but comparing them and selecting the one that best serves the needs of the patient. Yet, trying to compare modes by simply reading the operator's manuals is impractical. We propose an approach that first identifies the general goals of patient care and then matches them to specific technological capabilities of the available modes [14]. First, we assert that there are only three main goals of mechanical ventilation, safety (optimizing both gas exchange, and the risk of ventilator associated lung injury Fig. 92.7), comfort (optimizing synchrony between patient and ventilator Fig. 92.8), and liberation (optimizing the duration of mechanical ventilation Fig. 92.9) [10]. Next we realize that these general goals and their specific objectives lead naturally to clinical aims for individual patients. Once the patient's needs are assessed, treatment options in terms of mechanical ventilation modes can be identified using the general technical capabilities of ventilators and design features of specific modes.

In Table 92.3, we have identified the technological capabilities of currently available targeting schemes (Table 92.1) and grouped them according to the three goals of ventilation. Then we have listed the mode names from Table 92.2 and noted which

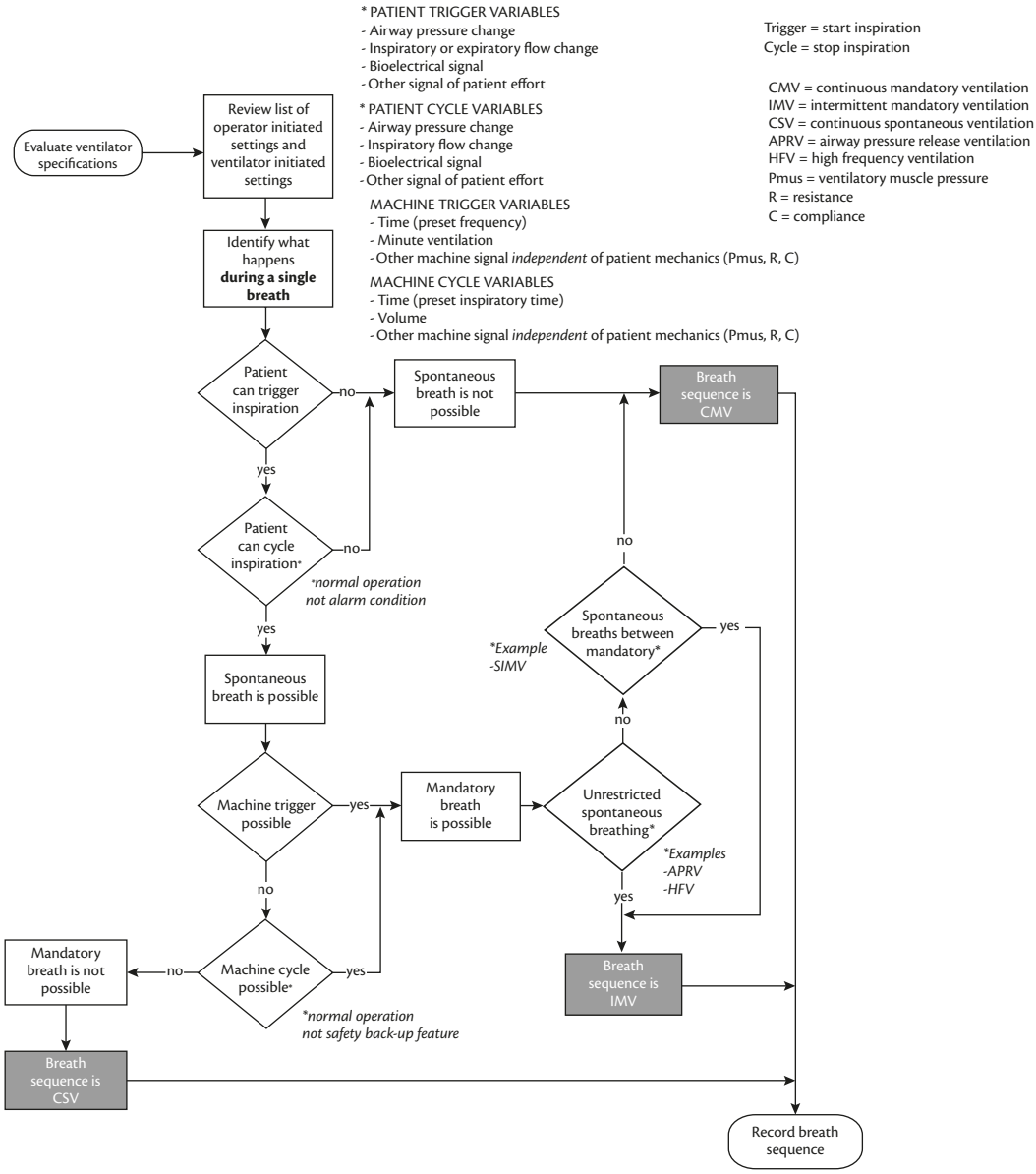


Fig. 92.6 Algorithm for determining the breath sequence of a mode.
Courtesy of Mandu Press Ltd., Cleveland Heights, Ohio.

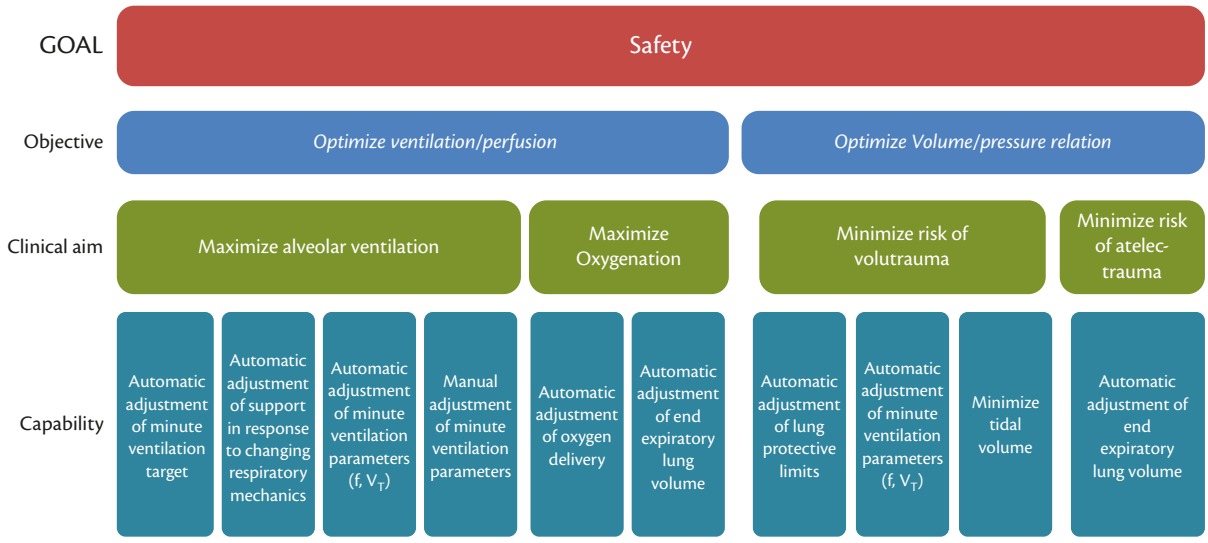


Fig. 92.7 Objectives, clinical aims, and ventilator technological capabilities for mechanical ventilation goal of safety.
Courtesy of Mandu Press Ltd., Cleveland Heights, Ohio.

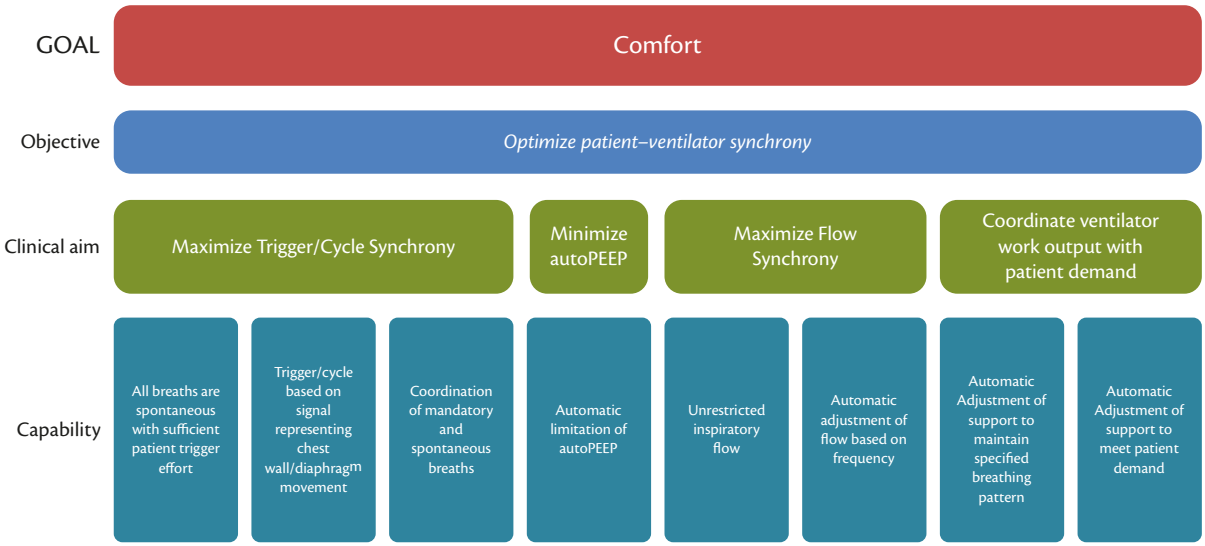


Fig. 92.8 Objectives, clinical aims, and ventilator technological capabilities for mechanical ventilation goal of comfort.
Courtesy of Mandu Press Ltd., Cleveland Heights, Ohio.

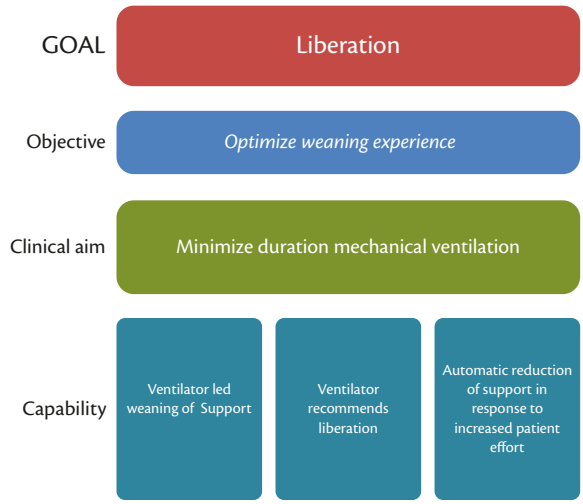


Fig. 92.9 Objectives, clinical aims, and ventilator technological capabilities for mechanical ventilation goal of liberation.
Courtesy of Mandu Press Ltd., Cleveland Heights, Ohio.

technological capabilities they offer. Note that some columns have no check marks because they represent capabilities of modes on other ventilators.

Conclusion

In this chapter we introduce a new approach to understanding the design and function of mechanical ventilators. These devices have become so complex that a formal classification system (taxonomy) is required to compare and contrast treatment options. We have shown how such a taxonomy can be constructed from 10 fundamental maxims of ventilator design. Finally, we have demonstrated how a formal description of ventilator technology can be used to match specific patient needs identified from clinical assessment to particular mode capabilities. This approach highlights the requirement for a thorough patient evaluation, identification of the goals of care and an understanding of ventilator technology.

Table 92.3 Comparison of technological capabilities for the modes in Table 92.2

Mode name	Mode tag	Automatic adjustment of minute ventilation target	Automatic adjustment of support in response to changing respiratory mechanics	Automatic adjustment of minute ventilation parameters (f, V_T)	Manual adjustment of minimum minute ventilation parameters (f, V_T)	Automatic adjustment of oxygen delivery	Automatic adjustment of end expiratory lung volume	Automatic adjustment of ventilation parameters within lung protective limits	Minimize tidal volume	Safety Capabilities	All breaths are spontaneous with patient effort	Trigger/cycle based on signal representing chest wall/diaphragm movement	Coordination of mandatory and spontaneous breaths	Automatic limitation of autoPEEP	Unrestricted inspiratory flow	Automatic adjustment of flow based on frequency	Automatic adjustment of support to maintain specific breathing pattern	Automatic adjustment of support proportional to patient demand	Comfort Capabilities	Ventilator initiated weaning of support	Ventilator recommends liberation	Automatic reduction of support in response to increased patient effort	Liberation Capabilities
Automode (Pressure Regulated Volume Control to Volume Support)	PC-IMVa,a		✓	✓	✓					3	✓		✓		✓				3			✓	1
Automode (Volume Control to Volume Support)	VC-IMVd,a		✓	✓	✓					3	✓		✓		✓				3			✓	1
Volume Support	PC-CSVa		✓							1	✓				✓				2			✓	1
Pressure Regulated Volume Control	PC-CMVa		✓		✓					2					✓				1			✓	1
Synchronized Intermittent Mandatory Ventilation (Volume Control)[1]	VC-IMVd,s				✓					1			✓		✓				2				0
Proportional Assist Ventilation Plus	PC-CSVr									0	✓				✓			✓	3				0
Volume Control Synchronized Intermittent Mandatory Ventilation	VC-IMVs,s				✓					1			✓						1				0
Pressure Support	PC-CSVs									0	✓				✓				2				0
BiLevel	PC-IMVs,s									0			✓		✓				2				0
Pressure Control Synchronized Intermittent Mandatory Ventilation	PC-IMVs,s									0			✓		✓				2				0
Automode (Pressure Control to Pressure Support)	PC-IMVs,s									0	✓		✓		✓				3				0
Pressure Control Assist Control	PC-CMVs									0					✓				1				0
Volume Control Assist Control	VC-CMVs				✓					1									0				0

[1] *Maquet Servo i ventilator*

PC, pressure control; VC, volume control; CMV, continuous mandatory ventilation; IMV, intermittent mandatory ventilation; CSV, continuous spontaneous ventilation Targeting scheme; s, setpoint; d, dual; r, servo; a, adaptive.

Courtesy of Mandu Press Ltd., Cleveland Heights, Ohio.

References

1. Cairo JM. (2012). *Pilbeam's Mechanical Ventilation*, 5th edn. St. Louis, MO: Mosby Inc.
2. Chatburn RL. (2007). Classification of ventilator modes: update and proposal for implementation. *Respiratory Care*, **52**(3), 301–23.
3. Chatburn RL. (2012). What's in a name? Response to letter to the editor. *Respiratory Care*, **57**(12), 2138–50.
4. Chatburn RL, Volsko TA, Hazy J, Harris LN, and Sanders S. (2012). Determining the basis for a taxonomy of mechanical ventilation. *Respiratory Care*, **57**(4), 514–24.
5. Sanborn WG. (1993). Microprocessor-based mechanical ventilation. *Respiratory Care*, **38**(1):72-109.
6. Chatburn RL and Daoud EG. (2012). Ventilation. In: Kacmarek RM, Stoller JK, and Heuer AH (eds) *Egan's Fundamentals of Respiratory Care*, 10th edn, pp. 225–49. St. Louis, MO: Mosby Elsevier.
7. Sassoon CSH. (2011). Triggering of the ventilator in patient-ventilator interactions. *Respiratory Care*, **56**(1), 39–48.
8. Rodarte JR and Rehder K. (1986). Dynamics of respiration. In: Fishman AP, Macklem PT, Mead J, and Geiger SR (eds) *Handbook of Physiology. The Respiratory System. Volume III, Mechanics of Breathing*, Part 1, pp. 131–44. Bethesda, MD: American Physiological Society.
9. Chatburn RL and Mireles-Cabodevila E. (2013). Basic principles of ventilator design and operation. In: Tobin MJ (ed.) *Principles and Practice of Mechanical Ventilation*, 3rd edn, pp. 65–97. New York, NY: McGraw-Hill.
10. Chatburn RL and Mireles-Cabodevila E. (2011). Closed-loop control of mechanical ventilation: description and classification of targeting schemes. *Respiratory Care*, **56**(1), 85–102.
11. Chatburn RL and Volsko TA. (2012). Mechanical ventilators. In: Kacmarek RM, Stoller JK, and Heuer AH (eds) *Egan's Fundamentals of Respiratory Care*, 10th edn, pp. 10006–1040. St. Louis, MO: Mosby Elsevier.
12. Chatburn RL and Volsko TA. (2016). Mechanical ventilators: classification and principles of operation. In: Hess DR, MacIntyre NR, Galvin WF, Mishoe SC (eds). *Respiratory Care: Principles and Practice*. 3rd edn, pp. 462–492. Philadelphia, PA: W.B. Saunders Co.
13. Chatburn RL. (2013). Classification of mechanical ventilators and modes of ventilation. In: Tobin MJ (ed.) *Principles and Practice of Mechanical Ventilation*, 3rd edn, pp. 45–64. New York, NY: McGraw-Hill.
14. Mireles-Cabodevila E, Hatipoglu U, and Chatburn RL. (2013). A rational framework for selecting modes of ventilation. *Respiratory Care*, **58**(2), 348–66.
15. Chatburn RL, Khatib ME, and Mireles-Cabodevila E. (2014). A taxonomy for mechanical ventilation: 10 fundamental maxims. *Respiratory Care*, **59**(11), 1747–63.
16. Volsko TA, Chatburn RL, and El-Khatib M. (2016). *Respiratory Care Equipment*. Burlington: Jones & Bartlett Learning.

CHAPTER 93

Setting rate, volume, and time in ventilatory support

Charles M. Oliver and S. Ramani Moonesinghe

Key points

- Ventilator rate, volume, and time parameters are interrelated directly, mechanically, and physiologically.
- The physiological consequences of mechanical ventilation and risks of ventilator-induced trauma may be exacerbated by lung pathology.
- Programming of parameters should be considered within the context of an individualized ventilation strategy to achieve adequate gas exchange, while minimizing attendant risks of mechanical ventilation.
- Recommended strategies should be modified within accepted limits to mitigate disease-specific risks.
- Parameters should subsequently be titrated against blood gas- and ventilator-derived targets and other clinical variables.

Introduction

While mechanical ventilation (MV) remains a cornerstone of critical care practice, understanding of its optimal usage continues to evolve. Striving for proposed physiological ideals has given way to strategies targeting more modest PaO_2, $PaCO_2$, and pH values, thereby reducing risks of volutrauma, barotrauma, atelectrauma, and bio-trauma, which may exacerbate or perpetuate lung injury [1,2].

Interactions between intrinsic pulmonary physiomechanics, pathological processes, and the effects of positive pressure ventilation are complex. Programming of ventilator parameters must therefore be considered within the context of an individualized ventilation strategy in order to achieve gas exchange targets, while minimizing the attendant risks of MV.

Rate, volume, and time

Rate, volume, and time parameters are interrelated directly, physiologically, and mechanically.

Minute ventilation ($\tilde{V}_{min}$) is the gas flow per minute, which is calculated as the product of the inspiratory volume, or tidal volume (V_T) and the ventilatory rate. V_T and rate are readily amenable to manipulation, and may be titrated to biochemical and physiological targets in MV.

Programming of absolute duration of inspiratory and expiratory phases of ventilation, and their ratio is necessarily limited by ventilatory rate. Furthermore, setting inspiratory time in volume-targeted modes may limit the magnitude of delivered gas flow and result in excessive system pressures. Disease-specific factors must be considered when setting expiratory time.

MV may be broadly classified as mandatory, assisted, or a combination. Rate, volume, and time values must be selected in mandatory modes, although this may be performed automatically. Spontaneous inspiration is augmented to a target pressure or volume in assisted modes and a back-up rate may be set to provide additional ventilator-delivered breaths. The duration of inspiration and expiration may be programmed in both mandatory and assisted modes.

Rate

In conventional mandatory ventilation a rate of 10–20 breaths/min will usually provide a $\tilde{V}_{min}$ sufficient to create and maintain favourable partial pressure gradients across alveolar membranes. Higher rates may be indicated in certain disease states and are routinely selected for children, infants, and neonates. Rates in excess of three times the physiological range are used in high frequency ventilation, and lower rates may be programmed for ventilator weaning and in individuals susceptible to gas-trapping.

Provided V_T remains constant, increasing ventilatory rate will increase alveolar ventilation, which may be beneficial. However, in addition to its additive role in ventilator-induced lung injury (VILI) [3], increasing ventilatory rate limits inspiratory and expiratory times, which may worsen gas exchange and predispose to complications in susceptible individuals as discussed in 'Targets in Pathophysiological States'.

Volume

Of the generated inspiratory volume (V_T), a proportion is unavailable for gas exchange. This 'dead space' volume comprises physiological (conducting airways and alveoli at which no gas exchange occurs) and apparatus dead space. While the former is relatively fixed, the latter should be minimized to optimize ventilatory efficiency. The flow of fresh gas ($\tilde{V}_A$) available for exchange in the alveolar compartment is therefore the product of ventilatory rate and what remains of V_T once dead space volume is accounted for:

$$\tilde{V}_A = r.\left[V_T - \left(V_D + V_{APP}\right)\right] \quad \text{[eqn 1]}$$

where $\tilde{V}_A$ is alveolar ventilation, r is rate, V_T is tidal volume, V_D is physiological dead space volume, and V_{APP}, apparatus dead space volume.

Provided alveolar perfusion matches ventilation, oxygenation and CO_2 elimination may be improved by increasing alveolar ventilation relative to dead space ventilation. It should, however, be noted that simply increasing rate will lead to a proportionally greater increase in dead space ventilation relative to $\tilde{V}_A$.

Tidal volume may be increased in positive pressure ventilation (PPV) by increasing generated inspiratory pressure with due attention to rate and time variables; however, the volume delivered is also dependent upon system compliance. Pathological processes resulting in differential regional compliance may cause asymmetrical distribution of gas flow and pressure inequalities in affected individuals. Such changes predispose to dynamic hyperinflation, over-distension of alveoli in more compliant lung units and exaggeration of physiological gas flow:perfusion ($\tilde{V}_A$:Q) mismatching.

Evidence of the potential harm caused by exposure to MV comes from studies of the pathogenesis of VILI and the acute respiratory distress syndrome (ARDS). While the aetiology of ARDS is likely to involve synergy between pulmonary insult and MV in predisposed individuals [4,5], VILI may develop in previously normal lungs in as little as 6hours [4,6,7]. Demonstrated associations include exposure to high end-inspiratory lung volumes (volutrauma) [8], shear stress resulting from cyclical inflation and deflation of differently compliant lung units (atelectrauma), and large transpulmonary pressure gradients [9].

Data from ARDS trials suggest that limitation of V_T to 4–8 mL/kg ideal body weight (IBW) [10,11] and limitation of plateau pressure (a surrogate for transpulmonary pressure) to less than 30–35 cmH_2O [10] may decrease early morbidity and mortality in affected individuals. However, due to increasing evidence of the potentially deleterious effects of high inflationary pressures and inspiratory volumes, such lung protective strategies are increasingly being adopted in the management of patients with previously normal lungs [12]. Targets include V_T 6–8 mL/kg IBW [13,14] and limitation of plateau pressure (P_{PLAT}) to 30 cmH_2O [12].

As can be seen from eqn 1, the limitation of V_T and P_{PLAT} without compensatory increase in rate may result in hypercapnoea in poorly compliant lungs. It may therefore be necessary to accept supraphysiological $PaCO_2$ or institute an alternative means of CO_2 removal.

Additional strategies to aid improved ventilation include the manipulation of time, rate, and mode variables to limit airway pressures and improve flow distribution, titration of positive end expiratory pressure (PEEP) to limit atelectrauma [15] and shunt, patient repositioning, and pharmacological agents.

Time variables

Time variables, which may be individually programmed or automatically determined include duration of inspiration and expiration and their ratio (I:E ratio). These variables are interdependent and limited by ventilatory rate; furthermore, their manipulation may predispose to complications.

To permit theoretical modelling, groups of alveoli and their terminal airways possessing similar mechanical characteristics are termed 'lung units'. The time required to fully inflate or deflate such units is determined by both compliance and resistance to flow, the product of which, the time constant (τ), determines the speed with which alveolar and proximal airway pressures reach equilibrium.

Many disease processes affect lung tissue mechanics and thus inspiratory (τ_i) and expiratory (τ_e) time constants, but because such changes are rarely homogenous, regional flow pattern variations occur. Lung units with low τ_i tend to fill quickly with a subsequent distribution of flow to more distensible units with greater resistance. PPV may therefore cause over-distension of compliant units and subsequent collapse of compressed units in a variety of pathologies, predisposing to complications and exaggerating $\tilde{V}_A$:Q mismatching.

Time variables may be controlled in both mandatory and assisted modes of ventilation; however, it is imperative to ensure synchrony with spontaneous effort to reduce distress, work of breathing, and breath stacking. Time variables must therefore be considered both individually and as components of an individualized strategy.

Inspiratory time

Inspiratory time (t_i) is the duration over which pressure is applied in PPV to deliver V_T and is typically set at 1 second when respiratory rate is 20 breaths/minute. Any increase in t_i occurs at the expense of expiratory time (t_e), unless rate is reduced to compensate.

Increasing t_i may improve oxygenation by permitting equilibration of pressure between differently compliant lung regions, increasing mean airway pressures, and preventing atelectasis. Reducing t_i predisposes to the complications of increased flow and system pressures in volume-controlled modes [8].

Expiratory time

Expiratory time (t_e) is typically set at 2 seconds when rate is 20 breaths/minute, and may only be maintained or increased at the expense of t_i at higher rates.

Pressures generated in PPV may be sufficient to overcome increased airway resistance and distend alveoli, but exhalation is passive and diminished if tissue elasticity is reduced. Conditions in which highly compliant alveoli empty into bronchioles with increased resistance to flow, such as chronic obstructive pulmonary disease (COPD), therefore require a longer t_e to permit lung unit emptying. If t_e is insufficient to permit emptying prior to inspiratory cycling, gas trapping and the generation of intrinsic PEEP ($PEEP_i$) may occur, with both respiratory and haemodynamic consequences.

I:E ratio

This is usually set at 1:1 to 1:2, but ratios of 1:2 to 1:4 may be required to prevent dynamic hyperinflation in severe airflow limitation. Awake patients may be more comfortable with shorter inspiratory times and high inspiratory flow rates.

Inverse ratio ventilation (IRV), in which t_i exceeds t_e, may be employed if adequate oxygenation cannot be achieved by increasing PEEP. It is thought that increased mean airway pressures and improved filling of lung units with high τ_i are responsible for its effects. Caution should be exercised in using IRV in patients with airflow limitation to avoid generation of $PEEP_i$.

Proposed benefits of IRV include:

- Reduced shunt due to prevention and resolution of atelectasis.
- Increased efficiency of CO_2 elimination due to delayed lung unit emptying.
- Lower V_T and transpulmonary pressures due to reduced $\tilde{V}_{min}$.

Suggested strategy

- Following a thorough clinical assessment, consider first whether lung physiomechanics are likely to be normal.

Table 93.1 Targets in the absence of overt pulmonary pathology

Rate	10–20 breaths/min
V_T	6–8 mL/kg IBW
I:E	1:2
P_{PLAT}	<30 cmH_2O

- Targets in the absence of overt pulmonary pathology are shown in Table 93.1.
- Adjust parameters in response to clinical examination, blood gas analysis, and monitoring. Recruitment manoeuvres may be required, particularly if a period of hypoventilation precedes institution of MV.

PaO_2 may be optimized by adjusting $\tilde{V}_{min}$, I:E ratio, PEEP, and FIO_2. Normocapnoea should not be pursued at the expense of exceeding pressure limits, unless there is urgent indication to do so. Development of a respiratory acidosis (pH < 7.25) should prompt reconsideration of pathology, mode of ventilation, and alternative methods of CO_2 removal.

Targets in pathophysiological states

Modify the parameters shown in the previous section considering predominant manifestations of pulmonary disease.

Airflow limitation

Narrowing of medium- and small-calibre airways significantly increases resistance to gas flow, disrupting regional and global pressure-flow relationships, and variably increasing time constants. Injudicious PPV programming in such individuals may result in volume redistribution, alveolar over-distension, and ventilator trauma.

Dynamic hyperinflation due to insufficient t_e and unfavourable I:E ratios exacerbates $\tilde{V}_A$/Q mismatching, and further increases the risk of trauma. $PEEP_i$ estimation may be necessary to avoid acute deterioration.

Restrictive lung disease

In the absence of significant airflow limitation, low compliance results in reduced τ. Affected lung units fill quickly, with rapid gas flow redistribution, $\tilde{V}_A$/Q mismatching and over-distension of relatively unaffected units. Attention to volume and pressure settings may mitigate risk of trauma in such individuals.

Emphysema

The characteristic destruction of lung parenchyma and diminishment of elastic recoil results in markedly increased compliance of affected tissue. Because tissue damage is patchy, with changes characteristic of causative agents and disease processes, affected units are slow to open and prone to over-distension. A low rate with long t_i and t_e should be set to permit filling and emptying of slower units, and P_{PLAT} limited to prevent trauma.

COPD

Because emphysematous changes co-exist with airflow limitation in COPD, both τ_i and τ_e may be significantly prolonged. A low rate and prolonged expiratory phase (I:E ratio 1:2.5 or 3.0) may allow for slow changes in airway flows and prevent gas trapping. Airway pressures must be limited to prevent over-distention and the potential for rupture of bullae.

ARDS

ARDS is characterized by absolute volume loss with decreased total system compliance [16], but pathological changes are not evenly distributed and even targeting tidal volumes of 6–8 mL/kg may over-distend aerated lung units and exacerbate shunt through compression atelectasis.

Optimal ventilatory strategies in ALI and ARDS remain the subject of debate, with some advocating bedside quantification of injured and healthy lung volumes in order to permit individualization of V_T targets and the limitation of regional distending pressures [17]. The weight of evidence supports limitation of V_T to 4–8 mL/kg IBW [10,11] and plateau pressure to less than 30–35 cmH_2O [10] as the least deleterious strategy.

References

1. Vincent J-L, Singer M, Marini JJ, et al. (2010). Thirty years of critical care medicine. *Critical Care*, **14**(3), 311.
2. Soni N and Williams P. (2008). Positive pressure ventilation: what is the real cost? *British Journal of Anaesthesia*, **101**(4), 446–57.
3. Hotchkiss JR, Blanch L, Murias G, et al. (2000). Effects of decreased respiratory frequency on ventilator-induced lung injury. *American Journal of Respiratory and Critical Care Medicine*, **161**(2), 463–8.
4. Gajic O, Dara SI, Mendez JL, et al. (2004). Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Critical Care Medicine*, **32**(9), 1817–24.
5. Howell DCJ and Bellingan GJ. (2009). Acute lung injury and acute respiratory distress syndrome (ALI/ARDS), in respiratory disease and its management. In: McLuckie A (ed.), pp. 1–7. Godalming: Springer-Verlag London Ltd.
6. Determann RM, Royakkers A, Wolthuis EK, et al. (2010). Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Critical Care, **14**(1): R1.
7. Dries DJ, Adams AB, and Manni JJ. (2007). Time course of physiologic variables in response to ventilator-induced lung injury. *Respiratory Care*, **52**(1), 31–7.
8. Dreyfuss D, Soler P, Basset G, and Saumon G. (1988). High inflation pressure pulmonary-edema—respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *American Review of Respiratory Disease*, **137**(5), 1159–64.
9. Pavone LA, Albert S, Carney D, Gatto LA, Halter JM, and Nieman GF. (2007). Injurious mechanical ventilation in the normal lung causes a progressive pathologic change in dynamic alveolar mechanics. *Critical Care*, **11**(3), R64.
10. (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *New England Journal of Medicine*, **342**(18), 1301–8.
11. Moran JL, Bersten AD, and Solomon PD. (2005). Meta-analysis of controlled trials of ventilator therapy in acute lung injury and acute respiratory distress syndrome: an alternative perspective. *Intensive Care Medicine*, **31**(2), 227–35.
12. Lipes J, Bojmehrani A, and Lellouche F. (2012). Low tidal volume ventilation in patients without acute respiratory distress syndrome: a paradigm shift in mechanical ventilation. *Critical Care Research and Practice*, **2012**, 416862.
13. Hubmayr RD. (2011). Point: is low tidal volume mechanical ventilation preferred for all patients on ventilation? Yes. *Chest*, **140**(1), 9–11.
14. Dennis D, Jacob W, and Van Heerden PV. (2012). Ventilation—how often are we correct? *Anaesthesia and Intensive Care*, **40**(4), 638–42.
15. Mols G, Priebe HJ, and Guttmann J, (2006). Alveolar recruitment in acute lung injuiry. *British Journal of Anaesthesia*, **96**(2), 156–66.
16. Gattinoni L and Pesenti A. (2005). The concept of 'baby lung'. *Intensive Care Medicine*, **31**(6), 776–84.
17. Mattingley JS, Holets SR, Oeckler RA, Stroetz RW, Buck CF, and Hubmayr RD. (2011). Sizing the lung of mechanically ventilated patients. *Critical Care*, **15**(1), R60.

CHAPTER 94

Respiratory support with positive end-expiratory pressure

Ignacio Martin-Loeches and Antonio Artigas

Key points

- Positive end-expiratory pressure (PEEP) is usually one of the first ventilator settings chosen when mechanical ventilation (MV) is initiated.
- A sufficient level of PEEP is necessary to prevent alveolar derecruitment, without developing alveolar overdistension, dead space ventilation, and hypotension.
- The ideal level of PEEP is that which prevents derecruitment of the majority of alveoli, while causing minimal overdistension.
- The level of PEEP should be individualized and higher PEEP might be used in the more severe end of the spectrum of patients (acute respiratory distress syndrome) with improved survival.
- A survival benefit for higher levels of PEEP has not been yet reported for any patient under MV but a higher PaO_2/FiO_2 ratio seems to be better in the higher PEEP group.

Introduction

Positive end-expiratory pressure (PEEP) is the pressure present in the airway (alveolar pressure) above atmospheric pressure that exists at the end of expiration. The term PEEP is defined in two particular settings. Extrinsic PEEP (PEEP applied by a ventilator) and intrinsic PEEP (PEEP caused by a non-complete exhalation that causes progressive air trapping). Applied (Extrinsic) PEEP—is usually one of the first ventilator settings chosen when mechanical ventilation (MV) is initiated. The application of PEEP has two primary purposes:

- To increase lung volume in patients who have acute lung restriction in order to improve arterial oxygenation by recruiting or stabilizing alveolar units, and to protect the alveoli against injury during phasic opening and closing of atelectatic units that produces hypoxaemia;
- To reduce the effort required for patients to trigger the ventilator or breathe spontaneously in the presence of dynamic hyperinflation and auto-PEEP.

It is important to consider that lung recruitment occurs during inspiration and PEEP is applied during expiration in order to maintain the alveolar units opened.

Physiological effects of PEEP

Applying PEEP increases alveolar pressure and alveolar volume. The increased lung volume increases the surface area by reopening and stabilizing collapsed or unstable alveoli. PEEP therapy can be effective when used in patients with a diffuse lung disease with a decrease in functional residual capacity (FRC). FRC is determined by primarily the elastic characteristics of the lung and chest wall, and in pulmonary diseases, such as ARDS, reduced because of the collapse of the unstable alveoli. Opening the alveoli with positive pressure improves the ventilation–perfusion match. After the shunt effect is modified to a ventilation–perfusion mismatch with PEEP (unoxygenated blood returning to the left side of the heart), lowered concentrations of oxygen can be used to maintain an adequate PaO_2. PEEP therapy may also be effective in improving lung compliance [1].

Lung protection ventilation is an established strategy of management to reduce and avoid ventilator induced lung injury and mortality. Levels of PEEP have been traditionally used from 5 to 12 cmH_2O; however, higher levels of PEEP have also been proposed and updated in order to keep alveoli open, without the cyclical opening and closing of lung units (atelectrauma). Several studies have evaluated the effect of modest versus high levels of PEEP in patients with and acute respiratory distress syndrome (ARDS) [2]. A survival benefit for higher levels of PEEP has not been yet reported for any patient under MV, but a higher PaO_2/FiO_2 ratio seems to be better in the higher PEEP group. In addition, higher levels of PEEP have been associated with improved survival (about 10%) among the subgroup of patients with ARDS.

How to set the PEEP

The ideal level of PEEP is often difficult to set but in general is that which the majority of lung units are set in order to maximize gas exchange and minimize over-distension. The main goal is to titrate the optimal level of PEEP defined as the level of PEEP that allows the lowest FiO_2 with an adequate level of oxygenation and avoiding complications induced by the level of PEEP. The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network have proposed to set individualized PEEP using a table that correlates the level of FiO_2 and PEEP based on the oxygenation (Table 94.1) [3]. Titrating PEEP according to the ARDS Net PEEP-FiO_2 ladder is strongly recommended. The benefit of PEEP might depend on the

Table 94.1 National Heart, Lung, and Blood Institute (NHLBI) ARDS Clinical Trials Network FiO_2/PEEP [3]

Lower PEEP group																	
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18	20	22	24
Higher PEEP group																	
FiO_2	0.3	0.3	0.4	0.4	0.5	0.5	0.6	0.6	0.7	0.8	0.8	0.9	1.0	1.0			
PEEP	12	14	14	16	16	18	18	20	20	20	22	22	22	24			

Adapted from *New England Journal of Medicine*, Brower RG et al., 'Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome', **351**(4), pp. 327–36. DOI: 10.1056/NEJMoa032193. Copyright © 2004, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

potential for alveolar recruitment. If the potential of recruitment is low, an increase in PEEP will not result in a beneficial effect on oxygenation with an accompanying higher risk for ventilator-induced lung injury, increased dead space that might potentially result in redistribution of pulmonary blood flow to non-ventilated regions of the lungs. If the increase of PEEP improves alveolar recruitment, the strain (distribution of pressure) might be reduced.

The potential for recruitment can be identified by the use of a 'PEEP trial'. In a 'PEEP trial', the PEEP is progressively increased. Ideally, only one variable—the amount of PEEP—is altered during the trial, with V_T, fraction of inspired oxygen (FiO_2), body position, and other factors that might affect oxygenation unchanged. An assessment for both favourable and adverse PEEP effects should be made at each level as PEEP increased. As the condition of the patient may change over time, to determine the effects of PEEP most clearly the intervals at each level must be kept short. When the increase of PEEP is associated with an improvement of PaO_2 and compliance and a decrease of PCO_2, an alveolar recruitment is expected. Conversely, if the alveolar recruitment is not achieved, there is a minimal improvement of oxygenation by an increase in dead space. The PEEP trial should be performed in a systematic manner whenever feasible [4].

It has been hypothesized that the level of PEEP can be determined by identifying pressure–volume (P–V) curve inflection points. Acquiring a dynamic curve presents the key to the curve's bedside application. The lower inflection point (LIP) on the total respiratory system P–V curve is widely used to set PEEP in patients with acute respiratory failure (ARF) on the assumption that LIP represents alveolar recruitment However, it is becoming widely accepted that the upper inflection point (UIP) of the deflation limb of the P–V curve represents the point of optimal PEEP (Fig. 94.1). New methods used to identify optimal PEEP, including computed tomography (CT), transthoracic lung ultrasound (LUS) and active compliance measurements, are currently being investigated. Using CT, it is possible to assess the pulmonary distribution of the increase in gas volume resulting from tidal ventilation and PEEP and to separate PEEP-induced lung overdistension from alveolar recruitment. In the mid-1990s, Gattinoni et al. [5] measured PEEP-induced alveolar recruitment on a single junta-diaphragmatic CT section by quantifying the decrease in non-aerated lung parenchyma characterized by CT attenuations ranging between −100 and +100 Hounsfield units (HU). In spite of the reference method for assessing PEEP-induced lung recruitment is lung CT, it is an important source of radiation, requires

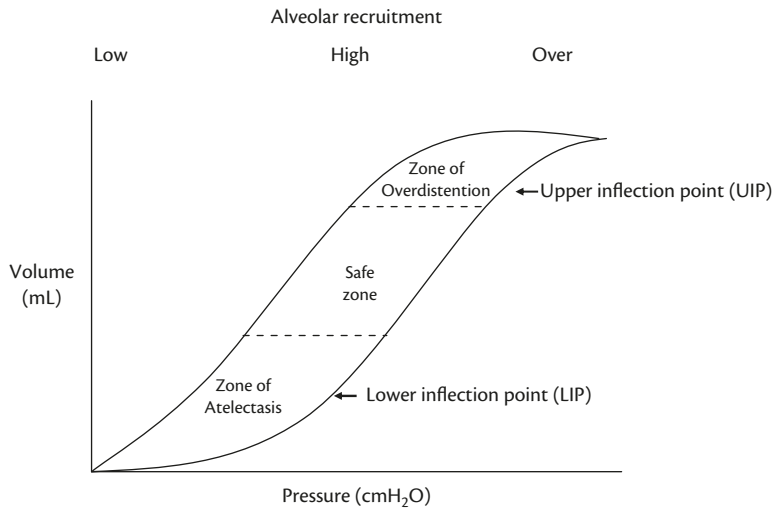


Fig. 94.1 The hysteresis of the pressure–volume curve of the lung. On inflation limb lungs need higher pressures to inflate than on deflation. On deflation limb, the higher lung volume can be maintained on lower pressure. Thus, once the lung is open it is more compliant. At the lower inflection point the lung opens up, compliance improves, and at the upper inflection point optimal lung volume is achieved. At over inflation, compliance decreases and lung injury occurs. The upper inflection point of the deflation limb of the P–V curve represents the point of optimal PEEP.

Table 94.2 Haemodynamic effects of PEEP

LV	1. ↓ **Preload** (a) ↓ in RV stroke volume: ◆ ↑ Pulmonary vascular resistance ◆ ↑ Pericardic pressure (b) ↓ LV telediastolic volume: ◆ Ventricular interdependence ◆ ↑ Pericardic pressure 2. ↓ **Afterload**: ↓ in LV transmural pressure 3. **Contractility**:↓ neurohormonal response?
Venous return	1. ↓ **Pulmonary venous return** (effect on RV) (a) ↓ RV preload (b) ↑ RV afterload (increased pulmonary vascular resistance)
RV	1. ↓**Venous return** (a) ↑ Intrathoracic pressure (b) ↑ Pericardic pressure (c) ↑ RV pressure (d) ↓ Transmural RA pressure 2. ↑ **Afterload** (a) ↑ Pulmonary vascular resistance (b) Compression of peri-alveolar capillaries 3. ↓ **Cardiac output**

transporting an often unstable and hypoxaemic patient outside the ICU with a time-consuming analysis of data. Other considerations such as the stress index and the measurement of oesophageal pressure have been recently proposed to assess the level of PEEP to avoid overdistension.

Finally, some considerations on how to set the PEEP should be taken into account in patients with acute respiratory failure (ARF) due to acute exacerbation of chronic obstructive pulmonary disease (COPD). The application of low levels of PEEP can result useful in order to reduce the magnitude of the inspiratory effort during assisted MV (or pressure support) and weaning, and therefore intrinsic PEEP. The application of PEEP in COPD patients requires close monitoring of the end-expiratory lung volume by inspection of flow/volume curves during application of increasing levels of PEEP. The presence of dynamic hyperinflation and expiratory flow limitation can be suspected based on the shape of the expiratory limb of the flow/volume curve (Fig. 94.1).

Haemodynamic effects of PEEP

Based on a better understanding of heart and lung interactions, lung overdistension (with the consequent effect on the pulmonary circulation and thus on the right ventricle) might be present with the application of excessive tension and deformation of the lung tissues (Table 94.2). These effects are determined in part by the stress (transpulmonary pressure) and strain (ratio tidal volume and FRC) applied to about 480 million of alveoli and 30,000 cycles/days. The vast majority of the studies that found an inverse relationship between high levels of PEEP and RV function were conducted before the studies that proposed to limit the tidal volume in the patients with ARDS and therefore these patients were ventilated with tidal volumes higher than 10 mL/kg ideal body weight.

As end-expiratory, end-inspiratory, and mean airway pressures are all increased in the presence of PEEP, PEEP induces an increase in the intrathoracic pressure with several hemodynamic effects [6]. Despite extensive investigation, the effect of PEEP on human cardiac physiology is complex, unpredictable, and has not been totally defined. It may also elevate mean systemic pressure (PMS), the static circulatory filling pressure that is the upstream pressure for venous return. A PEEP level of less than 10 cmH_2O rarely causes haemodynamic problems in the absence of intravascular volume depletion. The cardiodepressant effects of PEEP are often minimized with judicious intravascular volume support or cardiac inotropic support. Although peak pressure is related to the development of barotrauma, arterial hypotension is related to the mean airway pressure that may decrease venous return to the heart or decrease right ventricular function.

Except from the failing ventricle, PEEP usually decreases cardiac output. It is important to understand certain aspects of cardiac physiology to appreciate the effect of PEEP in cardiac output. Cardiac output is the product of heart rate and left ventricular stroke volume. In most pathophysiological states, stroke volume is the major determinant of cardiac output, while heart rate changes reflexively in response to changes in stroke volume. Stroke volume is influenced by four major factors:

- Diastolic ventricular filling, termed preload.
- Ventricular distensibility or compliance.
- Ventricular contractility.
- Ventricular afterload.

Preload and ventricular distensibility influence stroke volume by their effects on the heart during diastole, while contractility and afterload influence stroke volume during systole. At least three factors probably contribute to the decrease in cardiac output produced by PEEP decreased venous return (right ventricular filling), increased right ventricular afterload (regional or generalized lung overdistention can also stretch pulmonary vessels, which reduces their calibre and increases pulmonary vascular resistance) and decreased left ventricular distensibility (Fig. 94.2).

Decreasing PEEP

If PEEP is reduced prematurely, some alveoli may remain sufficiently unstable to collapse, which worsens oxygenation. If this happens, PEEP higher than the previous baseline level may be required to reopen the collapsed alveoli and, conceivably, the patient's requirement for MV may be unnecessarily prolonged.

Bacterial effects

The alveolar opening achieved with PEEP is likely to be responsible for this reduction in pneumonia risk, although the precise mechanism is unknown. PEEP is protective against pulmonary micro-aspiration by a protective counterbalance pressure. Various experimental studies have confirmed lower bacterial growth and a lower incidence of bacteraemia with strategies to maintain alveolar opening and reduce atelectasis after intratracheal instillation of bacteria into bronchial tree. The early application of PEEP in the non-hypoxaemic ventilated patients would stabilize the alveoli and can contribute to reducing the bacterial burden, and therefore the incidence of early-onset VAP.

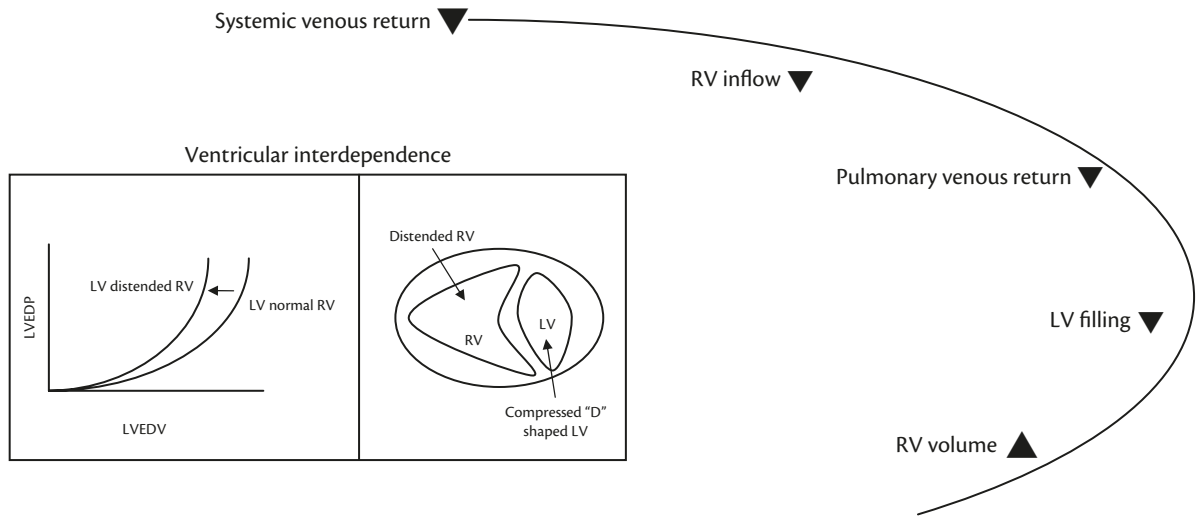


Fig. 94.2 Effect of positive end-expiratory pressure (PEEP) on left ventricular (LV) filling. See text.
Abbreviation: LVEDV, left ventricular end-systolic volume.

Hormonal effects

PEEP induces a rapid and intense antidiuresis with fall in fractional excretion of sodium (FE Na^+), whereas negative pressure breathing is associated with increased urinary flow. As discussed before, PEEP has haemodynamic effects, but also leads to indirect cardiovascular reflex activation or deactivation of high and low pressure baroreflexes, and to vasoactive hormonal release of antidiuretic hormone (ADH), renin, and norepinephrine.

Contraindications

There are no absolute contraindications to applied PEEP. However, applied PEEP can have adverse consequences (especially at high levels) and should be used cautiously in patients with unilateral lung disease, obstructive lung disease (without the presence of expiratory flow limitation), elevated peak and mean airway pressures, bronchopleural fistulae, hypovolaemia, elevated intracranial pressure, and pulmonary embolism (PEEP can worsen hypoxaemia in pulmonary embolism when adjacent unobstructed pulmonary vessels become compressed).

Complications

A classic paradigm of MV is that the systemic hypotension induced ventilation failure to produce the right ventricle (RV), and that this associated with high pressure and mainly with the use of PEEP. This paradigm comes from classical studies in which objective a progressive elevation of PEEP is associated with a progressive increase in central venous pressure and a fall in blood pressure. Thus, in clinical practice, it is common to have episodes of hypotension in a mechanically-ventilated patient. Between the responses are initial therapeutic volume expansion, initiation, or dose increase of inotropic agents, the reduction in the dose of sedatives and also the descent PEEP level with the intention of reducing the pressure intrathoracic. The possibility of right ventricular failure due to pulmonary hypertension, with a drop in systemic blood pressure related to the elevation of PEEP, is mainly produced in many situations with other conditions, such as hypovolaemia, the appearance of comorbid conditions that decrease the compliance lung (increased intra-abdominal pressure, restrictive lung disease, presence of auto-PEEP or pneumothorax) and the inappropriate use of appropriate modes of ventilation.

Another important point when PEEP is applied is the possibility to produce barotrauma. Pulmonary barotrauma is lung injury that results from the hyperinflation of alveoli past the rupture point. The most severe form is the development of pneumothorax, pneumomediastinum and subcutaneous emphysema.

References

1. Determann RM, Royakkers A, Wolthuis EK, et al. (2010). Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. *Critical Care*, **14**(1), R1.
2. Briel M, Meade M, Mercat A, et al. (2010). Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *Journal of the American Medical Association*, **303**(9), 865–73.
3. Brower RG, Lanken PN, MacIntyre N, et al. (2004). Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *New England Journal of Medicine*, **351**(4), 327–36.
4. Meade MO, Cook DJ, Guyatt GH, et al. (2008). Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *Journal of the American Medical Association*, **299**(6), 637–45.
5. Gattinoni L, Pelosi P, Crotti S, and Valenza F. (1995). Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **151**(6), 1807–14.
6. Luecke T and Pelosi P. (2005). Clinical review: positive end-expiratory pressure and cardiac output. *Critical Care*, **9**(6), 607–21.

CHAPTER 95

Volume-controlled mechanical ventilation

Kristy A. Bauman and Robert C. Hyzy

Key points

- Volume-controlled modes of mechanical ventilation guarantee flow and tidal volume, while airway pressures are variable.
- In volume-controlled modes, the clinician sets the flow pattern, flow rate, trigger sensitivity, tidal volume, respiratory rate, positive end-expiratory pressure (PEEP), and fraction of inspired oxygen (FIO_2).
- Patient ventilator synchrony can be enhanced by setting appropriate trigger sensitivity and inspiratory flow rate.
- I:E ratio is adjusted to improve oxygenation, avoid air trapping and enhance patient comfort.
- Low tidal volume ventilation in conjunction with plateau pressure limitation should be employed in patients with acute respiratory distress syndrome (ARDS).

Introduction

The goal of mechanical ventilation is to achieve adequate gas exchange, while minimizing haemodynamic compromise and ventilator-associated lung injury (VALI). There are a vast and ever increasing number of ventilator modes and settings to choose from. After endotracheal intubation, the first choice facing the clinician is between two basic modes of mechanical ventilation—pressure- and volume-controlled. In pressure control mode, peak inspiratory pressure is selected and tidal volumes are variable. In volume control mode, tidal volume is guaranteed at the expense of variable airway pressures. Volume-controlled ventilation, (also termed volume-cycled or volume-limited) can be delivered via several modes including controlled mechanical ventilation (CMV), assist control (AC) and synchronized intermittent mandatory ventilation (SIMV).

Ventilator settings for volume-controlled ventilation

Mode

In controlled mechanical ventilation, the minute ventilation (V_E) is determined by the set respiratory rate and tidal volume. This mode is used in patients with no spontaneous effort such as those in comatose states or pharmacologically paralysed. The ventilator does not respond to spontaneous breaths or changes in flow requirements. During AC ventilation, the clinician sets the minimum V_E as well, although the patient can increase V_E by triggering additional breaths. With each additional breath, the full preset tidal volume is delivered. Therefore, if a patient has a respiratory rate twice that of the preset frequency, the V_E will be effectively doubled. In SIMV mode, the mandatory ventilator breaths are synchronized with the patients' inspiratory effort. Additional inspiratory efforts either receive no additional ventilator assistance or pressure support may augment these breaths. With the exception of mandatory ventilator breaths, the tidal volume delivered is highly variable.

Controlled mechanical ventilation and AC volume-controlled modes control the tidal volume of each breath and provide most of the work of breathing. In patients who are critically ill, where control of ventilation and minimizing respiratory muscle oxygen consumption are paramount, controlled mechanical ventilation and AC may be the preferred modes. SIMV can provide partial or full ventilator support, ostensibly offering improved patient–ventilator synchrony and preservation of respiratory muscle strength [1]. AC and SIMV are the most commonly used modes of volume-controlled ventilation in medical and surgical intensive care units [2]. There are little data available regarding the benefits of one volume-controlled mode over another. In a multicentre observational study of ventilated critically-ill patients, there was no significant difference in clinical outcomes between those receiving AC ventilation versus those receiving SIMV with pressure support [3].

With volume-controlled modes, the clinician must set the flow pattern, flow rate, trigger sensitivity, tidal volume, respiratory rate, positive end-expiratory pressure (PEEP), and fraction of inspired oxygen (FIO_2).

Most mechanical ventilators currently available offer a pressure limited form of mechanical ventilation where the tidal volume is assured. The term utilized for this modality varies according to the designation created by the company. Although comparative studies are lacking the putative advantage of these modalities is to ensure an adequate tidal breath, while utilizing a pressure mode, which may afford greater patient-ventilator synchrony.

Flow pattern and flow rate

While the term volume-controlled ventilation is commonly used, the ventilator actually is controlling the inspiratory flow. Each breath terminates after delivery of the set tidal volume unless a pressure limit is exceeded. Flow can be delivered either in a constant pattern or a decelerating pattern. (Fig. 95.1) A constant flow pattern

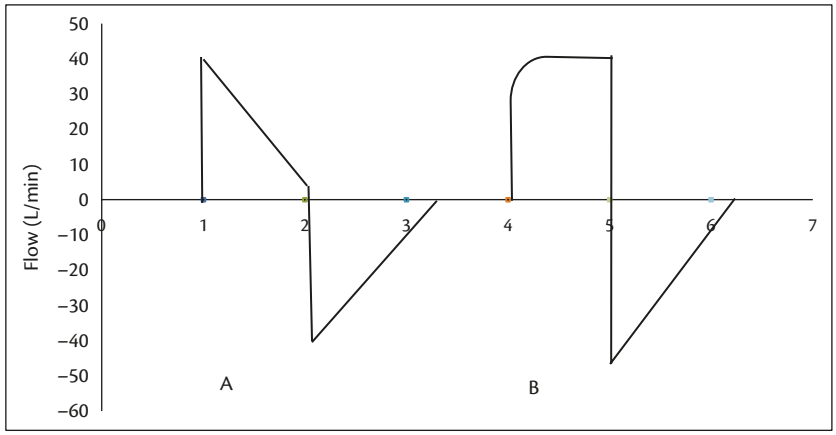


Fig. 95.1 Decelerating flow pattern (A). Constant flow pattern (B).
Adapted from Hess DR and Kacmarek RM. *Essentials of Mechanical Ventilation*, 2nd edn, Copyright 2002, with permission from McGraw-Hill Education.

provides nearly constant gas flow during the inspiratory cycle. It is often called a rectangular or square wave pattern. Tidal volume is delivered to the lungs equally throughout the entire inspiratory time (Ti). The airway pressure increases linearly with time.

The decelerating flow pattern is also termed a descending ramp flow pattern. Inspiratory flow is greatest at the beginning of inspiration and decreases throughout the inspiratory cycle. Most of the tidal volume is delivered early during inspiration and unless the flow rate is increased, the inspiratory time is lengthened with descending ramp flow. Peak inspiratory pressure is higher with constant flow and mean airway pressure is higher with descending ramp flow. An advantage of descending ramp flow is that the longer Ti can enhance alveolar gas distribution, improving oxygenation and ventilation. When switching between constant and descending ramp flow the ventilator must adjust either the peak flow rate or the Ti to maintain the set tidal volume.

In a spontaneously breathing individual, expiration is passive and expiratory time is longer than inspiratory time. Thus, the inspiratory to expiratory (I:E) ratio is less than 1. In patients receiving mechanical ventilation inspiratory time is a function of tidal volume and inspiratory flow. In mechanically-ventilated patients with airways obstruction and air trapping, dynamic hyperinflation can be avoided by shortening the inspiratory time. This may be accomplished on a breath-by-breath basis either by decreasing tidal volume, increasing the flow rate of gas administered, or by decreasing the number of breaths administered per minute.

The I:E ratio during volume-controlled ventilation be deliberately lengthened with important physiological effects. A longer inspiratory time increases mean airway pressure, increases intrathoracic pressure, can decrease cardiac output, particularly if hypovolaemia is present, increases oxygenation in patients with acute respiratory distress syndrome (ARDS), and can lead to air trapping [4].

Inverse ratio ventilation (IRV) can be used as a strategy to improve oxygenation in ARDS. IRV implies a prolonged inspiratory time with an I:E ratios exceeding 1:1. IRV is commonly employed with pressure-controlled ventilation, but can also be performed in volume-controlled ventilation through the use of a low flow rate or the administration of an inspiratory pause on every breath. While, in general, studies have demonstrated that it improves oxygenation, IRV has not been shown to improve clinical outcomes such as mortality or duration of mechanical ventilation. IRV is uncomfortable and often requires high levels of sedation or pharmacologic paralysis [5].

Triggering mechanism and sensitivity

In AC mode, the patient is able to trigger the ventilator to provide breaths. These breaths can be pressure- or flow-triggered. Pressure-triggered breaths are delivered when the patient exerts a specified negative-pressure deflection below the level of set PEEP or auto-PEEP, when present. Flow triggering occurs when the machine senses a decrease in flow of a set magnitude during exhalation. Triggering mechanism and sensitivity significantly influence inspiratory work of breathing and patient ventilator synchrony. Ineffective triggering is a form of ventilator asynchrony. As a result, triggering sensitivity should be set at the lowest required value that does not lead to auto-cycling or 'breath stacking'. Conversely, the sensitivity should not be set at such a value above which the patient has to overcome a significant amount of ventilator circuit or airways resistance to trigger a breath. This results in increased work of breathing and discomfort.

For example, a patient with significant air trapping due to obstructive airways disease may develop a significant amount of auto or intrinsic PEEP. If the trigger sensitivity is set at –2 cmH_2O and intrinsic PEEP is 10 cmH_2O, the patient will have to exert a negative-pressure deflection of –12 cmH_2O to trigger a breath. This can be recognized easily at the bedside as the patient will have obvious attempts to inhale with no ventilator breath delivered. The flow rate also is an important factor in work of breathing. The inspiratory flow rate should be set high enough in order to complete inhalation before the patient begins to exhale. Exhalation against a closed exhalation valve is distressing to a patient and best avoided. In general, the average flow rate should be four times the minute ventilation to avoid discomfort.

Tidal volume

Tidal volume should be set with individual pulmonary mechanics and physiology in mind. Present practice suggests tidal volumes in the range of 6–8 mL/kg ideal body weight are appropriate for most clinical circumstances. In order to avoid VALI, ideally plateau pressures should not be in excess of 30 cmH_2O, lower if possible, as

this is a continuous, not a threshold variable. In individuals with normal lungs, tidal volumes such as 10 mL/kg of ideal body weight are generally well-tolerated without generating high airway or plateau pressures. Nevertheless, clinicians should be cognizant of the fact that tidal volumes in excess of 700 mL have been associated with an increased risk of ARDS in post-operative patients with normal lungs. Persons with history of lung resection and pulmonary fibrosis typically can tolerate tidal volumes of 4–8 mL/kg. In ARDS, volume-controlled ventilation with tidal volumes of 6 mL/kg are recommended based upon the ARDS Network study demonstrating a 22% reduction in mortality in those receiving a low tidal volume strategy [6]. Low tidal volumes of less than 6 mL/kg may result in atelectasis; however, this can be offset by increases in PEEP. In controlled mechanical ventilation or AC modes the delivered tidal volume should be equivalent to exhaled tidal volume. Exceptions are the presence of an endotracheal tube cuff leak and pneumothorax with bronchopleural fistula.

Respiratory rate

The back-up respiratory rate should be chosen in order to satisfy the desired minute ventilation based upon pH and PCO_2 goals. In AC mode, however, if the patient triggers each breath, the set back-up rate may have no effect upon V_E. Ideally, the back-up rate is 2–4 breaths below the respiratory rate in patients receiving AC, permitting patients to determine their own minute ventilation and PCO_2.

PEEP and FIO_2

At initiation of mechanical ventilation, in most cases an FIO_2 of 1.0 and PEEP of 5 cmH_2O are recommended. These variables can be adjusted based upon patient condition and physiological goals. FIO_2 is later decreased in order to maintain an arterial saturation of at least 88% on arterial blood gas or 92% on pulse oximetry, allowing for the imprecision of the latter device.

Clinical uses

Volume-controlled ventilation is the most commonly used mode in inpatient settings. The major advantage is the delivery of a constant tidal volume, thus minute ventilation is assured. The peak inspiratory pressure will vary based upon compliance and resistance of the respiratory system. The vast majority of patients undergoing mechanical ventilation can be successfully and safely managed using conventional volume-controlled mechanical ventilation. There are no absolute indications for resorting to pressure-controlled modes, including in the initial management of patients with ARDS, where a low tidal volume strategy via volume-controlled ventilation has a proven mortality benefit. In the limited available studies comparing volume-controlled to pressure-controlled ventilation in persons with hypoxic respiratory failure, there have to date been no differences in clinically important variables, such as mortality.

Limitations

A major limitation of volume-controlled ventilation is that the flow pattern is fixed and will not change with changing demands of the patient. This increases the risk for patient-ventilator dys-synchrony. Pressure modes typically do allow for varied flow depending upon patient demand and may be preferred for this reason. Additional, in poorly compliant, stiff lungs, airway pressures during volume-controlled ventilation may be excessive leading to concern for ventilator-associated lung injury. In these instances, pressure-controlled ventilation may be advantageous.

References

1. Weisman IM, Rinaldo JE, Rogers RM, and Sanders MH. (1983). Intermittent mandatory ventilation. *American Reviews in Respiratory Diseases*, **127**(5), 641–7.
2. Esteban A, Anzueto A, Alia I, et al. (2000). How is mechanical ventilation employed in the intensive care unit? An international utilization review. *American Journal of Respiratory and Critical Care Medicine*, **161**(5), 1450–8.
3. Ortiz G, Frutos-Vivar F, Ferguson ND, et al. (2010). Outcomes of patients ventilated with synchronized intermittent mandatory ventilation with pressure support: a comparative propensity score study. *Chest*, **137**(6), 1265–77.
4. Hess DR and Kacmarek RM. (2002). *Essentials of Mechanical Ventilation*, 2nd edn. New York, NY: McGraw-Hill Companies, Inc.
5. Hess DR. (2011). Approaches to conventional mechanical ventilation of the patient with acute respiratory distress syndrome. *Respiratory Care*, **56**(10), 1555–72.
6. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *New England Journal of Medicine*, **342**(18), 1301–8.

CHAPTER 96

Pressure-controlled mechanical ventilation

Thomas Muders and Christian Putensen

Key points

- Pressure-controlled, time-cycled ventilation (PCV) enables the physician to keep airway pressures under strict limits in order to minimize the risk for ventilator-associated lung injury in patients with acute respiratory distress syndrome.
- During PCV inspiratory and expiratory pressures, and cycle times have to be chosen by the physician. These presets, as well as respiratory system mechanics determine (decelerating) inspiratory gas flow, tidal volume, and intrinsic positive end-expiratory pressure ($PEEP_i$).
- To avoid a harmful rise in tidal volume with improvement in respiratory system mechanics, continuous display, and tight monitoring of tidal volume is mandatory during PCV.
- When compared with flow-controlled, time-cycled ('volume-controlled') ventilation, PCV reduces peak airway pressure, while mean airway, and mean alveolar pressures and gas exchange improve. However, no consistent data exist, showing PCV to improve patient outcome.
- Airway pressure release ventilation (APRV) allows superimposed and unrestricted spontaneous breathing and, thereby, improves haemodynamics and gas exchange, whereas need for sedation, vasopressors and inotropic agents and duration of ventilator support decreases.

Introduction

Today's lung protective ventilatory strategies reduce tidal volume (V_T) to 6 mL/kg ideal body (iBW) [1] and limit airway pressures [1] to minimize risk for ventilator associated lung injury (VALI) and to improve outcome in patients with acute respiratory distress syndrome (ARDS).

In contrast to flow-controlled, time-cycled ventilation (= 'volume-controlled', VCV) using a squared flow control, during pressure-controlled (preset), time-cycled ventilation (PCV) a preset square-wave pressure is applied to the airway. PCV results in a decelerating inspiratory gas flow holding the alveoli inflated for a preset period of time. In this chapter, we try to point out the principle and special characteristics, and physiological effects of pressure-controlled, time-cycled, continuous mandatory mechanical ventilation (PC-CMV), a prototype of PCV. Furthermore, we will discuss important variants of PCV, such as assisted PCV (PC-A/C), pressure-controlled inverse-ratio ventilation (PC-IRV) and pressure-controlled airway pressure release ventilation (PC-APRV).

Principle characteristics of PCV

PCV results in a square-wave pressure to the airway and a decelerating inspiratory gas flow holding the alveoli inflated for a preset period of time (Fig 96.1). Flow will initially enter the lung rapidly to reach the preset airway pressure as quickly as possible. As the open and fast-filling alveoli fill, and their pressure reaches equilibrium with the preset pressure, flow will decelerate, whereas slow compartments continue to fill with gas. The ventilator will constantly adjust gas flow so that inspiratory pressure is maintained during the entire set inspiratory time. Flow will continue until the preset pressure reaches equilibrium with alveolar pressure throughout all lung units, which is indicated by the flow pattern decelerating to zero [2]. During expiration, pressure is released abruptly, and the lung will passively deflate against the set PEEP level. V_T depends mainly on respiratory compliance and resistance, and the difference between the preset pressure levels [2].

Input parameters of PCV

During PCV principally, inspiratory and expiratory pressures, and cycle times have to be chosen by the physician, but the way to determine these parameters depends on the ventilator.

Expiratory and inspiratory airway pressures

Apart from external positive end-expiratory pressure ($PEEP_e$) driving pressure (positive inspiratory pressure, PIP) as pressure increment above $PEEP_e$ or absolute inspiratory pressure (P_{INSP}) can be set (Fig. 1).

Ventilator rate, and expiratory and inspiratory time

Furthermore, ventilator rate (VR) and fractional inspiratory time (duty cycle, T_{INSP}/T_{TOT}) or VR, and inspiratory-to-expiratory ratio (I:E) has to be chosen. Alternatively, expiratory (T_{EXP}) and inspiratory (T_{INSP}) times can be set directly (Fig. 96.1).

Output parameters of PCV

Global and regional respiratory system mechanics (compliance and resistance) affect alveolar pressure (P_A), intrinsic PEEP ($PEEP_i$), inspiratory gas flow, V_T, total minute and alveolar ventilation, resulting from preset airway pressures and cycle times.

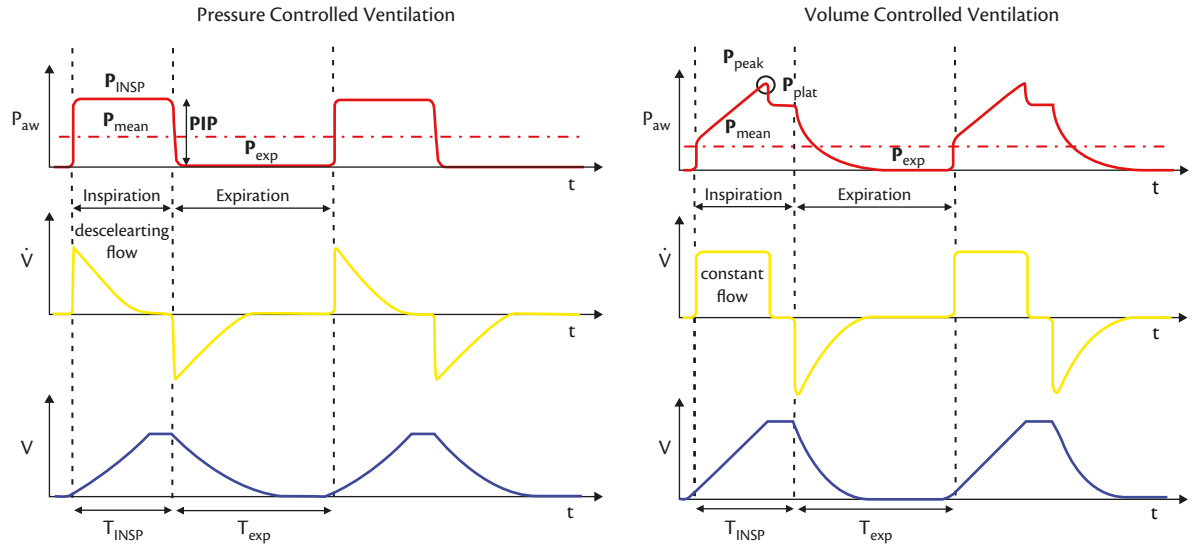


Fig. 96.1 Time (t) courses of airway pressure (P_{aw}), flow ($\dot{V}$), and volume (V) during pressure-controlled (PCV) (left) and volume-controlled (VCV) (right) mechanical ventilation.

P_{INSP}, inspiratory pressure; P_{exp}, expiratory pressure; P_{mean}, mean airway pressure; PIP, positive inspiratory pressure (= driving pressure); P_{peak}, Peak inspiratory pressure; P_{plat}, plateau pressure; T_{INSP}, inspiratory time; T_{exp}, expiratory time. See text for details.

Inspiratory flow

Depending on the respective ventilator, the abruptness of rise to peak flow can be modulated by setting slope or inspiratory rise-time. Rampant rise in flow might create some pressure overshoot that does not lead to elevated peak alveolar pressure and may not be associated with harm to the lung [3]. In contrast, longer rise-times creating a shallow increase to peak flow might be associated with a slow ramp of inspiratory pressure and have been reported to cause a delayed filling of the lung [4].

Mean airway pressure

Due to the squared waveform of the airway pressure during PCV, mean airway pressure ($\overline{P}_{aw}$, that is the is the integral of P_{aw} over time divided by duration of a single breath (T_{TOT}) can easily be calculated as

$$\overline{P}_{aw} = (PEEP_e \times T_{EXP} + P_{INSP} \times T_{INSP}) / T_{TOT} \quad \text{[eqn 1]}$$

Thus, during PCV changes in $\overline{P}_{aw}$ can directly be predicted from variations in preset airway pressures or cycle times. $\overline{P}_{aw}$ increases with increasing $PEEP_e$, P_{INSP} or I:E, whereas it decreases with decreasing $PEEP_e$, P_{INSP} or I:E (Fig 96.1). In contrast, changes in frequency maintaining I:E constant do not affect $\overline{P}_{aw}$.

Alveolar pressure

During PCV P_A can never exceed preset P_{INSP}. Mean alveolar pressure ($\overline{P}_A$) is closely related to mean airway pressure ($\overline{P}_{aw}$) and affected by minute ventilation (V_E) and inspiratory (R_I) and expiratory (R_E) resistances [3]:

$$\overline{P}_A = \overline{P}_{aw} + V_E \times (R_E - R_I) \quad \text{[eqn 2]}$$

If inspiratory and expiratory resistances are similar, changes in VR do not relevantly influence $\overline{P}_{aw}$. When R_E exceeds R_I, $\overline{P}_{aw}$ relevantly underestimates $\overline{P}_A$, and increments in VR may cause a noteless increase in $\overline{P}_A$. This phenomenon is pronounced when V_E is high and common in chronic obstructive lung diseases [3]. Peak P_A equilibrates to P_{aw} at end-inspiration when a sufficient inspiratory time is provided. With increasing VR and/or decreasing T_{INSP} peak, P_A falls below P_{INSP}, whereas end-expiratory P_A rises above $PEEP_e$ with increasing VR and/or decreasing T_{EXP} [3] creating $PEEP_i$ (Fig 96.2).

Intrinsic PEEP

$PEEP_i$ occurs when regional or total expiration remains incomplete within the T_{EXP} available leading to dynamic hyperinflation [5]. This dynamic phenomenon depends on a complex function of the respiratory mechanics and the input parameters of PCV [6].

$PEEP_i$ can be increased either by higher driving pressure (resulting in higher V_T during PCV), higher I:E ratio or higher VR (both shortening T_{EXP}). As described previously and in Fig. 96.2, changes in P_A are mainly affected by differences between R_I and R_E. Thus, increasing I:E ratio might elevate $PEEP_i$ up to maximal airway pressure, whereas pure increases in VR will reduce peak P_A and increase $PEEP_i$ [3].

Furthermore, higher respiratory time constants increase $PEEP_i$ for the same input parameters [5]. As the time constant (t) is equal to resistance (R) × compliance (C), high time constants are caused by high airway R and/or C, which may occur on a regional basis, e.g. in slow compartments, as well as for the whole respiratory system [7]. It is important to note that elevation in airway resistance also can be caused by the design of the ventilator circuit (e.g. narrow tubes, slow PEEP valves) [7].

In inhomogeneous lungs different $PEEP_i$ may occur [8] and mainly the slower compartments will profit from $PEEP_i$ in terms of alveolar recruitment, whereas fast compartments might be overinflated (Fig 96.2).

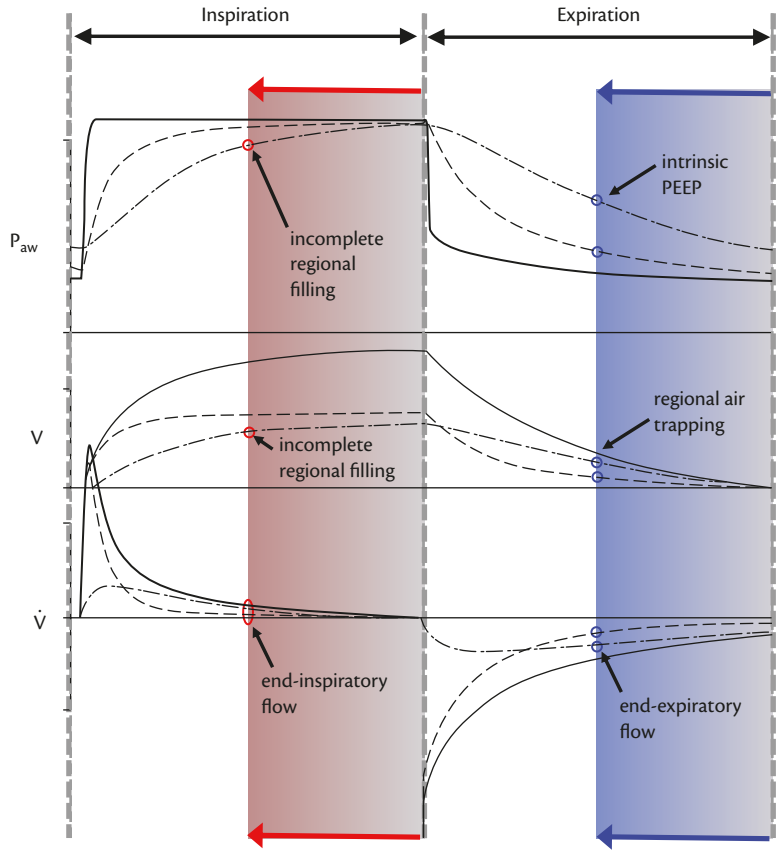


Fig. 96.2 Time courses of airway pressure (P_{aw}), volume (V), and flow ($\dot{V}$) during pressure controlled ventilation. Shortening inspiration (red arrow and area) can cause incomplete regional filling and persisting end-inspiratory flow. Shortening expiration (blue arrow and area) can cause intrinsic PEEP, regional air trapping, and persisting end-expiratory flow. See text for detailed influence of I:E ratio, inverse ratio, and respiratory frequency.

Tidal volume

In contrast to VCV, which ensures a preset V_T, during PCV V_T mainly depends on the difference between the preset pressure levels, VR or cycle times, and respiratory compliance and resistance. To enable a nearly-complete lung inflation T_{INSP} should be longer than three times the time constants of the respiratory system, leading to a minimal T_{INSP} of 1.0–1.5 s in healthy intubated adults. In obstructive patients, this time can rise to 2–4 s, whereas in patients suffering from ARDS, lung can be inflated within 0.8–1 s due to reduction in lung compliance [3]. Furthermore, incomplete lung emptying will decrease V_T. Therefore, T_{EXP} should be longer than three expiratory time constants. Hence, incomplete lung filling will occur with VR above 25–30 breaths/min. Generally, during PCV increasing I:E ratio mainly increases $PEEP_i$, whereas reductions in VR cause reduced peak P_A and increased $PEEP_i$, and thereby further decrease effective driving pressure. Thus, V_T is more affected by changes in VR than by altered I:E ratio (Fig 96.2).

At this point it is important to note, that V_T will change with changes in lung mechanics. When the lung is recovering over time and lung compliance improves, V_T will rise and may relevantly exceed the limits of lung protective ventilation. In this situation, inspiratory pressure has to be reduced to keep V_T below 6 mL/kg iBW. Therefore, respiratory mechanics and V_T have to be carefully monitored during PCV.

Alveolar and minute ventilation

As long as complete lung filling and emptying is ensured, increasing VR will improve total minute and alveolar ventilation, and thereby CO_2 elimination. At higher VR and decreases in T_{INSP}, peak P_A will not equilibrate to preset inspiratory pressure causing incomplete filling of slow lung compartments and a decline in V_T. As a consequence, functional dead space to tidal volume ratio will increase, and CO_2 elimination will be impaired by decreased alveolar ventilation. In clinical practice, with a fixed non-inverse I:E ratio, VR can be increased to improve CO_2 elimination until V_T decreases by 25–30%. A further increase in VR will be counterproductive due to increased dead space, even when V_E increases [3].

Physiological effects of PCV

The effects of using PCV when compared with VCV, while keeping all other parameters (VR, I:E ratio, PEEP and plateau pressure) constant can be summarized as follows.

Airway and alveolar pressures

During PCV decelerating flow reduces peak P_{aw}, but increases mean P_{aw} [9]. Homogeneity of regional peak P_A distribution within the lung is improved with PCV, reducing exposure of more diseased lung units to high pressures.

Ventilation distribution and pulmonary gas exchange

PCV seems to favour ventilation of slow lung units due to fast gas flow during early inspiration. As a consequence, $PaCO_2$ falls, since dead space ventilation is decreased, whereas arterial oxygenation is slightly improved [9]. However, clinical relevance of PCV-related advantages remains debatable.

Cardiovascular effects

The application of positive pressure ventilation generates an increase in airway and, therefore, in intrathoracic pressure, which in turn reduces venous return to the heart. This produces a reduction in right- and left-ventricular filling, and results in decreased stroke volume, cardiac output, and oxygen delivery [10]. For comparable mean airway pressures no differences in haemodynamic impairment were seen between PCV and VCV. Since influence of changes in ventilator settings on $\overline{P}_{aw}$ is more predictable with PCV, haemodynamic impairment should also be more predictable.

Ventilator-associated lung injury

Regional lung strain calculated from computed tomography scans is comparable between PCV and VCV [11]. Although, experimental data suggest PCV to reduce VALI, no consistent results have been seen with respect to reduced barotrauma or improved outcome in patients [12].

Variants of PCV

Assisted PCV

Assisted PCV (PC-A/C) enables the patient to trigger the ventilator and in opposite to pressure-support ventilation (PSV) time and not flow determines the cycle off. Compared with PSV, a risk of prolongation of T_{INSP} by not reaching the default expiratory triggering threshold (e.g. mask leaking, severe obstruction), and resulting insufficient drop in inspiratory flow is lower under assisted PCV [3]. Therefore, T_{INSP} must be adjusted to match the patient's spontaneous T_{INSP}, usually 0.6–1.2 seconds [13]. This gives more security for the patients, but also avoids freedom of ventilation pattern (restraining, for instance, the possibility of a spontaneous sigh and potentially increasing discomfort) [13].

With assisted PCV, breaths are triggered either by the patient's effort or by elapsed expiratory time, guaranteeing lower central apnoeas and sleep fragmentation. When compared with assisted VCV (flow-controlled, volume-cycled), assisted PCV results in lower peak P_{aw} and reduced workload [3].

Pressure-controlled inverse ratio ventilation

In healthy patients breathing for themselves, the ratio of the time spent in inspiration to that in expiration is about 1:2. Therefore, traditionally, the I:E ratio has been usually set at 1:2 or 1:1.5 to approximate the normal physiology. In inverse ratio ventilation (IRV) the T_{INSP} is prolonged (I:E ratio is inversed), thereby increasing $\overline{P}_{aw}$ and allowing the use of lower P_{aw} limits. This alternative ventilation strategy was initially developed to treat infants and adopted for adult patients with ARDS the early 1980s to improve severe hypoxaemia [8]. IRV can be delivered using pressure controlled, time-cycled ventilation (PC-IRV) [9] or flow-controlled ('volume-controlled'), time-cycled ventilation (VC-IRV) [8].

Principle of PC-IRV

The effects of changes in T_{INSP} and I:E ratio on P_{aw} and P_A can be summarized thus: the elongation of inspiratory time increases $\overline{P}_{aw}$, enables equilibration of peak P_A to preset P_{INSP}, and causes full lung inflation of even slow lung compartments. Shortening T_{EXP} leads to incomplete lung emptying and causes an increase in $PEEP_i$ [8,9]. Both mechanisms increase $\overline{P}_A$ and

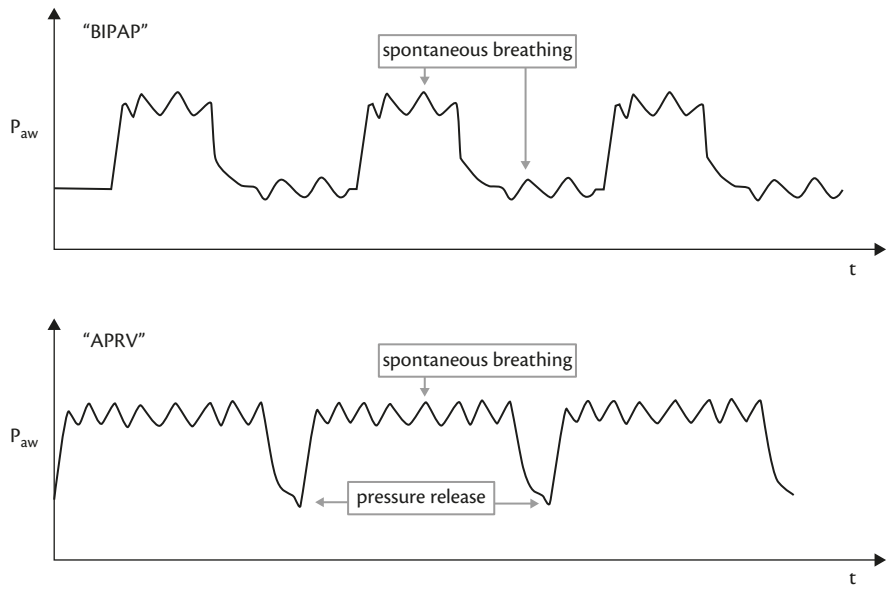


Fig. 96.3 Time courses of airway pressure (P_{aw}) biphasic-positive-airway-pressure (BIPAP) airway-pressure-release-ventilation (APRV). Both modes similarly provide a time-cycled switch between two different airway pressures and allow unrestricted spontaneous breathing at any time point and pressure. In the absence of spontaneous breathing BIPAP and APRV are equal to PCV. See text for details.

thereby transpulmonary pressure that is the driving force to recruit non-aerated alveoli and to prevent alveolar recollapse during expiration. This reduces intrapulmonary shunting and improves arterial oxygenation. Therefore, during IRV elevation in $\overline{P}_{aw}$ is a major determinant of improved oxygenation [5,14].

Physiological effects of PC-IRV

When compared with conventional mechanical ventilation using an increased $PEEP_e$ to reach the same magnitude of $PEEP_{TOT}$ as that produced intrinsically by IRV ($PEEP_{TOT} = PEEP_e + PEEP_i$), IRV had no advantage [15]. Furthermore, CT observations in experimentally-induced lung injury showed no improvement in lung aeration, but demonstrated that during IRV the upper, already well-aerated lung regions become even more aerated, whereas poorly- or non-aerated lung units localized in the dependent lung regions are less aerated when compared with conventional mechanical ventilation with essentially the same mean airway pressure and extrinsic/intrinsic PEEP [16].

A major problem during IRV is that $PEEP_i$ changes, due to altered respiratory mechanics for example, may not be immediately clinically evident. A remaining terminal flow at the end of the expiration indicates that a certain $PEEP_i$ exists, but it does not quantify the amount [8]. Therefore, careful monitoring and continuous display of V_T and expiratory flow has to be recommended during PC-IRV.

Limitation of PC-IRV

The long T_{INSP} of usually makes IRV incompatible with spontaneous breathing, and respiratory depressants or muscle relaxants must be administered to assure patient acceptance. Deep sedation sufficient to suppress respiratory efforts is known to cause significant cardiovascular depression [17]. Incompatibility with spontaneous breathing is a major limitation of IRV.

Airway pressure release ventilation (APRV)

APRV incorporates the characteristics of PCV, PC-IRV, spontaneous breathing, and partial ventilatory support into one technique with potentially widespread applicability. Based on the clinical and experimental data, APRV is indicated in patients with ARDS, and atelectasis after major surgery.

Principles of APRV

APRV provides a squared pressure pattern identical to PCV by time-cycled switches between two pressure levels in a high flow or demand valve continuous positive airway pressure (CPAP) circuit, while allowing unrestricted and unsupported spontaneous breathing in any phase of the ventilator cycle (Fig 96.3) [17,18].

The degree of ventilator support with APRV is determined by the duration of the two CPAP levels and the mechanically delivered V_T [17,18]. V_T depends mainly on respiratory compliance and the

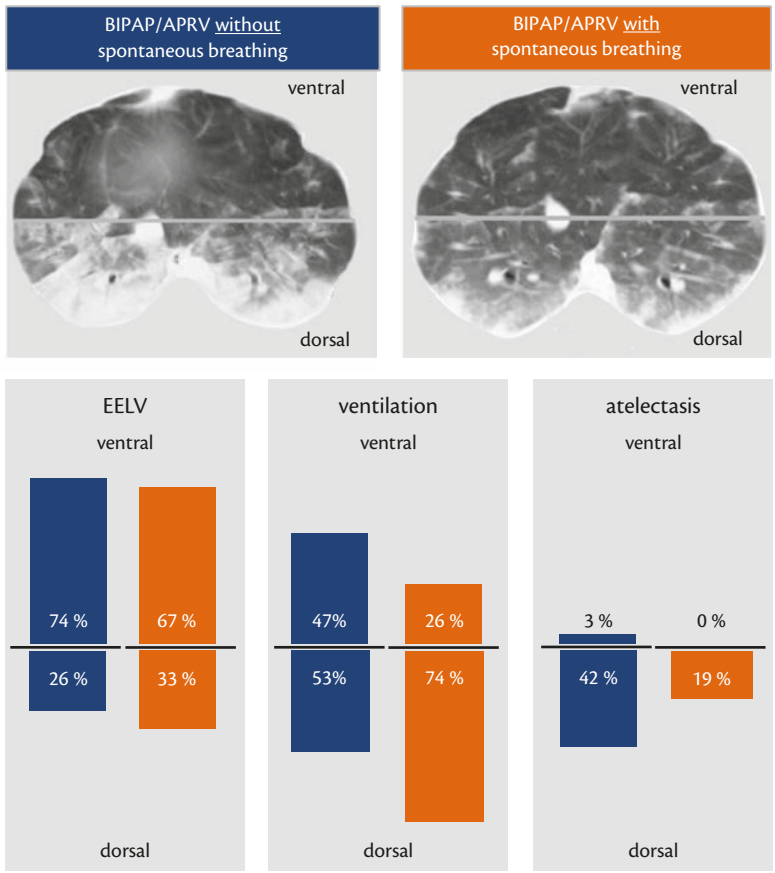


Fig. 96.4 Densitometric analysis of computed tomography scans (pig, experimental lung injury) during BIPAP/APRV with (orange) and without (blue) spontaneous breathing. Spontaneous breathing increase end-expiratory lung volume, decreases atelectasis and redistributed regional ventilation into dependent lung regions.
Data from Wrigge H et al., 'Spontaneous breathing with airway pressure release ventilation favors ventilation in dependent lung regions and counters cyclic alveolar collapse in oleic-acid-induced lung injury: a randomized controlled computed tomography trial', *Critical Care*, 2005, **9**(6), pp. R780–9.

difference between the CPAP levels. By design, changes in ventilatory demand do not alter the level of mechanical support during APRV. When spontaneous breathing is absent, APRV is not different from conventional PCV [17,18].

Synonyms used for APRV are biphasic positive airway pressure (BIPAP) [17] and bi-level airway pressure (Bilevel). BIPAP is identical to APRV except that no restriction is imposed on the duration of the low CPAP-level (release pressure) [17,18]. Based on the initial description, APRV keeps the duration of the low CPAP-level (release time) at 1.5 seconds or less (Fig 96.3).

Physiological effects of superimposed spontaneous breathing during APRV

As known from CT scans in patients with ARDS, alveolar collapse is primarily localized in the dependent lung regions (Fig 96.4), which correlates with intrapulmonary shunting and accounts entirely for the observed hypoxaemia [19]. If the diaphragm is relaxed, it will be moved by the weight of the abdominal cavity and intra-abdominal pressure towards the cranium. During spontaneous breathing, the posterior muscular sections of the diaphragm moves more than the anterior tendon plate [17]. Thereby, transpulmonary pressure will be increased especially in dependent lung regions. Periodic reduction of intrathoracic pressure, achieved by maintaining spontaneous breathing, promotes venous return to the heart and right- and left-ventricular filling and improves outflow from the right ventricle (the major determinant of pulmonary vascular resistance), thereby increasing cardiac output and oxygen delivery [17].

In clinical and experimental studies spontaneous breathing with APRV in is associated with recruitment of atelectasis and increased end-expiratory lung volume (Fig 96.4) [20], improved ventilation of dependent lung areas, and thereby improved ventilation–perfusion matching, a rise in cardiac output, oxygenation and oxygen delivery [17], whereas oxygen consumption remains unchanged despite the work of spontaneous breathing. Furthermore, tidal recruitment (cyclic collapse) that might be a major contributor to VALI is reduced [20] . Renal, intestinal, and cerebral perfusion have been shown to be increased [17].

When allowing spontaneous breathing, lower levels of sedation are possible. Less sedation helps in reducing the doses of vasopressor and inotropic agents, while maintaining cardiovascular function in a stable condition, and reducing the duration of ventilator support [17].

Limitations for APRV

In patients with left ventricular dysfunction, switching abruptly from controlled to supported ventilation with a simultaneous reduction in airway pressure might cause further decompensation due to augmentation right ventricular preload and increase in left ventricular afterload. Provided that satisfactory CPAP levels are applied, maintaining spontaneous breathing during APRV should not be a disadvantage and is not per se contraindicated in patients with ventricular dysfunction.

In concept, APRV does not provide breath-to-breath assistance of spontaneous inspiration. Thus, APRV is not expected to be an advantage in difficult-to-wean patients.

Because lower levels of sedation are used to allow spontaneous breathing, APRV should not be used in patients who require deep sedation for management of their underlying disease (e.g. cerebral oedema with increased intracranial pressure).

Acknowledgements

The authors would like to thank Stefan Kreyer, MD, DESA, staff anaesthesiologist at the Department of Anesthesiology and Intensive Care Medicine, University of Bonn, Germany, for his important input and support.

References

1. Brower RG and Rubenfeld RG. (2003). Lung-protective ventilation strategies in acute lung injury. *Critical Care Medicine*, **31**(4 Suppl.), S312–16.
2. Marik PE and Krikorian J. (1997). Pressure-controlled ventilation in ARDS: a practical approach. *Chest*, **112**(4), 1102–6.
3. Amato MB and Marini JJ. (2012). Pressure-controlled and inverse-ratio ventilation. In: Tobin MJ. (ed.) *Principles and Practice of Mechanical Ventilation*, 3rd edn, p. 1472. New York, NY: McGraw-Hill Professional.
4. Chiumello D, Pelosi P, Taccone P, Slutsky A, and Gattinoni L. (2003). Effect of different inspiratory rise time and cycling off criteria during pressure support ventilation in patients recovering from acute lung injury. *Critical Care Medicine*, **31**(11), 2604–10.
5. Mercat A, Diehl JL, Michard F, et al. (2001). Extending inspiratory time in acute respiratory distress syndrome. *Critical Care Medicine*, **29**(1), 40–4.
6. Marini JJ, Crooke PS, and Truwit JD. (1989). Determinants and limits of pressure-preset ventilation: a mathematical model of pressure control. *Journal of Applied Physiology*, **67**(3), 1081–92.
7. Burchardi H. (1996). New strategies in mechanical ventilation for acute lung injury. *European Respiratory Journal*, **9**(5), 1063–72.
8. Baum M, Benzer H, Mutz N, Pauser G, and Tonczar L. (1980). [Inversed ratio ventilation (IRV). Role of the respiratory time ratio in artificial respiration in ARDS.] *Der Anaesthetist*, **29**(11), 592–6.
9. Mercat A, Graïni L, Teboul JL, Lenique F, and Richard C. (1993). Cardiorespiratory effects of pressure-controlled ventilation with and without inverse ratio in the adult respiratory distress syndrome. *Chest*, **104**(3), 871–5.
10. Pinsky MR, Matuschak GM, and Itzkoff JM. (1984). Respiratory augmentation of left ventricular function during spontaneous ventilation in severe left ventricular failure by grunting. An auto-EPAP effect. *Chest*, **86**(2), 267–9.
11. Perchiazzi G, Rylander C, Vena A, et al. (1985). Lung regional stress and strain as a function of posture and ventilatory mode. *Journal of Applied Physiology*, **110**(5), 1374–83.
12. Esteban A, Alía I, Gordo F, et al. (2000). Prospective randomized trial comparing pressure-controlled ventilation and volume-controlled ventilation in ARDS. For the Spanish Lung Failure Collaborative Group. *Chest*, **117**(6), 1690–6.
13. Calderini E, Confalonieri M, Puccio PG, Francavilla N, Stella L, and Gregoretti C. (1999). Patient–ventilator asynchrony during noninvasive ventilation: the role of expiratory trigger. *Intensive Care Medicine*, **25**(7), 662–7.
14. Gattinoni L, Carlesso E, Valenza F, Chiumello D, and Caspani ML. (2004). Acute respiratory distress syndrome, the critical care paradigm: what we learned and what we forgot. *Current Opinion in Critical Care*, **10**(4), 272–8.
15. Zavala E, Ferrer M, Polese G, et al. (1998). Effect of inverse I:E ratio ventilation on pulmonary gas exchange in acute respiratory distress syndrome. *Anesthesiology*, **88**(1), 35–42.
16. Neumann P, Berglund JE, Andersson LG, Maripu E, Magnusson A, and Hedenstierna G. (2000). Effects of inverse ratio ventilation and positive end-expiratory pressure in oleic acid-induced lung injury. *American Journal of Respiratory and Critical Care Medicine*, **161**(5), 1537–45.

17. Putensen C, Muders T, Varelmann D, and Wrigge H. (2006). The impact of spontaneous breathing during mechanical ventilation. *Current Opinion in Critical Care*, **12**(1), 13–18.
18. Stock MC, Downs JB, and Frolicher DA. (1987). Airway pressure release ventilation. *Critical Care Medicine*, **15**(5), 462–6.
19. Gattinoni L, Presenti A, Torresin A, et al. (1986). Adult respiratory distress syndrome profiles by computed tomography. *Journal of Thoracic Imaging*, **1**(3), 25–30.
20. Wrigge H, Zinserling J, Neumann P, et al. (2005). Spontaneous breathing with airway pressure release ventilation favors ventilation in dependent lung regions and counters cyclic alveolar collapse in oleic-acid-induced lung injury: a randomized controlled computed tomography trial. *Critical Care*, **9**(6), R780–9.

CHAPTER 97

Pressure support ventilation

Hérnan Aguirre-Bermeo and Jordi Mancebo

Key points

- Pressure support ventilation (PSV) is an assisted ventilatory mode that is patient-triggered, pressure-limited, and flow cycled. During PSV, airway pressure is maintained nearly constant during the entire inspiration.
- PSV allows the patient to maintain a certain degree of control over respiratory rate and tidal volume.
- The main use of the modality is in withdrawal from mechanical ventilation because it unloads respiratory muscles and allows a gradual reduction of support until extubation.
- If not properly used (usually due to excessive levels of support), this modality generates high and abnormal tidal volumes, and wasted inspiratory efforts.
- The closed-loop modality could have important clinical implications in withdrawal of mechanical ventilation in specific groups of patients. It appears to be as good as usual care performed by experts and skilled teams.

Definition

Pressure support ventilation (PSV) is an assisted ventilatory mode that is patient-triggered (by pressure, airflow, or both), pressure-limited, and flow cycled. In this modality, the airway pressure is maintained almost constant during the entire inspiration. The ventilator provides assistance when the patient makes a breathing effort, and then, when inspiratory flow reaches a certain threshold level, cycling to exhalation occurs. The use of PSV is common in all intensive care units (ICUs), and it is the most commonly used method to wean patients from mechanical ventilation [1].

Mode characteristics

Trigger

In PSV, the clinician decides whether to use pressure or flow triggers to initiate ventilatory assist. The recommended pressure and flow triggers are, respectively, from –0.5 to –2.0 cmH_2O, and from 1 to 2 L/min [2].

Several studies have compared the use of pressure versus flow triggers, without finding any significant differences between the triggers. However, Aslanian et al. [2] found that the flow trigger was more effective in reducing breathing effort when used in PSV versus volume-controlled modality. In patients with intrinsic positive end-expiratory pressure ($PEEP_i$), the flow trigger can decrease inspiratory effort; moreover, low levels of external positive end-expiratory pressure (PEEP) are recommended to compensate for this $PEEP_i$, the dynamic flow limitation and for decrease the work of breathing [3].

Flow delivery

Once the ventilator is triggered, the machine provides an inspiratory flow (via a servo regulatory mechanism) to maintain the preset level of airway pressure (pressure support setting) nearly constant throughout the inspiration. The velocity of pressurization, which depends on the shape of the inspiratory flow waveform, is the time required for the ventilator to reach the pressure support setting at the onset of inspiration (rise time). Different pressurization rates have a profound effect on effort. Low pressurization rates produce a high inspiratory muscle effort, while high pressurization rates lower inspiratory muscle effort [4]. Visual inspection of the ventilator waveforms may be used to guide this setting. Tidal volume depends on the preset level of pressure support, the inspiratory effort of the patient, the cycling-off threshold level, and the mechanical characteristics (resistance and compliance) of the patient's respiratory system.

Cycling of expiration

During PSV, cycling from inspiration to expiration is triggered when the inspiratory airflow reaches a certain threshold value. The threshold value coincides, theoretically, with the end of inspiratory muscle effort. This flow value could be a percentage of peak flow (i.e. 25% of peak flow) or a fixed level (i.e. 5 L/min). The latest generation of ventilators allow the physician to set this flow threshold value [5]. Modification of the cycling-off criteria can influence inspiratory effort and patient–ventilator synchrony. In patients with chronic obstructive pulmonary disease (COPD), setting the cycling-off at higher percentages of peak inspiratory flow can improve patient–ventilator synchrony and reduce inspiratory muscle effort [6]. Thille et al. [7] have described a similar phenomenon in COPD and non-COPD patients. Tracings obtained during pressure support ventilation are shown in Fig. 97.1.

Physiological effects

Breathing pattern and respiratory effort

PSV allows the patient to retain control over the respiratory rate and tidal volume, a process referred to as physiological ventilation. PSV induces changes in the breathing pattern that affect tidal volume and respiratory rate, without, however, inducing major changes in minute ventilation. As a result, in most patients, tidal volume rises and the ventilator respiratory rate decreases as the

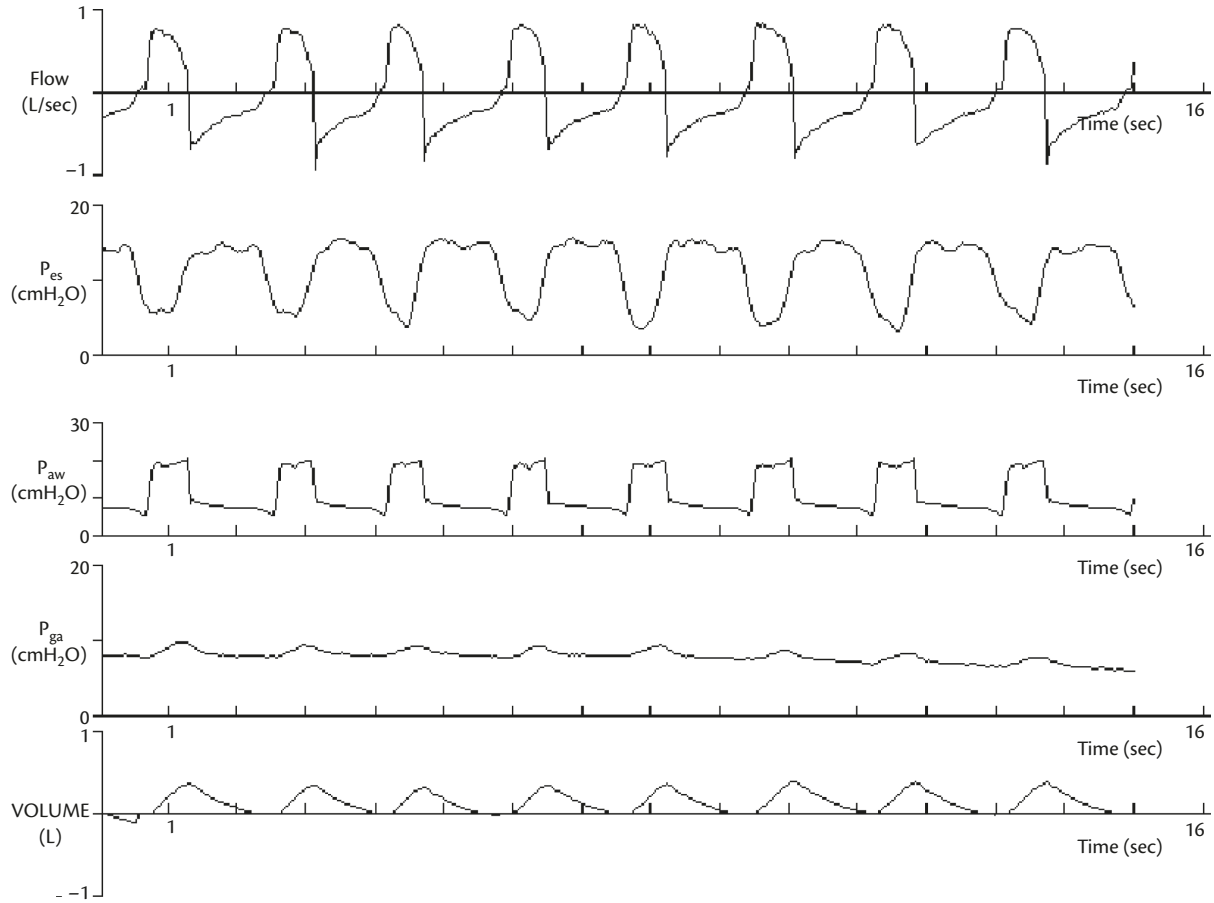


Fig. 97.1 From top to bottom: tracings of airflow (flow), oesophageal pressure (P_{es}), airway pressure (P_{aw}), gastric pressure (P_{ga}), and tidal volume (Volume) recorded in a patient breathing in PSV mode.

level of support is increased. Inappropriate low levels of support can generate low tidal volumes and a high respiratory rate, resulting in patient discomfort and hypercapnia; on the other hand, excessive levels of support may produce hyperinflation, the appearance of wasted inspiratory efforts, respiratory alkalosis, and even periods of apnoea.

Patient ventilator synchrony during PSV

Asynchronies can be present in all ventilator modalities and inappropriate ventilator settings can aggravate the frequency and severity of these asynchronies.

The patient–ventilatory synchrony achieved with PSV is good because it is able to recognize the beginning and the end of each spontaneous effort. However, asynchronies occur during PSV. Often, but not always, these asynchronies during PSV can be detected at the bedside by examining ventilator waveforms.

Thille et al. [8] found that assisted control modalities are associated with a higher prevalence of asynchronies compared with PSV. In their study, the most common asynchronies were ineffective triggering and double-triggering.

A study by Leung et al. [9] showed that high levels of support (above 60–70% of full support) generated wasted inspiratory efforts. A more recent study [7] found that the frequency of asynchronies can be decreased by lowering pressure-support levels.

Clinical usefulness and applications

Withdrawal of mechanical ventilation

In the process of withdrawal of mechanical ventilation, the support level should be reduced as quickly as the patient's clinical tolerance will permit. This reduction, therefore, must be made on an individual basis. The support levels are usually lowered by one or two steps per day (between 2 and 4 cmH_2O per step). A spontaneous breathing trial (SBT) should be conducted as soon as the physician suspects that weaning may be possible and the patient appears to be ready to breathe without ventilatory assistance. This trial can be performed by disconnecting the patient from the ventilator and attaching a T-piece to the endotracheal tube or, alternatively, the SBT can be performed by administering low levels of PSV with or without PEEP. Esteban et al. [10] showed that both methods (pressure support or a T-piece) are suitable for successful discontinuation of ventilator support. However, a recent study by Cabello and colleagues [11], showed that, in difficult to wean patients (those who had failed at least one SBT), the use of pressure support and PEEP modifies the breathing pattern, inspiratory muscle effort, and cardiovascular response when compared with the T-piece trial. In fact, of the 100% of difficult to wean patients who failed a T-piece trial, 79 and 57%, respectively, successfully completed subsequent PSV with PEEP and PSV without PEEP trials. For these reasons, it

is still unclear as to which SBT is best to predict successful extubation, and therefore weaning strategies must be individualized.

Initial suggested settings

As occurs in other ventilation modalities, all PSV settings must be adjusted individually in each patient. However, we can provide some suggestions for the initial PSV settings. These settings should be checked several times during the day and/or whenever the patient requires an adjustment.

First, the pressurization rate should be fast (short rise time), and the support level should be adjusted to produce a respiratory rate of approximately 25–30 breaths/min depending on the patient's comfort. Cycling off should be approximately 25% of peak inspiratory flow (a higher percentage is recommended in COPD patients). The FIO_2 and PEEP must be adjusted according to gas exchange and $PEEP_i$.

Closed-loop modality

A closed-loop, knowledge-based system has been designed to help in withdrawal from mechanical ventilation. The system continuously analyses physiological data (respiratory rate, tidal volume, and end-tidal CO_2 level) and adapts the level of pressure support to keep the patient within a 'comfort zone'. This comfort zone is defined as a respiratory rate that can vary freely from 15 to 30 breaths/min (up to 34 breaths in patients with neurological disease). The tidal volume should be above a minimum threshold and an end-tidal CO_2 level below a maximum threshold [12]. The level of pressure support is periodically adapted by the system in steps of 2–4 cmH_2O. The system automatically tries to reduce the pressure level to a minimal value, at which time a 'spontaneous breathing trial' with the minimal low-pressure support is performed by the system. Upon successful completion of this trial, a message on the screen recommends separation from the ventilator.

Lellouche et al. [12], showed that this system reduces the duration of mechanical ventilation and ICU stay compared with the usual intensive care weaning procedures. However, two recent studies have failed to fully confirm these results [13,14]. Rose et al. [13] reported that the automated system did not reduce weaning time in their study, in contrast to the positive findings of Lellouche and colleagues. However, this may be due to differences between the two studies, particularly in terms of patient severity, duration of ventilation, the patient–nurse ratio, and in ICU staffing levels. The study performed by Schadler et al. [14] also had several difference with the Lellouche et al. study. One important difference is that the Schadler study was performed in post-operative patients with nursing and medical staff who were skilled in the management of mechanical ventilation. The authors found that overall weaning times did not differ significantly between the control group and the experimental group, with the exception of a subgroup of 132 patients who had undergone cardiac surgery (24 hours in closed-loop versus 35 hours in control group, $p = 0.035$). Given the findings published to date, we can conclude that this closed-loop modality performs at least as well as experienced medical staff in weaning patients from mechanical ventilation.

References

1. Esteban A, Ferguson ND, Meade MO, et al. (2008). Evolution of mechanical ventilation in response to clinical research. *American Journal of Respiratory and Critical Care Medicine*, **177**(2), 170–7.
2. Aslanian P, El Atrous S, Isabey D, et al. (1998). Effects of flow triggering on breathing effort during partial ventilatory support. *American Journal of Respiratory and Critical Care Medicine*, **157**(1), 135–43.
3. Mancebo J, Albaladejo P, Touchard D, et al. (2000). Airway occlusion pressure to titrate positive end-expiratory pressure in patients with dynamic hyperinflation. *Anesthesiology*, **93**(1), 81–90.
4. Chiumello D, Pelosi P, Croci M, Bigatello LM, and Gattinoni L. (2001). The effects of pressurization rate on breathing pattern, work of breathing, gas exchange and patient comfort in pressure support ventilation. *European Respiratory Journal*, **18**(1), 107–14.
5. Brochard L and Lellouche F. (2006). Pressure support ventilation. In: Tobin MJ (ed.) *Principles and Practice of Mechanical Ventilation*, 2nd edn, pp. 221–50. New York, NY: McGraw-Hill Medical Publishing Division.
6. Tassaux D, Gainnier M, Battisti A, and Jolliet P. (2005). Impact of expiratory trigger setting on delayed cycling and inspiratory muscle workload. *American Journal of Respiratory and Critical Care Medicine*, **172**(10), 1283–9.
7. Thille AW, Cabello B, Galia F, Lyazidi A, and Brochard L. (2008). Reduction of patient–ventilator asynchrony by reducing tidal volume during pressure-support ventilation. *Intensive Care Medicine*, **34**(8), 1477–86.
8. Thille AW, Rodriguez P, Cabello B, Lellouche F, and Brochard L. (2006). Patient–ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Medicine*, **32**(10), 1515–22.
9. Leung P, Jubran A, and Tobin MJ. (1997). Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. *American Journal of Respiratory and Critical Care Medicine*, **155**(6), 1940–8.
10. Esteban A, Alia I, Gordo F, et al. (1997). Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. *American Journal of Respiratory and Critical Care Medicine*, **156**(2 Pt 1), 459–65.
11. Cabello B, Thille AW, Roche-Campo F, Brochard L, Gomez FJ, and Mancebo J. (2010). Physiological comparison of three spontaneous breathing trials in difficult-to-wean patients. *Intensive Care Medicine*, **36**(7), 1171–9.
12. Lellouche F, Mancebo J, Jolliet P, et al. (2006). A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. *American Journal of Respiratory and Critical Care Medicine*, **174**(8), 894–900.
13. Rose L, Presneill JJ, Johnston L, and Cade JF. (2008). A randomised, controlled trial of conventional versus automated weaning from mechanical ventilation using SmartCare/PS. *Intensive Care Medicine*, **34**(10), 1788–95.
14. Schadler D, Engel C, Elke G, et al. (2012). Automatic control of pressure support for ventilator weaning in surgical intensive care patients. *American Journal of Respiratory and Critical Care Medicine*, **185**(6), 637–44.

CHAPTER 98

High-frequency ventilation and oscillation

Mireia Cuartero and Niall D. Ferguson

Key points

- High-frequency oscillatory ventilation (HFOV) is a ventilatory mode that delivers pressure oscillations around a relatively constant mean airway pressure.
- Resultant tidal volumes with HFOV are very small—often smaller than the anatomic dead space—but adequate ventilation is achieved through a number of mechanisms generally related to enhanced mixing of gas within the lung.
- HFOV has been widely studied and adopted in the neonatal intensive care unit (ICU), where it may help reduce the incidence of chronic lung disease; it is also commonly used in the paediatric setting.
- In adults with acute respiratory distress syndrome (ARDS), HFOV is often effective in improving oxygenation among patients failing conventional ventilation.
- Despite being theoretically ideal for preventing ventilator-induced lung injury, recent trials indicate that HFOV does not reduce mortality in patients with moderate–severe ARDS.

Introduction

High-frequency oscillatory ventilation (HFOV) is a ventilation mode that achieves adequate alveolar ventilation despite using very low tidal volumes (V_T), at or below the dead space volume (V_D) (approximately 1–2 mL/kg), at frequencies significantly above normal physiological values (more than 3 breaths/second) [1]. Theoretically, it presents some advantages in its ability to apply a lung protective ventilation strategy and thereby avoid ventilator-induced lung injury (VILI) [2,3].

The modern history of HFOV began in 1971 when Jonzon presented a study about the circulatory effects of high-frequency ventilation [4]. The next year, Lunkenheimer et al. described the use of a ventilator based on an electromagnetic vibrator at very high respiratory frequencies (40 Hz) to clear CO_2 [5]. Previously, there had also been some studies reported in animal models. However, through his work in animals and neonates in the late 1970s and 1980s, A. C. Bryan is considered to be the father and developer of HFOV as it is currently known [6,7]. HFOV was initially introduced in the neonatal ICU, where it has been the subject of many randomized controlled trials (RCTs) [8], and it was also widely adopted in the paediatric intensive care unit (ICU). More recently, HFOV made the transition to adult critical care beginning in the late 1990s when technical improvements allowed for the oscillation of those weighing more than 35 kg. Since then, there have been many series and case reports of this ventilatory mode in adults failing conventional ventilation, and a few randomized trials in patients with acute respiratory distress syndrome (ARDS).

HFOV is one of a family of ventilatory modes termed high-frequency ventilation (HFV), and is the only one we will discuss in any detail here. Other members of this family include high frequency jet ventilation (HFJV) and high-frequency percussive ventilation (HFPV). Their differences are based on the manner of generating the high frequency—by an oscillating membrane with HFO, by jet catheter in HFJV, and with flow interruption in HFPV—and also by their ranges in frequency (2–15 Hz), on the type of wave (triangular or sinusoidal), the inspiratory–expiratory ratio (I:E) (constant or adjustable), and the type of expiration (active or passive) (Table 98.1).

Physiological effects of HFOV

The HFOV ventilator (see Fig. 98.1) is an oscillator with a diaphragm located in the inspiratory circuit. The ventilator pressurizes the patient circuit by means of a continuous flow of gas (bias flow) and a control valve allows modulation of the mean airway pressure (mP_{aw}). The gas is actively pushed in and pulled out of the patient by diaphragm, which oscillates according to an electrically-driven magnet or by bi-directional blower, depending on the model. The amplitude of displacement of the diaphragm can be modified by adjusting the power, which generates a peak-to-peak pressure gradient, displayed as ΔP on the more commonly-used SensorMedics 3100B oscillator. The oscillation frequency on this ventilator can be adjusted to between 180 and 900 cycles/min (3–15 Hz), although in adults frequencies between 5 and 10 Hz are most commonly used. The amplitude displacement of the diaphragm, the oscillation frequency, and the characteristics of the airway and respiratory system compliance determines the amplitude of the oscillations (or pressure difference ΔP) around the mean airway pressure (mP_{aw}).

During HFOV there is relative decoupling of oxygenation and ventilation. Oxygen is generally directly dependent on FIO_2 and mP_{aw}. Ventilation meanwhile, is directly proportional to power (ΔP) and inversely proportional to the applied frequency. CO_2 elimination is proportional to the frequency and the square of the tidal volume ($Vco_2 \alpha = f \times V_T^2$). Unlike conventional ventilation, where tidal volume (V_T) is relatively independent of respiratory

Table 98.1 Main characteristics of the different types of HFV

Type of HFV	Mechanism	Hz (breaths/min)	Exhalation	Pros	Cons
HFJV	Additional flow through a small-bore catheter placed within the endotracheal tube (Coanda effect)	1.7–2.5 (100–150)	Passive	Very efficient for removing CO_2	Risk of dynamic hyperinflation Unpredictable V_T Tracheobronchial injury
HFPV	HFV + conventional pressure-control breathing pattern	3.4–15 (200–900)	Passive	Improve secretion clearance	Much less studied
HFOV	Pressure oscillations around a mP_{aw}, resulting in very small V_T	3–15 (180–900)	Active	Decoupling of ventilation (depending on V_T and Hz) and oxygenation (depending on mP_{aw}).	Air leak syndrome Right heart failure Pneumothorax

HFJV, high frequency jet ventilation; HFPV, high-frequency percussive ventilation; HFOV, high-frequency oscillatory ventilation.

rate, during HFOV increasing frequency reduces inspiratory time and can have a strong influence on the resultant tidal volume, thus reductions in frequency usually lower $PaCO_2$. The V_T produced is often less than the volume of the anatomical dead space and is determined by the ΔP, the frequency, the airway resistance (mainly by endotracheal tube size), and respiratory system compliance. Even though the ΔP measured in the ventilator circuit can be as high as 90 cmH_2O, the transmission of this pressure to the alveoli is significantly attenuated, and is dependent on the diameter of endotracheal tube, the oscillation frequency, the resistance of the airway, and respiratory system compliance.

Because tidal volumes with HFOV are often lower than dead space volumes, the mechanisms of gas-transport mechanisms are complex and multiple (see Fig. 98.2) [9,10]. Adequate ventilation is achieved through the following phenomena:

- **Direct alveolar ventilation**: despite a very small V_T proximal alveoli may still be ventilated directly by bulk convection (the usual method of gas transport within the lung).
- **Turbulence in the large airways**: causing enhanced mixing.
- **Asymmetric velocity profiles**: due to the rapidly alternating high velocities of gas in the airway, a summation vector is created with a parabolic shape of penetration greater into the centre of the air than in the periphery. This leads to fresh gas entering through the middle of the airway, while expired gas tracks up the outside of the airway.

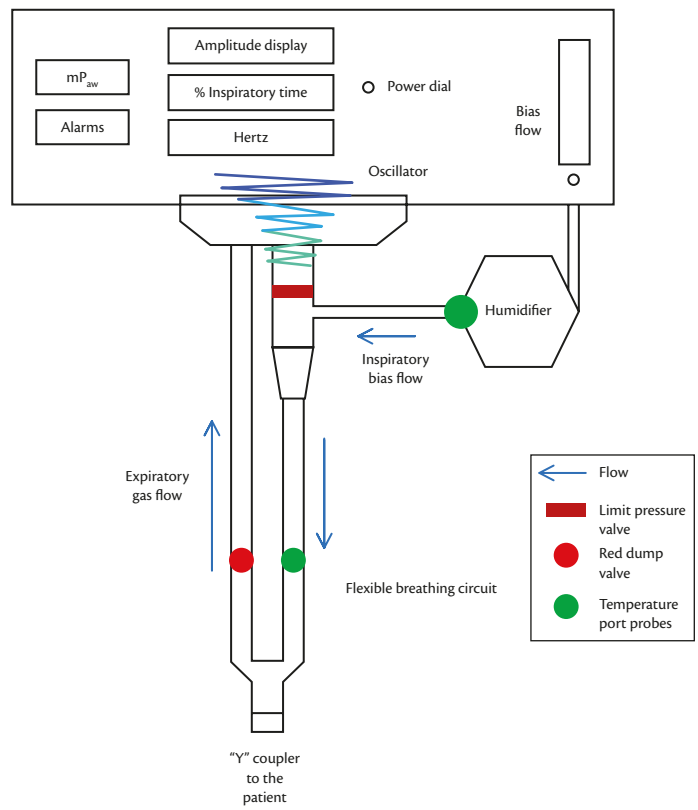


Fig. 98.1 Scheme of the HFOV circuit.

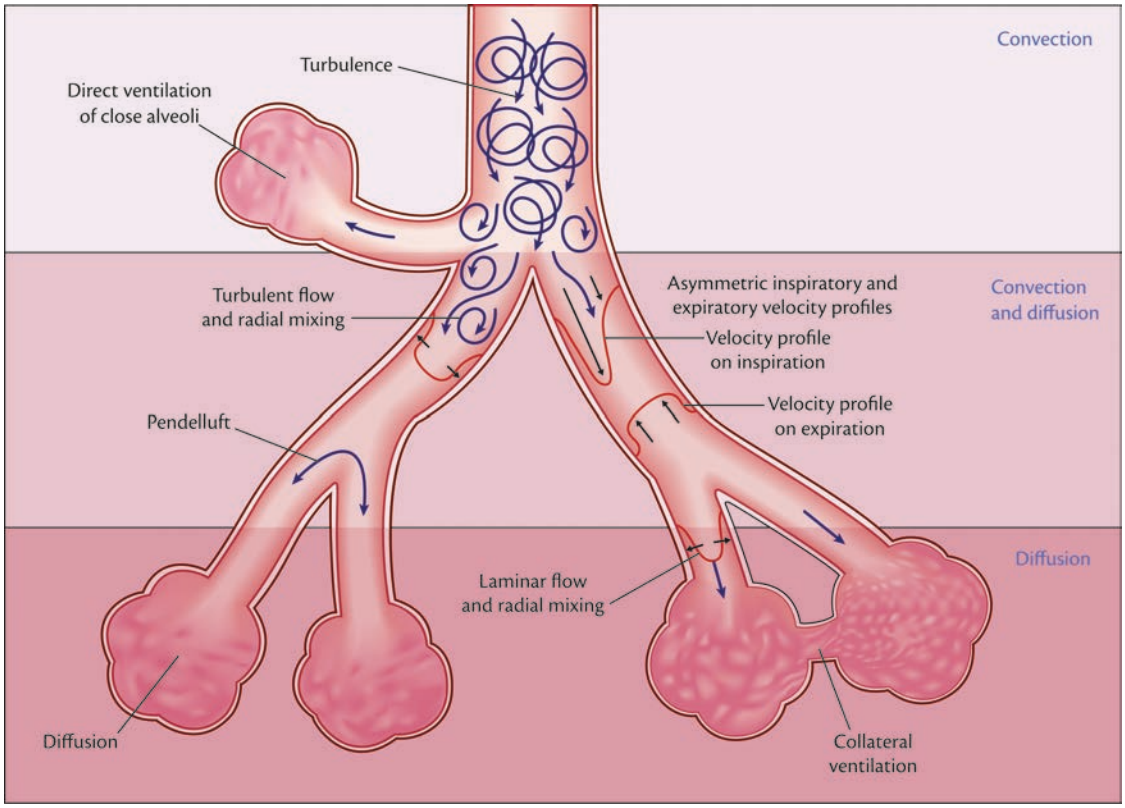


Fig. 98.2 Gas transport mechanisms.
From *New England Journal of Medicine*, Slutsky AS and Drazen JM, 'Ventilation with small tidal volumes', **347**(9), pp. 629–33. Copyright © 2002 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

- **Pendulum movement of air between alveolar units (pendelluft)**: this is the exchange of gas between adjacent lung units with differing time constants, due to the asymmetries in airflow impedances.
- **Increased dispersion**: this refers to the molecular dispersion of gas in the airway increases the sinusoidal deformation and radial forces at gas diffusion movements caused by the turbulence produced in the bronchial branches (Taylor dispersion).
- *Molecular diffusion*: displacement of the molecular gas from areas of higher to lower concentration. CO_2 has a higher diffusion constant than O_2.

The key action of HFOV is the constant maintenance of the mP_{aw}, in contrast to conventional modes, where even if the numerical value of mP_{aw} is similar, airway pressure varies greatly over the course of the respiratory cycle. The relatively constant mP_{aw} decreases the resistance to gas movement, facilitating and promoting the gas-transport phenomena described in the bulleted list previous to this paragraph. Moreover, the active recruitment of non-functional alveoli may be accomplished in a few hours, thanks to the constant high mean airway pressure.

Clinical implications

In 1980s Bryan and colleagues developed several physiological studies, which set the basis for our current knowledge of HFOV [7]. There have been several experimental animal studies to apply this mode to prevent VILI. Most of them, even when compared to 'protective' conventional ventilation, showed an improvement in pulmonary injury severity scores, in gas exchange and a decrease of some inflammatory markers (TNF, IL-1B, IL-6, IL-8, IL10, and TGF). Many case series were reported as a first clinical approach since that moment on.

From 1990s up to now, HFV has become standard practice in neonatal and paediatric ICU's in the treatment of newborns with respiratory distress syndrome. A recent meta-analysis [11], however, and the latest Cochrane review [12] comparing HFOV with conventional ventilation in preterm infants do raise some doubts about the real effectiveness of HFOV in the neonatal population. The 15 RCTs included in the Cochrane review showed no clear benefit with HFOV when their results were pooled. In those studies there are data suggesting some reduction in the rate of chronic lung disease (CLD) with HFOV, but that was not consistent across all them. Moreover, the introduction of HFOV into neonatal ICU's coincided with the simultaneous introduction of surfactant in the treatment of newborns with respiratory distress of prematurity. There is strong evidence that surfactant has led to a decreased mortality and morbidity, so a confounding effect cannot be ruled out. Therefore, further trials on elective HFOV in infants at higher risk of CLD could be conducted, although the feasibility of such trials may be questioned given the widespread adoption of HFOV in the neonatal and paediatric setting.

In adults, the first studies were set as a rescue therapy for patients with severe ARDS who were 'failing' conventional ventilation. Fort

et al. published the first of those case series, which suggested an improvement in oxygenation with HFOV [13]. Later on, Mehta and others showed similar results in subsequent case series [14]—HFOV appeared to be safe and effective in improving oxygenation in these extremely severe ARDS patients.

During the late 1990s several small RCT set out to explore those promising results further. The largest of these [15] randomized 148 patients with ARDS to either conventional mechanical ventilation (MV) with a V_T target of 6–10 mL/kg actual body weight, or to HFOV. There was no significant difference between groups in the primary outcome measure of survival without need for mechanical ventilation at 30 days. There was, however, an improvement in oxygenation and a non-significant trend towards lower mortality at 30 days with HFOV compared with the conventional MV (37 versus 52%, $P = 0.102$). Ten years later, however, it was clear that this and other trials were confounded by both small sample sizes and outdated control ventilation strategies. Thus, despite a meta-analysis showing a significant reduction in mortality [11], calls went out for larger trials comparing HFOV with lung-protective conventional ventilation in adults with ARDS. These trials were conceived on the premise that HFOV could be theoretically ideal for preventing VILI, based on the very small tidal volumes delivered, and the minimal swings in alveolar airway pressure, which might allow one to use higher pressures to recruit the atelectatic lung, while simultaneously avoiding tidal overdistention [16,17].

Recently, two large multicentre RCTs have been published, which shed light on the effects of HFOV on all-cause mortality. Both the Oscillation for ARDS (OSCAR; $n = 795$) trial [18] and the Oscillation for ARDS Treated Early (OSCILLATE; $n = 548$) trial [19] recruited patients with moderate–severe ARDS and assigned them to relatively early support with HFOV versus protective conventional MV (with V_T target 6 mL/kg and in the case of OSCILLATE, higher positive end-expiratory pressure). In contrast to prior studies, both of these trials found no evidence of improved survival in patients assigned to HFOV. Indeed, the OSCILLATE trial was stopped early because of concerns of a significantly higher mortality rate in the HFOV group (47 versus 35%).

Complications

HFOV, like any ventilatory mode, has related potential complications. None of the reported RCTs or case series, however, suggested any specific and clear complications at a higher rate than might be expected with conventional ventilation. The specific reasons for the higher mortality seen in the OSCILLATE trial remain uncertain, but among the postulated explanations are:

- Haemodynamic consequences related to higher airway pressures and sedation levels.
- Increased barotrauma and paradoxical increase in VILI.
- Increased sedation use.
- Chance alone.

A known complication of HFOV (and of conventional ventilation) is barotrauma, with the occurrence of air leak being reported in up to 25% of patients in some case series of rescue therapy. This ARDS population, however, is at higher risk of developing pneumothorax. The two recent large trials did not show statistically significant differences in barotrauma, although in OSCILLATE barotrauma rates did trend higher in the HFOV group.

Secondly, because the bias flow rate is insufficient to meet ventilatory demands, adults on HFOV usually requires larger doses of sedation and sometimes paralysis in order to blunt or eliminate their respiratory efforts, something that is often not the case in paediatric and neonatal populations. Transient muscle relaxation is often recommended during the initiation of HFOV, during recruitment manoeuvres and, in some specific conditions, such as air leak syndromes and severe hypoxaemia. In fact, a moderate amount of spontaneous breathing does not usually interfere with gas exchange during HFOV; changes in the mP_{aw} of plus or minus 5 cmH_2O can often be allowed. Moreover, although the use of neuromuscular paralysis and sedation are related with an overall increased mortality in the overall ICU population, they may improve survival when used in short-term and early stages of ARDS.

Another potential complication is the obstruction of the airway due to the lack of clearance of secretions. This effect is uncommon, and can be reduced by means of adequate humidification [13,19]. Nevertheless a sudden increase in $PaCO_2$ or unexplained increase in ΔP on the ventilator should be investigated with bronchoscopy to rule out endotracheal tube obstruction.

Finally, as with any kind of positive pressure ventilation, HFOV increases intrathoracic pressure, reducing venous return and even may potentially promote right heart failure, perhaps because of the constant mean airway pressure to which the right ventricle is exposed [15,20]. However, the presence of acute cor pulmonale is usually reversible in patients who recover from ARDS and does not increase long-term mortality.

Conclusion

HFOV produces effective exchange of CO_2 and O_2 with lower peak pressures at the alveolar level and a higher mean airway pressure. Indeed, applying a stable mP_{aw} produces minimal variations in pressures and ventilation volumes, keeping the lung volume above functional residual capacity largely constant. Therefore, HFOV is an interesting ventilatory modality, which has the potential to minimize ventilator-induced lung injury, at least in theory.

HFOV has become an established lung-protective modality in neonatal and paediatric intensive care, although further studies to support an improvement of mortality and morbidity could be conducted. In adults recent publications do not support the routine use of HFOV in patients with moderate-severe ARDS as there was no signal for benefit and even a suggestion of harm from one trial. While these findings do not necessarily apply to patients with severe hypoxaemia failing conventional ventilation, they do increase uncertainty about the role of HFOV even in these patients. In carefully selected patients who respond to lung recruitment, HFOV may still have a role in severe ARDS, but only after conventional ventilation settings have been optimized and after prone positioning has been considered.

References

1. Froese AB and Ferguson ND. (2012). Unconventional methods of ventilator support. In: Tobin MJ (ed.) *Principles and Practice of Mechanical Ventilation*, pp. 1–25. New York, NY: McGraw-Hill.
2. Amato MB, Valente CS, Machado D, et al. (1998). Effect of a protective-ventilation strategy on mortality in the acute respiratory distress. *New England Journal of Medicine*, **338**, 347–54.
3. Lee WL and Slutsky AS. (2001). Ventilator-induced lung injury and recommendations for mechanical ventilation of patients with

ARDS. *Seminars in Respiratory and Critical Care Medicine*, **22**(3), 269–80.
4. Jonzon A, Öberg P, Sedin G, and Sjöstrand U. (1970). High frequency low tidal volume positive pressure ventilation. *Acta Physiologica Scandinavica*, **80**(Vi), 21–2.
5. Lunkenheimer PP, Rafflenbeul W, Keller H, Frank I, Dickhut HH, and Fuhrmann C. (1972). Application of transtracheal pressure oscillations as a modification of 'diffusion respiration'. *British Journal of Anaesthesia*, **44**, 627.
6. Bryan A and Slutsky A. (1986). Long volume during high frequency oscillation. *American Review of Respiratory Disease*, **5**, 928–30.
7. Bryan AC. (2001). How it really happened the oscillations of HFO. *American Journal of Respiratory and Critical Care Medicine*, **163**(4), 816–17.
8. Parad RB. (2010). HFOV in preterms: an individual patients' data meta-analysis. *Lancet*, **375**(9731), 2054–5.
9. Jonzon A, Rondio Z, and Sedin G. (1983). Alveolar deadspace during high frequency positive pressure ventilation. *British Journal of Anaesthesia*, **55**, 1133.
10. Slutsky AS and Drazen JM. (2002). Ventilation with small tidal volumes. *New England Journal of Medicine*, **347**(9), 629–33.
11. Sud S, Sud M, Friedrich JO, et al. (2010). High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. *British Medical Journal*, **340**, c2327.
12. Henderson-Smart D, Cools F, Bhuta T, and Offringa M. (2008). Cochrane review: elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Evidence-Based Child Health: A Cochrane Review Journal*, **3**(3), 731–808.
13. Fort P, Farmer C, Westerman J, et al. (1997). High-frequency oscillatory ventilation for adult respiratory distress syndrome—a pilot study. *Critical Care Medicine*, **25**(6), 937–47.
14. Mehta S, Granton J, MacDonald RJ, et al. (2004). High-frequency oscillatory ventilation in adults: the Toronto experience. *Chest*, **126**(2), 518–27.
15. Derdak S, Mehta S, Stewart TE, et al. (2002). High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. *American Journal of Respiratory and Critical Care Medicine*, **166**(6), 801–8.
16. Hager DN, Fessler HE, Kaczka DW, et al. (2007). Tidal volume delivery during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. *Critical Care Medicine*, **35**(6), 1522–9.
17. Fessler HE, Derdak S, Ferguson ND, et al. (2007). A protocol for high-frequency oscillatory ventilation in adults: results from a roundtable discussion. *Critical Care Medicine*, **35**(7), 1649–54.
18. Young D, Lamb SE, Shah S, et al. (2013). High-frequency oscillation for acute respiratory distress syndrome. *New England Journal of Medicine*, **368**(9), 806–13.
19. Ferguson ND, Cook DJ, Guyatt GH, et al. (2013). High-frequency oscillation in early acute respiratory distress syndrome. *New England Journal of Medicine*, **368**(9), 795–805.
20. Guervilly C, Forel J-M, Hraiech S, et al. (2012). Right ventricular function during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. *Critical Care Medicine*, **40**(5), 1539–45.

CHAPTER 99

Prone positioning in the ICU

Paolo Taccone and Davide Chiumello

Key points

- Prone positioning optimizes lung recruitment and ventilation–perfusion matching, resulting in an improvement of gas exchange in 70–80% of acute respiratory distress syndrome (ARDS) patients. For this effect, patients with profound life-threatening hypoxaemia may be treated with prone positioning as a rescue manoeuvre.
- Independently from gas exchange, prone positioning may exert a protective role against ventilator-induced lung injury, reducing the unphysiological stress and strain to which the lung parenchyma is exposed during mechanical ventilation.
- The current clinical evidences support the use of prone position in the most severe form of ARDS (e.g. PaO_2/FiO_2 < 150 mmHg, need of high plateau pressure and high positive end-expiratory pressure (PEEP) level, diffuse pulmonary infiltrates), while it should be avoided in less severe patients for its potential adverse effects.
- Optimal dose of prone positioning is still undetermined. Based on the physiological rationale, we currently suggest to apply prone positioning as long as possible (e.g. >18–20 hours daily), until the resolution of the acute phase of ARDS.
- While prone positioning does not required any special equipment to be performed, it may significantly increase the risks of potentially life-threatening complications. Therefore, we recommend that prone positioning should be performed with great care by experienced personnel.

Introduction

Prone positioning (also known as 'proning', 'prone manoeuvre', or 'prone ventilation') refers to mechanical ventilation with patients positioned in prone position in contrast of standard supine (flat or semi-recumbent) position. The use of the prone positioning was proposed over 30 years ago as a means to improve arterial oxygenation in patients with acute respiratory distress syndrome (ARDS) [1]. Since then, extensive physiological research has been conducted to explore the possible mechanisms underlying the observed improvement in gas exchange, which involve changes in the distribution of both ventilation and pulmonary blood flow. Furthermore, it has been shown that, independently of gas exchange, prone positioning may reduce the harm of mechanical ventilation [2,3], which is known to adversely impact patient survival. In this chapter, we will summarize the physiological effect of prone positioning, as well as the clinical evidences supporting its use to reduce mortality in patients with ARDS [4,5].

Physiological effects of prone positioning

The effects of prone positioning on gas exchange results from a redistribution of lung ventilation and pulmonary perfusion. Indeed, in any body position, regional lung ventilation and pulmonary blood flow are influenced by the gravitational field of the earth. When we apply prone positioning to a patients, we reverse the vector of this gravitational force, with major consequences on inflation and perfusion distribution. As a secondary and less relevant effect, prone positioning also promotes postural drainage of secretions from the tracheobronchial tree, possibly ameliorating regional lung ventilation.

Distribution of ventilation

The distribution of alveolar lung inflation is different in prone and supine position [6]. In a normal subject lying flat in supine position, the pleural pressure, that is the determinant of alveolar dimension, results greater in the dorsal posterior region that in the non-dependent sternal region, mainly because of the hydrostatic pressure imposed by the weight of the lung tissue. Therefore, the non-dependent alveoli, located near the sternum, are more inflated than the dependent one in the dorsal region (see Fig. 99.1). In patients with ARDS, this inflation heterogeneity is exaggerated by the dramatic increase in lung weight due to the widespread inflammatory lung oedema. In this condition, the increase in pleural pressure gradient leads to an over inflation of the non-dependent region and a compression atelectasis of the dependent region. When the patient is turned in prone position, the inflation gradient is reversed, and the regional alveolar size is greater in dorsal regions and lower in ventral regions. Once again, the dependent lung regions (ventral) are collapsed [7]. Of note, in prone position the pleural pressure gradient is significantly decreased compared with supine position, resulting in a more homogeneous distribution of alveolar inflation (see Fig. 99.1). Accordingly, a reduced amount of collapsed lung parenchyma (i.e. more lung recruitment) and decreased alveolar over inflation is observed with prone positioning.

Another phenomenon has been recently emphasized to contribute to the redistribution of lung inflation during prone positioning, which is related to the position of the heart in the thorax. Indeed, while in supine position the cardiac mass has a direct compressive effect on the posterior regions of the lung (particularly the left lower lobe), in prone position the lungs are relieved from the heart weight [87], as this lies directly on the sternum. This effect may be particularly pronounced in patient with cardiomegaly.

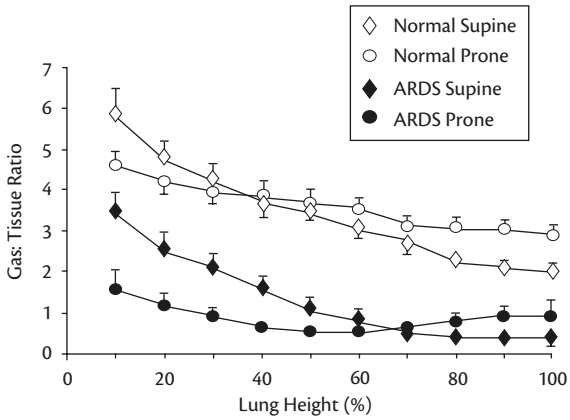


Fig. 99.1 Lung inflation (expressed as gas/tissue ratio measured by CT scan) for each lung section along the ventrodorsal axis (on the *x*-axis, level 0 represents the most non-dependent lung section, while *level 10* represents the most dependent one). Data have been collected on healthy subjects (open symbols) and ARDS patients (closed symbols). The degree of alveolar inflation reflected by the gas/tissue ratio is that observed in the supine (square symbols) and prone position (dot symbols), respectively.

Reproduced from Gattinoni L et al., 'Prone positioning in acute respiratory distress syndrome'. In: Tobin MJ, *Principles and Practice of Mechanical Ventilation*, © 2012 McGraw-Hill Education.

Distribution of perfusion

In normal subject, pulmonary blood flow progressively increases from the non-dependent to the dependent region of the lung, following gravitational distribution. In ARDS patients, factors other than gravity influence regional distribution of lung perfusion force, as hypoxic pulmonary vasoconstriction and extrinsic compression of the vessel by mechanical ventilation. Experimental studies have confirmed that in supine position ARDS leads to a high shunt fraction in the dorsal region (i.e. high perfusion and poor aeration). Interestingly, when the prone position is applied, perfusion distribution is less gravity-dependent than in the supine position, and a substantial fraction of pulmonary perfusion is maintained in the dorsal region. As this phenomenon is coupled to a recruitment of the dorsal region with prone position, the reopened alveoli continues to receive the majority of blood flow, resulting in a shunt reduction and a better matched ventilation/perfusion ratio [9].

Prone positioning and clinical outcome

Effect on oxygenation

Based on the results of many observational studies, as well as randomized controlled trials (RCTs), there is wide agreement that prone positioning increases arterial oxygen tension in most of the patients with ARDS. However, the degree of the response was variable, ranging from great improvement, to no change, and even a significant deterioration in a small fraction of patients. Among patients whose oxygenation improves, this improvement is usually progressive while in the prone position, showing a time-dependent effect. Furthermore, when returning to a supine position after a period in a prone position, some patients maintain an oxygenation benefit for hours, while other rapidly return to their basal supine oxygenation. Finally, the effect of prone positioning may change over the course of ARDS, usually decreasing in its benefit when lung pathology progresses from the oedematous phase to the fibrotic phase (i.e. after 7–10 days).

In conclusion, the short- and long-term oxygenation response while in the prone position are highly variable, probably because the individual response is strictly dependent on patients' underlying pathophysiological status. Notably, while several clinical variables have been investigated as possible predictors of this response, none of them have shown sufficient accuracy to be considered reliable at the bedside.

Effect on mortality

In the past, it has been suggested that prone positioning improves oxygenation, but in recent years there has been a progressive recognition that the prone position may decrease the stress and strain to which the lung parenchyma is exposed during mechanical ventilation [2,3]. Therefore, the possible survival advantage of prone positioning should be independent of oxygenation changes, which were constantly demonstrated to be uncorrelated with outcome, but it may be related to a decrease in the danger associated with mechanical ventilation (ventilator induced lung injury).

To date, five high-quality RCTs have addressed whether prone positioning might decrease the mortality of adult patients with ARDS:

- **The Prone-Supine study group** [10], enrolled 304 patients presenting with acute lung injury (ALI) or ARDS. This study investigates prone positioning applied for a mean of 7 hours daily, for a maximal period of 10 days (mean 4.7 days of treatment). Other relevant co-treatment, as mechanical ventilation settings were not protocolized. Although no effect on 6-month mortality was found in the overall study population, a post hoc analysis showed a trend towards reduced short-term mortality in the subgroup of patients which presented the most severe form of ARDS.
- **The Guerin et al. study** [11]: consisted of a larger population of 802 patients with hypoxaemic acute respiratory failure from various aetiologies (only about half of them fulfilled the ALI/ARDS criteria). The treatment protocol was 9 hours of prone positioning per day, applied until clinical criteria of improvement were matched (mean 4.1 days of treatment). No effect on primary outcome was found, and prone positioning was associated with a significant increase in adverse events.
- **The Mancebo et al. study** [12]: randomized 136 ARDS with diffuse radiologic pulmonary infiltrates. This study investigates a prolonged prone positioning strategy (mean 17 hours daily for 10.1 days of treatment), and included a lung protective mechanical ventilation protocol in both study arms. The findings of the study were negative, but there was a not statistically significant trend in intensive care unit (ICU) mortality reduction of about 15% in the treatment arm.
- **The Prone-Supine study II** [13]: enrolled 342 ARDS patients, using a prolonged prone positioning protocol (mean 18 hours daily for 8.3 days of treatment) and a protocolized protective mechanical ventilation strategy. Based on the result of the previous studies, patients were stratified at enrolment according to the severity of their hypoxaemia (severe hypoxaemia defined as PaO_2/FiO_2 ratio below 100). No significant effect on mortality was found in the overall population, while a trend in 6-month mortality reduction of about 10% was demonstrated in the most severely hypoxaemic patients.
- **The PROSEVA study** [14]: randomized 466 severe ARDS patients with a PaO_2/FiO_2 ratio lower than 150 with a positive end expiratory

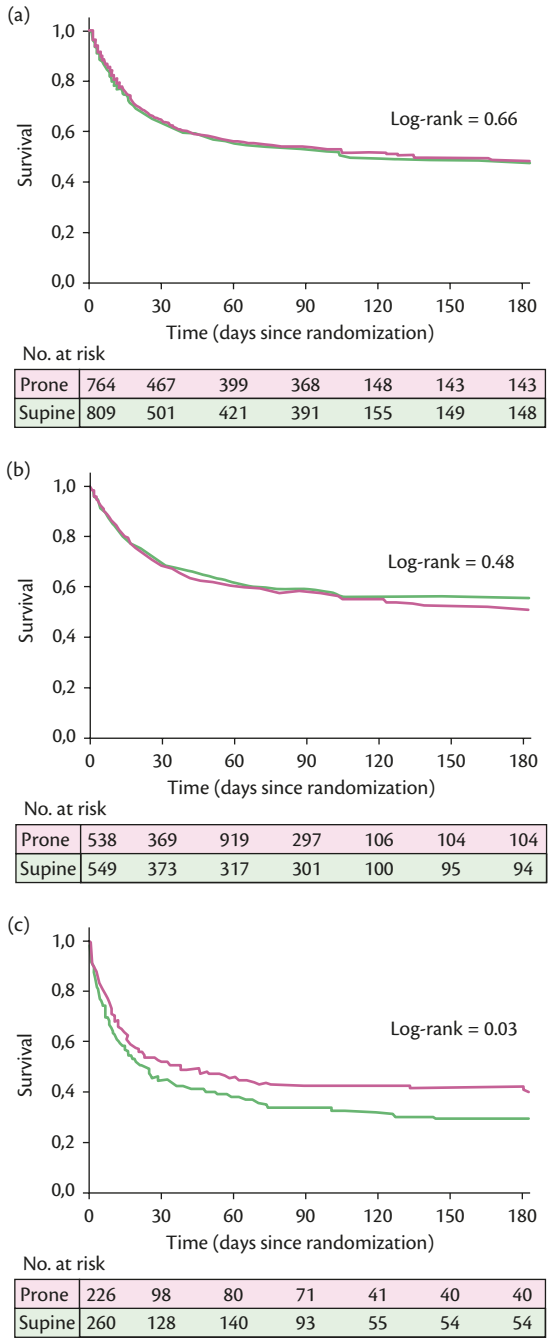


Fig. 99.2 Kaplan–Meier estimates of survival rates of the prone (solid line) and supine (dashed line) patients from a patient-level meta-analysis of the four largest RCTs investigating the effects of prone positioning on mortality [10–13]: (a) entire ARF population, (b) moderately hypoxaemic patients (PaO_2/FiO_2 100–200 mmHg at baseline, and (c) severely hypoxaemic patients (i.e. PaO_2/FiO_2 < 100 mmHg.
Reprinted by permission of Edizioni Minerva Medica from *Minerva Anestesiol* 2010; **76**, 448–54.

pressure (PEEP) higher than 5 cmH_2O to prone positioning for at least 16 hours or to supine position. The 28-day mortality rate was 16% in the Prone group compared with 32.8% in the supine group ($P < 0.001$). Patients were ventilated in the prone position for 73% of the 22.334 patient hours from the enrolment to the last session.

Notably, all these trials have different potential methodological bias, such as inadequate patient selection, underpowered population, possible suboptimal treatment strategy, and lack of standardization for relevant co-treatment (e.g. protective low tidal volume ventilation). However, the last trial published finally showed a definitive evidence supporting that prone positioning has a beneficial effect on survival in the most severely ill patients. Accordingly, two patients-level meta-analyses with different inclusion criteria were conducted in collaboration with trialists of the first four trials [4,5], aiming to study the interaction between the severity of hypoxaemia and the response to prone positioning. Both studies confirmed a survival advantage of prone positioning of about 10% in the most severely hypoxemic patients, with no significant heterogeneity among trials [5]. On the contrary, no effect was observed in patients with less severe hypoxaemia, discouraging the routine use of prone positioning in this subgroup of patients (see Fig. 99.2).

The hypothesis that prone positioning may be more effective in the most severe patients has a strong pathophysiological rationale. Indeed, these patients have been extensively demonstrated to present greater amount of pulmonary oedema, more widespread alveolar collapse and greater lung recruitability [18], and prone positioning exert its lung-protective effect mainly recruiting the collapsed regions of the lung.

Other outcomes

Prone positioning has been hypothesized to reduce the incidence of ventilator-associated pneumonia through improved reduction of secretion. Although some encouraging positive results, most trials evaluating VAP as an outcome were flawed by major limitations, and this finding should be taken cautiously [5].

Application of prone positioning

Patients selection

We believe that available clinical and preclinical data support the use of prone positioning in the management of patients with the most severe form of ARDS. In contrast, given the potentially harmful effects, prone positioning should not be routinely used in patients with less severe ARDS [4,5].

A practical question facing the physician at the bedside is which level of hypoxaemia should be used to identify ARDS patients that may possible benefit from prone positioning. Some RCT investigators proposed a threshold of PaO_2/FiO_2 ratio below 100 mmHg (with a PEEP higher that 5 cmH_2O) [10,13], others 150 mmHg [14]. However, although the PaO_2/FiO_2 ratio is correlated to the severity of the disease process, it is also highly dependent to other confounding factors (e.g. ventilatory strategy, PEEP response, haemodynamic status, fluid balance, etc.), and its reliability and reproducibility as a single indication criterion for prone treatment is questionable. Therefore, we currently suggest that clinicians should evaluate ARDS severity using a PaO_2/FiO_2 threshold (e.g. below 150) preferentially in conjunction with other markers of severity, as the direct/indirect evidence of high recruitability of the lungs (e.g. diffuse infiltrates at CXR or CT imaging), a severe impairment of respiratory mechanics (e.g. high plateau pressure), and a rapidly progressive deterioration of gas exchange unresponsive to conventional ventilation. Furthermore, a lack of oxygenation improvement should not be used as an absolute criterion to discontinue prone positioning. Indeed, as oxygenation response may depends to phenomenon unrelated to lung recruitment (as pulmonary blood flow

diversion) [19], it is not a reliable marker of lung protection during prone positioning.

There are very few absolute contraindications to prone positioning, as spinal instability and unmonitored increased intracranial pressure. Other conditions should be identify as relative contraindication, as open abdominal wounds, multiple trauma with unstabilized fracture, pregnancy, severe haemodynamic instability, and high dependency on airway and vascular access (e.g. extracorporeal membrane oxygenation support).

Positioning and timing of treatment

Prone positioning does not required any special equipment, and it can be safely performed manually by 3–5 specifically-trained health care personnel. Recently, some commercially-available beds have been specifically developed to perform the turning manoeuvre and/or maintain the positioning, but the reduction of workload and the possible advantage of procedure standardization must be weighed against the costs of these rather pricy devices.

In our clinical practice we start prone positioning as soon as the patients is diagnosed as having a severe form of ARDS. It is usual to wait a few hours to allow initial stabilization and perform any diagnostic procedures needed, but if the patient presents with an urgent life-threatening hypoxaemia, which is unresponsive to a highly-supporting mechanical ventilation (e.g. PaO_2 < 55 mmHg with PEEP > 20 cmH_2O and FIO_2 100%), prone positioning should be immediately assumed as a rescue manoeuvre.

The optimal daily duration of prone positioning is still unknown [5]. The final RCTs [12,13] applied a longer time of prone positioning compared with early trials [10,11] (i.e. 17–18 versus 7–9 hours/day), and the PROSEVA study, which used a prolonged prone position clearly showed a significant reduction in mortality [14].

Furthermore, the optimal timing and weaning criteria from prone positioning remain undetermined. Some trials suggested a shorter 'acute phase' protocol [10,11,14], while others prolonged the application of the treatment until the final phases of weaning from mechanical ventilation [12,13]. In the absence of certain information, based on the physiological rationale and clinical data available, currently suggested that a daily prone position be applied for as long as possible (e.g. >18–20 hours daily), until the resolution of the acute phase of ARDS (i.e. <7 days).

Finally, ventilation of patients in the prone positioning according to a lung-protective ventilation strategy is strongly recommended. Moreover, the use of prone positioning has been proposed in association to other non-conventional treatments [14,20] (e.g. inhaled nitric oxide, high-frequency oscillatory ventilation, extracorporeal membrane oxygenation), but the benefit of these combinations remained unpredictable and their use needs to be limited to selected patients in highly specialized centres.

Adverse events

Several side effects have been associated to the use of prone positioning, with some between-report differences in actual occurrence and incidence [10–14]. Some complications of prone positioning are reported as uncommon, but they may be dramatic and potentially life-threatening, especially in severely unstable patients (e.g. inadvertent extubation, displacement of thoracotomy tubes or extracorporeal membrane oxygenation access, major arrhythmias). Other less severe and more common adverse events include the displacement of vascular accesses, need for increased sedation or muscle relaxants, airway obstruction, transient desaturation, hypotension or increased use of vasopressor, and vomiting. Furthermore, dependent facial oedema, pressure ulcers, and some rare cases of nerve compression or retinal damage may occur, and they must be prevented or minimized by careful positioning and the use of adequate soft-padding.

Of note, one of the RCT published a demonstrated a significant increase in the rate of adverse events associated to a prolonged strategy of prone positioning [13]. However, we believe these increased risks may be partially explained by the increased frequency of turning manoeuvres required by the study protocol (i.e., every 4 hours). Therefore, we currently suggest reducing the number of turning as low as possible.

Conclusion

In conclusion, in order to minimize the potential risks, we suggest that prone positioning should be applied only by specifically-trained personnel with adequate experience in its use. A high level of attention of ICU staff is mandatory, especially during the turning manoeuvre, with maximal effort to prevent, or promptly recognize and correct, any possible major complication.

References

1. Piehl MA and Brown RS. (1976). Use of extreme position changes in acute respiratory failure. *Critical Care Medicine*, **4**(1), 13–14.
2. Valenza F, Guglielmi M, Maffioletti M, et al. (2005). Prone position delays the progression of ventilator-induced lung injury in rats: does lung strain distribution play a role? *Critical Care Medicine*, **33**(2), 361–7.
3. Broccard A, Shapiro RS, Schmitz LL, Adams AB, Nahum A, and Marini JJ. (2000). Prone positioning attenuates and redistributes ventilator-induced lung injury in dogs. *Critical Care Medicine*, **28**(2), 295–303.
4. Gattinoni L, Carlesso E, Taccone P, Polli F, Guerin C, and Mancebo J. (2010). Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis. *Minerva Anestesiologica*, **76**(6), 448–54.
5. Sud S, Friedrich JO, Taccone P, et al. (2010). Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive Care Medicine*, **36**(4), 585–99.
6. Gattinoni L, Taccone P, Valenza F, Pelosi P, and Mascheroni D. (2012). Prone positioning in acute respiratory distress syndrome. In: Tobin MJ (ed.) *Principles and Practice of Mechanical Ventilation*, 699–726. New York, NY: McGraw-Hill.
7. Gattinoni L, Pelosi P, Vitale G, Pesenti A, D'Andrea L, and Mascheroni D. (1991). Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. *Anesthesiology*, **74**(1), 15–23.
8. Albert RK and Hubmayr RD. (2000). The prone position eliminates compression of the lungs by the heart. *American Journal of Respiratory and Critical Care Medicine*, **161**(5), 1660–5.
9. Richter T, Bellani G, Scott Harris R, et al. (2005). Effect of prone position on regional shunt, aeration, and perfusion in experimental acute lung injury. *American Journal of Respiratory and Critical Care Medicine*, **172**(4), 480–7.
10. Gattinoni L, Tognoni G, Pesenti A, et al. (2001). Effect of prone positioning on the survival of patients with acute respiratory failure. *New England Journal of Medicine*, **345**(8), 568–73.
11. Guerin C, Gaillard S, Lemasson S, et al. (2004). Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. *Journal of the American Medical Association*, **292**(19), 2379–87.

12. Mancebo J, Fernandez R, Blanch L, et al. (2006). A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **173**(11), 1233–9.
13. Taccone P, Pesenti A, Latini R, et al. (2009). Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *Journal of the American Medical Association*, **302**(18), 1977–84.
14. Guerin C, Reignier J, Richard JC et al. (2013). Prone positioning in severe acute respiratory distress syndrome. *New England Journal of Medicine*, **368**, 2159–68.
15. Sud S, Sud M, Friedrich JO, and Adhikari NKJ. (2008). Effect of mechanical ventilation in the prone positioning on clinical outcomes in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *Canadian Medical Association Journal*, **178**(9), 1153–61.
16. Abroug F, Ouanes-Besbes L, Elatrous S, and Brochard L. (2008). The effect of prone positioning in acute respiratory distress syndrome or acute lung injury: a meta-analysis. Areas of uncertainty and recommendations for research. *Intensive Care Medicine*, **34**(6), 1002–11.
17. Alsaghir AH and Martin CM. (2008). Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. *Critical Care Medicine*, **36**(2), 603–9.
18. Gattinoni L, Caironi P, Cressoni M, et al. (2006). Lung recruitment in patients with the acute respiratory distress syndrome. *New England Journal of Medicine*, **354**(17), 1775–86.
19. Gattinoni L, Vagginelli F, Carlesso E, et al. (2003). Decrease in $PaCO_2$ with prone position is predictive of improved outcome in acute respiratory distress syndrome. *Critical Care Medicine*, **31**(12), 2727–33.
20. Pipeling MR and Fan E. (2010). Therapies for refractory hypoxemia in acute respiratory distress syndrome. *Journal of the American Medical Association*, **304**(22), 2521–7.

CHAPTER 100

Failure to ventilate in critical illness

Vito Fanelli and V. Marco Ranieri

Key points

- During assisted ventilation, patient and ventilator pumps share the work of breathing, avoiding both respiratory muscle atrophy and fatigue.
- Deterioration of patient/ventilator interplay causes asynchrony, which is associated with prolonged mechanical ventilation, and longer intensive care unit and hospital length of stay.
- Depending on the phase of the respiratory cycle, there are three types of asynchrony—asynchrony during the triggering phase; asynchrony during delivery of inspiratory flow; asynchrony during the cycling phase from inspiration to expiration.
- Bedside analysis of flow and airways pressure traces allows recognizing patient–ventilator asynchrony. Altered mental status, discomfort, activation of accessory inspiratory and expiratory muscles, tachycardia, and hypertension are all signs associated with patient ventilator asynchrony.
- Continuous adjustment of sedation, ventilator trigger, flow rate, and criteria of cycling from inspiration to expiration allow to minimize asynchronies.

Introduction

Mechanical ventilation is a life-saving therapy that is effective in reducing the work required to breathe and improves alveolar ventilation. Since its first description in 1952 during the polio epidemic, mechanical ventilation has become common practice for many physicians, and its technology has improved to provide better care for critically-ill patients [1].

In the most severe forms of acute respiratory failure, the use of deep sedation and neuromuscular blocking agents dictate the adoption of controlled mechanical ventilation. The medical practitioner sets ventilator parameters with the aim of reducing oxygen consumption, improving gas exchange and oxygen availability in the whole organism.

In less severe forms of respiratory failure or during the resolution phase of the disease that has imposed the use of mechanical ventilation, assisted controlled ventilation allows patients to contribute to work of breathing, thus avoiding deep sedation, muscle atrophy, and long-term dependency from the ventilator.

The most robust model that helps to understand the complex interaction between patient and ventilator during respiratory failure is the equation of motion that states [2]:

$$P_{mus} + P_{aw} = V'^{*}R = V_T^{*}E + PEEP_i \qquad \text{[eqn 1]}$$

where P_{mus} is the pressure developed by inspiratory muscles, P_{aw} is the pressure applied to respiratory system by the ventilator, V′ is the inspiratory flow, *R* is the airways resistance, V_T is the tidal volume, E is the elastance of the respiratory system and $PEEP_i$ is the intrinsic PEEP. Based on this equation, respiratory failure occurs when there is an imbalance between the inspiratory muscle generating force and the inspiratory load through its resistance, elastic, and $PEEP_i$ components. Therefore, mechanical ventilation restores the balance, helping respiratory muscle to overcome inspiratory load. In particular, during controlled mechanical ventilation, the contribution of inspiratory muscles (P_{mus}) is negligible, and the ventilator generates pressure (P_{aw}) to overcome the elastic (E) and resistive forces (*R*) of the respiratory system. This generates flow (V′) and changes in volumes (V_T). On the other hand, during assisted ventilation, both the inspiratory muscles and the ventilator pump work together to share the work required to overcome resistance and elastic loads, and the threshold pressure of $PEEP_i$. Any deterioration of this complex interplay causes patient–ventilator asynchrony, which exposes the patient to the risk of failure to ventilate, meaning no rest for their muscles and deterioration of gas exchange. The aim of this current chapter is to define the most common examples of asynchronies between patients and the ventilator, explaining physiopathological mechanisms and common solutions at the bedside. It is noteworthy that around 25% of intensive care unit (ICU) patients experiences asynchrony with the ventilator and those who are failing to ventilate because of asynchrony are exposed to many risks, including prolonged mechanical ventilation [3,4], longer ICU, and hospital length of stay [4].

Ideally, at the same moment when inspiratory muscles are contracting, patients should receive enough assistance from the ventilator to satisfy their ventilation needs and rest their muscles. This is until the switch from inspiration to expiration takes place. For this to happen, it is necessary that the ventilator promptly recognizes the inspiratory effort without delay, through an efficient trigger. Moreover, the machine should provide enough flow for the needs of the patient by matching the patient's neural inspiratory time with that of the ventilator. Toward this end, it is easily understood that

the perfect synchrony between patient and ventilator is a goal to achieve by the physician assessing the patient's ventilator demands [3]. Necessary interventions to improve patient–ventilator interaction can be made by a bedside analysis of flow and airway pressure traces that are displayed on the ventilator's screen [5].

There are three types of asynchrony:

- Asynchrony during the triggering phase.
- Asynchrony during delivery of inspiratory flow.
- Asynchrony during the cycling phase from inspiration to expiration.

This classification takes into account the phase of the respiratory cycle in which the asynchrony occurs [5].

Asynchrony between the patient's ventilatory drive and ventilator's trigger

Asynchrony during the triggering phase occurs when there is a discrepancy between the patient's ventilatory drive and the ventilator's trigger activation (Table 100.1). Inspiratory effort required to activate the trigger is an important part of the inspiratory effort [6]. Newer ventilators are equipped with pressure triggers that are as efficient as the flow triggers in terms of the time that elapses between effort and opening of the inspiratory valve. To date, due to the sensitivity of the trigger systems on newer ventilators, there is a greater risk of AutoTrigger than in their low-sensitivity counterparts. In fact, simple cardiac oscillations, movement of the condensate within the systems of the tubes or air leaks within the system, can activate the trigger [7]. The risk is that breaths, which are delivered by the ventilator without inspiratory effort, may lead to dynamic hyperinflation of the respiratory system, especially in heavily-sedated patients. Consequently, this removes every positive effect of assisted ventilation in terms of respiratory muscle activity. AutoTrigger may be recognized as a breath delivered by the ventilator that is not preceded by a drop in airway pressure as a consequence of inspiratory effort. In this case, it is important to verify the sensitivity of the trigger itself and adjust the level of sedation, such that the patient is not too deep [8].

Ideally, the patient's inspiratory effort should coincide with the 'breath' delivered by the ventilator. The algorithms of the most recent ventilators are based on indirect measurements of the patient's inspiratory time, such as flow or airway pressure signals. In fact, assuming the electrical activity of the diaphragm as the most useful measure to determine the beginning of the patient's neural inspiratory time, several studies have shown that the inspiratory time identified by the activity of the diaphragm differs significantly from that identified by the analysis of flow, oesophageal pressure and trans-diaphragmatic pressure [9]. The direct consequence of this discrepancy is that patient–ventilator asynchronies may be generated and they are essentially of two types–trigger delay and ineffective triggering (Table 100.1). Trigger delay is defined as a delay between the patient's inspiratory time (or the so-called neural trigger) and the breath delivered by the ventilator. The trigger delay can be caused mainly by a depressed respiratory drive [10,11] or by an increase in the elastic load caused by high levels of intrinsic PEEP ($PEEP_i$) [9,12]. In five ICU patients, Parthasarathy showed a significant delay between the beginning of inspiratory effort of the patient, measured by the electrical activity of the crural diaphragm, and the beginning of inspiratory flow [9]. Moreover, in this small cohort of patients, a correlation between the trigger delay and the level of $PEEP_i$ was noted. As a consequence, $PEEP_i$ represents a threshold that must be overcome before inspiratory flow could be delivered. It is important to note that in COPD patients with high levels of $PEEP_i$, the increase of the inspiratory effort required to match the value of $PEEP_i$ may have negative haemodynamic consequences. For example, an important inspiratory effort equal to an oesophageal pressure of –15 cmH_2O, in the presence of a value of $PEEP_i$ equal to 20 cmH_2O, leads to a significant increase in cardiac venous return and displacement of the interventricular septum with an altered diastolic filling of left ventricle [13]. The application of an external PEEP value, equal to about 80% of the value of $PEEP_i$, reduces inspiratory effort and improves haemodynamics [13].

Finally, an excessive elastic load may generate the second type of asynchrony—ineffective triggering. Ineffective triggering is defined as a reduction in oesophageal pressure of more than 1 cmH_2O that is not able to open the inspiratory valve, or has not achieved an increase of inspiratory flow >100 mL/sec [10]. At the bedside, ineffective triggering has been shown to represent nearly 90% of patient–ventilator asynchrony events [4] and it can be identified through the analysis of flow traces displayed on the mechanical ventilator. The start of this trigger is indicated by the point at which the expiratory flow decreases suddenly during expiration, altering its normal morphology and reaching the zero line. The time elapsed between this point and the point at which the airway pressure begins to rise is the 'triggering delay'. If a breath delivered by the mechanical ventilator does not follow this abrupt reduction in expiratory flow, ineffective triggering occurs (Table 100.1). Ineffective triggering is caused by high levels of ventilator assistance in either pressure-support or assisted-controlled ventilation [10]. It has been demonstrated that the amount of ineffective triggering is proportional to the level of assistance by the ventilator [10]; in fact, increasing the level of assistance reduces the work of breathing and the degree of dyspnoea, but also increases the number of ineffective triggering. It is important to note how breaths before ineffective triggering are characterized by larger tidal volumes, shorter expiratory time, and higher values of $PEEP_i$ [10,14]. Consequently, the increase in the elastic load due to the $PEEP_i$ threshold may be an important risk factor for ineffective triggering [10,12,14]. Of note, ineffective triggering has been associated with poor outcome, highlighting the need to recognize asynchrony and promptly correct it. In a cohort of 60 ICU patients under mechanical ventilation within 24 hours, those who showed ineffective triggering breaths were more that 10% of total breaths in 10 minutes of observation had poorer outcomes as demonstrated by longer duration of mechanical ventilation, fewer ventilator-free days and a lower likelihood of home discharge [4].

Many attempts have been made to reduce the time delay between a patient's inspiratory time and flow delivered by the ventilator. In this respect, synchrony during the triggering phase has been improved significantly with the neutrally-adjusted ventilatory assist (NAVA) ventilation mode [15]. In fact, with this method of assisted ventilation, the signal recognized by the ventilator to deliver the inspiratory flow is very close to the patient neural time and it uses neural electromyography activity of the diaphragm [15]. In this case, therefore, the trigger will not consist of changes in pressure or flow signals that are greatly influenced by the extent of respiratory elastic load. During NAVA, the level of assistance is proportional to every millivolt of electrical activity of the diaphragm, and the

Table 100.1 Different types of patient–ventilator asynchrony, in relation to the phase of the respiratory cycle in which are realized possible causes and remedies to implement

Type of asynchrony	Phase of respiratory cycle	Aetiology	Diagnosis	Solution
Asynchrony during triggering phase: ◆ Autotrigger. ◆ Trigger delay. ◆ Ineffective triggering.	Inspiration	**Autotrigger:** High trigger sensitivity; cardiac oscillations; movement of condense into tubing system; air leaks. **Trigger delay:** Depressed respiratory drive; over-assistance by the ventilator; increased elastic load ($PEEP_i$). **Ineffective triggering:** Depressed respiratory drive; over-assistance by the ventilator; Increased elastic load ($PEEP_i$).	**Autotrigger:** Lack of decrease in the airway pressure tracing at the beginning of inspiration. **Trigger delay:** Time delay between the abrupt decrease of expiratory flow (with distortion of morphology) until it reaches zero line and the beginning of airway pressure increase **Ineffective triggering:** Time delay between the abrupt decrease of expiratory flow (with distortion of morphology) until it reaches zero line and the beginning of airway pressure increase.	**Autotrigger:** Check trigger sensitivity; reduce the level of sedation; correct underlying respiratory alkalosis. **Trigger delay:** Reduce the level of sedation; reduce the level of assistance by the ventilator; minimize $PEEP_i$, essentially increasing expiratory time. **Ineffective triggering:** Reduce the level of sedation; reduce the level of assistance by the ventilator; minimize $PEEP_i$, essentially increasing expiratory time.
Asynchrony during the delivery of inspiratory flow: ◆ Rate of increase in airway pressure. ◆ Inspiratory flow.	Inspiration	Higher or lower rate of increase in airway pressure. Higher or lower inspiratory flow.	**Rate of increase in airway pressure:** Lower rate of increase in airway pressure is associated with increased work of breathing and patient's discomfort. **Inspiratory flow:** Higher inspiratory flow is associated with a decrease of inspiratory time and an increase of respiratory rate.	**Rate of increase in airway pressure:** Optimize the rate of increase in airway pressure to reduce dyspnoea and to avoid short inspiratory time, especially in patients with long time constant of respiratory system. **Inspiratory flow:** Titrate the inspiratory flow to patient's ventilation needs avoiding the miss concept that higher inspiratory flow reduces tachypnoea.
Asynchrony during the cycling phase from inspiration to expiration.	Expiration	Patient's neural inspiration lasts longer than ventilator inspiratory time. Patient's neural inspiration lasts less than ventilator inspiratory time.	Longer neural inspiration 'Double triggering', two breaths delivered by the ventilator for each inspiratory effort: the asynchronous breath lasts less the breath before. Shorter neural inspiration. Activation of expiratory muscle during ventilator inspiratory time. Consequently, it's possible to observe a sudden increase in the airway pressure at the end of inspiration.	Longer neural inspiration. Change the expiratory trigger in order to increase the duration of inspiration. This means the expiration begins after higher percentage of flow decay. Shorter neural inspiration. Change the expiratory trigger in order to decrease the duration of inspiration. This means the expiration begins after lower percentage of flow decay.

inspiration ends when the peak value of electrical activity of the diaphragm decreases to a fixed percentage. In this way, the level of assistance is proportional to the electrical activity of the diaphragm, leaving part of the work of breathing to the patient; it terminates when the diaphragm is relaxed and the electrical activity is decreased [16].

Asynchrony between the patient's ventilatory requirements and flow delivered by the ventilator

Good patient–ventilator synchrony is achieved even when the mean inspiratory flow is adjusted to the patient's ventilator requirements. In fact, flow asynchrony has been related to the increase in the speed of airway pressurization, the patient's ventilator drive, and the ventilator's performance [17]. Both airway pressurization rates that are too slow or too fast may produce discomfort for the patient [18] (Table 100.1). A slow rate of airway pressurization may not reduce the patient's dyspnoea and, indeed, increases the work of breathing, especially in the presence of impaired respiratory mechanics as in COPD or in patients with restrictive diseases [17]. In 11 COPD patients under assisted ventilation, the same inspiratory pressure was applied with a different rate of airway pressure increasing, ranging from 0.1 to 1.5 seconds. In this cohort of patients, Bonmarchand showed that progressively slower rates of airway pressure increasing were associated with an increased work of breathing, while respiratory rate, tidal volume, and $PEEP_i$ remained unchanged [17].

Asynchrony between inspiratory time of the patient and cycling of ventilator from inspiration to expiration

In ideal conditions, the patient's end of inspiration should coincide with the opening of the exhalation valve of the ventilator in order to allow passive expiration. In a controlled mode, cycling of the ventilator from inspiration to expiration is determined by the amount of inspiratory flow and the respiratory rate. On the contrary, in assisted ventilation mode, the algorithm of the ventilator must recognize the end of inspiration. In the pressure-support ventilation, cycling of the ventilator from inspiration to expiration occurs as a consequence of exponential decay of the inspiratory flow; in fact, the expiratory valve opens when the flow is reduced to a threshold value, usually expressed as 30% of peak flow. However, this criterion presents some issues [12], since the patient's inspiration may be shorter or longer than the time to deliver a given flow by the ventilator (Table 100.1). For example, if the flow delivered by the ventilator ends before the end of the patient's neural inspiration, an asynchrony may take place—the so-called 'double triggering' in which two breaths are delivered by the ventilator for a single inspiratory effort. This asynchrony is easily identifiable because the asynchronous breath is shorter than the preceding breath. In fact, the asynchronous breath begins at a higher volume of elastic equilibrium. It is possible to manipulate the expiratory trigger in modern ventilators by changing the decrease percentage of flow, which determines the cycling from inspiration to expiration. Therefore, manipulation of the expiratory trigger in order to increase the duration of inspiration avoids double triggering asynchrony (see Table 100.1).

In contrast, in patients with high values of time constants of the respiratory system, as in COPD patients, the mechanical ventilator may continue to deliver flow, even after the end of a patient's neural inspiration [19]. The time constant (τ) indicates the time necessary for the respiratory system to reach the volume of elastic equilibrium, and it is proportional to the value of airway resistance and compliance of the respiratory system according to the following formula:

$$\tau = R\,\mathrm{cmH_2O/L/sec} * C\,\mathrm{L/cmH_2O} \qquad \text{[eqn 2]}$$

where R indicates the value of airway resistance and C indicates the value of respiratory system compliance.

In COPD patients, the time constant of the respiratory system may be increased due to high values of expiratory resistance and compliance because of dynamic hyperinflation and/or expiratory flow limitation. Therefore, the longer time necessary for the flow to fall at threshold value determines that the inspiratory time of the ventilator to deliver flow is longer than the neural inspiration of the patient, causing asynchrony. In COPD patients with high constants equal to 0.54 and ventilated with a pressure support of 20 cmH_2O, a clear asynchrony has been shown consisting of activation of expiratory muscles during inspiratory flow delivered by the ventilator [20]. Consequently, this expiratory asynchrony is characterized by the sudden increase in airway pressure at the end of inspiration caused by activation of expiratory muscles. This asynchrony may be avoided by manipulating the expiratory trigger in order to reduce the ventilator's inspiratory time (see Table 100.1).

Conclusion

Optimization of patient–ventilator interactions can only be achieved through a continuous adjustment of ventilator trigger, flow rate, and criteria of cycling from inspiration to expiration. These fine adjustments imply an interpretation of ventilator waveforms as flow and airway pressure. Nevertheless, it is mandatory to observe patients at the bedside, looking for signs of asynchrony, such as altered mental status, discomfort, activation of accessory inspiratory and expiratory muscles, tachycardia, and hypertension.

References

1. Sassoon C. (2011). Triggering of the ventilator in patient–ventilator interactions. *Respiratory Care*, **56**(1), 39–51.
2. Purro A, Appendini L, De Gaetano A, Gudjonsdottir M, Donner CF, and Rossi A. (2000). Physiologic determinants of ventilator dependence in long-term mechanically ventilated patients. *American Journal of Respiratory and Critical Care Medicine* **161**(4 Pt 1), 1115–23.
3. Thille AW, Rodriguez P, Cabello B, Lellouche F, and Brochard L. (2006). Patient–ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Medicine*, **32**(10), 1515–22.
4. de Wit M, Miller KB, Green DA, Ostman HE, Gennings C, and Epstein SK. Ineffective triggering predicts increased duration of mechanical ventilation. *Critical Care Medicine*, **37**(10), 2740–5.
5. Georgopoulos D, Prinianakis G, and Kondili E. (2006). Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. *Intensive Care Medicine*, **32**(1), 34–47.
6. Sassoon CS, Giron AE, Ely EA, and Light RW. (1989). Inspiratory work of breathing on flow-by and demand-flow continuous positive airway pressure. *Critical Care Medicine*, **17**(11), 1108–14.
7. Imanaka H, Nishimura M, Takeuchi M, Kimball WR, Yahagi N, and Kumon K. (2000). Autotriggering caused by cardiogenic oscillation during flow-triggered mechanical ventilation. *Critical Care Medicine*, **28**(2), 402–7.
8. de Wit M, Pedram S, Best AM, and Epstein SK. (2009). Observational study of patient-ventilator asynchrony and relationship to sedation level. *Journal of Critical Care*, **24**(1), 74–80.
9. Parthasarathy S, Jubran A, and Tobin MJ. (2000). Assessment of neural inspiratory time in ventilator-supported patients. *American Journal of Respiratory and Critical Care Medicine*, **162**(2 Pt 1), 546–52.
10. Leung P, Jubran A, and Tobin MJ. (1997). Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. *American Journal of Respiratory and Critical Care Medicine*, **155**(6), 1940–8.
11. Tobert DG, Simon PM, Stroetz RW, and Hubmayr RD. (1997). The determinants of respiratory rate during mechanical ventilation. *American Journal of Respiratory and Critical Care Medicine*, **155**(2), 485–92.
12. Ranieri VM, Giuliani R, Mascia, et al. (1996). Patient–ventilator interaction during acute hypercapnia: pressure-support vs. proportional-assist ventilation. *Journal of Applied Physiology*, **81**(1), 426–36.
13. Ranieri VM, Dambrosio M, and Brienza N. (1996). Intrinsic PEEP and cardiopulmonary interaction in patients with COPD and acute ventilatory failure. *European Respiratory Journal*, **9**(6), 1283–92.
14. Ranieri VM, Grasso S, Fiore T, and Giuliani R. (1996). Auto-positive end-expiratory pressure and dynamic hyperinflation. *Clinics in Chest Medicine*, **17**(3), 379–94.
15. Sinderby C, Navalesi P, Beck J, et al. (1999). Neural control of mechanical ventilation in respiratory failure. *Nature Medicine*, **5**(12), 1433–6.

16. Colombo D, et al. (2008). Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. *Intensive Care Medicine*, **34**(11), 2010–18.
17. Bonmarchand G, Chevron V, Chopin C, et al. (1996). Increased initial flow rate reduces inspiratory work of breathing during pressure support ventilation in patients with exacerbation of chronic obstructive pulmonary disease. *Intensive Care Medicine*, **22**(11), 1147–54.
18. Chiumello, D., et al. (2001). The effects of pressurization rate on breathing pattern, work of breathing, gas exchange and patient comfort in pressure support ventilation. *European Respiratory Journal*, **18**(1), 107–14.
19. Racca F, Squadrone V, and Ranieri VM. (2005). Patient-ventilator interaction during the triggering phase. *Respiratory Care Clinics of North America*, **11**(2), 225–45.
20. Jubran A, Van de Graaff WB, and Tobin MJ. (1995). Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, **152**(1), 129–36.

CHAPTER 101

Ventilator trauma in the critically ill

Marcelo Amato and Andreas Wolfgang Reske

Key points

- Ventilator trauma refers to complications of mechanical ventilation that have an impact on morbidity and mortality.
- Two major forms of ventilator trauma may be distinguished, an acute form related to rupture of airspaces causing air leak syndrome and a subacute form causing protracted inflammatory responses.
- The most relevant consequence of airspace rupture is tension pneumothorax, which requires emergency intervention to prevent respiratory or haemodynamic collapse.
- Subacute ventilator trauma results from cyclic sublethal cell injury during mechanical ventilation and triggers intense, potentially self-perpetuating inflammatory responses.
- A marker-variable to monitor the risk of subacute ventilator trauma is driving-pressure. Because it is closely related to lung compliance and thus to the size of the lung compartment that remains functional, driving-pressure can aid in identifying disproportionate combinations of tidal volumes and lung compliance.

Introduction

Two major forms of ventilator trauma, occurring as complications of mechanical ventilation, can be conceptualized. The first form is the occurrence of extra-alveolar gas, also called gross barotrauma or air leak syndromes. Most air leak syndromes, such as pneumothorax or subcutaneous emphysema, cause acute problems. In contrast, the second form of ventilator trauma represents a subacute problem that can be easily obscured by complex critical illness. Except for extreme conditions found in experimental models, subacute ventilator trauma often causes protracted lung inflammation, fibrosis, and deterioration of lung function, contributing to systemic inflammation and organ failure. Clinical distinction of the two forms of ventilator trauma is not always straightforward. For example, gross barotrauma may cause venous gas embolism, leading to pulmonary hypertension, inflammation, and deterioration of gas exchange, ultimately mimicking the clinical picture of the subacute form. The recognition that subacute ventilator trauma may impair prognosis and increase mortality in mechanically-ventilated patients was one of most important discoveries of the last decades, and directly affected our daily practice of mechanical ventilation.

Gross barotrauma

Extra-alveolar gas usually escapes through ruptured alveoli or terminal airways at the junction with the vascular sheaths, due to large pressure gradients between intra-alveolar and interstitial spaces. Large pressure-gradients between these two regions are created not only during positive-pressure ventilation, but also during strong spontaneous efforts when very negative interstitial pressures are created. Gas accumulation in the pulmonary interstitium is called pulmonary interstitial emphysema. Gas may migrate through the interstitium, either peripherally, forming subpleural cysts, or centrally reaching the hilum and mediastinum. Pressurized mediastinal or subpleural gas collections can rupture and cause pneumothorax. Many pneumothoraces occurring during positive-pressure ventilation are under tension, necessitating prompt intervention to prevent respiratory or haemodynamic collapse. Gas can also spread along fascial planes to the neck, thorax, or abdomen, and cause subcutaneous emphysema or pneumoperitoneum.

The current incidence of gross barotrauma during a prolonged course of mechanical ventilation is below 10%, much lower than the figures reported before the advent of lung-protective mechanical ventilation. Although gross barotrauma is rarely the cause of death, its occurrence indicates severe underlying lung pathology, and is statistically correlated with increased morbidity and longer intensive care unit (ICU) stay. Common risk conditions for gross barotrauma are acute respiratory distress syndrome (ARDS), pneumonia, aspiration, and air trapping due to obstructive airway diseases. Such conditions are commonly associated with global airspace overstretching, as in asthma, or with localized overstretching, as in ARDS, where few lung regions remaining aerated (the '**baby lung**') must accommodate unevenly distributed tidal volumes [1].

Interestingly, gross barotrauma has not been necessarily associated with high positive end-expiratory pressure (PEEP), except for old studies using large tidal-volumes. In recent clinical studies limiting airway plateau-pressures below 35 cmH_2O, no clear association between high airway pressures and barotrauma could be detected.

Ventilator-induced lung injury

The subacute form of ventilator trauma, named 'ventilator-induced lung injury' (VILI) in experimental studies or, more conservatively (when the relative contributions of mechanical ventilation and

underlying disease are less clear), 'ventilator-associated lung injury' is histologically indistinguishable from the diffuse alveolar damage associated with ARDS. In lung samples from experimental animals and patients, light microscopy revealed alveolar haemorrhage, neutrophil infiltration, hyaline membranes, intra-alveolar and interstitial oedema, increased septum thickness, airspace collapse, and proliferation of macrophages and type II pneumocytes. Within terminal airways, alterations such as intraluminal inflammation, epithelial denudation, and necrosis have been described. Later, in a more chronic phase, alterations include bronchopulmonary dysplasia, cysts (dilated airways), airway remodelling, and fibroproliferation. Electron microscopy further reveals endothelial/epithelial abnormalities and tears, disruptions of the basement membrane, formation of intracapillary blebs, and an abnormal surfactant layer.

A key feature of mechanically-ventilated lungs, whether normal (during anaesthesia ventilation) or diseased, is the presence of non-aerated and unstable regions due to atelectasis, oedema or consolidation. Besides representing the disease itself, loss of aeration has been proposed as a central biophysical promoter of VILI. It was shown that, in the same lung, unstable lung regions were injured by VILI, whereas stable regions were not. The classical concept of mechanical interdependence suggests that pressures acting locally in non-uniformly expanded lungs at the boundaries between the atelectasis and aerated lung may be a multiple of the apparent transpulmonary pressure [2].

Synergistically with but also independent from non-uniform lung aeration, cyclic airspace overstretching, alveolar instability (due to surfactant dysfunction or negative transpulmonary pressures, for instance), and lung inflammation, have all been reported to precipitate or contribute to VILI. The sequelae of these mechanisms and the resulting intensity of VILI seem to depend on the intensity and duration of ventilation and are not restricted to mandatory ventilation. Among the physical mechanisms of VILI is the detachment of epithelial and endothelial cells from basement membranes and rupture of cellular and/or cytoskeletal structures. In addition to physical injury, a generalized pulmonary inflammatory response can cause and maintain VILI. Pulmonary inflammation involves neutrophil accumulation and activation in the pulmonary capillaries, the interstitial, and the alveolar spaces, and potentiates the destabilization of the alveolar–capillary barrier. The consequences are the development and dispersion of oedema, loss and inactivation of surfactant, loss of integrity of the alveolar compartment, and the transfer of bacteria and inflammatory mediators into the systemic circulation [3].

Accordingly, inflammatory cytokine concentrations (e.g. TNF-α, interleukin-(IL)-1β, IL-6, or IL-8) in broncho-alveolar lavage fluid or serum are associated with more injurious ventilation and with higher morbidity or mortality. Among the mechanisms by which cellular and subcellular pulmonary structures can sense injurious mechanical stimuli, and trigger and maintain local and systemic inflammatory or reparative responses are transformation of strain into (bio)chemical signals (mechanotransduction), stress failure of cytoskeletal structures (necrosis), and impairment of the alveolar barrier (decompartimentalization). These mechanisms can be activated also by unilateral injury or even without ultrastructural damage [3].

Several of the afore-mentioned pathomechanisms have the potential to become self-perpetuating. Proteinaceous oedema, for example, increases the lung weight and inactivates surfactant, which aggravates collapse of the dependent lung regions, worsens the non-uniformity of lung aeration and amplifies the negative effects of mechanical interdependence. The latter in turn alters vascular transmural pressures, promotes the development and distribution of lung oedema, and impairs ventilation-to-perfusion matching. Surfactant depletion and dysfunction, as another example, creates negative perivascular pressures, which together with altered alveolar–capillary barrier permeability, promote the development of oedema.

Seminal studies observed that adding PEEP to injurious mechanical ventilation attenuates VILI and may interrupt the viscious cycle described in the previous paragraph. The generalized readout of such experiments is that PEEP attenuates VILI when the end-inspiratory volume or plateau pressures are maintained unchanged [4,5]. To explain such beneficial effects, many facets of the application of PEEP need to be considered. First, adding PEEP to mechanical ventilation with unchanged plateau pressure reduces the amplitude of both pressure and cyclic (over)stretching. Applying PEEP to a non-uniformly expanded lung reduces the amount of non-aerated lung units, stabilizes unstable lung units, and reduces both non-uniformity and oedema.

Effects on remote organs

The clinical consequences of VILI are not limited to the lung. Injurious ventilation can have deleterious systemic effects. Accordingly, the most common cause of death in ARDS patients is not intractable hypoxaemia, but a systemic inflammatory response syndrome and multiple organ dysfunction. Interactions between local pulmonary, systemic and distal organ inflammation may help explaining the decreases in serum levels of inflammatory cytokines, associated with decreased morbidity and mortality observed in recent trials of lung-protective mechanical ventilation [6].

Barotrauma versus volutrauma

After the recognition of subacute ventilator trauma unrelated to air leaks, it was proposed to replace the old term *barotrauma* (i.e. pressure-induced trauma) by **volutrauma** (volume-induced trauma). The rationale for this new terminology came from two remarkable observations:

- Chest strapping, by significantly decreasing chest-wall compliance, minimized VILI despite the application of very high positive airway pressures.
- Negative pressure ventilation, by cyclic application of vacuum around the chest wall, could produce severe VILI—despite atmospheric airway pressure.

Tidal volumes generated in the first experiment were small, but very high in the second experiment. Thus, injury was not solely related to high airway pressures—it only occurred when high tidal volumes were concomitantly generated [4].

Although representing an improvement, the term **volutrauma** was later shown to be also imprecise. It became evident that high tidal volumes are not always injurious. Conversely, in lungs with gross collapse and low tidal-compliance, VILI can occur despite 'protective' tidal volumes (as low as 4 mL/kg). To better estimate injury risks, it was later proposed that tidal volumes should be individualized according to both the potential size of the whole lung (normalized by height or ideal body weight), but also according to

the size of the functional lung compartment (spared from disease) that accommodates the tidal volume. This reduced functional lung volume in ARDS patients has been termed the **baby lung** [1]. The lung areas within the **baby lung** that are spared from collapse, are particularly exposed to VILI because they are exposed to significantly increased mechanical work. Since shunt makes gas exchange less efficient, the spared zones have to achieve the whole ventilation task. Studies using positron emission tomography have shown that the most inflamed areas in injured, mechanically-ventilated lungs are the ones receiving the highest ventilation, and not the silent, non-aerated regions.

Stress, strain and cyclic lung stress

Trying to circumvent the main limitations of the terms **barotrauma** and **volutrauma**, the engineering terms **stress** and **strain** were recently proposed for defining risk-constellations for VILI.

Stress represents an evolution of **barotrauma**. Risk is now defined in proportion to transpulmonary pressures (airway minus pleural pressure) and it becomes possible to explain the attenuation of VILI by chest strapping. It is also possible to explain the pronounced VILI associated with negative pressure or vigorous spontaneous ventilation—strongly negative pleural pressures may generate high transpulmonary pressures even against atmospheric airway pressure.

Conversely, **strain** represents an evolution of **volutrauma** and risk is now defined in proportion to resting lung volume. **Strain** equals the ratio between end-inspiratory lung volume and functional residual capacity (when central airways are submitted to atmospheric pressure). Thus, it can be explained why even small tidal volumes can be injurious in patients with gross lung collapse—the resting lung volume (the denominator) decreases and **strain** becomes high.

One main limitation of the **stress/strain** approach is its physical reductionism: it assumes that **stress** on the structure can be estimated as a quasi-linear function of **strain**. In fact, a complex structure like the lung, composed of different cell types attached to a network of extracellular matrix, elastic and collagen fibres, reacts to physical deformation in a markedly non-linear manner. For instance, the response of pneumocytes to surface deformations depends on their repair capabilities. There is a clear threshold, beyond which further **strain** causes cell wounds and uncontrolled transmembrane ion traffic. The lung has a very large reserve of alveolar surface, which is folded during resting conditions. Therefore, the delicate lung surface will be stressed only when unfolding is no longer possible. Below this threshold, prolonged large variations in surface area (i.e. during a marathon race) are tolerated without significant injury. Assuming that this non-linearity is constitutive for lung function, the interchangeable use of **strain/stress** becomes troublesome. The assessment of **stress** requires oesophageal pressure measurement as a surrogate of pleural pressure, which is rarely reliable in supine patients with massive atelectasis. Proper **strain** calculation requires whole-lung computed tomography and many approximations for the calculus of recruitment and true 'surface deformation' (as opposed to surface unfolding). In conclusion, the actual **stress** will hardly be represented by in vivo **strain** measurements, especially when considering measurement errors at the bedside.

Another limitation of the **stress/strain** engineering perspective is the omission of consideration of the 'pace of deformation'—vital cells easily adapt to sustained deformations by the neoformation of cell membranes, but they rarely survive rapid, large changes of alveolar surface area. It has been shown that **strain** preconditioning helps cells to stand a subsequent large deformation [3]. Translated to a larger scale, increasing end-expiratory volumes by application of PEEP may have preconditioning effects protecting against injury by high inspiratory lung volumes (**strain**). This would be another explanation for protective effects of PEEP.

Bedside estimate of cyclic lung stress

Based on the principles exposed previously, absolute end-inspiratory thresholds should be de-emphasized for assessing the risk of VILI. Cyclic deformation-thresholds should be proposed instead. Variables indicating cyclic **stress** variations (pressure swings) applied to the lung tissue seem preferable to markers of area/volume deformation, since the latter are difficult to assess at the bedside. Transpulmonary pressures should be included in the consideration of ventilator settings: increased pleural pressures might counterbalance **stress**, while negative pleural pressures may amplify stress.

A marker-variable fulfilling most of the aforementioned characteristics is **driving-pressure** [7]. During controlled mechanical ventilation, **driving-pressure** is the difference between end-inspiratory and end-expiratory pressures, both measured during the brief pauses while flow is zero. It represents the total cyclic pressure gradient applied across the respiratory system for elastic expansion of lung plus chest wall. Thus, part of the total **driving-pressure** applied to the respiratory system is counteracted by chest wall elastance, which means that cyclic lung stress would be better represented by isolated measurements of transpulmonary pressure. Nevertheless, the simplification of using **driving-pressure** as a marker-variable is convenient because it renders estimation of pleural pressure unnecessary and it is also reasonable because lung elastance during acute diseases is typically 5–10 times higher than chest wall elastance [7]. Therefore, the majority (80–90%) of **driving-pressure** is indeed applied to the lung. Moreover, obesity and intra-abdominal hypertension usually cause positive offsets in pleural pressures, but rarely increase chest-wall elastance, which is relatively constant among patients.

Assuming that **driving-pressure** mirrors cyclic changes in transpulmonary pressure shows why this variable has the best predictive power for VILI in experimental and human studies, and outperforms simple measurements of plateau pressure or tidal volume [7]. Moreover, **driving-pressure** can be calculated as the ratio between tidal volume and compliance. Because the size of the **baby lung** is positively correlated to compliance, **driving-pressure** will indirectly account for the size of the **baby lung**—for a given tidal volume [1].

For application of **driving-pressure** as a surrogate of cyclic **stress**, a **driving-pressure** threshold would aid in limiting cyclic deformation and VILI. Obviously, no well-established threshold can yet be proposed. However, in all recent trials testing lung-protective ventilation strategies, reduction of **driving-pressure** (usually to below 15 cmH_2O) was associated with reduced morbidity and mortality [7]. This **driving-pressure** threshold is also supported by millions of patients who undergo uncomplicated anaesthesia ventilation, where **driving-pressure** is commonly below 15 cmH_2O.

The **driving-pressure** concept can also be applied in the presence of spontaneous breathing efforts when some reasonable assumptions are made. If the respiratory system compliance can be

measured during a preceding period of controlled ventilation, the tidal volume during subsequent assisted spontaneous efforts allows estimation of the total **driving-pressure** applied to the system by ventilator and inspiratory muscles. Using this approach, potentially injurious combinations of compliance and tidal volume can be identified. For instance, a tidal volume of 500 mL measured during low levels (e.g. 5 cmH_2O) of pressure support, together with a recent compliance measurement of 20 mL/cmH_2O, indicates that a very high total **driving-pressure** of 25 cmH_2O is applied, deserving the same concern as if it was observed during controlled ventilation.

Conclusion

Still today, acute and subacute ventilator trauma cause significant extra-morbidity and -mortality in mechanically-ventilated patients. The traditional concepts of barotrauma and volutrauma evolved to more sophisticated considerations about physical stress and strain applied to the delicate lung tissue. By representing integrated information about cyclic lung stress and specific responses of the lung tissue, **driving-pressure** can work as a marker-variable to predict the risks of VILI at the bedside.

References

1. Gattinoni L and Pesenti A. (2005). The concept of 'baby lung'. *Intensive Care Medicine*, **31**, 776–84.
2. Mead J, Takishima T, and Leith D. (1970). Stress distribution in lungs: a model of pulmonary elasticity. *Journal of Applied Physiology*, **28**, 596–608.
3. Plataki M and Hubmayr RD. (2010). The physical basis of ventilator-induced lung injury. *Expert Reviews in Respiratory Medicine*, **4**, 373–85.
4. Dreyfuss D, Soler P, Basset G, and Saumon G. (1988). High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *American Reviews of Respiratory Diseases*, **137**, 1159–64.
5. Webb HH and Tierney DF. (1974). Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *American Reviews of Respiratory Diseases*, **110**, 556–65.
6. Slutsky AS and Imai Y. (2003). Ventilator-induced lung injury, cytokines, PEEP, and mortality: implications for practice and for clinical trials. *Intensive Care Medicine*, **29**, 1218–21.
7. Amato MBP, Meade MO, Slutsky AS, et al. (2015). Driving pressure and survival in the acute respiratory distress syndrome. *New England Journal of Medicine*, **372**, 747–55.

PART 4.7

Weaning ventilatory support

CHAPTER 102

Assessment and technique of weaning

Martin J. Tobin

Key points

- Several studies suggest that most patients weaned successfully could have tolerated the weaning attempts had they been initiated a day or more earlier. Such data emphasize the need for the early use of screening tests.
- A screening test should have a high sensitivity. The ratio of respiratory frequency to tidal volume (f/V_T) has been evaluated in more than 25 studies—its average sensitivity is 0.89.
- Weaning involves undertaking three diagnostic tests in sequence, measurement of predictors, a weaning trial, and a trial of extubation.
- Of the techniques used for a weaning trial, IMV has been repeatedly shown to be inferior to the use of T-tube trials or pressure support.
- Six randomized trials have evaluated the usefulness of protocols in the management of weaning. Three revealed no benefit, two had major methodological problems, leaving only one supporting the use of protocols.

Introduction

Although mechanical ventilation is often lifesaving, the high risk of complications makes it imperative to disconnect patients from the ventilator at the earliest possible time [1]. This process is usually referred to as weaning, an unfortunate term because the word means a gradual reduction in a process [2]. Most patients move quite abruptly from a period of high-level support to unassisted breathing.

The timing of this process is critical. Several randomized controlled trials (RCTs) have revealed most patients who received mechanical ventilation for a week or longer were able to tolerate ventilator discontinuation on the first day that weaning-predictor tests were measured [3,4]. Many of these patients may have tolerated extubation a day or so earlier.

Many physicians view weaning predictors as something to perform at the point they think a patient might be able to tolerate disconnection from the ventilator. However, weaning predictors have the greatest potential for enhancing clinical management if performed at a time when physicians have considerable doubt as to whether or not a patient is ready for ventilator disconnection.

One of the main sources of weaning delay is the failure to **think** the patient just **might** come off the ventilator. Psychological research suggests much of this delay in ventilator weaning results from clinicians being overconfident in their intuition that a patient is not ready for a weaning trial [2]. Another source of error is the failure to pay close attention to pretest probability, i.e. failure to recognize the importance of Bayesian principles in clinical-decision making.

Assessment of patient readiness for weaning

By alerting physicians to a patient's readiness to tolerate unassisted ventilation—hours or days before he or she would otherwise order a spontaneous breathing trial—weaning-predictor tests circumvent the cognitive errors inherent in clinical decision-making [2].

Weaning-predictor tests function solely as a screening test. The goal of a screening test is not to miss anybody with the condition under consideration. It should have a low false-negative rate and a higher false-positive rate is acceptable [5]. An ideal screening test has a high sensitivity [2,5].

Weaning uses three diagnostic tests in sequence—measurement of predictors, a weaning trial, and a trial of extubation [2]. The sequential nature of the testing leads to particular problems in studies undertaken to investigate the reliability of a predictor test. One is spectrum bias where a new study population contains fewer (or more) sick patients than the population in which a diagnostic test was originally developed [5,6]. A second is test-referral bias, where the results of a test under evaluation are used to select patients for a reference-standard test, e.g. passing a weaning trial that leads to extubation [5,6]. A third factor is base-rate fallacy [6,7]. Consider a diagnostic test for a disease that has a false-positive rate of 5% and false-negative rate of 0%, and the incidence of the disorder (under consideration) is 1 per 1000 persons. A randomly selected person undergoes diagnostic testing. The result comes back positive. What is the chance this person has the disease? Most physicians answer 95%. The correct answer is 1.96% [7]. Physicians who answer 95% are failing to take into account the pretest probability of the disorder. Thus, they fall into the trap of base-rate fallacy.

Pretest probability is the estimate of the likelihood of a particular condition (weaning outcome) before a diagnostic test is undertaken [2]. Post-test probability (typically expressed as positive- or negative-predictive value) is the new likelihood after the test results are obtained. A good diagnostic test achieves a marked increase (or decrease) in the post-test probability (over pretest probability) (Fig. 102.1). For every test the change between

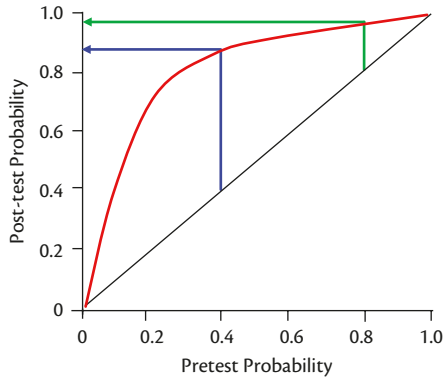


Fig. 102.1 Relationship between pre- and post-test probability for a good weaning-predictor test, sensitivity of 0.9 and specificity of 0.9, is characterized by the red curve. If pretest probability of weaning success is 0.40, Bayes' theorem dictates that a positive result on the weaning-predictor test will yield a post-test probability of 0.86. If pretest probability is 0.80, post-test probability will be 0.97. The increase between pretest and post-test probability in the second instance (21%, 0.17/.80) is only a fraction of that in the first instance (115%, 0.46/0.40) despite the sensitivity and specificity being identical. Thus, a high pretest probability markedly decreases the apparent reliability of a weaning-predictor test.

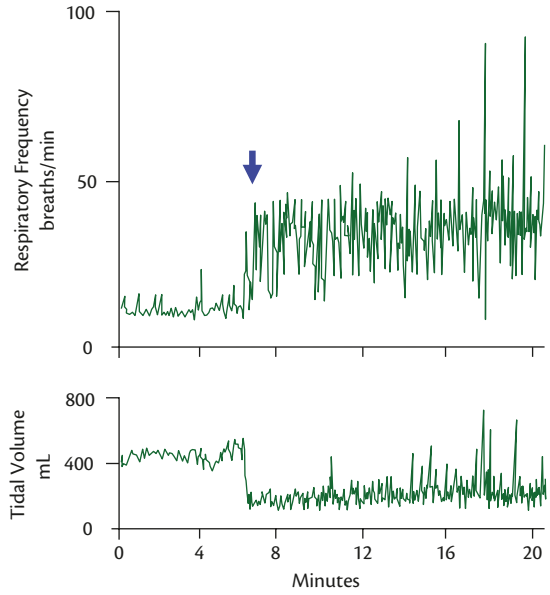


Fig. 102.2 A time-series, breath-by-breath plot of respiratory frequency and tidal volume in a patient who failed a weaning trial. The arrow indicates the point of resuming spontaneous breathing. Rapid, shallow breathing developed almost immediately after discontinuation of the ventilator.

pre- and post-test probability is determined by Bayes' theorem [6]. Three factors determine the magnitude of the pre- to post-test change—sensitivity, specificity, and pre-test probability. Sensitivity and specificity are commonly assumed to remain constant for a test. In truth, test-referral bias, a common occurrence in studies of weaning tests, leads to major changes in sensitivity and specificity [5]. Likewise, major changes in pre-test probability arise as a consequence of spectrum bias [5].

Frequency-to-tidal volume ratio

Weaning-failure involves several different physiological abnormalities [8]. The combination of a low tidal volume and elevated respiratory frequency is recognized as the physiological hallmark of weaning failure (Fig. 102.2) [9]. Patients who fail a weaning trial typically demonstrate rapid shallow breathing in the first few minutes after they are disconnected from the ventilator [10] quantified as the ratio of respiratory frequency to tidal volume (f/V^T) [11]. The higher the f/V_T, the more severe the rapid, shallow breathing and the greater the likelihood of unsuccessful weaning. An f/V_T of 100 best discriminates between successful and unsuccessful attempts at weaning [11]. The measurement should be obtained during spontaneous breathing because measurements of f/V_T in the presence of pressure support or CPAP will result in inaccurate predictions of weaning outcome [2].

The initial evaluation of f/V_T was reported in 1991 [11]. Since then, this test has been evaluated in more than 25 studies. Sensitivity ranges from 0.35 to 1 [6]. Specificity ranges from 0 to 0.89 [6]. At first glance, this wide scatter suggests that f/V_T is an unreliable predictor of weaning outcome. This was also the viewpoint of an Evidence-Based Medicine Task Force that undertook a meta-analysis of the studies [12,13]. The Task Force, however, failed to take account of test-referral bias and spectrum bias [2,5]. When data from the studies (included in the meta-analysis) were compared with the test characteristics in the original 1991 report, taking into account Bayesian pretest probability, the weighted Pearson correlation coefficient was 0.86 ($P < 0.0001$) for positive-predictive value and 0.82 ($P < 0.0001$) for negative-predictive value (Figs. 102.3 and 102.4) [6]. The average sensitivity in all of the studies on f/V_T was 0.89, and 85% of the studies reveal sensitivities higher than 0.90 [6]. This sensitivity compares well with commonly used diagnostic tests [2].

Diagnostic screening requires a simple test performed at a time when pre-test probability is low (less than 50%) [2]. A screening test should be cheap, easy to perform, pose minimal risk to patients, and provide a quick answer. A spontaneous breathing trial that involves 30–120 minutes of monitored performance is the antithesis of a screening test.

Techniques of weaning

When a screening test is positive, the clinician proceeds to a confirmatory test [5]. The goal of a positive result on a confirmatory test is to rule in a condition, i.e. the likelihood of a patient tolerating a trial of extubation is high. An ideal confirmatory test has a low rate of false-positive results (i.e. a high specificity) [5]. Unfortunately, the specificity of a spontaneous breathing trial is not known. Indeed, its specificity will never be known because its determination would require an unethical experiment—extubating all patients who fail a weaning trial and counting how many require reintubation [2].

T-tube trials

During a T-tube trial, the patient is completely disconnected from the ventilator and required to breathe spontaneously, while receiving an enriched supply of oxygen through a T-tube circuit. If the

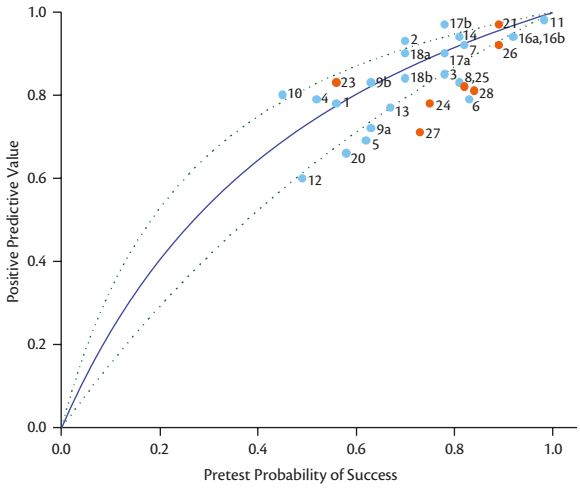


Fig. 102.3 Positive-predictive value (post-test probability of successful outcome) for f/V_T plotted against pretest probability of successful outcome. Studies included in EBM Task Force meta-analysis are indicated by blue symbols; additional studies are indicated by red symbols. The curve is based on the sensitivity and specificity originally reported by Yang and Tobin[2411] and Bayes' formula for 0.01-unit increments in pretest probability between 0.00 and 1.00.[226] The lines represent the upper and lower 95% confidence intervals for the predicted relationship of the positive predictive values against pretest probability. The observed positive-predictive value in each study (indicated a separate number) is plotted against the pretest probability of weaning success (prevalence of successful outcome).

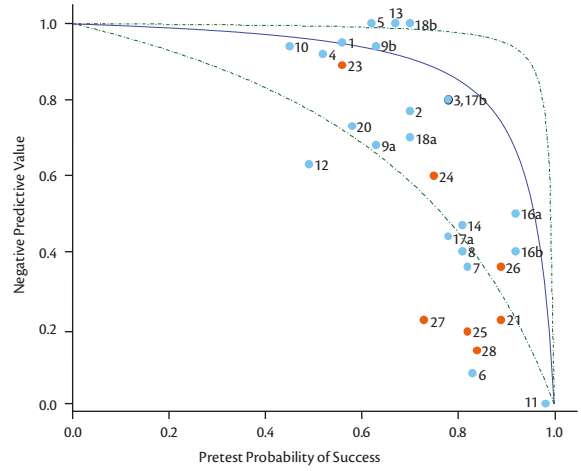


Fig. 102.4 Negative-predictive value (post-test probability of unsuccessful outcome) for f/V_T. The curve, its 95% confidence intervals, and placement of a study on the plot are described in the legend of Fig. 102.3. The observed negative-predictive value in each study (indicated a separate number) is plotted against the pretest probability of weaning success (prevalence of successful outcome).

trial is successful, the patient is extubated. If the trial is unsuccessful, the patient is typically given at least 24 hours of respiratory muscle rest with full ventilator support before another T-tube trial is performed [2].

Intermittent mandatory ventilation

Intermittent mandatory ventilation (IMV) was the most popular method of weaning for many years [14]. With IMV, the mandatory rate from the ventilator is reduced in steps of 1–3 breaths per minute, and an arterial blood gas is obtained about 30 minutes after each rate change. Titrating the number of ventilator-supported breaths in accordance with the results of arterial blood gases provides no information regarding a patient's work of breathing (which may be excessive) [9].

Pressure support

When pressure support is used for weaning, the level of pressure is reduced gradually (decrements of 3–6 cm H_2O) and titrated on the basis of the patient's respiratory frequency [3]. When the patient tolerates a minimal level of pressure support, he or she is extubated. What exactly constitutes a 'minimal level of pressure support' has never been defined [9].

Comparison of weaning methods

Two RCTs revealed weaning time was three times longer with IMV than with the use of T-tube trials [3,4]. In a study involving patients with respiratory difficulties on attempted weaning, T-tube trials halved the weaning time compared with pressure support [4]. In another study, the weaning time was similar with the two methods [3]. Performing trials of spontaneous breathing once a day is as effective as performing such trials several times a day, but much simpler [4]. In patients not expecting to pose any particular difficulty with weaning, a half-hour trial of spontaneous breathing is as effective as a 2-hour trial [15]. In a recent study of patients requiring prolonged mechanical ventilation, the rate of successful weaning was more than 40% higher with trials involving unassisted breathing through a tracheostomy than with pressure support [16].

Weaning by protocol versus usual care

Six RCTs compared the use of protocols with usual care in the management of weaning [2]. Three found protocolized weaning was without benefit. Data from two of the other studies, although sometimes viewed as evidence of the benefit of protocolized weaning, contain internal validity problems of such magnitude that the data cannot be accepted as supportive. This leaves only one of the six studies supportive of the use of protocols [2].

In a RCT to determine whether the inclusion of f/V_T in a weaning protocol influenced weaning time Tanios et al. [17] found weaning duration was longer in the f/V_T protocol group than in the non-protocol group. In this study, patients who had a f/V_T of 105 or less progressed to a weaning trial, whereas patients with a f/V_T of 106 or higher were returned to the ventilator. When conducting research, this is exactly how a protocol must be specified and followed. No flexibility is permitted. However, it is not clinically realistic to slavishly comply with a protocol that decides an entire day of ventilator management on a one-unit difference in a single measurement of f/V_T. Rather, customizing knowledge of each patient outperforms the inflexible application of a protocol.

Extubation

Decisions about weaning and decisions about extubation are commonly combined [18]. When a patient tolerates a weaning trial without distress, a clinician feels reasonably confident that the patient will be able to sustain spontaneous ventilation after extubation. Before removing the endotracheal tube, however, the clinician must also judge whether or not the patient will be able to maintain a patent upper airway after extubation.

Of patients who are expected to tolerate extubation without difficulty, approximately 10–20% fail and require reintubation [3,4]. Mortality among patients who require re-intubation is more than six times higher than patients who can tolerate extubation [15]. The reason for the higher mortality is unknown. It might be related to the development of new problems after extubation or to complications associated with reinsertion of a new tube. A more likely explanation is that the need for re-intubation reflects greater severity of the underlying illness [18].

Many find it convenient to extubate a patient once he or she can breathe comfortably on a pressure support of about 7 cmH_2O and PEEP 5 cmH_2O based on the belief that such 'minimal ventilator settings' are simply overcoming the resistance engendered by an endotracheal tube [19]. This ignores the inflammation and oedema that develops in the upper airways after an endotracheal tube has been in place for a day or more. On removal of the tube, the mucosal swelling produces an increase in upper airway resistance. Straus et al. [20] demonstrated the respiratory work dissipated against the supraglottic airway after extubation is almost identical to the work dissipated against an endotracheal tube before extubation. Thus, applying any level of pressure support causes underestimation of the respiratory resistance a patient will encounter after extubation. The addition of a small amount of pressure support produces surprisingly large reductions in inspiratory work in ventilated patients: 5 cmH_2O decreases inspiratory work by 31–38% and 10 cmH_2O decreases work by 46–60% [19]. Independently, addition of 5 cmH_2O of PEEP can decrease work of breathing by as much as 40% in ventilated patients [19]. In the case of a patient who might experience cardiorespiratory difficulties after extubation, it is sensible to ensure that the patient is able to breathe comfortably for about 30 minutes in the complete absence of pressure support or PEEP before removal of the endotracheal tube.

Conclusion

In conclusion, to minimize the likelihood of either delayed weaning or premature extubation, a two-step diagnostic strategy is recommended—measurement of weaning predictors followed by a weaning trial. Because each step constitutes a diagnostic test, clinicians must be mindful of the scientific principles of diagnostic testing when interpreting the information generated by each step. The critical step is to contemplate the possibility that a patient **just might** be able to tolerate weaning. Such diagnostic triggering is assisted through use of a screening test, which is the rationale for measurement of weaning-predictor tests. Importantly, one should not postpone this first step by waiting for a more complex diagnostic test, such as a T-tube trial. Because of the many complex facets of pulmonary pathophysiology that impinge on ventilator disconnection, weaning requires individualized care at a high level of sophistication.

References

1. Tobin MJ. (2001). Advances in mechanical ventilation. *New England Journal of Medicine*, **344**, 1986–96.
2. Tobin MJ and Jubran A (2012). Weaning from mechanical ventilation. In Tobin MJ. (ed.) *Principles and Practice of Mechanical Ventilation*, 3rd edn, pp. 1185–220. New York, NY: McGraw-Hill, Inc.
3. Brochard L, Rauss A, Benito S, et al. (1994). Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *American Journal of Respiratory and Critical Care Medicine*, **150**, 896–903.
4. Esteban A, Frutos F, Tobin MJ, et al. (1995). A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *New England Journal of Medicine*, **332**, 345–50.
5. Feinstein AR (1985). *Clinical Epidemiology: The Architecture of Clinical Research*. Philadelphia, PA: Saunders.
6. Tobin MJ and Jubran A. (2006). Variable performance of weaning-predictor tests: Role of Bayes' theorem and spectrum and test-referral bias. *Intensive Care Medicine*, **32**, 2002–12.
7. Casscells W, Schoenberger A, and Graboys TB. (1978). Interpretation by physicians of clinical laboratory results. *New England Journal of Medicine*, **299**, 999–1001.
8. Laghi F, Cattapan SE, Jubran A, et al. (2003). Is weaning failure caused by low-frequency fatigue of the diaphragm? *American Journal of Respiratory and Critical Care Medicine*, **167**, 120–7.
9. Tobin MJ, Laghi F, and Jubran A. (2012). Ventilatory failure, ventilator support, and ventilator weaning. *Comprehensive Physiology*, **2**, 1–51.
10. Tobin MJ, Perez W, Guenther SM, et al. (1986). The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. *American Reviews of Respiratory Disease*, **134**, 1111–18.
11. Yang KL and Tobin MJ. (1991). A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *New England Journal of Medicine*, **324**, 1445–50.
12. MacIntyre NR, Cook DJ, Ely EW Jr, et al. (2001). Evidence-based guidelines for weaning and discontinuing ventilatory support: A collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest*, **120**(Suppl. 6), 375S–95S.
13. Meade M, Guyatt G, Cook D, et al. (2001). Predicting success in weaning from mechanical ventilation. *Chest*, **120**, 400S–24S.
14. Sassoon CS (2012). Intermittent mechanical ventilation. In: Tobin MJ (ed.) *Principles and Practice of Mechanical Ventilation*, 3rd edn, pp. 17–98. New York, NY: McGraw-Hill.
15. Esteban A, Alia I, Tobin MJ, et al. (1999). Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. *American Journal of Respiratory and Critical Care Medicine*, **159**, 512–18.
16. Jubran A, Grant BJB, Duffner LA, et al. (2013). Weaning from prolonged mechanical ventilation. Effect of pressure support vs unassisted breathing through a tracheostomy collar on weaning duration in patients requiring prolonged mechanical ventilation: a randomized trial. *Journal of the American Medical Association*, **309**, 671–7.
17. Tanios MA, Nevins ML, Hendra KP, et al. (2006). A randomized, controlled trial of the role of weaning predictors in clinical decision making. *Critical Care Medicine*, **34**(10), 2530–5.
18. Tobin MJ and Laghi F. (2012). Extubation. In: Tobin MJ (ed.) *Principles and Practice of Mechanical Ventilation*, 3rd edn, pp. 1221–36. New |York, NY: McGraw-Hill Inc.
19. Tobin MJ. (2012). Extubation and the myth of 'minimal ventilator settings'. *American Journal of Respiratory and Critical Care Medicine*, **185**(4), 349–50.
20. Straus C, Louis B, Isabey D, et al. (1998). Contribution of the endotracheal tube and the upper airway to breathing workload. *American Journal of Respiratory and Critical Care Medicine*, **157**, 23–30.

CHAPTER 103

Weaning failure in critical illness

Annalisa Carlucci and Paolo Navalesi

Key points

- Weaning failure is defined as either unsuccessfull mechanical ventilation discontinuation or extubation failure.
- Both are associated with increased morbidity and mortality.
- An impaired balance between respiratory muscles force and respiratory system impedance (load) is the main cause of weaning failure. Weak cough and increased upper airway resistances are also implicated in the aetiology of extubation failure.
- A systematic approach to assess readiness by means of a spontaneous breathing trial is crucial to reduce the risk of extubation failure.
- In selected cases, non-invasive ventilation and intensive physiotherapy may facilitate discontinuation of mechanical ventilation and avert extubation failure.

Definition and outcome

Weaning failure has been defined as either failure to discontinue mechanical ventilation or a need for re-intubation within 48–72 hours after extubation (extubation failure) [1].

The former is generally assessed as an inability to breath spontaneously through an endotracheal tube for a relatively short period of time, commonly 30–120 minutes, the so-called spontaneous breathing trial (SBT) [1]. SBT failure is predominantly consequent to an excessive load for the capacity of the respiratory muscles [1].

Extubation failure encompasses a more complex phenomenon. On the one hand, it can be consequent to the incapacity to maintain the spontaneous unassisted breathing after removal of the endotracheal tube, suggesting an increase of the load imposed on the respiratory muscles after extubation. On the other hand, it can be due to the inability to maintain patent the upper airway without necessarily requiring mechanical ventilation or to incapacity to adequately clear secretions [1].

Both discontinuation and extubation failure constitute major clinical and economic burdens. Failure to discontinue mechanical ventilation is associated with increased morbidity and mortality. In particular, patients who require more than 7 days of mechanical ventilation after the first attempt of withdrawal are characterized by a high rate of death [2]. Extubation failure is also associated with an increased risk of death, ranging between 40 and 50% [3], which is correlated with the aetiology of extubation failure and the delay in re-intubation [4]. A high incidence of pneumonia and clinical deterioration before re-intubation are considered to play a predominant role in worsening outcome [1–3]. Table 103.1 summarizes the major causes of weaning failure.

Epidemiology

The time for weaning accounts for 40–50% of the total duration of mechanical ventilation, depending on the reason for initiating mechanical ventilation [1]. In a recent observational multicentre study including 2714 intubated patients who met criteria for weaning readiness, 45% failed at least one attempt. Of these patients, 39% were extubated within 7 days (difficult weaning) and 6% after 7 days (prolonged weaning) after the first attempt [2].

Extubation failure is reported to be as high as 15–18% of planned extubations; about one-third of extubation failures occurs within the first 12 hours and approximately two-thirds within the first 24 hours [1,4].

Causes of failure of mechanical ventilation discontinuation

Readiness for discontinuation of mechanical ventilation is commonly assessed, when overall clinical stability is achieved, which implies that all the acute problems are overcome, the patient is haemodynamically stable, a high FiO_2 is not required, positive end-expiratory pressure (PEEP) values not exceeding 5 cmH_2O are used, and comfortable breathing and adequate gas exchange are obtained with no or minimal (7–8 cmH_2O) inspiratory support [1].

Discontinuation failure may depend on a multiplicity of factors and is often consequent to more than one single cause. Irrespective of the underlying disorder leading to the need for mechanical ventilation, the most common mechanism is an unfavourable balance between the force generating capacity of the respiratory muscles and the load they must face [1,5]. Any treatment able to reduce the load and/or to augment muscle force may favour discontinuation success [5]. A highly unfavourable unbalance between force and load represents the most common cause of early SBT failure, which is sometimes unpredictable when the patient receives even a minimal assistance. Indeed, an inspiratory support as low as 5 cmH_2O can reduce the respiratory work by nearly 40% [6].

Failure can occur later in the course of the trial. Sometimes an inspiratory load that is tolerable at the beginning of the trial increases throughout the SBT. In a series of chronic obstructive pulmonary disease (COPD) patients undergoing SBT, Jubran et al. found that that airway resistance significantly increased throughout the trial (from 9 ± 2 cmH_2O to 15 ± 2 cmH_2O) within 45 minutes in the patients who failed, while it did not vary in those who succeeded [7]. The increase in pulmonary resistance in the course of

Table 103.1 Causes of weaning failure

	Weaning failure	
	MV discontinuation failure	**Extubation failure**
Causes	**Increased load (respiratory system impedance)**: ◆ Increased airway resistance ◆ Reduced respiratory system compliance ◆ $PEEP_i$ **Decreased respiratory muscle force**: ◆ Neuromuscular disease ◆ ICU-acquired CINM ◆ Prolonged controlled MV ◆ Hyperinflation ◆ Poor nutritional status **Cardiac dysfunction** **Cerebral dysfunction**: ◆ Altered consciousness ◆ Psychological and psychiatric disorders (delirium, depression) ◆ Sedation	**Deteriorated force/load balance** **Increased upper airway resistance**: ◆ Laryngeal inflammation ◆ Laryngeal oedema ◆ Tracheal obstruction (stenosis, granuloma) **Inability to clear secretions**

MV, mechanical ventilation; $PEEP_i$, auto- or intrinsic positive end-expiratory pressure; ICU, intensive care unit; CINM, critical illness neuro-myopathy.

the SBT may suggest a mechanism related to the cardio-pulmonary interaction [7]. In fact, a remarkable increase of the inspiratory negative intrathoracic pressure swings leads to a rise in both cardiac preload (i.e. venous return) and afterload (i.e. left ventricular transmural pressure), which may cause pulmonary congestion and oedema of the bronchial wall, and consequently worsens pulmonary mechanics and increases the magnitude of the load imposed on the respiratory muscles. Thus, an unrecognized or latent cardiac dysfunction can become evident when interrupting the ventilator support to resume spontaneous breathing [1].

A critical reduction of the force-generating capacity of the respiratory muscles may also lead to a failure to discontinue mechanical ventilation. This is quite common in mechanically-ventilated patients with neuromuscular diseases. Besides, the respiratory muscles can be weakened because of ICU-acquired critical illness neuromyopathy (CINM), which may occur as a complication of sepsis and multiple organ failure, hyperglycaemia and in patients receiving neuromuscular blocking agents for days, aminoglycosides, and/or steroids [8]. Also, diaphragm disuse atrophy complicates the clinical course of patients undergoing controlled mechanical ventilation. After 5–6 days of controlled mechanical ventilation the force-generating capacity of the diaphragm was found to be reduced by two-third [9]. This was associated with histobiochemical signs of diaphragmatic injury and atrophy, with a significant correlation between duration of mechanical ventilation and magnitude of diaphragmatic injury [9]. A physiological study performed on patients who had received prolonged mechanical ventilation showed that the recovery from inspiratory muscle weakness is a major determinant of 'late' weaning success [10]. A poor nutritional status may also play a role in decreasing muscle force [1]. Finally, in patients with lung hyperinflation because of diseases causing prolonged expiratory time constant and/or expiratory flow limitation, such as asthma and COPD, the force-generating capacity of the diaphragm is reduced because the muscle fibres, though well-functioning, are already shortened at end expiration [11].

Cerebral dysfunctions affecting the level of consciousness [12] or determining psychological or psychiatric disorders, such as ICU-acquired delirium and depression may contribute to discontinuation failure [1].

Causes of extubation failure

Any of the causes of discontinuation failure may also be implicated in the pathogenesis of extubation failure. This holds especially true whenever readiness for discontinuation of mechanical ventilation is not systematically tested with a SBT [6,12].

In some cases, after removal of the endotracheal tube, the inspiratory load may rise up consequent to an increase in upper airway resistance due to laryngeal inflammation and oedema. However, a physiological study showed that the work of breathing necessary to overcome supraglottic airway resistance soon after extubation is on average rather close to that formerly imposed by the endotracheal tube [13]. In patients with prolonged intubation complications leading to tracheal obstruction, such as tracheal stenosis, granuloma, and tracheomalacia may also cause extubation failure [14].

In patients successfully completing SBT, weak cough and the inability to clear secretions may afterwards cause extubation failure not predicted by the conventional parameters used to assess readiness for discontinuation of mechanical ventilation [1]. In a prospective study on 115 patients who passed the SBT and were ready to be extubated, a peak expiratory flow during glotic-free cough ≤60 L/min was associated with a five-fold increase in extubation failures [15].

Preventing strategies

Although conventionally considered as a specific period of the time spent on mechanical ventilation, the process of weaning should start as soon as mechanical ventilation is instituted and include any intervention aimed at facilitating resumption of spontaneous breathing through the native airway. If, on the one hand, discontinuation of mechanical ventilation and extubation should be considered as soon as possible to avoid the consequences of unnecessary prolonged intubation, on the other hand, because of their detrimental consequences, both discontinuation and extubation failures must be prevented.

The methodology used to assess readiness for withdrawal of mechanical ventilation and extubation is crucial. A systematic approach to determine readiness utilizing standardized meaningful physiological and clinical criteria may improve weaning and extubation outcome [12]. Assessing readiness by means of the SBT represents a cornerstone of this process. Anyhow, the wide variability of the methods used to perform the SBT, i.e. T-piece trial, minimal levels of CPAP and low values of inspiratory support, may affect the SBT outcome [2].

Based on the aforementioned experimental data, although never proved by clinical studies, a rapid switch from controlled to assisted modes of mechanical ventilation should in principle reduce the risk of diaphragm atrophy and injury. The ventilator settings are also important. Unnecessarily high levels of mechanical support may

result in excessively low patient's respiratory drive and effort, which is associated with poor patient-ventilator interaction and increased risk of prolonged mechanical ventilation [16]. Avoiding excessive sedation can also improve the outcome of weaning [17].

In some patients with underlying chronic respiratory disorders intubated for treatment of severe hypercapnic acute on chronic respiratory failure, an early extubation followed by immediate application of non-invasive ventilation (NIV) may help to speed up the process of discontinuation, while reducing the risk of developing ventilator associated pneumonia [18].

NIV can be also successfully used to decrease the re-intubation rate in patients at increased risk of extubation failure, such as those with underlying chronic or cardiac disorders, prior weaning failure, and numerous comorbidities [19]. In particular, in patients who develop hypercapnia during the SBT, prophylactic application of NIV at extubation reduces the rate of re-intubation and mortality [20].

In patients at risk of developing extubation failure because of ineffective clearing of secretions, intensive physiotherapy may be helpful. The use of mechanical cough assistance may prevent extubation failure consequent to sputum retention, especially in patients with weak cough [1].

References

1. Boles JM, Bion J, Connors A, et al. (2007). Weaning from mechanical ventilation. *European Respiratory Journal*, **29**, 1033–56.
2. Peñuelas O, Frutos-Vivar F, Fernández C, et al. (2011). Characteristics and outcomes of ventilated patients according to time to liberation from mechanical ventilation. *American Journal of Respiratory and Critical Care Medicine*, **184**, 430–7.
3. Thille AW, Harrois A, Schortgen F, Brun-Buisson C, and Brochard L. (2011). Outcomes of extubation failure in medical intensive care unit patients. *Critical Care Medicine*, **39**, 2612–18.
4. Epstein SK and Ciubotaru RL. (1998). Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. *American Journal of Respiratory and Critical Care Medicine*, **158**, 489–93.
5. Vassilakopoulos T, Zakynthinos S, and Roussos C. (1998). The tension-time index and the frequency/tidal volume ratio are the major pathophysiologic determinants of weaning failure and success. *American Journal of Respiratory and Critical Care Medicine*, **158**, 378–85.
6. Tobin MJ. (2012). Extubation and the myth of 'minimal ventilator settings'. *American Journal of Respiratory and Critical Care Medicine*, **185**, 349–50.
7. Jubran A and Tobin MJ. (1997). Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *American Journal of Respiratory and Critical Care Medicine*, **155**, 906–15.
8. de Jonghe B, Lacherade JC, Sharshar T, and Outin H. (2009). Intensive care unit-acquired weakness: risk factors and prevention. *Critical Care Medicine*, **37**, S309–15.
9. Jaber S, Petrof BJ, Jung B, et al. (2011). Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. *American Journal of Respiratory and Critical Care Medicine*, **183**, 364–71.
10. Carlucci A, Ceriana P, Prinianakis G, Fanfulla F, Colombo R, and Nava S. (2009). Determinants of weaning success in patients with prolonged mechanical ventilation. *Critical Care*, **13**, R97.
11. Similowski T, Yan S, Gauthier AP, Macklem PT, and Bellemare F. (1991). Contractile properties of the human diaphragm during chronic hyperinflation. *New England Journal of Medicine*, **325**, 917–23.
12. Navalesi P, Frigerio P, Moretti MP, et al. (2008). Rate of reintubation in mechanically ventilated neurosurgical and neurologic patients: evaluation of a systematic approach to weaning and extubation. *Critical Care Medicine*, **36**, 2986–92.
13. Straus C, Louis B, Isabey D, Lemaire F, Harf A, and Brochard L. (1998). Contribution of the endotracheal tube and the upper airway to breathing workload. *American Journal of Respiratory and Critical Care Medicine*, **157**, 23–30.
14. Rumbak MJ, Walsh FW, and Anderson WM. (1999). Significant tracheal obstruction causing failure to wean in patients requiring prolonged mechanical ventilation: a forgotten complication of long-term mechanical ventilation. *Chest*, **115**, 1092–5.
15. Smina M, Salam A, Khamiees M, Gada P, Amoateng-Adjepong Y, and Manthous CA. (2003). Cough peak flows and extubation outcomes. *Chest*, **124**, 262–8.
16. Thille AW, Cabello B, Galia F, Lyazidi A, and Brochard L. (2008). Reduction of patient-ventilator asynchrony by reducing tidal volume during pressure-support ventilation. *Intensive Care Medicine*, **34**, 1477–86.
17. Strøm T, Martinussen T, and Toft P. (2010). A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet*, **375**, 475–80.
18. Burns KE, Adhikari NK, Keenan SP, and Meade MO. (2010). Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Systematic Reviews*, **8**, CD004127.
19. Nava S, Gregoretti C, Fanfulla F, et al. (2005). Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. *Critical Care Medicine*, **33**, 2465–70.
20. Ferrer M, Sellarés J, Valencia M, et al. (2009). Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet*, **374**, 1082–8.

PART 4.8

Extracorporeal support

CHAPTER 104

Extracorporeal respiratory and cardiac support techniques in the ICU

Claire Westrope and Giles Peek

Key points

- Extra-corporeal life support (ECLS) is an essential tool for the modern intensivist and surgeon.
- The addition of extracorporeal therapy should be considered when pathology is reversible and conventional therapy is failing.
- There are different types of extracorporeal therapies, each with their own nuances, which need to be understood in order to be used effectively and appropriately.
- Techniques required for providing successful ECLS in adult respiratory and cardiac failure are described in this chapter.
- Increasing use of mobile extracorporeal membrane oxygenation (ECMO) and extracorporeal cardiopulmonary resuscitation (ECPR) demonstrate how extracorporeal support has progressed and advanced in recent years.

Background

Extracorporeal life support (ECLS) is a general term to describe prolonged, but temporary support of heart and lung function using mechanical devices. Device applications require a combination of vascular access catheters, connecting tubing, a blood pump, a gas exchange device (oxygenator), a heat exchanger, measuring and monitoring devices, and systemic anticoagulation.

There are various sub-types of ECLS (with varying degrees of overlap) including:

- Extracorporeal lung assist ECLA (low flow extracorporeal membrane oxygenation (ECMO) to prevent intubation or minimize ventilation).
- ECMO (high flow ECLS to replace lung and/or heart function, used synonomously with ECLS).
- Extracorporeal carbon dioxide removal ($ECCO_2R$, same as lung assist).
- Extracorporeal cardiopulmonary resuscitation (ECPR, emergency cardiac support in cardiac arrest).

When blood pumps alone are used for cardiac support then ECLS is termed as left ventricular assist device (LVAD), right ventricular assist device (RVAD), or biventricular assist device (BiVAD).

The Extracorporeal Life Support Organization's (ELSO) recent international summary (July 2012) [1] shows that to date over 50,000 patients have been treated with ECLS (Fig. 104.1). Adult respiratory activity has increased year-on-year (Fig. 104.2) following the publication of the CESAR trial [2] and successful use of ECMO in the H1N1 outbreaks of 2009 and 2010, which have raised awareness of ECMO use in adults globally [3].

With improved knowledge and experience in adult respiratory extracorporeal techniques, use in adult cardiac support has also increased (Fig. 104.3).

ECLS techniques

Team

No ECMO programme can be run without a dedicated team with extensive knowledge of and ability to manage all of the following—patient selection, patient transport (including mobile ECMO), ECMO circuit, ECMO circuit–patient interaction, ECMO complications, specific patient and disease management pre, during and post-ECMO, and advanced ventilator techniques for pre- and post-ECMO patients. This requires engagement and teamwork across several disciplines.

ECMO circuit

The ECMO/ECLS circuit has undergone significant changes in the last few years, which has resulted in a shorter more biocompatible circuit.

The essential components (venous drainage line, blood pump, or oxygenator with gas supply, heat exchanger, arterial return) of an ECMO circuit are shown in Fig. 104.4.

Newer tubing materials and heparin coating have resulted in ELCS circuits causing less patient systemic inflammatory response, having decreased heparin requirement for systemic anticoagulation and reduced thrombotic complications.

The traditional silicone oxygenator has been replaced by the hollow fibre polymethlypentene (PMP) oxygenators, which have lower resistance, better gas exchange, lower priming volumes, increased efficiency, cause less consumption of platelets and clotting factors, and survive longer.

Mendler type centrifugal blood pumps are superseding the occlusive roller pump and the first generation centrifugal pump. These are smaller and non-occlusive, and so are inherently safer. The central hole in the rotor of the Mendler type pump prevents clot

ECLS Registry Report

International Summary

July, 2012

Extracorporeal Life Support Oraganization
2800 Plymouth Road
Building 300, Room 303
Ann Arbor, MI 48109

Overall Outcomes

	Total Patients	*Survived ECLS*		*Survived to DC or Transfer*	
Neonatal					
Respiratory	25,746	21,765	85%	19,232	75%
Cardiac	4,797	2,928	61%	1,912	40%
ECPR	784	496	63%	304	39%
Pediatric					
Respiratory	5,457	3,556	65%	3,061	56%
Cardiac	5,976	3,855	65%	2,913	49%
ECPR	1,562	843	54%	630	40%
Adult					
Respiratory	3,280	2,094	64%	1,808	55%
Cardiac	2,312	1,243	54%	891	39%
ECPR	753	276	37%	207	27%
Total	50,667	37,056	73%	30,958	61%

Fig. 104.1 Total patients treated with ECLS. ELSO Registry Report International Summary July 2012.
Provided from the Extracorporeal Life Support Organization July 2012 Registry Report, with permission.

Adult Respiratory (18 years and over)

Annual Respiratory Adults Runs

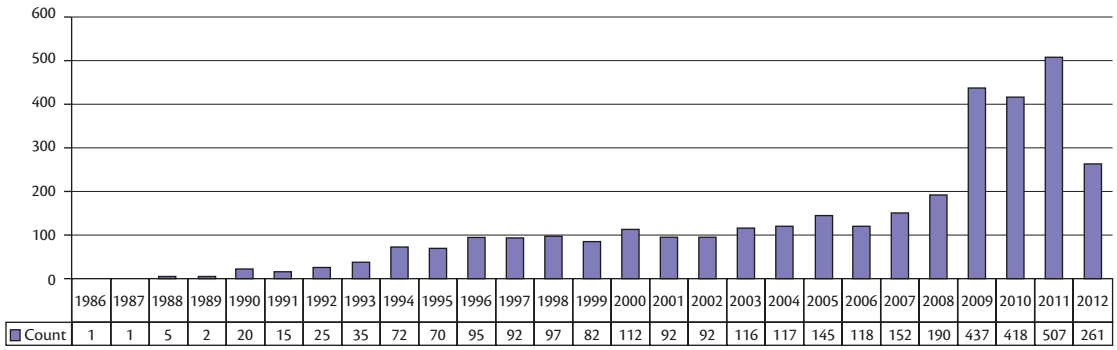


Fig. 104.2 Adult respiratory runs. ELSO Registry Report International Summary July 2012.
Provided from the Extracorporeal Life Support Organization July 2012 Registry Report, with permission.

Annual cardiac Runs (16 years old and over)

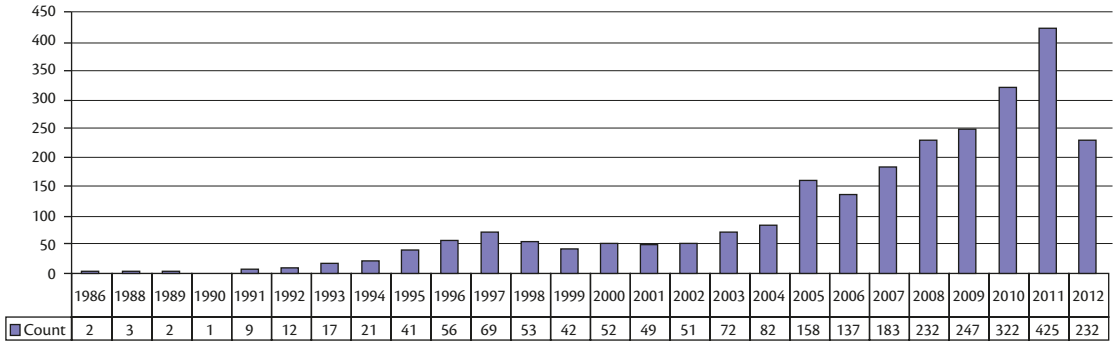


Fig. 104.3 Adult cardiac runs. ELSO Registry Report International Summary July 2012.
Provided from the Extracorporeal Life Support Organization July 2012 Registry Report, with permission.

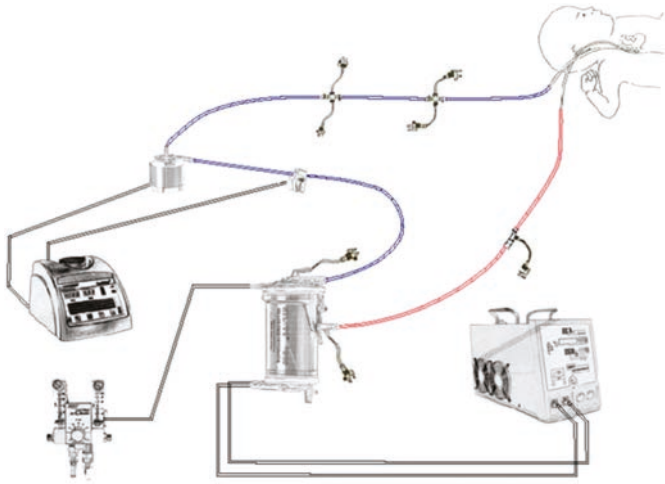


Fig. 104.4 ECLS Circuit.

build-up and has improved heat dissipation, making it mechanically more reliable. ECLS circuits overall are shorter as centrifugal pumps generate active suction and do not depend on gravity for venous drainage. They generate a new problem of negative pressure on the drainage side of the circuit. The main disadvantage of this negative pressure is that it increases the risk of air entrainment if access ports are placed in the drainage side of the circuit. As air in the circuit is the nemesis of the ECMO specialist removing circuit access ports from the drainage side of the circuit and placing them post-centrifugal pump/pre-oxygenator (i.e. in the positive pressure side of the circuit) almost completely eliminates the risk of air entrainment.

Fig. 104.5 illustrates how the ECMO circuit has changed over the years with the first photo showing the simplified modern circuit.

Definite proof that new systems (centrifugal pump, PMP oxygenator) are better than traditional systems (silicone oxygenator and roller head occlusive pump) is lacking, but various single centre reports are encouraging. Sivarjan et al. [4] compared two groups of paediatric ECMO patients in different time periods, 1998 (Biomedicus centrifugal pump and silicone oxygenator) and 2001 (Jostra centrifugal pump and quadrox oxygenator). Patient survival improved from 24 to 49% in the latter group and mechanical complications per 10,000 hours fell from 70 to 50; pump heads used from 160 to 110 and oxygenators from 130 to 110.

Mobile ECMO

Despite advances in technology, a significant number of adult patients fail maximal medical therapy and ultimately require ECMO. A proportion of these patients can be moved to an ECMO centre in a timely manner by conventional means, but increasingly they rapidly become too unstable, requiring emergency cannulation/ECPR in their own centre, and transport on ECMO to an ECMO centre.

Advances in technology and experience mean that ECMO centres should now consider mobile ECMO retrieval as a standard part of their service provision.

This requires medical, nursing, and perfusion professionals to be available round the clock, and trained in ECMO and transport medicine. It also requires a dedicated transport system (trolley and vehicle), which can be adapted to the transport mode (air/rotary/fixed wing).

Veno-venous ECLS support

In veno-venous (VV) ECLS support blood is drained from the venous circulation and re-infused back into the venous circulation after passing through the extracorporeal circuit. It requires the patient to have adequate cardiac output to pump the oxygenated blood around the body. Oxygenation is proportional to ECMO flow. High flow VV ECLS is for oxygenation (ECMO) and low flow for CO_2 removal ($ECCO_2R$).

Cannulation for VV support is traditionally through the right internal jugular vein into the right atrium and via the femoral vessels, and the degree of ECMO support provided depends on cannula size and site. Percutaneous access over a wire via the Seldinger technique has been a major advantage in ECMO cannulation. Traditionally, a two cannula approach is used in adults. A 23–28F (external diameter) single lumen catheter inserted into the inferior vena cava (IVC) via either femoral vein and a second 23–28F cannula inserted into the right atrium (RA) via the right internal jugular vein will give adequate support for most adult patients (up to 5 L/min flow). Direction of flow is optional, drainage from the neck (with a shorter cannula) allows higher flow, but has more recirculation while drainage from the groin gives less drainage and recirculation, but may

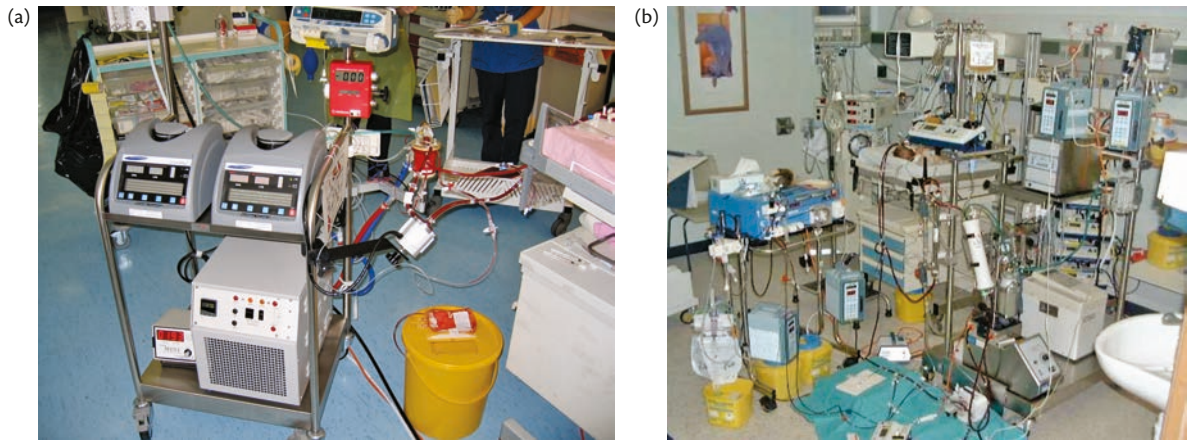


Fig. 104.5 Changes to ECMO circuit over time with panel (a) showing the simplified modern circuit and panel (b) showing the older more complex circuit.

provide better oxygen delivery. Additional drainage cannulae can be placed in the other femoral vein with drainage from IVC and RA, and reinfusion into IVC, if flow is inadequate.

Recently, the bicaval double lumen venous cannula has allowed a single point of venous access with inherently low levels of recirculation making ECMO much more efficient. The Bicaval double lumen cannula, Avalon Elite® (Maquet) is designed to be inserted percutaneously via the right internal jugular vein with its tip placed in the IVC. Drainage holes placed proximally and distally to sit in SVC and IVC minimize recirculation as oxygenated blood is returned via a separate return hole placed in the middle of these two drainage ports and directed toward the tricuspid valve (Fig. 104.6).

Cannulae are available in sizes 16–31F and provide adequate flows in most patients up to 100 kg. Insertion requires X-ray screening to confirm wire then cannula position in IVC and to minimize complications, particularly misplacement/pneumothorax and cardiac perforation. If additional flow is required, a second femoral drainage cannula (23f biomedicus) can be inserted percutaneously into the lower IVC via either femoral vein.

Advantages of the bicaval double lumen cannula include single site access (reducing the risk of vascular injury, cannula site bleeding, and infection) and reduced circuit length (less contact activation, mobile ECMO, improved patient mobility). A perceived disadvantage of the bicaval cannula is a reduced ECMO flow compared with two single cannulae. However, as there is reduced recirculation this does not impact on oxygen delivery. It is recommended that flows should be maintained above 2.5 L/min in adults in order to avoid clot formation.

VV ECMO can provide total CO_2 removal, but provides less O_2 delivery than veno-arterial (VA) support. It relies on adequate pumping of the native heart to distribute the extracorporeal oxygenated blood to the body. Many centres default to VA ECMO support in patients who have high inotropic requirements secondary to severe respiratory failure. However, one potential benefit of VV support is that the highly oxygenated blood returned back to the right atrium flows through the heart and into the coronary arteries, resulting in improved oxygen delivery to the myocardium and cardiac function.

The goal of ECMO for respiratory failure is to support gas exchange so that the iatrogenic side effects of intensive care treatment (such as ventilator-associated lung injury and sedation complications) can be minimized. Patients are therefore transitioned immediately to 'rest settings' on the ventilator, this is either a low frequency, high PEEP, low positive inspiratory pressure (PIP) strategy (i.e. 25/15 rate 10, FiO_2 0.3) or a low pressure high-frequency oscillatory ventilation approach, i.e. MAP 10–15 cmH_2O for patients with severe barotrauma and air leak. Once the acute phase of the illness has passed patients are either extubated or (more commonly) tracheostomized, while still on ECMO, woken up, and allowed to breathe for themselves. Many teams are now able to mobilize patients on ECMO.

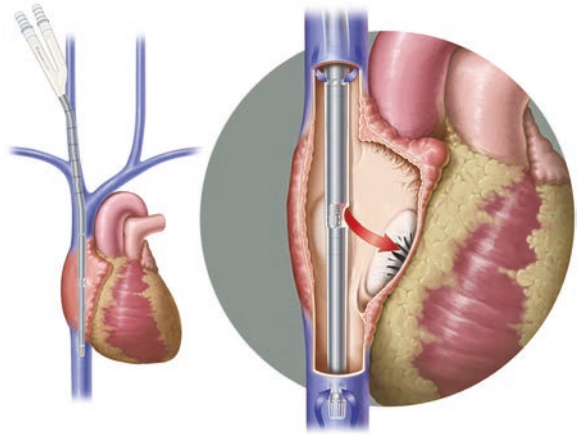


Fig. 104.6 Bicaval double lumen cannula.
Reproduced from Manquet Cardiopulmonary AG.

VA support

VA support in adult patients is reserved for those cases with profound cardiac failure or in the situation of cardiac arrest when it is termed as ECPR.

Blood is drained from the venous system (from RA via RIJ or IVC via the femoral vein and returned into the arterial system via the aorta (via common carotid, axilliary, or the femoral artery).

The right internal jugular is preferred for venous drainage as it is the shortest route, but femoral venous access is sometimes more easily achievable. Direct right atrial access after cardiac surgery is also possible if the sternum is left open, although the risk of infection is high and the decision whether to change the cannula insertion site to percutaneous in the neck or groin should be made early.

Historically, the common carotid artery was the preferred route for the arterial return cannula, largely as a result of early ECMO experience with VA support in neonates. Because the carotid artery could be ligated distally, distal perfusion was not required, and it delivered fully oxygenated blood direct to the aortic root. Unfortunately, 15% of adults develop an intracranial ischaemic injury following carotid ligation. The right femoral artery is now the preferred site for arterial return (it is usually slightly bigger than the left). In centres who perform purely VA ECMO for all adult cardiac and respiratory indications, the femoral artery is directly accessed using a cut-down technique, a distal perfusion cannula is placed electively into the superior femoral artery and then the arterial cannula (17, 19, or 21F) is inserted into the femoral artery under direct vision. This minimizes compromise to the distal collateral circulation of the leg. Other centres electively insert a distal perfusion catheter into the posterior tibial artery once the patient has stabilized on ECMO. Whichever technique is used for femoral artery cannulation, the associated leg should be monitored hourly for signs of compromised distal perfusion. Compartment syndrome of the leg requiring fasciotomies is not an infrequent complication of VA ECMO.

Total bypass of the cardiopulmonary system during VA ECMO is not recommended. Some blood is required to flow through the patient's heart to supply the coronary arteries. As the blood going through the heart in VA ECMO is deoxygenated, oxygenation of coronary artery blood is dependent on oxygenation via ventilatory support of the lungs. It is routine, therefore, for the amount of ventilatory support to be higher in VA ECMO (FiO_2 routinely 40% or above), although care should still be taken to minimize ventilator-induced lung injury.

An adverse effect of VA ECMO is that it increases left ventricular afterload, which may result in complete left ventricular failure. Chemical afterload reduction may not be adequate to manage the

situation. Patients can require a left atrial vent (line into left atrium connected to the venous drainage line of ECMO circuit) if the chest is open or an atrial septosomy. If a patient has these interventions it should be noted that mixed venous saturations taken from the venous line below the vent will be falsely elevated, as oxygenated blood from the left heart will be vented into the right atrium or the venous side of the ECMO circuit, and so a true mixed venous gas should be taken proximal to the site of mixing. Near-infrared spectroscopy (NIRS) can be a useful adjunct in tailoring oxygen delivery in this situation.

The goal of VA ECMO is to provide adequate haemodynamics, oxygenation, and perfusion, while optimizing the conditions for cardiac and respiratory rest and recovery.

Other extracorporeal respiratory therapies

Mini ECMO/novalung™/ILA active™

In recent years miniature extracorporeal lung assist (ECLA) devices have become available, e.g. Novalung™ (Germany). These devices require percutaneous cannulation of the femoral artery and vein, utilizing the patient's own blood pressure to drive blood across the low resistance oxygenator. More recently, Novalung has released the ILA active™ device, which allows venous cannulation only using a double lumen cannula (24F NOVAPORT twin™) and relying on a centrifugal pump to drive blood through the oxygenator. Novalung is limited to lower flows 1–2 L/min and are only able to provide CO_2 removal to support patients with moderate respiratory failure. The technique can avoid the need for intubation and mechanical ventilation in high-risk patients, shorten the duration of mechanical ventilation and allow suitable patients to be awake and mobile prior to lung transplantation. The ILA active™ device will allow flow up to 8l/min, but would require a larger cannula than 24F to achieve this flow, so it is usually used in low flow $ECCO_2R$ mode. Other $ECCO_2R$ devices include A-Lung and DECAP.

Adult ECPR

Use of ECPR is relatively new. It can be viewed as an extreme form of cardiac support using VA ECMO cannulation for cardiac arrest. Cannulation is usually of the femoral vessels (artery and vein) using percutaneous techniques.

Adult in-hospital cardiac arrest results in an 80% mortality (survival range 10–40% depending on underlying rhythm at onset of the arrest) [5]. ELSO registry data shows survival to hospital discharge of 29% in 591 adults who required ECPR [1]. Shin et al. [6] demonstrated that when ECMO was used early as part of an overall plan for the resuscitation of adults with cardiac arrest, there was improved survival and quality of life when compared with conventional CPR. This was only demonstrated when ECMO was considered (within 10 minutes of onset of arrest) and implemented (within 60 minutes of arrest) early. In the event of an unexpected arrest, even with an unsuccessful outcome ECPR and VA ECMO support may give relatives and clinical teams time to reflect and come to terms with the loss of the patient.

Conclusion

ECLS is an essential tool for the modern intensivist, cardiologist and surgeon. The addition of extracorporeal therapy should be considered in all cases when pathology is potentially reversible and conventional therapy is clearly failing.

References

1. Extracorporeal Life Support Organization (2015). *ECLS Registry Report International Summary*. Ann Arbor, MI: ELSO. Available at: www.elsonet.org
2. Peek J, Mugford M, Tiruvoipati R, et al. (2009). Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*, **374**, 1351–63.
3. Noah MA, Peek GJ, Finney SJ, et al. (2011). Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *Journal of the American Medical Association*, **306**(15), 1659–68.
4. Sivarjan VB, Best D, Brizard CP, et al. (2010). Improved outcomes of paediatric extracorporeal support associated with technology change. *Interactive Cardiovascular Surgery*, **11**, 400–5.
5. Meaney PA, Nadkarni VM, Kern KB, et al. (2010). Rhythms and outcomes of adult in-hospital cardiac arrest*. *Critical Care Medicine*, **38**(1), 101–8.
6. Shin TG, Choi JH, Jo IJ, et al. (2011). Extracorporeal cardiopulmonary resuscitation in patients with in hospital cardiac arrests. A comparison when compared with conventional CPR. *Critical Care Medicine*, **39**, 1–7.

CHAPTER 105

Treating respiratory failure with extracorporeal support in the ICU

Giacomo Bellani and Antonio Pesenti

Key points

- Veno-venous extracorporeal life support is a solid tool in rescuing patients with severe hypoxaemia.
- While a low-flow bypass can remove comparatively high amounts of CO_2 from blood, oxygenation is limited by venous haemoglobin saturation and therefore requires high extracorporeal blood flows.
- As shown by several data registries, a shorter duration of mechanical ventilation before initiation of extracorporeal support is associated with a decreased mortality rate.
- The recent improvements in efficacy and safety of extracorporeal support technology might lead to an earlier application of this technique to remove CO_2, decreasing the need for ventilation and, hence, decreasing ventilator-induced lung injury.
- Extracorporeal support still bears severe risks of complications. Centralizing patients to selected specialized centres with a high case volume is likely to improve the outcome of the treatment.

Historical background

Extracorporeal respiratory support technology was developed in the 1940s as an essential tool in cardiac surgery. Its successful use in an adult patient with acute respiratory distress syndrome (ARDS) was first described in 1971 by J. D. Hill. Following this first report, one multicentre randomized trial was conducted, but no effect on mortality was observed in patients treated with extracorporeal membrane oxygenation (ECMO) [1]. The trial was doomed by a very high incidence of severe bleeding and by the use of immature technology. The result of this and other studies led to an almost complete stop of ECMO in adults, confining its application to newborns [2]. The reasons leading to the failure of the adult early trial might probably be identified in the continuous lung damage caused by an injurious setting of mechanical ventilation (MV) in spite of extracorporeal support. Subsequently, Kolobow and Gattinoni suggested the concept that by removing CO_2 through an artificial lung, ventilation could be reduced virtually down to zero [3], allowing to put the lung at rest minimizing the negative effect of ventilation.

Present status of ECMO

The concept of ECMO is apparently very simple [4,5]—blood is diverted from the patient to an artificial lung for gas exchange (oxygenation and CO_2 removal) and then returned into the patient's circulation once arterialized. The bypass may be veno-arterial, veno-venous, or arteriovenous (Table 105.1). While a low-flow bypass can remove comparatively high amounts of CO_2 from the blood, oxygenation is limited by venous haemoglobin saturation and, therefore, requires high extracorporeal blood flows, in the range of 3–5 L/min. Several technical improvements led to a profound change in the safety and applicability of ECMO in recent years, and even allowed to transfer patients undergoing ECMO [6]. Surgical was largely replaced by percutaneous cannulation [7], with a greater bedside applicability and less bleeding complications. Moreover, double lumen cannulas [8], specifically designed to minimize recirculation, allow for single vessel access for both drainage and reinfusion. The introduction of heparin-coated surface for tubings and artificial lungs drastically reduced the need for systemic anticoagulation. Roller pumps were largely abandoned in favour of centrifugal pumps. Until the late 1990s, the flat sheet silicon rubber membrane artificial lungs were the standard of care. These oxygenators required a large priming volume, and had a very high flow resistance. A revolution in oxygenators came from the introduction of hollow-fibre membrane oxygenators whose initial problems with plasma leakage are now largely solved since polymethylpentene membranes came into use. These oxygenators have a much lower priming volume and resistance to blood flow (tens, rather than hundreds of mmHg/L/min). The very low resistance of these circuits permitted the design a pumpless system, which takes advantage of the arteriovenous pressure gradient to pump blood through the oxygenator; this circuit type is not very efficient in oxygenating blood, due to the relatively low blood flow and the high haemoglobin saturation of the blood entering the oxygenator [9]. However, the efficient CO_2 removal allows a decrease in traditional ventilation needs.

Table 105.1 Extracorporeal respiratory support

Technique	Blood flow	Bypass type	Main suggested indications
Extracorporeal membrane oxygenation (ECMO)*	3–5 L/min	Veno-venous Veno-arterial	Rescue of hypoxia in ARDS
Extracorporeal CO_2 removal	0.5–2.5 L/min	Veno-venous Arteriovenous	Prevention of VILI in ARDS COPD Bronchopleural fistulas with air leaks Bridge to transplant

*Brings CO_2 removal as a fringe benefit.

ECMO as a rescue procedure for the severely hypoxic patient

ECMO has been mainly proposed as salvage-therapy for the most severe ARDS patients. The substitution for the lung's gas exchange function reduces the ventilatory requirement and warrants viable levels of oxygenation.

An important contribution in this field came from the Extracorporeal Life Support Organization (ELSO) [10], which collected in 1986 from data of patients treated with ECMO in 130 centres, mainly located in the United States. In 2009 the results from 1473 patients were published, constituting the largest published dataset on this topic. Notwithstanding the severe hypoxaemia (median PaO_2/FiO_2 was 57 mmHg) and high peak inspiratory pressure (median 40 mmHg) before ECMO institution, the survival rate was 50%. Interestingly, one of the factors associated with a lower mortality was a short duration of mechanical ventilation prior to ECMO. This underlines the importance of an early initiation of ECMO in the most severe patients, rather than a last desperate rescue after failure of 'traditional' therapies. Another important case series was published by the group of the Karolinska hospital [11]. The authors reported data from 16 patients with a very high lung injury score (average 3.5): the survival rate was 76%. Patients were managed with minimal sedation, with the use of pressure support ventilation, and accepting arterial saturation as low as 70%.

Until recently, however, no randomized trial had proven a clear survival in patients with ARDS treated with ECMO. In 2009, the publication of the results of the CESAR trial provided the first formal evidence in favour of ECMO application in adults [12]. This study was conducted in the UK and followed a particular design, modelled on the template of a previous ECMO study in neonates. Adult patients (18–65 years) with severe, but potentially reversible respiratory failure were enrolled. Severe respiratory failure was defined as a Murray score ≥3 or uncompensated hypercapnia with a pH <7.20. Patients randomized to ECMO were transferred to the ECMO centre in Leicester; control patients continued the conventional treatment according to the best available clinical practice. In most of the patients assigned to the treatment group, veno-venous ECMO via percutaneous cannulation was used. The system was designed to provide full substitution of pulmonary gas exchange with high blood flows (> 5 L/min), and high gas exchange surfaces. The average duration of bypass was 9 days. During ECMO the ventilator settings were gradually reduced to allow lung rest, limiting the peak inspiratory pressure to 30 cmH_2O and respiratory rate to 10 breaths/min. In 5 years, 180 patients were enrolled onto the study. Survival at 6 months or the absence of severe disability was achieved in 63% of the ECMO patients, comparing very favourably with 47% of the control group. This accounted for one life without severe disability saved every six patients treated. In spite of the peculiarity of the study design, this is the first, long-expected, positive randomized clinical trial on adult ECMO application. These results are achieved through lung protection by the total or almost total substitution of the lung gas exchange function.

An important impulse to the early use of ECMO in ARDS came from the experience with the recent outbreak of H1N1 influenza. The pandemic was characterized by a high incidence of severe respiratory complications. Different series of patients with H1N1 infection requiring ICU admission have been described in Mexico, Canada, Australia, and United States. All patients required MV with high PEEP and frequent use of rescue therapies. Davies et al. have recently described a series of 68 patients with H1N1-associated ARDS treated with ECMO in 15 Australian ICUs—the median duration of extracorporeal support was 10 days and the overall mortality was 21% [13].

To cope with the H1N1 influenza epidemic outbreak in Italy, the Italian Ministry of Health organized a multicentre network for the transferring of more severe patients to specialized centres equipped to apply ECMO treatment. Eight of the 14 ECMO centres were also able to start ECMO in outside centres and transport the patient to the referral hospital, while on ECMO. Thus, if patient transportation was considered risky, patient was connected to ECMO at bedside and then transferred while on ECMO to the tertiary centre. Between August 2009 and March 2010, 60 patients with suspected H1N1 affected by severe ARDS were treated with ECMO, H1N1 diagnosis being confirmed later in 49. Twenty-eight patients were transported while on ECMO. Overall ICU discharge survival was 68%. No major complications were reported during the transportation of patients in ECMO. In keeping with the data of the ELSO registry, non-survivors had a longer duration of mechanical ventilation when compared with survivors, in addition to higher SAPS II and SOFA scores [14].

A smaller case series from Marseille, France had been previously published [15], where nine patients with H1N1 were treated with ECMO; six of these had been connected to ECMO in a referral hospital by a mobile team.

A similar system was set up in the UK, with similar results. The British ECMO group recently published a cohort study in which ECMO-referred patients, defined as all patients with H1N1-related ARDS, who were transferred to one of the four adult ECMO centres in the UK, were matched with similar non-ECMO-treated H1N1 ARDS patients using data from a concurrent, longitudinal cohort study. Detailed demographic, physiological, and comorbidity data were used in three different matching techniques. The hospital mortality rate for ECMO-referred patients was almost one half of that for non–ECMO-referred patients in all the three matching used [16].

Future perspectives in extracorporeal respiratory support: extracorporeal gas exchange to avoid injury from mechanical ventilation

Ventilator-induced lung injury (VILI) has been known as a potential mechanism of lung injury, which can further aggravate ARDS.

The benefits of reduction of tidal volume and plateau airway pressure reduction are well known, but the need for CO_2 removal, even if hypercapnia is tolerated to a certain extent, represent a limiting factor to a further ultra-preventive lung strategy. In this respect, CO_2 removal by ECMO could dramatically decrease the ventilatory needs. As stated, in order to effectively remove a large fraction of total CO_2 production (without the need for an effective oxygenation), a lower blood flow is required, further reducing the size of the cannulas, the need for anticoagulation and the invasiveness of the technique. Terragni et al. showed that extracorporeal CO_2 removal by a low flow device allows the reduction of tidal volume from 6 to 4 mL/kg, with a reduction of circulating inflammatory cytokines and lung hyperinflation. However, more data are necessary in order to understand whether extracorporeal CO_2 removal is able to improve the outcome of ARDS patients [17].

Pushing this concept to its furthest end, ECMO could be conceived as an alternative to MV and endotracheal intubation, although some preliminary reports indicate that COPD patients failing non-invasive ventilation might successfully be managed with [low flow] ECMO and avoid intubation [18].

Conclusion

The fire of ECMO has been smouldering under the ashes for many years, but improved technologies, deeper knowledge of the risk of VILI and flu pandemics gave a new burst to its flame. Clinicians should use ECMO with caution, in order to avoid unnecessary risks for their patients. The role of ECMO in severe hypoxia is hardly debatable, but, in such cases, an early application of the technique and a centralization of cases to a few specialized experienced centres (taking advantage of ECMO provided by mobile teams also for a safe patient transport) are mandatory to success. We will hopefully learn, in the next years, if low flow CO_2 removal will become a lighthouse for safer, less invasive ventilation, eventually finding its place, in some patients.

References

1. Zapol WM, Snider MT, Hill JD, et al. (1979). Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *Journal of the American Medical Association*, **242**(20), 2193–6.
2. Bartlett RH, Roloff DW, Custer JR, Younger JG, and Hirschl RB. (2000). Extracorporeal life support: the University of Michigan experience. *Journal of the American Medical Association*, **283**(7), 904–8.
3. Gattinoni L, Agostoni A, Pesenti A, et al. (1980). Treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO_2. *Lancet*, **2**(8189), 292–4.
4. Pesenti A, Zanella A, and Patroniti N. (2009). Extracorporeal gas exchange. *Current Opinions in Critical Care*, **15**(1), 52–8.
5. Brodie D and Bacchetta M. (2011). Extracorporeal membrane oxygenation for ARDS in adults [Review]. *New England Journal of Medicine*, **365**(20), 1905–14.
6. Isgro S, Patroniti N, Bombino M, et al. (2011). Extracorporeal membrane oxygenation for interhospital transfer of severe acute respiratory distress syndrome patients: 5-year experience. *International Journal of Artificial Organs*, **34**(11), 1052–60.
7. Pesenti A, Rossi GP, Pelosi P, Brazzi L, and Gattinoni L. (1990). Percutaneous extracorporeal CO2 removal in a patient with bullous emphysema with recurrent bilateral pneumothoraces and respiratory failure. *Anesthesiology*, **72**(3), 571–3.
8. Pesenti A, Kolobow T, Riboni AE, et al. (1982). Single vein cannulation for extracorporeal respiratory support. *Life Support Systems*, **1**(Suppl.), 165–7.
9. Kopp R, Bensberg R, Wardeh M, Rossaint R, Kuhlen R, and Henzler D. (2012). Pumpless arterio-venous extracorporeal lung assist compared with veno-venous extracorporeal membrane oxygenation during experimental lung injury. *British Journal of Anaesthesia*, **108**(5), 745–53.
10. Brogan TV, Thiagarajan RR, Rycus PT, Bartlett RH, and Bratton SL. (2009). Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database. *Intensive Care Medicine*, **35**(12), 2105–14.
11. Linden V, Palmer K, Reinhard J, et al. (2000). High survival in adult patients with acute respiratory distress syndrome treated by extracorporeal membrane oxygenation, minimal sedation, and pressure supported ventilation. *Intensive Care Medicine*, **26**(11), 1630–7.
12. Peek GJ, Mugford M, Tiruvoipati R, et al. (2009). Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*, **374**(9698), 1351–63.
13. Davies A, Jones D, Bailey M, et al. (2009). Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. *Journal of the American Medical Association*, **302**(17), 1888–95.
14. Patroniti N, Bellani G, Saccavino E, et al. (2012). Respiratory pattern during neurally adjusted ventilatory assist in acute respiratory failure patients. *Intensive Care Medicine*, **38**(2), 230–9.
15. Roch A, Lepaul-Ercole R, Grisoli D, et al. (2010). Extracorporeal membrane oxygenation for severe influenza A (H1N1) acute respiratory distress syndrome: a prospective observational comparative study. *Intensive Care Medicine*, **36**(11), 1899–905.
16. Noah MA, Peek GJ, Finney SJ, et al. (2011). Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *Journal of the American Medical Association*, **306**(15), 1659–68.
17. Terragni PP, Del Sorbo L, Mascia L, et al. (2009). Tidal volume lower than 6 mL/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology*, **111**(4), 826–35.
18. Kluge S, Braune SA, Engel M, et al. (2012). Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation. *Intensive Care Medicine*, **38**(10), 1632–9.

PART 4.9

Aspiration and inhalation

CHAPTER 106

Aspiration of gastric contents in the critically ill

Sara Froio and Franco Valenza

Key points

- Several pulmonary syndromes may occur after aspiration, depending on the amount and nature of the aspirated material, the frequency of aspiration, and the host's response to the aspirated material.
- Aspiration of gastric contents results in a chemical burn of the tracheobronchial tree and pulmonary parenchyma, causing pneumonitis.
- Aspiration pneumonia may involve fluid or particulate matter, which are not inherently toxic to the lung, but can cause airway obstruction or reflux airway closure.
- The causative micro-organism in aspiration pneumonia, similar to community-acquired pneumonia, are thought to be bacteria residing in the oral cavity. In the treatment of aspiration pneumonia, use of antimicrobials for pneumonia itself is important.
- The aspiration of gastric contents is generally preventable by good anaesthetic practice and attention to details in the intensive care unit.

Introduction

Aspiration is defined as the inhalation of oropharyngeal or gastric contents into the larynx and lower respiratory tract. Several pulmonary syndromes may occur after aspiration, depending on the amount and nature of the aspirated material, the frequency of aspiration, and the host's response to the aspirated material. Aspiration pneumonitis is a chemical injury caused by the inhalation of sterile gastric contents, whereas aspiration pneumonia is an infectious process caused by the inhalation of oropharyngeal secretions that are colonized by pathogenic bacteria. Other aspiration syndromes include airway obstruction, lung abscess, exogenous lipoid pneumonia, and chronic interstitial fibrosis [1,2].

The three syndromes that are most frequently seen clinically and are best studied are chemical pneumonitis, bacterial infection, and airway obstruction. Although there is some overlap among these syndromes, they are distinct clinical entities. This chapter focuses on the pathophysiology, clinical features, and management of these three syndromes (Table 106.1).

The lack of specific and sensitive markers of aspiration complicates the epidemiological study of aspiration syndromes. Furthermore, most studies do not distinguish between aspiration pneumonitis and aspiration pneumonia.

The risk of aspiration pneumonitis is approximately 10% after a drug overdose. This condition is very common in patients with reduced consciousness level due to general anaesthesia, particularly during pregnancy, where there is increased intra-abdominal pressure and delayed gastric emptying. The most recent report suggests an incidence of 1 in 3000 patients receiving general anaesthesia. However, mortality remains very high and accounts for 10–30% of all deaths related to anaesthesia. The elderly, particularly the nursing home population, is at increased risk of aspiration secondary to both an increased incidence of pharyngeal dysmotility and gastro-oesophageal reflux. Aspiration pneumonia and pneumonitis are the most common causes of death in patients with dysphagia caused by neurological disorders [1].

Conditions that predispose to aspiration of gastric content include:

- Reduced consciousness resulting in a compromise of the cough reflex and glottic closure.
- Neurological dysphagia.
- Disorders of the upper gastrointestinal (GI) tract, including oesophageal disease, surgery involving the upper airways or oesophagus, and gastric reflux.
- Disruption of the gastro-oesophageal junction due to tracheostomy, endotracheal intubation, bronchoscopy, upper endoscopy, and nasogastric feeding.
- General anaesthesia.
- Extremes of age.

Clinical syndromes

Aspiration pneumonitis

Pathophysiology

The term aspiration pneumonitis refers to the aspiration of substances that are toxic to the lower airways, independent of bacterial infection. Gastric acid is the most frequently encountered and the most completely studied substance that can initiate an inflammatory reaction. Historically, the syndrome most commonly described as aspiration pneumonitis is Mendelson's syndrome, reported in 1946 in patients who aspirated while receiving

Table 106.1 Classification of aspiration syndromes

Syndromes	Pulmonary sequelae	Clinical features	Management features
Aspiration pneumonitis	Chemical injury	Dyspnoea, tachycardia Hypoxaemia	Tracheal suction Antibiotics for superimposed infection
Aspiration pneumonia	Bacterial infection	Usually insidious onset Cough, fever, purulent sputum **Radiograph**: infiltrate involving dependent pulmonary segment or lobe	Antibiotics
Airways obstruction	Mechanical obstruction	**Dependent upon level of obstruction**: ◆ Acute dyspnoea ◆ Cyanosis ◆ Apnoea **Pulmonary oedema**	Tracheal suction Extraction of particulate matter

general anaesthesia during obstetrical procedures. Mendelson revealed the importance of acid in the pathogenesis of this syndrome when he showed that acid gastric contents introduced into the lungs of rabbits caused severe pneumonitis that was indistinguishable from that caused by an equal amount of 0.1 N hydrochloric acid. Later, it was shown that if the pH of gastric contents was neutralized before aspiration, the pulmonary injury was minimal. In experimental studies, the severity of lung injury increased significantly as the volume of the aspirate increases and as its pH decreases [3,4].

The pathophysiology of acid pneumonitis has been studied in experimental animals by intratracheal inoculation of sterile hydrochloric acid. These animal models require an inoculum that has a pH of ≤2.5 and that is relatively large (usually 1–4 mL/kg). This would translate to an inoculum of at least 25 mL of gastric acid in adult humans. It is probable that smaller volumes produce a more subtle process that either escapes clinical detection or causes a less fulminant form of pneumonitis. The clinical observation that patients with oesophageal or gastric reflux experience frequent bouts of recurrent pneumonitis, often accompanied by pulmonary fibrosis, supports this concept [5–7].

Aspiration of gastric contents results in a chemical burn of the tracheobronchial tree and pulmonary parenchyma, causing an intense parenchymal inflammatory reaction. Experimental animal studies have shown that the toxic effects of acid are immediate and extensive. Within 3 minutes there is atelectasis, due to acid denaturation of surfactant, peribronchial haemorrhage, pulmonary oedema, and degeneration of bronchial epithelial cells [8].

By 4 hours, the alveolar spaces are filled with polymorphonuclear leucocytes and fibrin. Hyaline membranes are seen within 48 hours. The lung at this time is also grossly oedematous, haemorrhagic, and with alveolar consolidation.

At first, the caustic effects of the low pH of the aspirate are directed to the cells lining the alveolar–capillary interface—a second phase is associated with the infiltration of neutrophils into the alveoli and lung interstitium, with histological findings characteristics of acute inflammation. The mechanisms of the lung injury after gastric aspiration involve the release of pro-inflammatory cytokines, especially tumour necrosis factor-alpha (TNFα) and interleukin IL-8. In animal studies, neutropenia, inhibition of neutrophil function, inactivation of IL-8, and complement inactivation attenuate the acute lung injury induced by acid aspiration.

Under normal condition the gastric contents are sterile because of acidity. Bacterial infection does not have an important role in the early stages after the aspiration of gastric contents, but it may occur at later stages. Colonization of gastric contents may occur when the pH in the stomach is increased by the use of antacids. In addition, there may be gastric colonization by Gram-negative bacteria in patients who receive enteral feeds, as well as in patients with gastroparesis or small bowel syndrome [9,10].

Clinical features and diagnosis

The diagnosis of acid pneumonitis is usually presumptive.

The following clinical features should raise the possibility of chemical pneumonitis:

- Abrupt onset of symptoms with prominent dyspnoea.
- Fever that is usually low grade.
- Cyanosis and diffuse crackles on lung auscultation.
- Severe hypoxaemia and infiltrates on chest radiograph involving dependent pulmonary segments.

The dependent lobes in the upright position are the lower lobes. However, aspiration that occurs while patients are in the recumbent positions may result in pneumonia in the superior segments of the lower lobes and the posterior segments of the upper lobes. After a suspected aspiration, chest X-ray abnormalities typically appear within 2 hours. If performed, bronchoscopy demonstrates erythema of the bronchi, indicating acid injury.

The course of the disease varies. In one retrospective review of 50 cases, three outcomes were observed:

- 12% of patients had a fulminant course and died shortly after aspiration presumably from acute respiratory distress syndrome (ARDS).
- 62% had a rapid clinical improvement with clearing of the chest radiograph.
- 26% had initial rapid improvement, but then developed new expanding infiltrates on chest X-ray, which probably represented secondary bacterial infection or the development of ARDS superimposed on the acid injury [11].

Management

Patients with an observed aspiration should be placed in the head-down position on the right side and should have also immediate tracheal suction to maintain a clear airway. However, this manoeuvre will not protect the lungs from chemical injury, which occurs instantly in a manner that has been compared with a 'flash burn'. The acid inoculum is rapidly neutralized by the physiological response. Pulmonary lavage is futile, since the full extent of injury has usually occurred by the time the diagnosis is recognized.

The major therapeutic approach is to correct hypoxia and support pulmonary function by assisted ventilation or positive-pressure oxygen. Endotracheal intubation should be considered for patients who are unable to protect their airways.

The use of corticosteroids in the treatment of chemical pneumonitis is controversial. Studies in animals have failed to demonstrate beneficial effects of corticosteroids on pulmonary function, lung injury, alveolar–capillary permeability, or outcome after acid aspiration. Furthermore, given the failure of two multicentre, randomized controlled trials to demonstrate a benefit of high-dose corticosteroids in patients with ARDS, the administration of corticosteroids cannot be recommended [12–14].

Although it is common practice, the prophylactic use of antibiotics in patients in whom aspiration is suspected or witnessed is not recommended. Similarly, the use of antibiotics shortly after aspiration in patients in whom a fever, leukocytosis, or a pulmonary infiltrate develops is discouraged, since the antibiotic may select for more resistant organisms in patients with an uncomplicated chemical pneumonitis. However, empirical antibiotic therapy is appropriate for patients who aspirate gastric contents, and who have small-bowel obstruction or other conditions associated with colonization of the gastric contents. Antibiotic therapy should be considered for patients with aspiration pneumonitis that fails to resolve within 48 hours following aspiration. Empirical therapy with broad-spectrum agents is recommended; antibiotics with anaerobic activity are not routinely required. Sampling of the lower respiratory tract (with a protected specimen brush or by broncho-alveolar lavage) and quantitative culture in intubated patients may allow targeted antibiotic therapy, or in patients with negative cultures, the discontinuation of antibiotics.

Aspiration pneumonia

Pathophysiology

Aspiration pneumonia develops after the inhalation of colonized oropharyngeal material. Aspiration of colonized secretions from the oropharynx is the primary mechanism by which bacteria gain entrance to the lungs. The causative micro-organism in aspiration pneumonia, similar to community-acquired pneumonia, are thought to be bacteria residing in the oral cavity. In fact, the risk of aspiration pneumonia is lower in patients without teeth and in patients who receive aggressive oral care.

Any condition that increases the volume or the bacterial burden of oropharyngeal secretions in a person with impaired defence mechanisms may lead to aspiration pneumonia.

This condition is generally less fulminant than acid pneumonitis and the actual episode of aspiration is seldom observed.

Clinical features and diagnosis

In patients with aspiration pneumonia, unlike those with aspiration pneumonitis, the episode of aspiration is frequently not witnessed and the diagnosis is often inferred when a patient at risk of aspiration has radiographic evidence of an infiltrate in characteristic bronchopulmonary segment. The presenting findings in aspiration pneumonia due to bacterial infection are variable depending on the time when the patient is seen during the course of the infection, the bacterial agents involved, and the status of the host.

Compared with most cases of community-acquired pneumonia, the course of the disease in this type of aspiration pneumonia often evolves slowly. The majority of patients presents with the common manifestations of pneumonia, including cough, fever, purulent sputum and dyspnoea, but the process evolves over a period of days or weeks instead of hours. If not treated, these patients have a high incidence of cavitation and abscess formation in the lungs in later stages [15].

Organisms that assume the greatest importance in terms of pathogenetic potential are anaerobic bacteria. Expectorated sputum is unsuitable for anaerobic culture because of inevitable contamination by the normal flora of the mouth. There is a limited experience with quantitative cultures of specimens obtained at bronchoscopy by a protected brush or broncho-alveolar lavage. In current practice, anaerobic bacteria are virtually never detected in pulmonary infections due to the lack of access to specimens that are uncontaminated with the normal flora of the upper airways, such as needle aspirated, trans-tracheal aspirates and pleural fluid.

Most patients with aspiration pneumonia acquired in the community have infection of mixed agents (anaerobic and aerobic bacteria such as *S. pneumoniae, S. aureus, H. influentiae*, and Enterobacteriaceae). By contrast, patients with nosocomial aspiration pneumonia commonly involve a mixture of anaerobes and Gram-negative bacilli such as *E. coli, Klebsiella*, and *Pseudomonas*. One recent prospective study of 95 patients from a long-term care facility admitted to an intensive care unit with pneumonia and risk factors for aspiration found that Gram-negative bacilli were the most common isolates (49%) followed by anaerobes (16%) and *S. aureus* (12%) [16].

One explanation for the difference in organisms accompanying anaerobic bacteria in hospitalized patients is the high frequency of upper airway colonization by enteric Gram-negative bacilli.

Management

In contrast to chemical pneumonitis, antibiotics are the most important component of treatment of aspiration pneumonia due to bacterial infection. The choice of antibiotics should depend on the setting in which the aspiration occurs, as well as the patient's general health. Historically, the antibiotic of choice for the treatment of aspiration pneumonia and lung abscess involving anaerobic bacteria was penicillin, usually given intravenously or orally in high doses. However, a recent trial evaluated the efficacy of agent with specific anaerobic activity, such as clindamycin and metronidazole. Antibiotic agents with activity against Gram-negative organism, such as third-generation cephalosporins, fluoroquinolones, and piperacillin, are usually required.

When anaerobic bacteria are suspected, clindamycin (600 mg iv every 8 hours) is suggested as first line therapy. Alternative agents, as suggested by clinical trials, are amoxicillin-clavulanic acid (875 mg po bd) or the combination of metronidazole (500 mg po or endovenous tds) plus amoxicillin (500 mg po tds). For nosocomial aspiration pneumonia aerobic bacteria, especially Gram-negative

bacilli and *S. aureus*, are usually more important than the anaerobes and therapy should be directed at these organisms [17].

The usual duration of therapy for cases that are not complicated by cavitation or empyema is 7–10 days. Patients with lung abscesses need a longer course of antibiotics, usually until there is radiographic clearance or significant improvement.

Airway obstruction

Pathophysiology

Aspiration pneumonia may involve fluid or particulate matter, which are not inherently toxic to the lung, but can cause airway obstruction or airway closure.

Typical fluids that are aspirated and are not toxic to the lungs per se, include saline, barium, ingested fluid (including water), and gastric contents with a pH exceeding 2.5. Aspiration of large volumes of non-toxic fluid produces abrupt suffocation by mechanical obstruction. Failure to clear the airways may be impaired in patients who lack an effective cough reflex due to a neurological deficit or coma [18].

Clinical features and diagnosis

Patients who have aspirated gastric material may present with dramatic signs and symptoms. In solid particle aspiration, the severity of respiratory obstruction depends on the relative size of the particle that is aspirated and the calibre of the lower airways. When smaller particulate reaches peripheral airways causing complete or partial obstruction, the initial symptom is cough due to bronchial irritation. Chest radiograph shows atelectasis or obstructive emphysema. When major bronchi are involved there may be severe dyspnoea, cyanosis, wheezing, chest pain, pulmonary oedema, hypotension, and hypoxaemia with rapid progression to severe ARDS and death.

Bacterial superinfection is a frequent complication when the obstruction persists for more than 1 week.

Management

The obvious therapeutic modality for the aspiration of large volume of non-toxic fluids is immediate tracheal suction. In the absence of a residual pulmonary infiltrate, no further treatment is indicated.

The immediate suggested treatment when major bronchi are involved is the Heimlick manoeuvre to dislodge the particle. When the obstruction is only partial, the primary therapeutic modality is removal of the particles with fibre optic or rigid bronchoscopy.

Prevention

The main aim of aspiration treatment is prevention. Patient at risk must be identified, including emergency cases, pregnant women, and diabetics. A good anaesthetic practice and attention to detail for patients in the intensive care unit (ICU) are required. Safe intubation needs to be fasted after a rapid sequence induction with correct use of cricoid pressure.

The accepted minimum time for solid food to be emptied from the stomach in adults is 6 hours. Other approaches to prevention include the use of awake intubation and the use of balloon-tipped nasogastric tubes to attempt to occlude the cardia. Another element in prevention is the prophylactic use of anti-acids. A number of agents given pre-operatively have been shown to both increase effectively the pH and to reduce the volume of gastric contents.

In the ICU, similar preventive measures should be applied for intubation of patients, many of whom will also have nasogastric tubes inserted. Even a tracheostomy does not completely eliminate the risk of aspiration.

Bacterial colonization of gastric contents and oropharyngeal secretions, with subsequent aspiration to the lower airways are the most commonly recognized pathogenic factors for the development of nosocomial pneumonia.

Safe extubation is also an important factor in ICU, where patients can have an endotracheal tube in position several days. Patients must be able to cough and have an adequate gag reflex, the stomach contents must be aspirated, and the patient should be placed in the sitting position.

It has been recently observed that both body position and the time the patient is kept in that position are factors that increase the risk of aspiration of gastric contents to lower airways, increasing the risk of nosocomial pneumonia development. This suggests that the semi-recumbent position could be a non-cost prophylactic measure for nosocomial pneumonia.

A number of research groups are studying factors that affect aspiration from the oropharynx into the lower airways in mechanically-ventilated patients as the type of endotracheal cuff, with low-volume high-pressure cuffs.

In ICU patients, once nasogastric feeding has commenced, preventing gastric dilatation by regular aspiration of gastric contents to determine effectiveness of gastric emptying is essential. In patients with gastroparesis leading to gastric distention and regurgitation, the use of post-pyloric tube for feeding may have advantages [19,20].

Measures that should be implemented to prevent silent aspiration include elevating the head (of the bed), oral care, and adequate nutrition to prevent muscle deterioration.

References

1. Marik PE. (2001). Aspiration pneumonia and aspiration pneumonitis *New England Journal of Medicine*, **344**(9), 665.
2. Bartlett JG and Gorbach SL. (1975). The triple threat of aspiration pneumonia. *Chest*, **68**, 560.
3. Mendelson CL. (1946). The aspiration of stomach contents into the lungs during obstetric anesthesia. *American Journal of Obstetrics and Gynecology*, **52**, 191–205.
4. Tebeaut JR. (1952). Aspiration of gastric contents: an experimental study. *American Journal of Pathology*, **28**, 51–67.
5. Fisk RL, Symes JF, Aldridge LL, and Couves CM. (1970). The pathophysiology and experimental therapy of acid pneumonitis in ex vivo lungs. *Chest*, **57**, 364.
6. Mays EE, Dubois JJ, and Hamilton GB. (1972). Pulmonary fibrosis associated with tracheobronchial aspiration. A study of the frequency of hiatal hernia and gastroesophageal reflux in interstitial pulmonary fibrosis of obscure etiology. *Chest*, **69**, 512.
7. Johnson LF and Rajagopal KR. (1988). Aspiration resulting from gastroesophageal reflux. A cause of chronic bronchopulmonary disease. *Chest*, **93**, 676.
8. Davidson BA, Knight PL, Wand Z, et al. (2005). Surfactant alterations in acute inflammatory lung injury from aspiration of acid and gastric particulates. *American Journal of Physiology - Lung Cellular and Molecular Physiology*, **288**, L699–708.
9. Garvey BM, McCambley JA, and Tuxen DV. (1989). Effects of gastric alkalinization on bacterial colonization in critically ill patients. *Critical Care Medicine*, 17: 211–16.
10. Bonten MJ, Gaillard CA, van der Geest S, et al. (1995). The role of intragastric acidity and stress ulcus prophylaxis on colonization and

infection in mechanically ventilated ICU patients: a stratified, randomized, double-blind study of sucralfate versus antacids. *American Journal of Respiratory and Critical Care Medicine*, **152**, 1825.
11. Bynum LJ and Pierce AK. (1976). Pulmonary aspiration of gastric content. *American Reviews in Respiratory Diseases*, **114**, 1129.
12. Bernard GR, Luce JM, Sprung CL, et al. (1987). High-dose corticosteroides in patients with the adult respiratory distress syndrome. *New England Journal of Medicine*, **317**, 1565.
13. Bone RC, Fisher CJ, Jr, Clemmer TP, Slotman GJ, and Metz CA. (1988). Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. *Chest*, **94**, 448.
14. Wynne JW, DeMarco FJ, and Hood CI. (1981). Physiological effects of corticosteroids in foodstuff aspiration. *Archives of Surgery*, **116**, 46.
15. Bartlett JC. (1993). Anaerobic bacterial infections of the lung and pleural space. *Clinical Infectious Diseases*, **16**(Suppl. 4), S248.
16. El-Solh AA, Pietrantoni C, Bhat A, et al. (2003). Microbiology of severe aspiration pneumonia in institutionalized elderly. *American Journal of Respiratory and Critical Care Medicine*, **167**, 1650.
17. Kadowaki M, Demura Y, Mizuno S, et al. (2005). Reappraisal of clindamicyn IV monotherapy for treatment of mild-to-moderate aspiration pneumonia in elderly patients. *Chest*, **127**, 1276.
18. Colebatch HJ and Halmagyi DF. (1964). Reflex airway reaction to fluid aspiration. *Journal of Applied Physiology*, **17**, 787.
19. Bonten MJ, Gaillard CA, van der Hulst R, et al. (1996). Intermittent enteral feeding: the influence on respiratory and digestive tract colonization in mechanically ventilated intensive care unit patients. *American Journal of Respiratory and Critical Care Medicine* **154**, 394.
20. Bonten MJ, Gaillard CA, van Tiel FH, van der Geest S, and Stobberingh EE. (1994). Continuous enteral feeding counteracts preventive measures for gastric colonization in intensive care unit patients. *Critical Care Medicine*, **22**, 939.

CHAPTER 107

Inhalation injury in the ICU

Silvia Coppola and Franco Valenza

Key points

- Smoke inhalation causes three types of injuries—thermal injury to the upper airways, chemical injury to the tracheobronchial tree, and systemic poisoning.
- When a patient presents with known or suspected smoke inhalation, the patient's airway, breathing, and circulation should be immediately and repeatedly assessed.
- Carbon monoxide and hydrogen cyanide interfere with the delivery and utilization of oxygen.
- Prevention or early diagnosis, and treatment of associated life-threatening complication are necessary to decrease morbidity and mortality after inhalation injury.
- Bronchoscopy is currently a standard diagnostic regimen for inhalation injury.

Introduction

Inhalation injury is an acute respiratory tract insult caused by steam or toxic inhalant, such as fumes, gases, and mists. Inhalation injury may occur without cutaneous burn injury, although the two injuries usually occur together [1]. Inhalation injury continues to be one of the most serious associated injuries, complicating the care of thermally-injured patient. Prevention or early diagnosis, and treatment of this associated life-threatening complication are necessary to decrease its associated morbidity and mortality. Airway injury is present in up to one-third of patients with major burns, and the risk of concurrent pulmonary damage is directly related to the extent of the body surface area burned [2]. Inhalation injury greatly increases the incidence of respiratory failure and acute respiratory distress syndrome (ARDS). It is also the cause of most early deaths in burn victims. [1] The mortality rate following smoke inhalation ranges from 45 to 78% [3–5].

Pathophysiology

Three mechanisms are responsible alone or in combination with inhalation injury—thermal injury to the respiratory tract, chemical injury of airways and lung parenchyma due to exposure to irritating gases and particulate matter, and systemic oxygen supply impairment.

Thermal injury

The inhalation of extremely hot smoke may produce thermal injury to the upper airway. Direct thermal injury below the vocal cords is very unusual because of the efficient heat-exchanging system of the mucous membranes of the upper airway and the limited capacity of dry air to conduct heat. Thermal injury due to smoke inhalation may very rapidly cause erythema, ulceration, and life-threatening intra-oral, pharyngeal, or laryngeal oedema. The oedema may also be progressive during the first 18–24 hours [1]. Therefore, early recognition of thermal injury is very important to perform tracheal intubation before oedema progresses to airway obstruction. Lower airway mucosal oedema is usually not clinically evident until 24 hours after exposure. This oedema can cause damage to the tracheal and bronchial mucosa resulting in bronchorrhoea (that may not appear until 36 hours after exposure), ulceration, and damage to the ciliary system. Tracheal and bronchial epithelial sloughing may also occur [5–7].

Chemical injury

Chemical injury of the airway can be caused by irritants or cytotoxic compounds. The type and volume of the irritants generated by combustion can vary depending on the material burned, the temperature of the fire, and the amount of oxygen present in the fire environment.

Gases with high water solubility such as ammonia, hydrogen chloride, and sulphur dioxide, react with water in the mucous membranes of the upper airway, and produce strong acids and alkalis leading to irritation, ulceration, and oedema of the mucosal surface. This irritation is well perceived by the victims provoking escape responses. Less water-soluble gases (nitrogen oxides, phosgene, chlorine) are transported to the lower airway. Since these lipid-soluble constituents are not as irritating, protracted exposures are more likely before irritation and inflammatory reaction of the upper and lower airways occur [8]. Moreover, smoke contains particulate matter, usually less than 0.5 mm in size, which is formed by the incomplete combustion of organic material. These small particles easily reach all parts of the respiratory tract including the alveoli.

A short duration of exposure to highly reactive irritants may result in loss of cilia and epithelial erosions of the tracheobronchial tree.

When irritant gasses and particulate matter reach the terminal bronchioles, they can initiate an inflammatory reaction [5,7].

Oxygen delivery impairment

The tissue hypoxia is multifactorial, including the inspiration of air with a FiO_2 of less than 0.15 during the fire and the impaired delivery and utilization of oxygen (O_2) by the tissues. Fires occurring in enclosed spaces rapidly remove the available O_2 from the environment. Asphyxiant gases lower the ambient oxygen tension. Both mechanisms lead to hypoxaemia in the victims.

Carbon monoxide (CO) and hydrogen cyanide are the two major tissue asphyxiants, which interfere with the delivery and utilization of O_2.

The decrease of the O_2 delivery to the brain and other organs interferes with mental and physical capabilities. Gases that produce significant hypoxaemia are indirectly toxic to the heart. If hypoxaemia progresses, the aerobic metabolism shifts to the anaerobic pathway leading to metabolic acidosis.

Injury activates the inflammatory cascade resulting in histologically evident inflammatory changes of the respiratory mucosa within 2 hours of injury. In addition, inflammatory mediators such as thromboxane have been shown to decrease mucociliary activity. Both direct toxic injury, as well as the release of inflammatory mediators, allow particles and toxins to exert their effects on other local defence mechanisms and initiate a cascade of parenchymal damage and bacterial infection [6].

It is thought that inhalation of burn products, as well as respiratory tract thermal injury can impair surfactant function and production. Lung injury models have shown that increased capillary permeability leads to reduced surfactant production causing a loss of force that maintain alveolar patency thus resulting in alveolar collapse [7].

Of particular importance is the fact that inhalation injuries have been proven to increase the risk of pneumonia in burned ICU patients. The risk for pneumonia depends on the impaired function of alveolar macrophages, polymorphonuclear leukocytes, and mucociliary clearance mechanisms. Age >60 years and total burn surface area >20% have been shown to be associated with the development of pneumonia [9]. Both factors might prolong the length of stay and, thus, the risk of pneumonia. The mortality for the combination of inhalation injury and nosocomial pneumonia can reach 50–86% [4]. The root cause of this synergistic effect has to do with both direct lung injury from inhalation, as well as systemic inflammation and immune dysfunctions. Endogenous organisms that often cause infections are those present in the oral and respiratory tract or in the gut at the time of admission. These include *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Proteus mirabilis*, and *Escherichia coli*. Exogenous organisms include methicillin-resistant *S. aureus, Acynetobacter, Pseudomonas aeruginosa*, and other opportunistic organisms. Early infections tend to originate from endogenous organisms, whereas infections at a later time tend to be from exogenous organisms. Recognition and understanding of the pathogens involved in inhalation injury and the time for the onset of infections are important to tailor effective antimicrobial therapy and avert serious complications. ARDS is a complication that may develop several days after the exposure. During thermal injury, inflammatory mediators increase vascular permeability, recruit immune cells, and reduce surfactant function [10]. Thus, burn and inhalation injury carry a significant risk in the development of ARDS that results in a fairly high mortality rate (50–60%) [9].

Diagnosis

An accurate diagnosis of the inhalation burn injury in the early stage is essential for achieving a good prognosis. However, this is not entirely true because the inhalation burn injury has a latent period for 3–4 days prior to the occurrence of respiratory complications. For this reason, inhalation injury is difficult to diagnose and need to be suspected on the basis of a history of smoke exposure in an enclosed space [11].

Patients can be symptomatic within minutes or be asymptomatic for several hours. Symptomatic patients may show some of the following symptoms—mental confusion, unconsciousness, burns to face, lips, mouth and neck, burned nasal or facial hair, soot in the mouth, around the nares or in sputum, hoarseness, and laryngeal stridor. Symptoms of inhalation injury below the glottis include—dyspnoea, bronchorrhoea, wheezing sounds, productive cough, and increased labour in breathing. Bronchospasm and upper airway oedema can occur rapidly. Lower airway oedema can be asymptomatic for up to 24 hours [1].

Inhalation injury should be suspected in the presence of a high carboxyhaemoglobin level after exposure to smoke in an enclosed space. Nevertheless, carboxyhaemoglobin levels may not be reliable if O_2 has been administered or significant time has passed from initial exposure to carbon monoxide (CO). Arterial blood gases may be initially normal. The presence of hypoxaemia and hypercarbia is suggestive of pulmonary injury. All victims of smoke inhalation should be evaluated for cyanide and CO poisoning. Carbon monoxide and hydrogen cyanide poisoning may produce metabolic acidosis and a decreased difference in arteriovenous O_2 content due to tissue hypoxia.

Until 1–2 days after the onset of inhalation burn injury, abnormal findings cannot be identified on a chest radiography or on arterial blood gas analysis. Chest X-ray may show some abnormalities 24–48 hours after the injury, such as atelectasis, and interstitial and alveolar infiltrates that could suggest the presence of pulmonary infection or oedema. Computed tomography may be useful for the diagnosis of delayed respiratory sequelae, such as bronchiectasis, pulmonary fibrosis [12]. Laryngoscopy and bronchoscopy can be performed and have a very high accuracy in the diagnosis of the full extent of the airway injury. The initial exploration may not reveal injured areas for the first 24 hours. This technique may show mucosa erythema, oedema, blisters, ulcerations, presence of particulate matter. Inhalation injury should be assessed by examination of both the upper and lower airway, since any of those may be affected independently. It has been reported that the findings seen on bronchoscopy are useful in predicting the progression of acute lung injury. Fibre optic bronchoscopy is considered the most direct diagnostic method for the definitive diagnosis of inhalation injury and is considered to be more accurate than the diagnosis based on clinical manifestations and signs [13,14].

The literature suggests that the shock phase of burning can lead to colour changes in the airway epithelium that are caused by poor perfusion affecting the correct estimation of the depth of the injury. Fibrescopic bronchoscopy should be performed 3 days after injury, after the shock phase, in order to obtain more accurate results. In conclusion, fibre optic bronchoscopy can evaluate airway epithelial congestion, oedema, erosion haemorrhage, epithelial necrosis, and slough-off. For patients with malignant arrhythmias, refractory hypoxaemia, or severe, uncorrectable bleeding diathesis, bronchoscopy is not recommended [14].

Ventilation–perfusion radionuclide scanning with Xenon-133 is a reliable method for identification of small airway obstruction. This technique is indicated in case of normal findings on chest X-ray and bronchoscopy to determine the extent of the inhalation injury [4].

Pulmonary function tests may give information about respiratory rate, lung compliance, and decreased vital capacity [10]. However,

they are usually difficult to perform due to the critical condition of the patients.

Management

When a patient presents with smoke inhalation, immediate assessment of the patient's airway, breathing, and circulation is indicated. This should take only a few seconds to perform.

The cornerstone of management includes management of airways patency, adequate fluid resuscitation and mechanical ventilation when required, and vigilant surveillance for infectious complications [6].

Intubation is justified if any of the following signs are present—stridor, use of accessory respiratory muscles, respiratory distress, hypoventilation, deep burns to the face or neck, or blistering or oedema of the oropharynx. If these findings are absent, the oropharynx should be examined, followed by laryngoscopy if there is erythema. Some centres routinely perform bronchoscopy, rather than laryngoscopy. Other centres consider that laryngoscopy is preferable to bronchoscopy, because thermal injuries tend to be limited to the supraglottic airways and the appearance of the subglottic airways does not definitively affect management or predict the need for ventilator support [15].

Upper airway oedema or blistering seen during laryngoscopic examination should prompt intubation. Intubation with a large lumen endotracheal tube is preferable to facilitate optimal management of secretions and bronchoscopy. Humidified oxygen may help avoid inspissation [11].

In contrast, in the absence of upper airway oedema or blistering, close observation for 24 hours is reasonable, particularly if serial laryngoscopies are performed. If upper airway oedema is going to occur, it will usually manifest within 24 hours of the exposure.

For patients who are intubated, the endotracheal tube should be left in place until resolution of the upper airway oedema has been documented. Changing the endotracheal tube and failed extubation requiring re-intubation are dangerous in the presence of upper airway oedema and should be avoided [3].

When intubation is necessary, the use of succinylcholine or other depolarizing agents may be appropriate for patient intubation if neuromuscular blockade is required. These drugs are contraindicated for intubation in burn patients 48 hours after injury, since they may worsen post-burn hyperkalaemia.

Patients who do not require intubation should receive supplemental oxygen at a fraction of inspired oxygen of 100%. The purpose of a high concentration of supplemental oxygen is to quickly reverse tissue hypoxia, and to displace CO and cyanide from protein binding sites [6].

Subsequent management of the patient with smoke inhalation consists of monitoring the patient for the development of upper airway compromise due to thermal injury, as well as the development of lower airway sequelae due to direct toxin damage. The former tends to occur within 24 hours of exposure and is managed by intubation until the upper airway oedema subsides, which generally occurs in 3–5 days [3]. The latter tends to occur within 12–36 hours, has a variable duration and is managed by aerosolized bronchodilatators [8].

The hallmark of ventilator management during the treatment of inhalation injury is to minimize further damage and inflammation to lung tissue, and provide adequate ventilation and oxygenation. The increased capillary permeability, coupled with changes in surfactant, results in increased opening alveolar pressures and extensive atelectasis. Studies have shown that increasing positive end expiratory pressure (PEEP) above hydrostatic pressures can prevent collapse of these regions. However, because hydrostatic pressures are not equally distributed and atelectasis tends to occur in dependent lung regions, increasing PEEP to overcome the collapse in these regions could lead to overdistention of other regions, resulting in barotrauma [11]. One way of counteracting the mechanical ventilation-induced damage to lung parenchyma could be the high frequency ventilation (HFV) that uses rapid respiratory rates and small tidal volumes. Several trials of HFV in patients with acute lung injury have shown improvements in oxygenation and ventilation. However, sample sizes for these studies have not been large enough to show a significant survival benefit [6]. Extracorporeal membrane oxygenation is used in situations in which mechanical ventilation fails to provide adequate oxygenation or elimination of carbon dioxide.

Because of the increased pulmonary vascular permeability, the fluid management strategy incorporates providing minimal amounts of fluid to maintain adequate haemodynamic parameters and urine output [6].

Inhalation injury predisposes the patient to nosocomial infections by opportunistic organisms. Prophylactic antibiotic coverage did not show any benefits; on the contrary, it may lead to increased antimicrobial resistance by these organisms. Currently, broad spectrum antibiotics are used when infections or sepsis is suspected. Once an infection agent is identified by culture or Gram stain, the antibiotic therapy is directed at that source.

The presence of CO poisoning, a non-inflammatory form of inhalation injury, should always be considered in those patients suspected of having inhalation injury. CO interferes with oxidative metabolisms by decreasing the oxygen-carrying capacity of the blood, shifting the oxygen–haemoglobin dissociation curve to the left and binding to cytochrome oxidase. For these reasons, any patients suspected of inhalation injury should receive 100% oxygen via a tight-fitting non-rebreathing mask until CO poisoning is excluded and the carboxyhaemoglobin level is less than 10%. The half-life of carboxyhaemoglobin is reduced from approximately 240 minutes at an FIO_2 of 0.21 to around 75–80 minutes at an FIO_2 of 1.0. Hyperbaric oxygen decreases the half-life of carboxyhaemoglobin to approximately 20 minutes [16]. Hyperbaric oxygen treatment has been shown to have an advantage over normobaric oxygen treatment for CO poisoning [6].

A release of hydrogen cyanide also occurs in the smoke of residential fires during combustion of polyurethane, acrylonitrile, and nylon. Hydrogen cyanide can be present in 50% of all fires and its toxicity is synergic with that of carbon monoxide. Cyanide poisoning is nearly impossible to confirm during the initial hours following smoke inhalation because cyanide levels cannot be measured soon enough to be clinically useful. The symptoms and signs are non-specific, and may be due to CO poisoning or an alternative inhaled toxin (including coma, central apnoea, cardiac dysfunction, severe acidosis, high mixed venous oxygen, and low arteriovenous O_2 content difference) [17].

Cyanide inhalation is a potentially life-threating occurrence that requires immediate intervention.

Cyanide, by virtue of its uncoupling of oxidative phosphorylation, is a known cellular toxin. In the patient with an unexplained severe acidosis, tachycardia, and tachypnoea, yet a normal arterial

oxygen content, cyanide poisoning may be present and treatment should be initiated. The first treatment consists of creating a cyanide link in the form of a ferric ion on haemoglobin by the delivery of inhaled amyl nitrite (Amyl Nitrite®) or intravenous sodium nitrite (Nithiodote®). Further treatment includes supplying substrate, such as thiosulphate, which transfers a sulphur group to cyanide and converts it to thiocyanate, which is excreted by the kidneys. A third therapeutic agent, is hydroxycobalamin (Cyanokit®) that combines with cyanide to form the inactive compound cyanocobalamin and is usually given intravenously as a 5-g dose, which should be doubled for patients with blood cyanide levels greater than 40 μmol/L [17].

References

1. El-Helbawy RH and Ghareeb FM. (2011). Inhalation injury as prognostic factor for mortality in burn patients. *Annals of Burns and Fire Disasters*, **24**(2), 82–8.
2. Soejmima K, Schmalstieg FC, Sakurai H, et al. (2001). Pathophysiological analysis of combined burn and smoke inhalation injuries in sheep. *American Journal of Physiology—Lung Cellular and Molecular Physiology*, **280**, L1233–41.
3. Heimbach DM and Waeckerle JF. (1988). Inhalation injuries. *Annals of Emergency Medicine*, **17**, 1316–20.
4. Shirani KZ. (1987). The influence of inhalation injury and pneumonia on burn mortality. *Annals of Surgery*, **205**, 82–7.
5. Haponik EF, Crapo RO, Herdon DN, et al. (1988). Smoke inhalation. *American Reviews of Respiratory Diseases*, **138**, 1060–3.
6. Monafo WW. (1996). Initial management of burns. *New England Journal of Medicine*, **335**, 1581–6.
7. Weiss SM and Lakshiminarayan S. (1994). Acute inhalation injury. *Clinical Chest Medicine*, **15**, 103–6.
8. Toon MH, Maybauer MO, Greenwood JE, et al. (2010). Management of acute smoke inhalation injury. *Critical Care and Resuscitation*, **12**, 53–61.
9. Ching-Chun Lin AA, Liem Cho-Kai Wu, Yi-Fan Wu, Jui-Yung Yang, and Chung-Ho Feng. (2011). Severity score for predicting pneumonia in inhalation injury patients. *Burns*, **38**, 203–7.
10. Slutzer AD, Kinn R, and Said SI. (1989). Bronchiectasis and progressive respiratory failure following smoke inhalation. *Chest*, **95**, 1349.
11. Clark WR Jr. (1992). Smoke inhalation: diagnosis and treatment. *World Journal of Surgery*, **16**, 24–9.
12. Tasaka S, Kanazawa M, Mori M, et al. (1995). Log-term course of bronchiectasis and bronchiolitis obliterans as late complication of smoke inhalation. *Respiration*, **62**, 40.
13. Bingham Hg, Gallagher TJ, and Powell MD. (1987). Early bronchoscopy as a predictor of ventilatory support for burned patients. *Journal of Trauma*, **27**, 1286–8.
14. American Burn Association (2003). Inhalation injury: diagnosis. *Journal of the American College of Surgeons*, **196**, 307–12.
15. Masanes MJ, Legendre C, Lioret N, et al. (1995). Using bronchoscopy and biopsy to diagnose early inhalation injury. Macroscopic and histologic findings. *Chest*, **107**, 1365–9.
16. Ilano AL and Raffin TA. (1990). Management of carbon monoxide poisoning. *Chest*, **97**, 165–9.
17. Beasley DMG and Glass WI. (1998). Cyanide poisoning: pathophysiology and treatment recommendations. *Occupational Medicine*, **48**, 427–31.

PART 4.10

Acute respiratory distress syndrome

CHAPTER 108

Pathophysiology of acute respiratory distress syndrome

Lorraine B. Ware

Key points

- ARDS can occur in disparate clinical settings including both children and adults, both medical and surgical patients, and in both the immunocompetent and the immunocompromised.
- Common aetiologies of ARDS include sepsis, pneumonia, severe traumatic injury and aspiration of gastric contents.
- Clinical identification of cases of ARDS is based on the acute onset of both radiographic infiltrates and significant hypoxaemia.
- Alveolar flooding causes decreased lung compliance, ventilation perfusion mismatch, and shunt leading to increased work of breathing and hypoxaemia.
- The pathophysiology of ARDS is complex and involves acute lung inflammation, increased permeability of the lung endothelial and epithelial barriers, inhibition of surfactant function, impairment of alveolar fluid clearance mechanisms and systemic inflammation.

Clinical presentation

The acute respiratory distress syndrome (ARDS) is a common clinical syndrome with an estimated incidence in the United States of 180,000 cases per year [1]. ARDS can occur in disparate clinical settings, and is seen in both children and adults, in medical and surgical patients, and in both the immunocompetent and the immunocompromised. Common aetiologies of ARDS include sepsis, pneumonia, severe traumatic injury, and aspiration of gastric contents [2]. Less common aetiologies include acute pancreatitis, transfusion-associated acute lung injury (TRALI), ischaemia reperfusion injury, drug overdose, fat embolism, and near drowning. Environmental factors, such as alcohol abuse and cigarette smoke exposure may increase the risk of developing ARDS in at risk patients.

Regardless of the underlying cause, ARDS is characterized by the acute onset of non-cardiogenic pulmonary oedema leading to increased work of breathing and acute hypoxaemic respiratory failure. The majority of patients require invasive mechanical ventilation. Although ARDS is defined by its pulmonary manifestations, multi-organ system failure is common and contributes to morbidity and mortality. Current mortality rates in unselected patients are in the 30–50% range. Mortality rates in clinical trials tend to be lower due to exclusion of patients with severe comorbidities. Morbidity is likewise high; survivors have both short- and long-term sequelae, including pulmonary function abnormalities, cognitive impairment, and other neurologic problems [3].

Diagnosis and clinical definitions

The diagnosis of ARDS should be considered in any patient presenting with acute respiratory failure, and an appropriate risk factor for ARDS, such as sepsis, pneumonia, or severe trauma. Although recent efforts have been aimed at identifying patients at risk for ARDS [4] or with early ARDS [5], the clinical definitions of ARDS, established by expert consensus, are intended for diagnosis of established ARDS. The Berlin definitions [6], the most recent, are a minor modification of the 1994 American European Consensus Conference definitions [7]. Diagnosis is based on the acute onset (within 1 week) of radiographic infiltrates consistent with acute pulmonary oedema (Fig. 108.1) accompanied by hypoxaemia as assessed by the arterial to inspired oxygen fraction. In addition, there should be no clinical evidence of a cardiogenic cause of pulmonary oedema. Echocardiography to exclude a cardiac cause should be considered in patients without a risk factor for ARDS [6]. Despite the simplicity of the definitions, they are under-utilized and the diagnosis of ARDS is often missed leading to under-treatment. The need for arterial blood gas measurement may be one factor that limits uniform application of ARDS definitions, particularly in children. Several investigators have studied the use of the oxygenation saturation (as measured by pulse oximetry) to inspired oxygen ratio [SpO_2/FiO_2] as a substitute for the PaO_2/FiO_2 ratio in determining the severity of hypoxemia across various patient populations [8].

Pathologically, ARDS is characterized by diffuse alveolar damage (Fig. 108.2) [2]. This injury pattern is consistent regardless of the underlying cause of ARDS. Invasive diagnosis of ARDS by lung biopsy is not commonly undertaken due to the morbidity and mortality associated with lung biopsy in the critically ill. Of note, in autopsy studies, neither the American European Consensus Conference [9] nor the Berlin ARDS definitions [10] have high specificity for diffuse alveolar damage. Other pathological diagnoses that were made at autopsy in patients who met the Berlin definition of ARDS include pneumonia, abscess, tuberculosis, cancer, pulmonary embolism, acute pulmonary oedema, pulmonary haemorrhage, interstitial pneumonia/fibrosis, and severe emphysema, underscoring the fact that a variety of clinical conditions can present with clinical features consistent with ARDS [10].

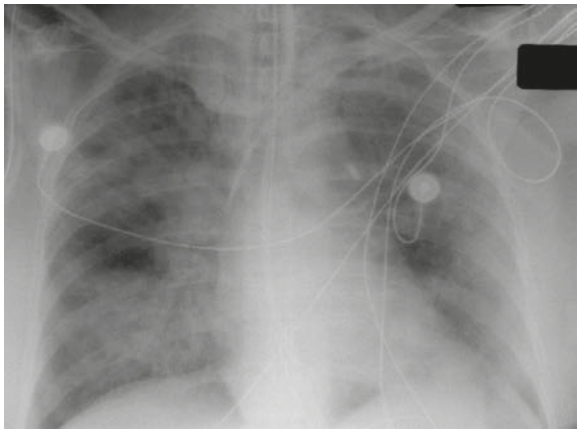


Fig. 108.1 Frontal chest radiograph of a patient with ARDS.

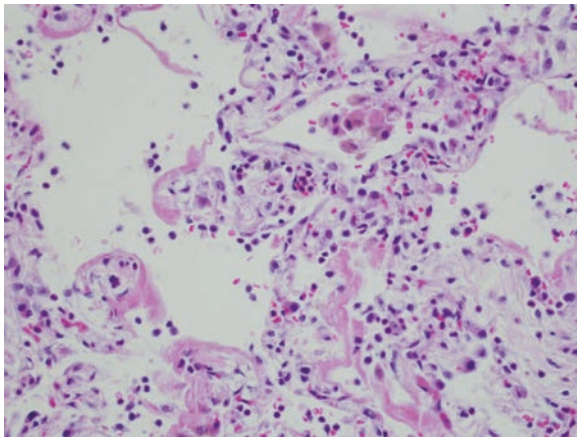


Fig. 108.2 Photomicrograph (×400) of lung tissue from a patient with ARDS showing diffuse alveolar damage with hyaline membrane formation, and intra-alveolar and interstitial neutrophilic inflammation.

Physiological mechanisms of impaired gas exchange and alterations in pulmonary mechanics in ARDS

Acute non-cardiogenic pulmonary oedema is a prominent clinical feature of ARDS. Pulmonary oedema formation in ARDS is caused by increased lung endothelial and alveolar epithelial permeability. Increased endothelial permeability leads to increased rates of filtration of fluid and solute from the lung microvasculature into the lung interstitium. In the absence of increased epithelial permeability, oedema fluid accumulates in the peribronchial interstitial space, and is drained from the peribronchial interstitium by the lung lymphatics that arise in this space. The early interstitial phase of non-cardiogenic pulmonary oedema may not be recognized clinically since interstitial oedema alone does not typically cause significant hypoxaemia and pulmonary oedema may not be visible on chest radiograph until lung water content increases by over 30%.

Although some patients with very mild lung injury may have only interstitial oedema, increased alveolar epithelial permeability due to injury to the epithelial barrier combined with fluid filtration rates that exceed the capacity of the lung lymphatics for fluid removal leads to frank alveolar flooding. Alveolar flooding is a major cause of hypoxaemia in ARDS. Lung units that are flooded contribute to ventilation–perfusion mismatch and intrapulmonary shunt. Inactivation of surfactant by alveolar fluid accumulation may also cause atelectasis of alveolar units, contributing to ventilation–perfusion mismatch and shunt.

Both interstitial and alveolar oedema decrease lung compliance contributing to the increased work of breathing, as well as to the need for ventilation with relatively high distending pressures to deliver sufficient tidal volumes to maintain alveolar ventilation. Accumulation of pulmonary oedema fluid in the peribronchial interstitial space can increase airway resistance, further contributing to increased work of breathing.

Although increased permeability is the primary cause of pulmonary oedema in ARDS, any increases in pulmonary microvascular hydrostatic pressure will raise the driving force for oedema fluid formation across the permeable alveolar–capillary barrier. Increased pulmonary microvascular hydrostatic pressure is common in patients with ARDS [11]. As is discussed in more detail in the chapter on treatment of ARDS, treatment to lower pulmonary microvascular hydrostatic pressure can reduce duration of mechanical ventilation in ARDS likely due to diminished pulmonary oedema formation [11].

Although plain chest radiographs may suggest that pulmonary oedema is diffusely distributed throughout the lung in ARDS, computed tomography demonstrates substantial heterogeneity in oedema distribution [12]. In some patients, particularly those with an extra-pulmonary cause of ARDS [13], pulmonary oedema is indeed diffuse, while others have more focal oedema which tends to be concentrated in dependent regions with less dependent regions appearing more normal.

Molecular mechanisms of acute lung injury and ARDS

A variety of cellular and molecular mechanisms contribute to the pathophysiology of ARDS [14]. Although our understanding of the pathophysiological pathways has improved substantially in the past two decades, therapies targeted at specific mechanisms of injury have largely been ineffective, perhaps due to the complexity and redundancy of injury pathways. In addition, many of these pathways are critically important in host defence.

Inflammation

Dysregulated inflammation is a pathophysiological hallmark of ARDS. Innate immune response pathways are activated in ARDS by pattern recognition receptor binding by either pathogen-derived or cell injury-derived molecules that serve as danger signals. Pattern recognition receptors, such as the Toll-like receptors are highly expressed on the lung epithelium and alveolar macrophages. Activation of these receptors leads to pro-inflammatory signalling, and robust cytokine and chemokine production, activating alveolar macrophages and recruiting neutrophils from the vasculature into the alveolar space. Intracellular pattern recognition receptors such as the Nod-like receptors can also be activated leading to inflammasome activation, caspase-1 cleavage, and release of the pro-inflammatory cytokines interleukin-1 and interleukin-18. Activated neutrophils can release a variety of potentially injurious products, including proteases, oxidants, lipid mediators, histones, and neutrophil extracellular traps, networks of extracellular

antimicrobial factors, and chromatin that can cause endothelial injury. Although these neutrophil-derived mediators are important for host defence against pathogens, excessive, rather than controlled production can contribute to lung injury.

Molecular mechanisms of increased endothelial permeability

The integrity of the lung endothelial barrier is maintained by adherens junctions that are formed by structural proteins, including endothelial-specific VE-cadherin. Factors that stabilize and destabilize the adherens junctions regulate endothelial permeability [15]. Destabilizing factors that may increase permeability in ARDS include pro-inflammatory agonists, such as thrombin, vascular endothelial growth factor, TNF, interleukin-1, microbial products such as lipopolysccharide and leukocyte signals. These factors can disrupt the adherens junction by disrupting homophilic bonds between VE-cadherin molecules. Stabilizing factors include sphingosine-1 phosphate, a glycosphingolipid, and the Robo/Slit signalling pathway. Other endothelial stabilizing agonists include angiopoietin-1, atrial natriuretic peptide, activated protein C, and ATP. Although targeting endothelial stabilization pathways is an attractive avenue for development of potential therapies for ARDS and sepsis, increased endothelial permeability also facilitates leukocyte margination, a process that is critically important for host defence.

Molecular mechanisms of epithelial injury and permeability

The alveolar epithelium is an important site of injury in ARDS that contributes to increased alveolar–capillary barrier permeability and pulmonary oedema formation. In ultrastructural studies of patients dying with ARDS, epithelial lesions range from mild injury with cytoplasmic swelling, vacuolization, and bleb formation to frank necrosis and complete loss of the epithelial layer [16].

In addition to impairing barrier function, injury to the lung epithelium facilitates leukocyte migration, reduces surfactant production and inhibits the clearance of pulmonary oedema fluid from the airspace. Alveolar fluid clearance is normally driven by transcellular active transport of sodium and chloride across the lung epithelial layer from the airspace into the interstitium, which creates a mini-osmotic gradient for resorption of water. In patients with ARDS, intact lung epithelial fluid transport function is associated with better clinical outcomes suggesting that the degree of alveolar epithelial injury is an important determinant of clinical severity of lung injury. In addition to simple loss of barrier function, a variety of other mechanisms have been identified that impair alveolar fluid clearance in ARDS including deleterious effects of pro-inflammatory cytokines, oxidants, and hypoxia.

Regulation of lung epithelial permeability has not been as well studied as endothelial permeability. In general, the lung epithelial barrier is much tighter than the endothelial barrier. Like the endothelium, the epithelial barrier is maintained by cadherin-mediated adherens junction bonds and tight junctions, but contains epithelial specific E-cadherin, rather than VE-cadherin. Recent evidence suggests that the tight junction proteins claudins may be critical regulators of lung epithelial permeability in ARDS.

Ventilator-induced lung injury

Although mechanical ventilation is an important supportive therapy for patients with ARDS, ventilation with high volumes, and high pressures can injure the normal lung and exacerbate injury and oedema formation in the injured lung. There are several mechanisms by which mechanical ventilation is injurious. Because of heterogeneity in the distribution of alveolar consolidation, tidal volumes are delivered predominantly to alveoli that are relatively uninjured, leading to over distension. Alveolar over distension can cause capillary stress failure with endothelial and epithelial injury and initiation of a pro-inflammatory cascade, as well as release or metalloproteinases and oxidative stress. Clinical trials aimed at reducing alveolar over distension by reducing tidal volume have improved clinical outcomes in ARDS [17]. In addition to alveolar over distension, the repeated collapse and re-opening of atelectatic alveoli in areas where surfactant function is impaired can be pro-inflammatory. However, therapies targeted at maintaining alveolar recruitment have not yet had a major impact on clinical outcomes, perhaps because it is difficult in an individual patient to improve alveolar recruitment without causing alveolar over distension.

Dysregulated coagulation and fibrinolysis

In patients with ARDS, both intra- and extravascular coagulation and fibrinolytic pathways are dysregulated [18]. Intra-alveolar fibrin deposition, as evidenced by hyaline membrane formation, is promoted by increased procoagulant, and decreased anticoagulant and fibrinolytic mediators in the airspace. Tissue factor, a potent activator of the extrinsic coagulation cascade, is elevated in the airspace in ARDS, and is associated with increased procoagulant activity. Active tissue factor is also shed into the airspace on membrane-bound microvesicles. Levels of the endogenous anticoagulant protein C are decreased and high levels of plasminogen activator inhibitor-1 impair fibrinolysis.

The systemic procoagulant antifibrinolytic state in ARDS is characterized by increased circulating levels of tissue factor, and PAI-1 and decreased levels of protein C. Microvascular thrombosis occurs both systemically and in the lung in ARDS. Systemic microvascular thrombosis probably contributes to the frequent occurrence of multi-organ system failure in patients with ALI/ARDS. Microvascular thrombosis in the lung capillary bed contributes to ventilation–perfusion mismatch and elevated pulmonary dead space fraction.

Initiation of coagulation is a potent pro-inflammatory stimulus that has been postulated to amplify lung inflammation in ARDS. Thrombin generation induces neutrophil adhesion to the endothelium, expression of selectin, and activation of platelet receptors. Fibrin generation also increases vascular permeability, activates endothelial cells, and induces neutrophil adhesion and margination. However, anticoagulant therapies have not been effective at reducing mortality in clinical ARDS or sepsis. Several recent experimental studies suggest that procoagulant pathways are critically important in regulating barrier permeability and host defence in ARDS, findings that could explain the lack of clinical benefit of anticoagulant strategies.

Resolution of ARDS

Although patients with ARDS continue to die from refractory respiratory failure and multi-organ system failure, with improvements in supportive care and ventilator management, the majority of patients (>50%) with ARDS now survive to hospital discharge.

Although ARDS survivors may have chronic neurological and cognitive impairments related to critical illness, lung function in survivors of ARDS gradually returns to normal or near normal. By 1 year, only modest decrements in diffusing capacity for carbon monoxide may persist. In order for normal lung function to be restored, a variety of resolution pathways need to be activated.

In order for lung epithelial integrity to be restored, the alveolar epithelium must be repopulated to replace injured and necrotic cells. Alveolar epithelial type I cells, which cover the majority of the alveolar surface are regenerated through proliferation and differentiation of the more injury-resistant alveolar epithelial type II cells. Recent evidence also suggests a role for broncho-alveolar stem cells that reside in the broncho-alveolar junction. Therapies that accelerate alveolar epithelial regeneration, such as keratinocyte growth factor can improve experimental lung injury suggesting that epithelial regeneration is a key determinant of outcome of ARDS. Endothelial integrity must also be restored, but this process is less well understood.

Resolution of pulmonary oedema is mediated by alveolar epithelial fluid transport, which requires an intact alveolar epithelium. Although various mediators such as beta-adrenergic agonists have been identified that accelerate the rate of alveolar fluid clearance in animal and human lungs, clinical trials have been disappointing [19,20].

Resolution of inflammation is a coordinated process that involves termination of pro-inflammatory signalling, elaboration of anti-inflammatory signals such as lipoxin A4, resolvin E1, and clearance of apoptotic neutrophils by alveolar macrophages. Recent experimental evidence suggests that T-regulatory lymphocytes are important regulators of resolution of lung inflammation, enhancing neutrophil apoptosis, and suppressing cytokine secretion, in part by release of TGF-beta.

References

1. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. (2005). Incidence and outcomes of acute lung injury. *New England Journal of Medicine*, **353**(16), 1685–93.
2. Ware LB and Matthay MA. (2000). Medical progress: the acute respiratory distress syndrome. *New England Journal of Medicine*, **342**, 1334–49.
3. Herridge MS, Tansey CM, Matte A, et al. (2011). Functional disability 5 years after acute respiratory distress syndrome. *New England Journal of Medicine*, **364**(14), 1293–304.
4. Gajic O, Dabbagh O, Park PK, et al. (2011). Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. *American Journal of Respiratory and Critical Care Medicine*, **183**(4), 462–70.
5. Levitt JE, Bedi H, Calfee CS, Gould MK, and Matthay MA. (2009). Identification of early acute lung injury at initial evaluation in an acute care setting prior to the onset of respiratory failure. *Chest*, **135**(4), 936–43.
6. Ranieri VM, Rubenfeld GD, Thompson BT, et al. (2012). Acute respiratory distress syndrome: the Berlin Definition. *Journal of the American Medical Association*, **307**(23), 2526–33.
7. Bernard GR, Artigas A, Brigham KL, et al. (1994). The American–European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *American Journal of Respiratory and Critical Care Medicine*, **149**, 818–24.
8. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, and Ware LB. (2007). Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or acute respiratory distress syndrome. *Chest*, **132**(2), 410–17.
9. Esteban A, Fernandez-Segoviano P, Frutos-Vivar F, et al. (2004). Comparison of clinical criteria for the acute respiratory distress syndrome with autopsy findings. *Annals of Internal Medicine*, **141**, 440–5.
10. Thille AW, Esteban A, Fernandez-Segoviano P, et al. (2013). Comparison of the Berlin Definition for Acute Respiratory Distress Syndrome with Autopsy. *American Journal of Respiratory and Critical Care Medicine*, **187**(7), 761–7.
11. Wheeler AP, Bernard GR, Thompson BT, et al. (2006). Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *New England Journal of Medicine*, **354**(21), 2213–24.

*12. Gattinoni L, Bombino M, Pelosi P, et al. (1994). Lung structure and function in different stages of severe adult respiratory distress syndrome. *Journal of the American Medical Association*, **271**, 1772–9.

13. Pelosi P, D'Onofrio D, Chiumello D, et al. (2003). Pulmonary and extrapulmonary acute respiratory distress syndrome are different. *European Respiratory Journal*, **42**(Suppl.), 48s–56s.
14. Matthay MA, Ware LB, and Zimmerman GA. (2012). The acute respiratory distress syndrome. *Journal of Clinical Investigation*, **122**(8), 2731–40.
15. Vandenbroucke E, Mehta D, Minshall R, and Malik AB. (2008). Regulation of endothelial junctional permeability. *Annals of the New York Academy of Sciences*, **1123**, 134–45.
16. Bachofen M and Weibel ER. (1977). Alterations of the gas exchange apparatus in adult respiratory insufficiency associated with septicemia. *American Review of Respiratory Diseases*, **116**, 589–615.
17. The Acute Respiratory Distress Syndrome Network. (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *New England Journal of Medicine*, **342**, 1301–8.
18. Ware LB, Bastarache JA, and Wang L. (2005). Coagulation and fibrinolysis in human acute lung injury—new therapeutic targets? *Keio Journal of Medicine*, **4**, 142–9.
19. Matthay MA, Brower RG, Carson S, et al. (2011). Randomized, placebo-controlled clinical trial of an aerosolized beta(2)-agonist for treatment of acute lung injury. *American Journal of Respiratory and Critical Care Medicine*, **184**(5), 561–8.
20. Gao Smith F, Perkins GD, Gates S, et al. (2012). Effect of intravenous beta-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *Lancet*, **379**(9812), 229–35.

CHAPTER 109

Therapeutic strategy in acute respiratory distress syndrome

Charlotte Summers and Geoffrey Bellingan

Key points

- Acute respiratory distress syndrome (ARDS) is not a single condition, hence a variety of supportive and therapeutic approaches may be required for optimal management.
- The mainstay of ARDS management is the identification and treatment of the pre-disposing condition, together with supportive care, which includes lung-protective ventilation, and even prone ventilation in more severe cases.
- Fluid restriction, after patients are appropriately resuscitated, is probably of benefit.
- The early, and short-term, use of cisatracurium in more severe ARDS cases may improve outcome over and above lung-protective ventilation.
- There are currently no licensed pharmacological therapies for ARDS, although there are a number of novel agents under development.

Introduction

Acute respiratory distress syndrome (ARDS) is a pathological syndrome characterized by arterial hypoxaemia and bilateral pulmonary infiltrates, in the absence of evidence of left atrial hypertension (see Fig. 109.1a). Histologically, the syndrome features epithelial and endothelial injury, with diffuse alveolar damage, hyaline membrane formation, and infiltration of neutrophils and macrophages into the pulmonary interstitium observed (see Fig. 109.1b), and fibrosis can be prominent. Until recently, the diagnosis of ARDS was made in accordance with the America-European Consensus Conference (AECC) criteria established in 1994, however, an updated 'Berlin' definition was produced in 2012 [1]. It is important to remember that almost all clinical studies to date have utilized the AECC criteria, and also that ARDS is not a single disease, but rather a constellation of conditions with similar pathophysiology, and thus there may not be one unifying clinical treatment.

Supportive care

Treatment of predisposing factor and intercurrent infection

The development of ARDS is associated with several risk factors including pneumonia, non-pulmonary sepsis (e.g. peritonitis), aspiration of gastric contents, major trauma, transfusion, and acute pancreatitis. Diagnosis and appropriate treatment of predisposing factors is key to clinical management. It may be necessary, particularly in the immune-compromised host, to undertake invasive diagnostic procedures, such as bronchoscopy, to establish a diagnosis. Furthermore, it has been shown that intercurrent pulmonary infection occurs in 34–70% of patients with ARDS [2], necessitating vigilance for the subsequent development of infection in ARDS patients.

Lung protective mechanical ventilation

It is well established that mechanical ventilation using tidal volumes of 6 mL/kg predicted body weight (PBW), and a plateau pressure less than 30 cmH_2O, confers a mortality benefit, and should be undertaken whenever possible [3]. A trial of high versus low positive end expiratory pressure (PEEP) in patients receiving 6 mL/kg PBW ventilation, with a plateau pressure below 30 cmH_2O, did not find any significant difference between groups, suggesting that the level of PEEP may not be as critical as the need for low tidal volume ventilation in all patients with ARDS [4]. However, retrospective subgroup analysis has suggested that higher PEEP levels may be of benefit in severe ARDS.

Non-conventional gas exchange technologies

There has been significant interest in the use of non-conventional gas exchange technologies, including extracorporeal membrane oxygenation (ECMO), extracorporeal carbon dioxide removal ($ECCO_2R$) and oscillatory devices. To date, none of these devices have been proved to be of universal benefit in ARDS, although it is possible that there may be sub-populations of ARDS patients (e.g. H1N1 influenza patients and ECMO [5]) that derive benefit from these interventions.

Fluid management

Close attention to fluid balance has long been thought to be important in the management of ARDS, and a theoretical case can be made for minimizing the use of fluid therapy, once the patient is adequately resuscitated, to reduce the formation of pulmonary oedema, but the evidence to support this strategy is not conclusive. In 2006, the FACCT study [6] found that a conservative fluid management strategy (in those patients who had been fully resuscitated) was not associated with decreased 60-day mortality when compared with a more liberal regimen. However, improvements in pulmonary physiological values, and a reduction in the duration

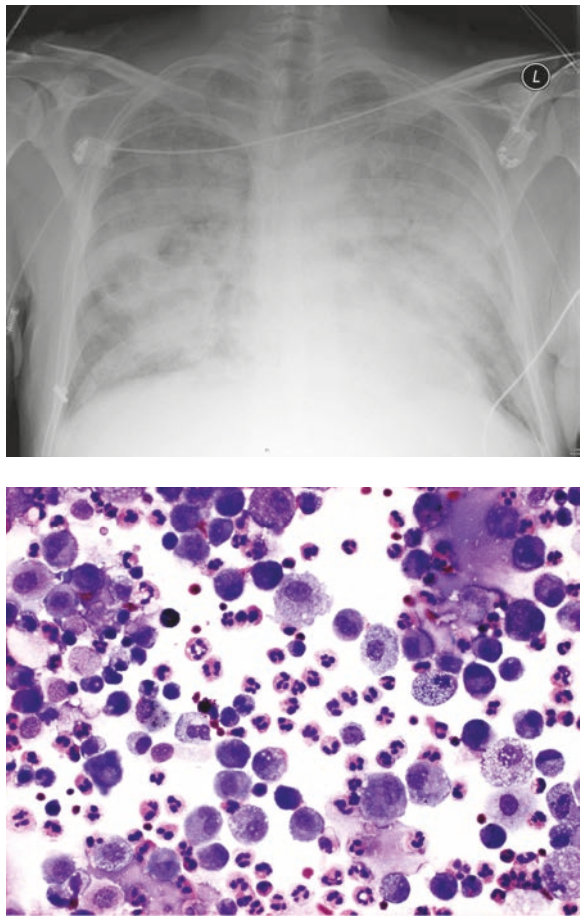


Fig. 109.1 (a) Chest radiograph illustrating the bilateral pulmonary infiltrates of ARDS. (b) Inflammatory cells present within the broncho-alveolar lavage fluid of patient with chest radiograph shown in Fig. 109.1a.
Images courtesy of Dr Jatinder Juss, University of Cambridge, UK.

of mechanical ventilation and intensive care stay were observed in the conservative fluid group, with no associated increase in renal failure, need for renal replacement therapy, or non-pulmonary organ failures. Subsequently, a retrospective study examined data from patients enrolled in the lung-protective ventilation ARDSnet clinical trial, finding that a cumulative negative fluid balance on day 4 after the diagnosis of ARDS was independently associated with lower hospital mortality, and increased ventilator- and ICU-free days.

Blood transfusion

Transfusion-related ARDS, or transfusion-related acute lung injury (TRALI), is defined as the development of ARDS during or within 6 hours following transfusion of one or more units of blood or blood components. A recent study identified both recipient (shock, chronic alcohol abuse, liver surgery, current smoking, positive fluid balance before transfusion, and peak airway pressure >30 cmH_2O if mechanically ventilated) and transfusion (plasma or whole blood from female donor, volume of HLA class II antibody, and volume of antihuman neutrophil antigen positivity) related risk factors for TRALI. Interestingly, in contrast to previous studies, an increase in the incidence of TRALI associated with older red blood cell units was not observed [7].

Nutrition

The provision of supportive care involves the administration of nutrition to the ARDS patient. A multicentre study examining the role of trophic (25% of caloric requirement) feeding found no benefit over full standard feeding in terms of ventilator-free days, organ-failure free days, ICU-free days, or incidence of infection [8]. The benefit of dietary supplementation with n-3 fatty acids, gamma-linoleic acid (GLA), and antioxidants on both clinical and physiological outcomes in ARDS has been proposed by several small randomized studies, although a large multicentre double-blinded, placebo-controlled randomized trial to examine the effects of dietary supplementation on ventilator-free days was stopped early on futility grounds, and the intervention group had significantly more reported side effects attributed to the therapy [9]. Currently, there is no evidence to support a specific feeding regimen in ARDS patients, over and above the evidence to suggest that adding parenteral nutrition to enteral nutrition, to facilitate the early meeting of caloric goals, may be detrimental in critically-ill patients.

Neuromuscular blockade

Neuromuscular blockade is often used in ARDS to permit lung-protective ventilation, although concerns have been raised about the potential of these agents to induce ICU-acquired weakness. A multicentre double-blinded placebo-controlled randomized trial of short-term cisatracurium therapy showed a decrease in the adjusted 90-day mortality of more severe ARDS patients, i.e. those with a PaO_2/FIO_2 ratio below 150 mmHg, who received lung-protective ventilation [10]. Paralysis was commenced within 48 hours of patients fulfilling study entry criteria, and was continued for 48 hours according to a standardized protocol. No increase in the incidence of ICU-acquired weakness was observed between the study groups. It remains to be seen in further planned trials, whether the improved mortality seen was due to the effect of neuromuscular blockade, or a specific effect of cisatracurium.

Pharmacological therapies for acute lung injury

Hydroxymethyglutaryl-coenzyme A reductase inhibition (statin therapy)

Hydroxymethyglutaryl-coenzyme A reductase inhibitors, or statins, have been shown to have pleotropic immunomodulatory effects, in addition to their cholesterol-reducing action. Hence, interest has developed in their use as potential anti-inflammatory agents in ARDS. Observational studies examining the impact of prehospital statin use have produced conflicting results, with some suggesting prehospital statin use was associated with a reduced risk of developing ARDS and/or severe sepsis, and others reporting no effect. A single centre, double-blinded placebo-controlled randomized trial of simvastatin showed no significant reduction in pulmonary oedema (extravascular lung water, EVLW), or improvement in pulmonary physiological variables over 14 days, and no improvement in clinical outcomes, although the study was under-powered to detect clinical outcome differences [11]. Furthermore, a multicentre randomized controlled trial (RCT) of rosuvastatin in sepsis-induced ARDS (SAILS; ClinicalTrials.gov: NCT00979121) has recently been stopped, on grounds of futility, after the recruitment of 745

patients. Currently, there is no evidence to support the clinical use of statins in ARDS, particularly as the latest multicentre, HARP2, has shown no benefit (ISTCTN 88244364).

Corticosteroids

Due to the inflammatory nature of ARDS there has been much interest in the use of corticosteroid therapy. Several studies have shown no benefit from the use of high-dose short-course corticosteroids early in the clinical course of ARDS, and a double-blinded placebo RCT in patients diagnosed with ARDS for at least 7 days prior enrolment found no benefit of methylprednisolone, and in fact a significantly increased mortality amongst patients diagnosed with ARDS at least 14 days prior to commencing corticosteroid therapy [12]. However, interest remains in the use of low-dose corticosteroids for established ARDS, with several clinical trials planned.

Beta-adrenergic receptor agonists

Alveolar fluid clearance has been shown to be defective in ARDS. Previous studies demonstrating the ability of beta-adrenergic receptor agonists to improve the resolution of pulmonary oedema led to multicentre randomized controlled trials of both intravenous [13] and aerosolized [14] salbutamol in ARDS. Both studies were stopped early, the aerosolized study on grounds of futility, and the intravenous study due to a significantly increased 28-day mortality in the intervention arm. The lack of benefit of beta-adrenergic agonist therapy on mortality and ventilator-free days was consistent between the two studies, with both concluding that the routine use of this therapy in ARDS patients cannot be recommended. Furthermore, there is evidence that intravenous salbutamol usage in ARDS may be associated with worsened outcomes.

Surfactant

Decreased surfactant levels and altered surfactant composition have been identified in the lungs of patients with ARDS. Clinical trials of replacement therapy with synthetic surfactants have not proved successful, despite significant improvements in oxygenation and a multicentre RCT of large volume natural porcine surfactant replacement, within 36 hours of the onset of ARDS, showed no benefit and a trend towards increased mortality and adverse events in the treatment group [15].

Inhaled nitric oxide

The ventilation–perfusion mismatch, and pulmonary hypertension, often observed in ARDS has led to clinical trials of inhaled nitric oxide therapy. Nitric oxide is a potent pulmonary vasodilator, and also has anti-inflammatory properties. Unfortunately, meta-analysis has shown that inhaled nitric oxide, whilst associated with improved oxygenation in ARDS patients, does not lead to shortened duration of mechanical ventilation, or improved survival [16].

Emerging therapies

Interferon beta

Adenosine is a key regulator of endothelial cell permeability. Preclinical studies have suggested that using interferon beta to induce CD73, a cell surface enzyme that de-phosphorylates AMP to adenosine, may be of benefit in ARDS by improving endothelial barrier function [17]. Interferon beta therapy is currently undergoing phase III clinical trials in ARDS.

Aspirin

The accumulation of activated platelets and neutrophils within the pulmonary vasculature has been demonstrated to be a key step in the pathogenesis of ARDS. Preclinical studies show that platelet inhibition with aspirin leads to improved outcomes in animal models of ARDS [18]. Clinical trials of aspirin therapy are underway in both Europe and the United States (Clinicaltrials.gov: NCT01504867 and NCT02326350).

Biologics

Recently, much interest has developed within the pharmaceutical industry for new therapies for ARDS, leading to the development of novel agents, such as a domain antibody to inhibit the p55 TNF receptor [19].

Cell-based therapies

A multicentre phase one clinical trial to investigate the role of allogeneic bone marrow-derived mesenchymal stem cells (MSCs) for the treatment of ARDS is currently underway in the United States (ClinicalTrials.gov: NCT01775774). However, engraftment in the lung does not seem to be the major therapeutic effect of MSCs, rather the effect derives from their capacity to secrete paracrine factors that modulate immune responses and alter the host responses to injury. Preclinical work has shown that clinical-grade, cryopreserved allogeneic human MSC are therapeutic in a human, ex vivo, *E. coli* pneumonia model, but the antimicrobial effects of the MSCs could be largely duplicated by KGF, a major paracrine product of MSCs [20]. A phase II trial investigating the efficacy and safety of intravenous KGF in ARDS is currently also under way (ISRCTN95690673).

References

1. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. (2012). ARDS definition task force. Acute respiratory distress syndrome: the Berlin definition. *Journal of the American Medical Association*, **307**(23), 2526–33.
2. Andrews CP, Coalson JJ, Smith JJ, et al. (1981). Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury. *Chest*, **80**, 254–8.
3. The NHLBI Acute Respiratory Distress Syndrome Network (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *New England Journal of Medicine*, **342**, 1301–8.
4. The NHLBI ARDS Clinical Trials Network (2004). Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *New England Journal of Medicine*, **351**, 327–36.
5. Noah MA, Peek GJ, Finney SJ, et al. (2011). Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A (H1N1). *Journal of the American Medical Association*, **306**, 1659–68.
6. The NHLBI ARDS Clinical Trial Network (2006). Comparison of two fluid-management strategies in acute lung injury. *New England Journal of Medicine*, **354**(24), 2564–75.
7. Toy P, Gajic O, Bacchetti P, et al. (2012). Transfusion-related acute injury: incidence and risk factors. *Blood*, **119**(7), 1757–67.
8. The NHLBI ARDS Clinical Trials Network (2012). Initial trophic vs full enteral feeding in patients with acute lung injury. *Journal of the American Medical Association*, **307**(8), 795–803.

9. The NHBLI ARDS Clinical Trial Network (2011). Enteral omego-3 fatty acid, gamma-linolenic acid, and anti-oxidant supplementation in acute lung injury. *Journal of the American Medical Association*, **306**(14), 1574–81.
10. Papazian L, Forel J-M, Gacouin A, et al. (2010). Neuromuscular blockers in early acute respiratory distress syndrome. *New England Journal of Medicine*, **363**(12), 1107–16.
11. Craig TR, Duffy MJ, Shyamsundar M, et al. (2011). A randomized clinical trial of hydroxymethygluteryl-coenzyme a reductase inhibition for acute lung injury (The HARP study). *American Journal of Respiratory and Critical Care Medicine*, **183**(5), 620–6.
12. The NHLBI ARDS Clinical Trial Network (2006). Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *New England Journal of Medicine*, **354**(16), 1671–84.
13. Gao Smith F, Perkins GD, Gates S, et al. (2012). Effect of intravenous beta-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicenter, randomized controlled trial. *Lancet*, **379**(9812), 229–35.
14. The NHLBI ARDS Clinical Trial Network (2011). Randomized, placebo-controlled clinical trial of an aerosolized beta-2-agonist for treatment of acute lung injury *American Journal of Respiratory and Critical Care Medicine*, **184**(5), 561–8.
15. Kesecioglu J, Beale R, Stewart TE, et al. (2009). Exogenous natural surfactant for treatment of acute lung injury and the acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **180**(10), 989–94.
16. Adhikari NK, Burns KE, Friedrich JO, et al. (2007). Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *British Medical Journal*, **334**, 779–86.
17. Bellingan G, Maksimov M, Howell DC, et al. (2014). The effect of intravenous interferon beta-1a (FP-1201) on lung CD73 expression and acute respiratory distress syndrome mortality: an open label study. *Lancet Respiratory Medicine*, **2**(2), 98–107.
18. Looney MR, Nguyen JX, Hu Y, et al. (2009). *Journal of Clinical Investigation*, **119**(11), 3450–461.
19. Bertok S, Wilson MR, Morley PJ, et al. (2012). Selective inhibition of intra-alveolar p55 TNF receptor attenuates ventilator-induced lung injury. *Thorax*, **67**(3), 244–51.
20. Lee JW, Krasnodembskaya A, McKenna DH, et al. (2013). Therapeutic effects of human mesenchymal stem cells in ex vivo human lungs injured with live bacteria. *American Journal of Respiratory and Critical Care Medicine*, **187**(7), 751–60.

PART 4.11

Airflow limitation

CHAPTER 110

Pathophysiology and causes of airflow limitation

David V. Tuxen

Key points

- Control dynamic hyperinflation during mechanical ventilation by using low minute ventilation, low tidal volume, and high inspiratory flow to achieve a plateau pressure ≤25 cmH_2O.
- Accept high peak inspiratory pressure that results from high inspiratory flow so long as plateau pressure is safe.
- Recognize lactic acidosis from salbutamol.
- Avoid myopathy by avoiding or minimizing neuromuscular blockade.
- Reduce the ventilator rate if a pneumothorax is suspected to protect the second lung.

Introduction

Airflow limitation occurs in asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, bronchiolitis obliterans, and a component of airflow limitation can accompany a number of other less common conditions.

Both acute severe asthma and exacerbations of chronic airflow limitation can be life-threatening emergencies, requiring urgent medical treatment and ventilatory support. If these are not available or instigated in a timely way, cardiorespiratory arrest can occur, resulting in death or hypoxic cerebral injury. Even after instigation of invasive ventilatory support the risk is not over, as both medical therapy and the ventilator technique also have significant risk of morbidity and mortality. Understanding the mechanism of these problems is key to avoiding them.

Pathophysiology and causes of airflow limitation

The pathogenesis of asthma has both genetic and environmental factors. There is an increase in worldwide prevalence [1]. Reduced exposure to childhood infections as a result of antibiotics and a more hygienic lifestyle are believed to lead to increased IgE-dependent airway inflammation and bronchial hyperreactivity (the 'hygiene hypothesis') with local allergen exposure determining the specific antibody responses [2]. Triggers of acute asthma can be non-specific (cold air, exercise, pollutants), specific allergens (house mite, pollen, animal danders), modifiers of airway control (aspirin, β-blockers), or stress or emotion. No precipitant can be identified in over 30% of exacerbations.

Two patterns of acute severe asthma have been identified [3]. Usual acute severe asthma is the more common group (80–90%), with progression of symptoms over many hours or days, often with a background of poor control and recurrent presentations. This group is predominantly female, triggered by upper respiratory infections and responds slowly to treatment. Pathology is dominated by mucous inspissation and chronic bronchial wall inflammation with eosinophilia [3]. 'Hyperacute', 'fulminating', 'asphyxic', or 'sudden onset' severe asthma is where the interval between onset of symptoms and intubation is less than 3 hours [3–5]. This presentation is less common (approximately 10–20% of life-threatening presentations) and tends to occur in younger male patients with relatively normal lung function, but high bronchial reactivity. Massive respiratory allergen exposure, cold air or exercise and psychosocial stress are the most frequent triggers [3]. This group characteristically has neutrophilic inflammation, typically responds quickly to bronchodilators and is thought to be mainly due to bronchial smooth muscle contraction.

COPD also has both host and environmental factors. Environmental factors include tobacco smoke, air pollution, indoor fumes (e.g. from solid biomass fuel) and poor socio-economic status. The biggest single factor in over 95% of patients with COPD is tobacco smoking. Marijuana smoking may cause premature and quite advanced bullous emphysema due to extremely hot and toxic inhaled smoke held at peak inspiration for prolonged periods of time [6]. Host factors are the balance between circulating proteases and antiproteases (e.g. alpha-1 antitrypsin deficiency) and the intake of antioxidant vitamins (A,C,E) [7]. Only approximately 15% of smokers develop COPD.

In both asthma and COPD, reduced expiratory airflow is primarily due to increased small airway resistance usually due to varying combinations of mucosal oedema and hypertrophy, secretions, bronchospasm, airway tortuosity, and airflow turbulence. In COPD, the loss of lung parenchyma and its elastic tissues (the emphysema component) further reduces expiratory airflow by a decrease in elastic support of the small airways and reduced lung elastic recoil. Reduction of lung elastic recoil pressure is due both to loss of lung elastin and loss of alveolar surface tension from alveolar wall destruction.

Common problems associated with treatment

Dynamic hyperinflation

The majority of critically-ill patients who require mechanical ventilation do not have airflow limitation; their lungs return to

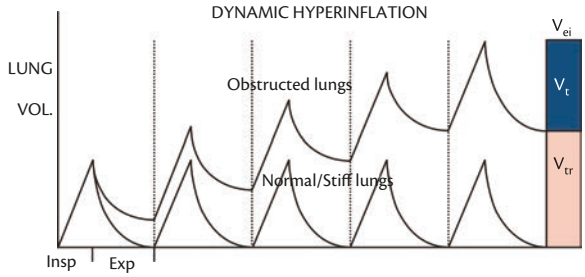


Fig. 110.1 Comparison of the initial effects of mechanical ventilation on lungs with and without airflow limitation. Dynamic hyperinflation is the result of incompletely exhaled gas being 'trapped' by the arrival of the next breath.
V_t, tidal volume; V_{tr}, trapped gas volume above FRC; V_{ei}, end-inspiratory lung volume above FRC; FRC, functional residual capacity.
Data from Tuxen D and Lane S, 'The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe airflow obstruction', *American Review of Respiratory Disease*, 1987, **136**, pp. 872–9.

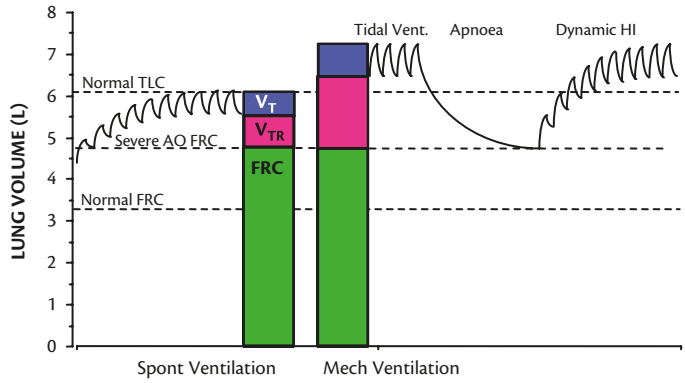


Fig. 110.2 Comparison of dynamic hyperinflation (HI) between spontaneous ventilation and mechanical ventilation in severe airflow limitation [8,10]. Dotted lines show normal total lung capacity (TLC), normal FRC and the elevated FRC in severe airflow obstruction (AO). The effects of periods of apnoea during mechanical ventilation are shown.
Data from Tuxen D and Lane S, 'The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe airflow obstruction', *American Review of Respiratory Disease*, 1987, **136**, pp. 872–9; and Williams T, et al., 'Risk factors for morbidity in mechanically ventilated patients with acute severe asthma', *American Review of Respiratory Disease*, 1992, **146**(3), pp. 607–15.

functional residual capacity or passive relaxation volume at the end of tidal expiration (Fig. 110.1) where the recoil pressures of the lungs (to collapse) and chest wall (to expand) are balanced.

This is not the case in a patient with any significant airflow limitation. Slower expiratory flow results in incomplete exhalation of the inspired tidal volume (V_T) in the expiratory time available and part of the inspired volume is trapped by the arrival of each new breath after commencement of mechanical ventilation ('gas trapping', Fig. 110.1). The lungs undergo dynamic hyperinflation [8]. The expiratory time to complete exhalation in severe airflow limitation may be 30–90 sec [8]. Gas trapping does not continue indefinitely, but increases lung volume over 6–12 breaths until an equilibrium point is reached where the inspired V_T (which could not be completely expired at lower lung volumes) is able to be expired in the same expiratory time [8]. This equilibrium point is enabled by two factors—the increase in lung elastic recoil pressure and in small airway calibre, both of which normally occur as lung volume increases. The three primary determinants of this equilibrium point are the volume going in (V_T), the time for it to come out (determined both by respiratory rate and inspiratory flow or the I:E ratio) and, of course, the severity of airflow limitation.

In moderate airflow limitation with spontaneous breathing this process is adaptive; it allows the desired minute ventilation to be achieved at a higher lung volume, albeit with increased work of breathing and loss of inspiratory reserve. When airflow limitation becomes severe during spontaneous breathing, dynamic hyperinflation will continue to total lung capacity (Fig. 110.2). Hypercapnia occurs in the absence of fatigue as a result of the physical limits on inspiration and expiration, where the maximum achievable minute ventilation is less than that required for normocapnia. Of course, at this lung volume, the inspiratory muscles length is very short and has little mechanical advantage over the already maximally-inflated chest wall and so muscle fatigue can rapidly occur with worsening hypercapnia.

Once mechanical ventilation is commenced, ventilation is easily increased, resulting in more dynamic hyperinflation to above total lung capacity (Fig. 110.2) where hypotension and risk of pneumothorax will readily occur [9].

The passive relaxation volume of the lung, i.e. the functional residual capacity (FRC) after prolonged expiration (30–90 sec in a paralysed patient), is elevated in moderate to severe airflow obstruction by airway closure that occurs throughout expiration. In severe asthma requiring mechanical ventilation FRC is 50% above normal [10] and only 1.4 L below total lung capacity (Fig. 110.2). A period of 30–90 sec apnoea during mechanical ventilation will allow the lungs to exhale all dynamically-trapped gas and return to this FRC (Fig. 110.2) with release of circulatory compromise [11]. Restoration of ventilation will return the lungs to their previous hyperinflation within 6–10 breaths (Fig. 110.2). It has been shown that ventilation to end-inspiratory lung volumes above total lung capacity (TLC) greatly increases the risk of hypotension and pneumothorax, while ventilation that keeps the plateau pressure (P_{plat}) ≤25 cmH_2O reduces that risk [9].

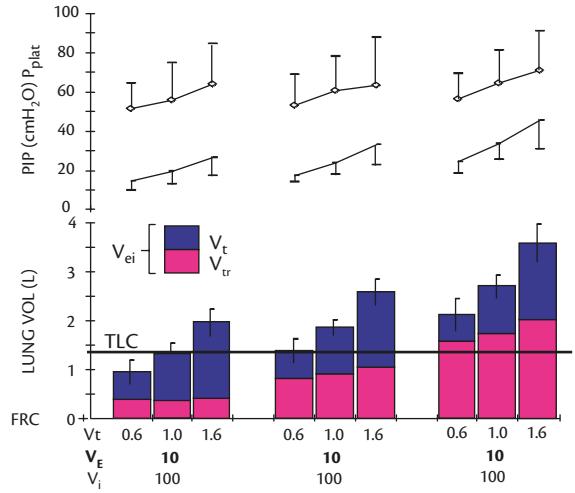
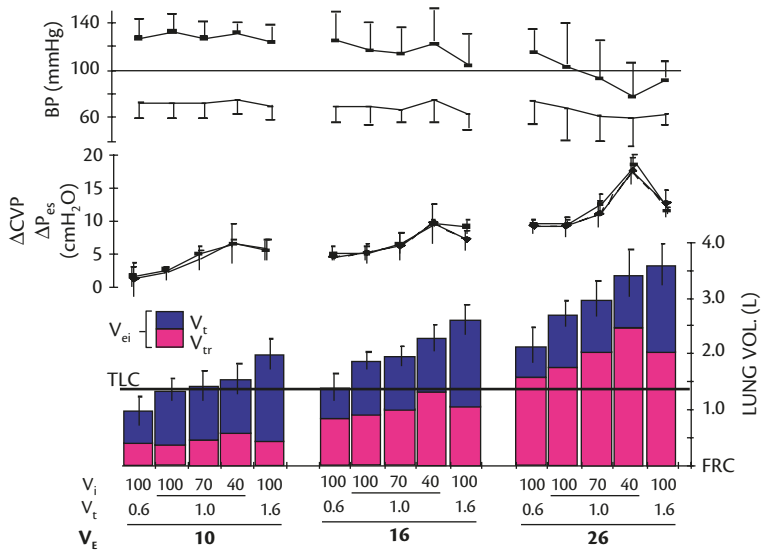


Fig. 110.3 The effects of minute ventilation (V_E) on trapped gas (V_{tr}) above FRC, end-inspiratory lung volume (V_{ei}), peak inspiratory pressure (PIP) and plateau airway pressure (P_{plat}) at a constant inspiratory flow setting (V_I). The effect of different V_t and ventilator rate combinations to achieve each V_E [8].



Tuxen & Lane. Am Rev Respir Dis 1987; 136: 872-879

Fig. 110.4 The effects of different mechanical ventilation patterns on blood pressure, central, and oesophageal pressures on patients with severe airflow limitation [8].
V_t, tidal volume; V_{TR}, trapped gas volume above FRC; V_{ei}, end-inspiratory lung volume above FRC; FRC, functional residual capacity; BP, blood pressure; CVP, central venous pressure; P_{es}, oesophageal pressure.

The biggest single ventilator variable affecting the trapped gas volume (Fig. 110.3) is the minute ventilation (V_E, Fig. 110.3) [8]. A large V_T slightly increases trapped gas levels at each level of V_E, but greatly increases the end-inspiratory lung volume with risk of pneumothorax. The changes in central venous and oesophageal pressures, and the reductions in mean arterial pressure most directly relate to the end-expiratory lung volume [8] (Fig. 110.4). The only ventilator pattern that places all patients below the safety line equivalent to TLC is a low V_T and a low V_E (Fig. 110.3).

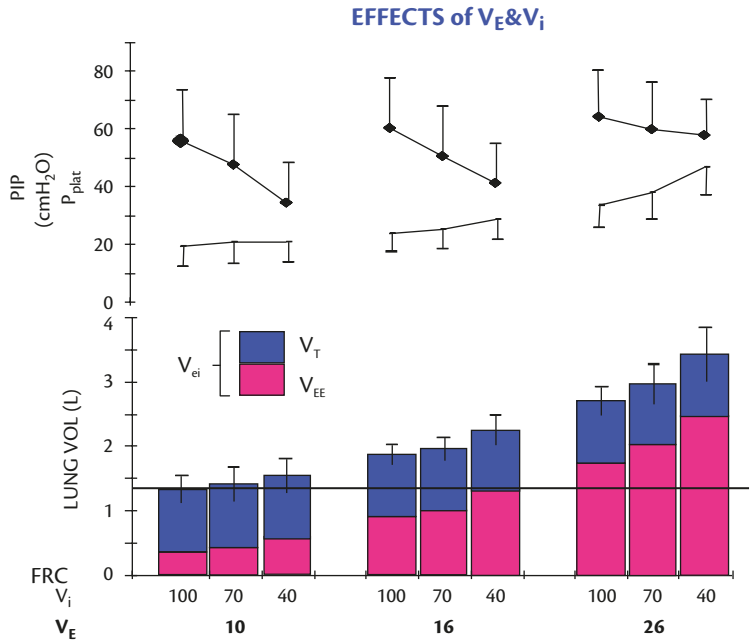


Fig. 110.5 The effects of reducing V_i from 100 to 40 L/min, at each level of V_E, on V_{ei}, PIP and P_{plat} [8].
V_{ei}, end-inspiratory lung volume above FRC; FRC, functional residual capacity; V_E, minute ventilation, V_{TR}, trapped gas; P_{plat}, plateau airway pressure; V_i, constant inspiratory flow setting; V_{EE}, end-expiratory.

In patients requiring mechanical ventilation for severe asthma, the minute ventilation required to normalize $PaCO_2$ and pH can require a high level of V_E. If these levels of V_E are used, the result is excessive dynamic hyperinflation in most patients, significant risk of hypotension and pneumothorax, and increase in asthma ventilation mortality [9,12]. Safe ventilation should result in an end-inspiratory lung volume (V_{ei}) ≤20 mL/kg (1.4 L) and a P_{plat} of less than 25 mLH_2O. This usually requires a V_E of ≤115 mL/kg/min (≤8 L/min), which will result in most patients being initially hypercapnic.

At any given V_T and respiratory rate, putting the V_T in quickly (high inspiratory flow, short inspiratory time) will result in a longer expiratory time and less gas trapping (Fig. 110.5) [8].

During volume controlled ventilation, the use of a high inspiratory flow (V_i) in the presence of airflow limitation will result in a high peak inspiratory pressure (PIP), but a lower P_{plat}. When the V_i is turned down there is a very gratifying reduction in PIP at every level of minute ventilation, but hidden beneath this falling airway pressure is an increasing P_{plat} (Fig. 110.5) that may convert a patient from a safe to an unsafe level of dynamic hyperinflation [8,12].

A safe level of dynamic hyperinflation (P_{plat} 25 cmH_2O) with a high PIP may not need change, accepting that high PIP is necessary in severe asthma to allow inspiration of a safe tidal volume over a short time inspiratory time. A high PIP in the presence of otherwise safe ventilation has never been shown to cause harm in severe airway obstruction.

Treatment-induced lactic acidosis

Both intravenous salbutamol and continuously nebulized salbutamol can, and often do, cause lactic acidosis [13,14]. Over the course of 1–2 hours, particularly after a bolus dose of intravenous salbutamol, the lactate level may rise as high as 12 mmol/L [15]. The benefits of nebulized salbutamol in acute severe airway obstruction are beyond question [16]. Intravenous salbutamol has never been shown to have additional benefit above maximal doses of nebulized salbutamol [13,17], but has the theoretical advantage of reaching airways that are completely occluded and, hence, inaccessible to nebulized salbutamol.

It is commonly used in acute severe asthma refractory to initial treatment in some countries. Thus, intravenous salbutamol may improve airflow limitation, but may concurrently increase dyspnoea, distress, and fatigue by the production of lactic acid. This resolves rapidly with infusion reduction or cessation. With continued infusions, the lactic acidosis is usually resolved within 24 hours. This phenomenon is shared with other intravenous beta-agonists. The mechanism is not clear, but is probably a direct effect on intracellular metabolism.

Necrotizing myopathy after prolonged ventilation

It has now been widely reported [15,18,19] that patients with severe asthma who receive prolonged neuromuscular blockade or even effective paralysis by heavy sedation [20] can suffer from an acute necrotizing myopathy. This characterized by generalized weakness and hyporeflexia, which can range from mild weakness (not delaying ICU discharge) to profound weakness requiring prolonged mechanical ventilation, rehabilitation, and significant disability at 12 months. Sensation is intact. Electromyography shows a myopathic pattern, sometimes with false features of neuropathy. Serum creatine kinase (CK) levels are always abnormal and levels may range from mild elevation to greater than 10,000 IU. Levels do not correlate well with weakness as a muscular person may have a large, but transient CK rise with minimal weakness and an elderly person with poor muscle mass might have small elevations for an extended time period with severe weakness. Muscle biopsy shows three characteristic features:

- Non-uniform muscle wasting with pale staining.
- Nuclear crowding, but lack of inflammatory infiltrate.
- Vacuolation (Fig. 110.6).

Myopathy severity has been shown to correlate with dose of neuromuscular blocking agents received [15].

Ventilation-induced circulatory collapse

A small subset of patients have such severe asthma that the usual safe ventilation results in extreme dynamic hyperinflation with acute circulatory collapse and apparent electromechanical dissociation within a short time of commencing mechanical ventilation. If this phenomenon is not recognized early it can lead to prolonged, futile standard resuscitation, eventually leading

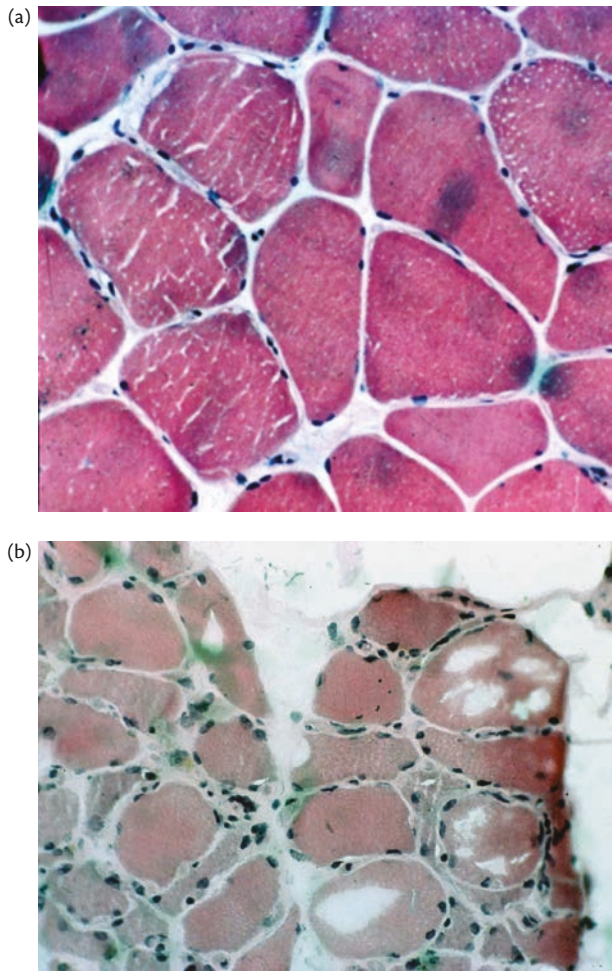


Fig. 110.6 Comparison of a normal muscle biopsy (a) with one from a patient with severe necrotizing myopathy following prolonged neuromuscular blockade for refractory asthma (haematoxylin and eosin staining). Note the non-uniform muscle wasting, nuclear crowding, absence of inflammatory infiltrate, and vacuolation (b).

Reproduced with kind permission from David Tuxen.

to asystole, and brain damage or death. A period of apnoea or much reduced minute ventilation will usually result in circulatory improvement. Additional fluid resuscitation and inotropes may also be required.

Pneumothorax

Pneumothoraces in severe airflow limitation are most commonly caused by excessive dynamic hyperinflation, central venous cannulation, or intercostal insertion of an intravenous cannula for a suspected pneumothorax. They are almost always under tension during mechanical ventilation because the airways themselves expand during inspiration, and collapse during expiration resulting in a valve-like effect and airway closure prevents the lung from collapsing and sealing the air leak. Such a pneumothorax will significantly reduce ventilation to that lung and increase ventilation to the second lung greatly increasing the risk of bilateral tension pneumothoraces. While either an urgent chest X-ray (if mild hypotension) or an intercostal catheter insertion (if severe hypotension) is required promptly, the first action should be a reduction in ventilation to prevent a pneumothorax in the second lung.

References

1. Mattes J and Karmaus W. (1999). The use of antibiotics in the first year of life and development of asthma: which comes first? *Clinical & Experimental Allergy*, **29**(6), 729–32.
2. Busse WW, Lemanske RF, Jr. (2001). Asthma. *New England Journal of Medicine*, **344**(5), 350–62.
3. Restrepo RD and Peters J. (2008). Near-fatal asthma: recognition and management. *Current Opinions in Pulmonary Medicine*, **14**(1), 13–23.
4. Wasserfallen J, Schaller M, Feihl F, and Perret C. (1990). Sudden asphyxic asthma: a distinct entity? *American Reviews in Respiratory Diseases*, **142**, 108–11.
5. Woodruff PG, Emond SD, Singh AK, and Camargo CA, Jr. (1998). Sudden-onset severe acute asthma: clinical features and response to therapy. *Academic Emergency Medicine*, **5**(7), 695–701.
6. Niewoehner DE. (2010). Clinical practice. Outpatient management of severe COPD. *New England Journal of Medicine*, **362**(15), 1407–16.
7. Britton JR, Pavord ID, Richards KA, et al. (1995). Dietary antioxidant vitamin intake and lung function in the general population. *American Journal of Respiratory Critical Care Medicine*, **151**(5), 1383–7.
8. Tuxen D and Lane S. (1987). The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe airflow obstruction. *American Reviews in Respiratory Diseases*, **136**, 872–9.
9. Williams T, Tuxen D, Scheinkestel C, Czarny D, and Bowes G. (1992). Risk factors for morbidity in mechanically-ventilated patients with acute severe asthma. *American Reviews in Respiratory Diseases*, **146**(3), 607–15.
10. Tuxen D, Williams T, Scheinkestel C, Czarny D, and Bowes G. (1992). Use of a measurement of pulmonary hyperinflation to control the level of mechanical ventilation in patients with severe asthma. *American Reviews in Respiratory Diseases*, **146**(5), 1136–42.
11. Pepe P and Marini J. (1982). Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction. *American Reviews in Respiratory Diseases*, **126**, 166–70.
12. Tuxen D, Williams T, Scheinkestel C, Czarny D, and Bowes G. (1993). Limiting dynamic hyperinflation in mechanically ventilated patients with severe asthma reduces complications. *Anaesthesia & Intensive Care*, **21**(5), 718 (Abs).
13. Tuxen D. (1996). Mechanical ventilation in asthma. In: Evans T and Hinds C (eds) *Recent Advances in Critical Care Medicine*, Number 4, pp. 165–89. London: Churchill Livingstone.
14. Prakash S and Mehta S. (2002). Lactic acidosis in asthma: report of two cases and review of the literature. *Canadian Respiratory Journal*, **9**(3), 203–8.
15. Douglass J, Tuxen D, Horne M, et al. (1990). Acute myopathy following treatment of severe life threatening asthma (SLTA). *American Reviews in Respiratory Diseases*, **141**, A397.
16. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) (2007). Available at: http://www.ginasthma.org/local/uploads/files/GINA_Report_072007_1.pdf (accessed 28 October 2015).
17. Travers AH, Rowe BH, Barker S, Jones A, and Camargo CA, Jr. (2002). The effectiveness of IV beta-agonists in treating patients with acute asthma in the emergency department: a meta-analysis. *Chest*, **122**(4), 1200–7.
18. Williams T, O'Hehir R, Czarny D, Horne M, and Bowes G. (1988). Acute myopathy in severe asthma treated with intravenously administered corticosteroids. *American Reviews in Respiratory Diseases*, **137**, 460–3.
19. Hansen-Flaschen J, Cowen J, and Raps E. (1993). Neuromuscular blockade in the Intensive Care Unit. More than we bargained for. *American Reviews in Respiratory Diseases*, **147**, 234–6.
20. Leatherman J, Fluegel W, David W, Davies S, and Iber C. (1996). Muscle weakness in mechanically ventilated patients with severe asthma. *American Journal of Respiratory and Critical Care Medicine*, **153**, 1686–90.

CHAPTER 111

Therapeutic approach to bronchospasm and asthma

Brett G. Sampson and Andrew D. Bersten

Key points

- Risk factors for life-threatening asthma include chronic severe asthma, taking ≥3 asthma medications, previous intensive care unit admissions, previous invasive ventilation, and psychosocial factors.
- β_2 agonists, anticholinergics, and corticosteroids are the mainstay of treatment.
- A ventilation strategy of hypoventilation and permissive hypercapnoea minimizes barotrauma and dynamic hyperinflation.
- Hypotension, cardiovascular collapse, and cardiac arrest may result from dynamic hyperinflation, tension pneumothorax, acute right heart failure, or arrhythmia.
- Non-established therapies include leukotriene antagonists, non-invasive ventilation, and extracorporeal support.

Clinical assessment

A focused asthma history and examination enables grading of severity (Box 111.1). Risk factors for life-threatening asthma include chronic severe asthma, taking ≥3 asthma medications, previous intensive care unit (ICU) admissions, previous invasive ventilation, and psychosocial factors [1,2]. Chest examination should assess for pneumothorax, lung collapse, and hyperinflation. A 'silent chest' from maximally hyperinflated lungs may portend respiratory arrest. Alternative diagnoses, including left ventricular failure, inhaled foreign body, upper airway obstruction, and vocal cord dysfunction should be considered, especially if unresponsive to bronchodilator therapy.

Vocal cord dysfunction

Early recognition of vocal cord dysfunction (VCD), the inappropriate adduction of the vocal folds during respiration, may prevent β_2 agonist toxicity and unnecessary intubation. VCD may mimic refractory asthma, affects 4–10% of asthma clinic patients, is more common in females, and a physical cause is identified in only 25% [3]. Diagnosis is by fibre optic observation of paradoxical vocal cord movement and possibly by computed tomography (CT) of the larynx [3].

β_2 agonist toxicity

Adverse effects of β_2 agonists range from tolerable side effects to serious toxicity. Side effects include tachycardia, arrhythmia, hypertension, hypotension, tremor, hypokalaemia, worsening of V/Q mismatch, and hyperglycaemia. β_2 agonist toxicity may cause lactic acidosis with respiratory compensation, which can be mistakenly attributed to worsening or unresponsive asthma; often leading to further inappropriate β_2 agonist administration [4]. β_2 agonist toxicity is most often seen with intravenous (iv) infusions and continuous nebulization. ICU admission for closely supervised cessation, or reduction, of β_2 agonist therapy allows safe resolution of the hyperlactataemia.

Chest radiograph

A chest radiograph is indicated in unresponsive severe asthma, when lower respiratory tract infection or barotrauma is suspected, after initiation of ventilation, and if the diagnosis is in doubt.

Pulse oximetry and arterial blood gas analysis

Pulse oximetry enables accurate titration of oxygen therapy. Hypoxaemia from V/Q mismatch and mucous plugging is common in severe asthma. Hypocapnoea and respiratory alkalosis from hyperventilation is seen initially in severe asthma. Normal $PaCO_2$ or hypercapnoea usually represents more severe asthma, especially if the $PaCO_2$ is rising on serial measurements. Arterial blood gas sampling is indicated to confirm hypoxaemia, and to measure $PaCO_2$, pH, and lactate. Lactic acidosis and hypokalaemia from β_2 agonist toxicity can be detected by arterial blood gas analysis.

Therapeutic management

Oxygen

Humidified oxygen should be applied to maintain SpO_2 between 94 and 98% [2]. Hyperoxia from uncontrolled oxygen administration can worsen V/Q mismatch by releasing hypoxic vasoconstriction, leading to increasing hypercapnoea.

β_2 agonists

Inhaled short-acting β_2 agonists are the first line treatment. β_2 agonist via metered dose inhalers (MDI) and spacer is more effective in cooperative patients than nebulization. Typically, four to eight puffs of salbutamol are administered 1–4-hourly [2,5]. Oxygen-driven nebulization is recommended in life-threatening asthma as delivery by MDI and spacer method is usually not possible. Nebulized salbutamol (5 mg every 15–30 minutes) is a common initial regimen, increasing the dosing interval to 1–4 hours according to

Box 111.1 Clinical features of severe and life-threatening acute asthma

Acute severe asthma

Any one of:

- Respiratory rate ≥25/min.
- Heart rate ≥110.
- Inability to complete sentences in one breath.
- PEFR 33–50% best or predicted.*
- Pulsus paradoxus > 15 mmHg.**

Life-threatening asthma

Any of the following in a patient with severe asthma:

- Altered conscious state.
- Exhaustion.
- Arrhythmia.
- Hypotension.
- Cyanosis.
- Silent chest.
- Poor respiratory effort.
- PEFR <33% best or predicted.*
- SpO_2 < 92%.
- PaO_2 < 8 kPa (60 mmHg).
- Normal or rising $PaCO_2$.

*PEFR may not be possible in severe and life-threatening asthma, and may worsen bronchospasm.
**Absence of pulsus paradoxus does not exclude severe and life-threatening asthma.

response [2]. Continuous nebulization, e.g. salbutamol 5–10 mg/hour, may be more effective than intermittent administration [6]. Despite a lack of evidence, and a higher risk of toxicity, iv infusions of β_2 agonist may be considered in life-threatening asthma unresponsive to continuous nebulization, e.g. salbutamol 5-20 micrograms/min. An iv bolus of 100–300 micrograms of salbutamol may be life-saving in the unintubated patient *in extremis*. While unresponsiveness to maximal β_2 agonist therapy may suggest refractory asthma or a complication of asthma (Box 111.2), alternative diagnoses, and β_2 agonist toxicity should always be considered.

Box 111.2 Complications of severe and life-threatening acute asthma

- Pneumothorax, pneumomediastinum, pneumopericardium.
- Atelectasis.
- Mucous plugging.
- Respiratory arrest.
- **β_2 agonist toxicity**: arrhythmias, tremor, lactic acidosis, hypokalaemia.

Anticholinergics

Combining nebulized ipratropium bromide (500 micrograms 4–6-hourly) with nebulized β_2 agonist produces significantly greater bronchodilation than β_2 agonist alone [1,2,7]. An initial three doses 20 minutes apart might have additional benefit.

Corticosteroids

Prednisolone 50 mg daily (or 100 mg hydrocortisone 6-hourly if the oral route is not possible) should be commenced as early as possible and continued for at least 5 days [1,2]. Following recovery of the acute exacerbation, systemic steroids should be stopped or returned to maintenance dose, without tapering and inhaled steroids recommenced.

Magnesium sulfate

A single iv dose (1.2–2 g iv over 20 minutes) may be beneficial in severe and life-threatening asthma in patients who are unresponsive to maximal bronchodilator therapy [1,2,8]. However, evidence for the nebulized route is lacking [8]. While serious side effects from a single dose are uncommon, iv magnesium may cause respiratory muscle weakness, hypotension, flushing, sedation, areflexia, and arrhythmias, and therefore, repeat doses should be avoided.

Adrenaline

A slow iv bolus dose of 0.2–1 mg, over 3–5 minutes, followed by an infusion of 1–20 micrograms/min may be effective in selected patients. Subcutaneous and intramuscular adrenaline (0.3–0.5 mg) appears to be efficacious and safe in the prehospital environment for near fatal asthma that is unresponsive to β_2 agonists.

While there is insufficient evidence for iv adrenaline in acute severe asthma, it may avert invasive ventilation when a patient is in extremis [9].

Heliox

Helium/oxygen mixtures (e.g. Heliox 70:30) may decrease resistance to airflow, enhance delivery of nebulized bronchodilators, and improve pulmonary function in severe acute asthma [10]. However, the existing evidence does not support its use in asthma [1,10].

Anaesthetic agents

Ketamine infusion (0.5-2 mg/hr) has been reported to induce bronchodilation and avoid intubation in severe asthma [11], but there is insufficient evidence to recommend its use. The use of volatile anaesthetic agents (e.g. halothane) in ventilated patients has been described; hypotension, myocardial depression, and rebound bronchospasm, as well as the requirement for an anaesthetic machine with scavenging have limited their use.

Aminophylline

Aminophylline does not provide additional bronchodilation beyond that achieved by β_2 agonist therapy in adults [1,12]. However, aminophylline is beneficial in children with unresponsive severe acute asthma [13]. Aminophylline has a narrow therapeutic index and unfavourable side effect profile (headache, nausea, vomiting, cardiac arrhythmias, and seizures).

Leukotriene antagonists

Leukotriene antagonists have shown early promise in the treatment of acute asthma [14,15], but their use is currently limited to clinical trials.

Ventilatory support

Dynamic hyperinflation and intrinsic PEEP

Dynamic hyperinflation is the progressive increase in lung volume occurring when severe airflow limitation prevents complete exhalation before onset of the next breath (commonly known as 'gas trapping') [16]. Functional residual capacity (FRC) progressively increases, shifting tidal ventilation into higher lung volumes, resulting in flattening of the diaphragm, mechanical disadvantage, and increased elastic load. Together with the underlying increase in resistive work, the minute ventilation required to maintain normocapnoea eventually becomes unachievable, resulting in hypercapnic respiratory failure.

Intrinsic positive end expiratory pressure ($PEEP_i$) results from incomplete exhalation with progressively higher end-expiratory lung volumes and failure of alveolar pressure to return to zero at end expiration [16]. $PEEP_i$ measured as the airway pressure after an end-expiratory occlusion is the most common method used; however, this requires a relaxed patient and sufficient time for equilibration. Due to the heterogeneous distribution of inflammation and bronchospasm (and consequently dynamic hyperinflation and $PEEP_i$), $PEEP_i$ should be considered an average value. Also, airway closure may prevent regional $PEEP_i$ from being measured underestimating gas trapping (Fig. 111.1) [16].

During spontaneous and supported ventilation, inspiratory effort must overcome $PEEP_i$ and reduce airway pressure below extrinsic PEEP ($PEEP_e$), or below atmospheric pressure if no $PEEP_e$ is applied, before inspiratory flow can occur. This additional elastic load contributes to increased work of breathing and respiratory insufficiency. During supported or triggered ventilation a low level of $PEEP_e$ (typically 5 cmH_2O), which is less than the $PEEP_i$, can reduce inspiratory (threshold) work and allow easier triggering of the ventilator. During controlled ventilation, when there is no spontaneous respiratory effort, the traditional approach is to set $PEEP_e$

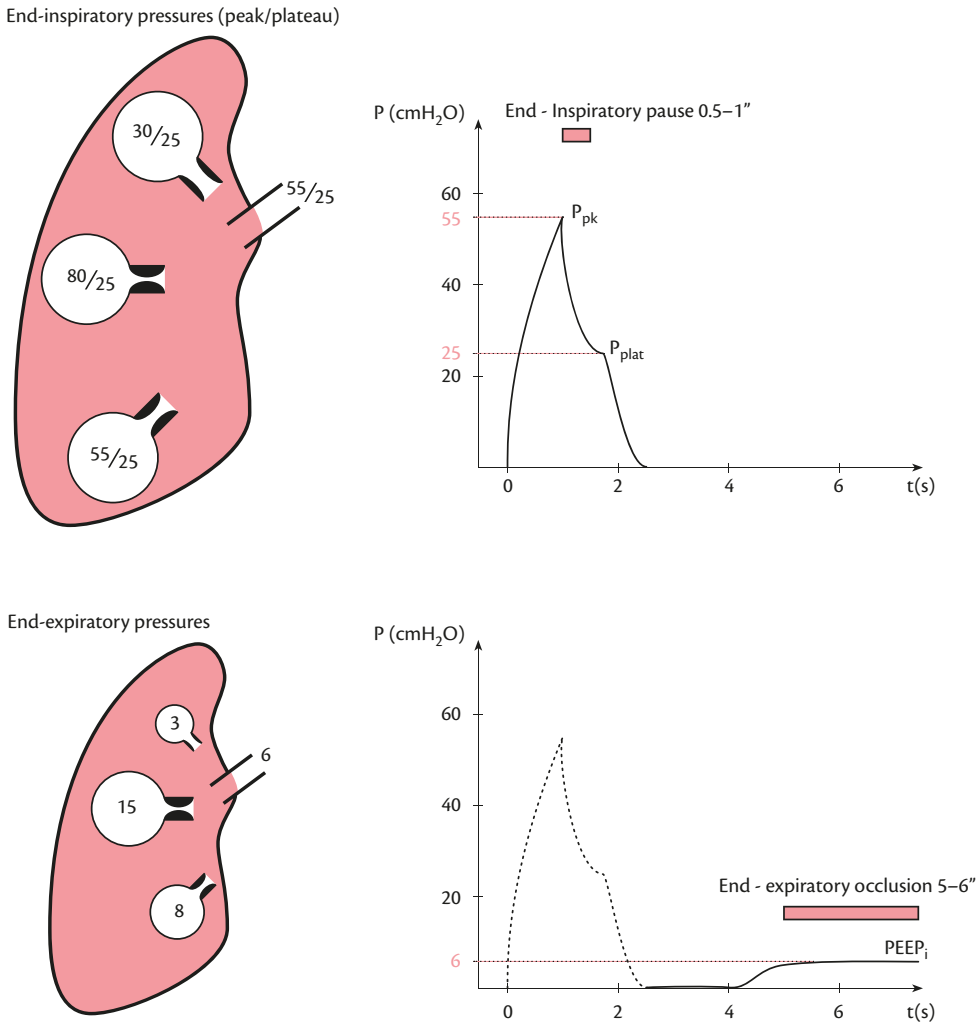


Fig. 111.1 Schematic representation of the heterogeneous distribution of airflow limitation and lung mechanics at end-inspiration and end-expiration in acute asthma. The figure represents the lung at both end-inspiration and end-expiration with associated airway time curves and relevant pressures during controlled mechanical ventilation in a relaxed patient. At end-inspiration a 0.5-second pause results in a fall from a peak airway pressure (P_{pk}) to the plateau airway pressure (P_{plat}) followed by a fall to the set $PEEP_e$ of 0 cmH_2O. The difference between P_{pk} and P_{plat} is determined by the average inspiratory resistance and the inspiratory flow rate. As there is heterogeneous distribution of resistance, different lung units have different P_{pk}, but a constant P_{plat}. The average P_{pk} and P_{plat} is also shown in the major conducting airway. At end-expiration differences in resistance between lung units results in heterogeneous degrees of gas trapping and $PEEP_i$. The result of an end-expiratory occlusion is shown in the airway pressure time relation with a rise in pressure to the average $PEEP_i$ (6 cmH_2O) occurring over some seconds.

to zero to prevent further increases in lung volume. However, one study suggests that an empirical trial of $PEEP_e$ during controlled ventilation may paradoxically relieve over inflation [17].

Non-invasive ventilation

Although non-invasive ventilation (NIV) has potential benefits, there is insufficient evidence to support its use in asthma [18]. NIV applied $PEEP_e$ (5 cmH_20) may reduce the inspiratory effort required to overcome $PEEP_i$, shorten inspiratory time and improve minute ventilation; without worsening dynamic hyperinflation. Other possible benefits include reduced V/Q mismatch, improved response to bronchodilators, avoidance of mechanical ventilation, improved PEFR and FEV1, and shorter ICU and hospital stay. However, NIV has potential serious complications including gastric insufflation, aspiration, hypotension, and pneumothorax. A trial of NIV may be warranted in cooperative patients with severe asthma, but must not delay intubation and invasive ventilation. Non-invasive positive pressure ventilation (NPPV) is the most studied mode of NIV in asthma, with inspiratory positive airway pressures (IPAP) of 12–15 cmH_2O and an expiratory positive airway pressure (EPAP) of 5 cmH_2O [18].

Invasive ventilation

The decision to intubate should be made by an experienced clinician after a period of observation, taking into consideration the rapidity of asthma onset, response to treatment and projected clinical course. It may be safe to withhold intubation in hypercapnic hyperacute asthma responding to treatment, but may be necessary in normocapnic chronic severe asthma with exhaustion. Absolute indications for intubation include respiratory and cardiac arrest, severe hypoxaemia, severe exhaustion, and rapidly deteriorating conscious state [19].

Induction with ketamine may provide additional bronchodilation [19]. Intubation-induced bronchospasm may be attenuated by maximal pre-induction β_2 agonist therapy; intravenous lidocaine has not been shown to be effective [19]. Once endotracheal tube placement is confirmed, slow hand ventilation (4–10 breaths/min) will maximize expiratory time until connection to the ventilator. A ventilation strategy that provides adequate oxygenation, while avoiding dynamic hyperinflation is required. This mandates a prolonged expiratory time with accompanying relative hypoventilation and permissive hypercapnoea. Prolonged expiratory time may be safely achieved with volume control ventilation at an initial tidal volume of 5–7 mL/kg and respiratory rate of 6–12/min. CO_2 clearance may be improved by incrementally increasing tidal volume and reducing respiratory rate (preserving constant minute ventilation) to reduce the anatomical dead space ventilation fraction. $PEEP_e$ is usually set at zero to prevent further increases in lung volume and dynamic hyperinflation. Inspiratory flow rates should be initially set at 30–60 L/min. Although higher inspiratory flow rates (70–100 L/min) may reduce inspiratory time, resultant high peak airway pressures may expose over distended, well-ventilated lung units to barotrauma (Fig. 111.1). A constant inspiratory flow pattern offers the advantage of a simple estimate of inspiratory resistance when an inspiratory pause is used and prevents dissipation of visco-elastic forces aiding expiratory flow. However, the peak airway pressure will be higher than if a descending ramp inspiratory flow pattern is used. Adjustments of tidal volume, respiratory rate and inspiratory flow should be made to maintain a $P_{plat} < 25$ cmH_2O. Acidaemia from permissive hypercapnoea is usually well tolerated. Sodium bicarbonate administration may be of benefit if the pH is below 7.15, although it can worsen intracellular acidosis. Deep sedation and intermittent neuromuscular blockade are usually required in the early ventilation period to avoid asynchrony.

Box 111.3 Complications of invasive ventilation in acute asthma

- **Dynamic hyperinflation**:
  - Barotrauma; pneumothorax (tension), pneumomediastinum, pneumopericardium.
  - Hypotension (↓ right ventricular preload).
  - Cardiac arrest (pulseless electrical activity).
  - Acute right heart failure.
- Patient-ventilator asynchrony.
- Ventilator-associated lung injury.
- Ventilator-associated pneumonia.
- Myopathy (corticosteroids and neuromuscular blockade).
- Gastric mucosal ulceration.

Withdrawal of ventilation

Withdrawal of ventilation may be attempted once airflow limitation has improved, suggested by a decreasing Pplat and PEEPi. Sedation is reduced, respiratory rate increased and pressure support ventilation commenced once spontaneous respiratory effort returns. PEEPe (3-7 cmH_20) may be cautiously introduced to assist triggering and reduce work of breathing.

Complications of ventilation

Hypotension, cardiovascular collapse, and cardiac arrest may result from dynamic hyperinflation, tension pneumothorax, acute right heart failure, or arrhythmia (Box 111.3). Cardiac arrest with pulseless electrical activity can occur from severe dynamic hyperinflation alone or from tension pneumothorax. Return of circulation after disconnection from the ventilator (for up to 60 seconds), the apnoea test, is both diagnostic and therapeutic for dynamic hyperinflation. Tension pneumothorax is difficult to diagnose and confirmation by chest radiograph should occur unless the patient is in cardiac arrest. Management is with chest drain insertion by blunt dissection; needle thoracentesis should be avoided to prevent iatrogenic pneumothorax. Complications such as myopathy and ventilator-associated pneumonia may prolong ventilator dependence.

Acute necrotizing myopathy associated with deep sedation, corticosteroids, and prolonged neuromuscular blockade may prolong ventilation weaning and slow overall recovery. Neuromuscular blockade should be used sparingly and systemic corticosteroid ceased as soon as possible to reduce the risk of myopathy. Mucous plugging and lung collapse may require bronchoscopic airway toilet.

Extracorporeal support

Extracorporeal support has been described in life-threatening asthma; registry data demonstrated an 83.3% survival to hospital discharge, compared with 50.8% in non-asthmatics [20].

References

1. British Thoracic Society Guideline on the Management of Asthma. Available at: www.brit-thoracic.org.uk/clinical-information/asthma/ (accessed 2 June 2014).
2. National Heart Lung and Blood Institute. Guidelines for the Diagnosis and Management of Asthma (EPR-3). Available at: www.nhlbi.ni.gov/guidelines/asthma/ (accessed 2 June 2014).
3. Ayres JG and Mansur AH. (2011). Vocal cord dysfunction and severe asthma: considering the total airway. *American Journal of Respiratory and Critical Care Medicine*, **184**, 2–3.
4. Rodrigo GJ and Rodrigo C. (2005). Elevated plasma lactate level associated with high dose inhaled albuterol therapy in acute severe asthma. *Emergency Medicine Journal*, **22**, 404–8.
5. Cates CJ, Crilly JA, and Rowe BH. (2006). Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database of Systematic Reviews*, Issue 2. Art. No.: CD000052.
6. Camargo Jr CA, Spooner C, and Rowe BH. (2003). Continuous versus intermittent beta-agonists for acute asthma. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD001115.
7. Rodrigo GJ and Castro-Rodriguez JA. (2005). Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax*, **60**, 740–6.
8. Song WJ and Chang YS. (2012). Magnesium sulfate for acute asthma in adults: a systematic literature review. *Asia Pacific Allergy*, **2**, 76–85.
9. Smith D, Riel J, Tilles I, Kino R, Lis J, and Hoffman JR. (2003). Intravenous epinephrine in life-threatening asthma. *Annals of Emergency Medicine*, **41**, 706–11.
10. Rodrigo G, Pollack C, Rodrigo C, Rowe BH. (2003). Heliox for nonintubated acute asthma patients. *Cochrane Database of Systematic Reviews*, **4**, CD002884.
11. Shlamovitz GZ and Hawthorne T. (2011). Intravenous ketamine in a dissociating dose as a temporizing measure to avoid mechanical ventilation in adult patient with severe asthma exacerbation. *Journal of Emergency Medicine*, **41**, 492–4.
12. Parameswaran K, Belda J, and Rowe BH. (2000). Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. *Cochrane Database of Systematic Reviews*, **4**, Art. No.: CD002742.
13. Yung M and South M. (1998). Randomised controlled trial of aminophylline for severe acute asthma. *Archives of Diseases of Childhood*, **79**, 405–10.
14. Camargo CA Jr, Gurner DM, Smithline HA, et al. (2010). A randomized placebo-controlled study of intravenous montelukast for the treatment of acute asthma. *Journal of Allergy and Clinical Immunology*, **125**, 374–80.
15. Ramsay CF, Pearson D, Mildenhall S, and Wilson AM. (2011). Oral montelukast in acute asthma exacerbations: a randomised, double-blind, placebo-controlled trial. *Thorax*, **66**, 7–11.
16. Marini JJ. (2011). Dynamic hyperinflation and auto-positive end-expiratory pressure: lessons learned over 30 years. *American Journal of Respiratory and Critical Care Medicine*, **184**, 756–62.
17. Carmez MP, Borges JB, Tucci MR, et al. (2005). Paradoxical responses to positive end-expiratory pressure in patients with airway obstruction during controlled ventilation. *Critical Care Medicine*, **33**(7), 1519–28.
18. Keenan SP, Sinuff T, Burns KE, et al. (2011). Canadian Critical Care Society Noninvasive Ventilation Guidelines Group. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. *Canadian Medical Association Journal*, **183**, E195–214.
19. Brenner B, Corbridge T, and Kazzi A. (2009). Intubation and mechanical ventilation of the asthmatic patient in respiratory failure. *Proceedings of the American Thoracic Society*, **6**, 371–9.
20. Mikkelsen ME, Woo YJ, Sager JS, Fuchs BD, Christie JD. (2009). Outcomes using extracorporeal life support for adult respiratory failure due to status asthmaticus. *American Society for Artificial Internal Organs Journal*, **55**, 47–52.

CHAPTER 112

Therapeutic strategy in acute or chronic airflow limitation

Francesco Macagno and Massimo Antonelli

Key points

- Oxygen therapy is used for the hypoxia in acute exacerbation of chronic obstructive pulmonary disease (AECOPD). The objective is to reach PaO_2 60 mmHg (8 kPa; SpO_2 90%.). The Venturi mask is the best method for administering oxygen.
- Inhalation therapy with beta 2 agonists, and anticholinergics reduce bronchial tone and dynamic hyperinflation. This type of administration is superior to intravenous administration and has significantly reduced side effects. Prednisolone at the daily dosage of 0.5 mg/kg for a duration of 8–15 days causes a reduction of hospital stay and therapeutic failures.
- In AECOPD patients, bacterial infections account for 50% of the cases of exacerbation. The first-line antibiotics are co-amoxiclav, third-generation cephalosporin, or fluoroquinolones.
- The early use of non-invasive ventilation (NIV) with conventional medical therapies decreases the need for intubation, and reduces the risk of complications and mortality in patients with acute or chronic respiratory failure. The treatment can be started for pH values between 7.25 and 7.35. Pressure support is the most used mode of ventilation and different interfaces can be used to improve tolerance and increase the success rate. In case of In AECOPD patients with previous negative trials of weaning, NIV can be used for reducing the weaning time, and prevent re-intubation.
- The failure of non-invasive treatment requires endotracheal intubation and mechanical ventilation. To reduce the risk of volutrauma and the worsening of the hyperinflation, tidal volumes between 6 and 8 mL/kg can be used with low respiratory rates and longer expiratory times.

Introduction

The medical history of a chronic obstructive pulmonary disorder (COPD) patient is characterized by the recurrence of worsening symptoms whose severity is closely related to compromised respiratory function, modifications in the intrapulmonary gas exchanges and comorbidities.

The objective of the initial evaluation of these patients is to increase the success of diagnostic tools, in order to provide the assistance proportional to the severity of the clinical condition. The fragility of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) accounts for their frequent hospitalization and their high intensive care unit (ICU) risk.

The decision-making process for hospital admission of a patient with AECOPD must take into account various aspects, including the severity of the clinical picture, the socio-economic situations, and family context. Advanced age, male gender, previous or current tobacco use, concomitant illnesses, nutritional state, important respiratory function deterioration, frequency of hospitalizations, altered intrapulmonary gas exchange, and long-term oxygen therapy constitute all negative predictors for the development of AECOPD.

In addition to clinical evaluation, arterial blood gas sampling (ABG), chest X-ray evaluation, serum electrolytes, albumin depletion, and biomarkers, such as NTproBNP, C reactive protein (CRP) and pro-calcitonin (PCT) also play an important role for prognosis. In a differential diagnosis of AECOPD patients, pneumothorax or a pulmonary embolism must be ruled out, especially when inflammation markers are negative [1].

Therapy for AECOPD is varied and the need for hospitalization must be always carefully evaluated, considering the risk factors related to the presence of multi-resistant pathogens or the need of invasive procedures.

Oxygen therapy

Oxygen therapy is the most effective and commonly used therapy for the treatment of hypoxia. The prolonged use of oxygen requires an accurate monitoring of blood gases and continuous oximetry. Arterial blood gas analysis allows the simultaneous evaluation of PaO_2, $PaCO_2$, and pH. A reasonable target for hospitalized patients might be PaO_2 60 mmHg (8 kPa), which correspond to a peripheral oxygen saturation (SpO_2) close to 90%. The attempt to improve PaO_2 values through the progressive increase of FiO_2 is not justified, due to the haemoglobin dissociation curve–small increases of SpO_2 require high inhaled fractions (FiO_2). The consequent risk is the respiratory centres depression, due to the altered physiologic response, resulting in CO_2 retention and subsequent pH worsening. The Venturi mask is the most used method for administering oxygen. This equipment ensures a quite precise administration of FiO_2. As an alternative, nasal cannula or transtracheal catheters can be used. A useful decisional algorithm is that proposed by the Infectious Disease Society of America and American Thoracic Society (IDSA_ATS) illustrated in Fig. 112.1 [2].

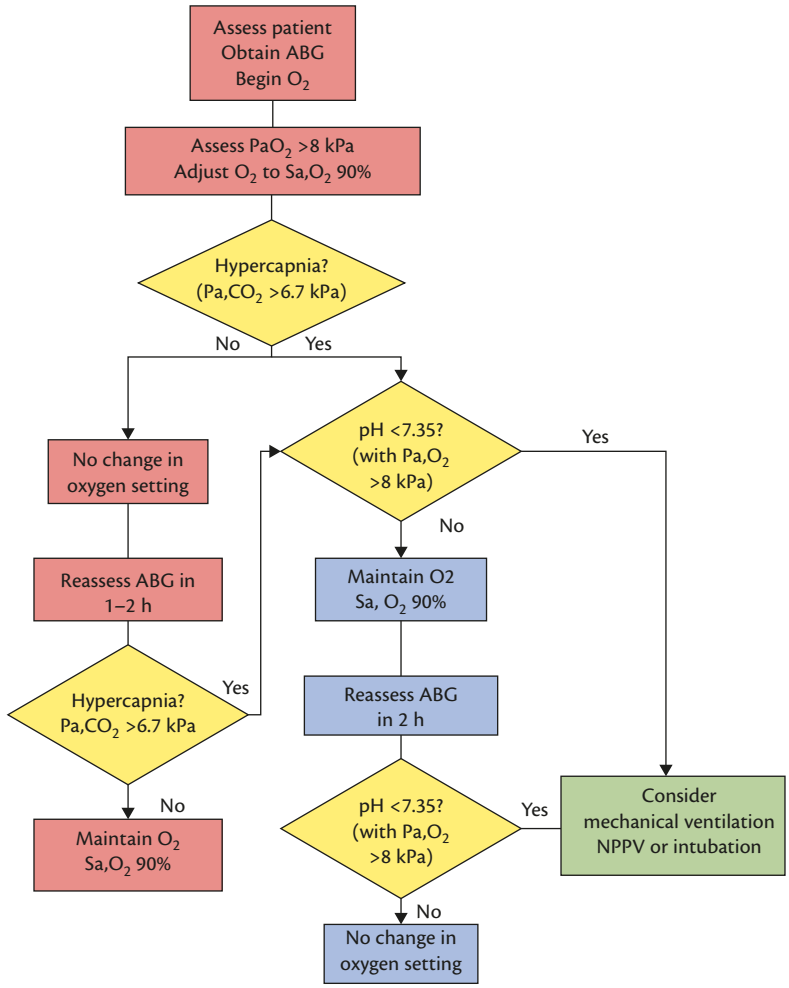


Fig. 112.1 ATS/ERS TASK FORCE: Standards for the diagnosis and treatment of patients with COPD.
Reproduced with permission of the European Respiratory Society: *Eur Respir J* June 2004 **23**, 932–46; doi:10.1183/09031936.04.00014304.

Bronchodilators

At present, three kinds of bronchodilators are normally used—beta 2 agonists, anticholinergics, and methylxantine. Their main effect is to reduce bronchial tone, dynamic hyperinflation, respiratory fatigue, and dyspnoea.

In AECOPD, beta 2 agonists and anticholinergics are commonly administered via inhalation. This route is superior to intravenous administration and significantly reduces side effects. Usually the nebulized dose of salbutamol (the most used beta 2 agonist) varies from 2.5 to 5 mg qds. Nebulized ipratropium (the most used anticholinergic) dose is 0.5 mg bd. Due to its many side effects, theophylline has a narrow therapeutic index. Theophylline serum levels correlate with both therapeutic and toxic effects. Concentrations of 10–20 mg/L are needed to produce bronchodilation with a minimum of side effects. Serum levels exceeding 20 mg/L are associated with an unacceptable incidence of adverse reactions. Theophylline levels above 35 mg/L increase the incidence of seizures and cardiac arrhythmias. Studies have suggested that low dose theophylline (at plasma concentrations below 10 mg/L) has some anti-inflammatory effect on the COPD airway. Low doses seem to increase the anti-inflammatory effects of steroids by increasing the activity of the histone deacetylase [3].

Inhalation therapy can be performed using nebulizers, pre-dosed aerosols, or powders for inhalation. The choice depends on the method, circumstances, and clinical conditions of the patient.

Corticosteroids

Corticosteroids for oral and systemic use now play an established role in AECOPD. Random control clinical studies have confirmed the effectiveness of prednisolone at the dosage of 0.5 mg/kg daily for a duration of 8–15 days. In particular, a reduction in hospital stay and therapeutic failures has been observed with an improvement in lung function and the reduction of dyspnoea. Longer treatments have not confirmed their effectiveness, with high risk of side effects as hyperglycaemia, osteoporosis, and muscular weakness.

Antibiotics

The use of antibiotics in AECOPD plays an important role because bacterial infections account for 50% of exacerbations. The presence of symptoms including leukocytosis, fever, variation of secretion volume, and characteristics, and the presence of markers such as the PCT or reactive protein C RPC) can help the diagnosis, limiting the prescription of empirical antibiotics to cases with high suspicion

Table 112.1 Antimicrobial therapy in acute exacerbations of chronic obstructive pulmonary disease (AECOPD)

Category	Likely pathogens	Antimicrobial treatment
Uncomplicated AECOPD Age <65 years; FEV1 > 50% predicted; <4 exacerbations/year; no comorbid conditions	*H. influenza* (more prevalent); *S. pneumoniae; M. catarrhalis; H. parainfluenzale*; viral; *M- pneumonie; C. pneumonie.*	Macrolide (azithromycin and clarithromycin); Doxycycline; 2nd or 3rd generation cephalosporin; Respiratory quinolone (moxifloxacin, gatifloxacin, gemifloxacin: against penicillin-resistant *S. pneumonie*)
Complicated AECOPD Age ≥65 years; FEV1 < 50% predicted; ≥4 exacerbations/year; Comorbid conditions	*H. influenza* (more prevalent); *S. pneumoniae; M. catarrhalis; H. parainfluenzale*; viral; *M. pneumonie; C. pneumonie*; Gram-negative enteric bacilli	Respiratory quinolone (moxifloxacin, gatifloxacin, gemifloxacin: against penicillin-resistant *S. pneumonie*); amoxicillin/clavulanate
Complicated AECOPD at risk for *Pseudomonas aeruginosa* infection FEV1 < 35% predicted; recurrent courses of antibiotics or steroids; bronchiectasis	*H. influenza* (more prevalent); *S. pneumoniae; M. catarrhalis; H. parainfluenzale*; viral; *M. pneumonie; C. pneumonie*; Gram-negative enteric bacilli; *Pseudomonas aeruginosa.*	Fluoroquinolone with antipseudomonal activity (ciprofloxacin and levofloxacin)

of infection. The overall objective is to decrease the development of multiresistant strains and mortality risk. Although there is no definite consensus regarding the most appropriate therapy and given the heterogeneousness of various pathogens in question, the proposed first-line antibiotics are co-amoxiclav, third-generation cephalosporin or fluoroquinolones. In case of community-acquired pneumonia the presence of comorbidities, such as COPD requires a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]; strong recommendation; level I evidence) or a β-lactam plus a macrolide (strong recommendation; level I evidence; Table 112.1) [4].

Mechanical ventilator support

In AECOPD, the increase of the airway resistances and the need for greater minute ventilation exacerbate the limitation of expiratory flow, increasing dynamic hyperinflation and intrinsic PEEP (positive end-expiratory pressure). This leads to an increase in respiratory effort with deterioration of respiratory muscle function. When respiratory muscles have exhausted their capacity to maintain adequate alveolar ventilation, CO_2 retention leads to worsening respiratory acidosis. Ventilatory support represents a milestone of the treatment of exacerbated AECOPD patients.

The rationale to start a form of ventilator assistance is well summarized in Fig. 112.2.

Non-invasive ventilation

NIV must be considered the first option in AECOPD patients and acute respiratory failure if there are no contraindications, such as severe impairment of consciousness, facial trauma, or incapability to control the airways or intolerance. The effectiveness of NIV lies in the reduction of the workload of the respiratory muscles with reduction of dyspnoea and respiratory rate and a subsequent improvement of the respiratory gases and pH [5].

The main advantages of an early trial of NIV are the easy and prompt application, and its possible use outside the ICU. Many prospective randomized and controlled studies have verified the effectiveness of NIV in the treatment of acute or chronic respiratory failure. Compared with traditional treatments, early application of NIV improves survival, reduces the need for endotracheal intubation and related complications, and reduces the length of stay in ICU and hospital. Treatment of patients with light to moderate respiratory failure characterized by pH values between 7.25 and 7.35 has shown a failure rate not higher than 20%. The treatment of more severe and later conditions had failure rates close to 50% and inversely correlated to the severity of respiratory acidosis. In these cases, the use of NIV as an alternative to invasive ventilation does not increase mortality, while reducing the risk of complications as ventilator-associated pneumonia (VAP) or difficult weaning [6]. The use of NIV in critically-ill patients should be avoided when contraindications or the impairment of consciousness (Glasgow coma scale <10) are present and, in case of shock, serious arrhythmias or acute coronary syndrome, serious agitation, and vomiting with the risk of inhalation. NIV failures are more frequent during the first hours of use and are mainly related to the severity of the acidosis, mental deterioration, and comordities. The lack of improvement of gas exchanges during the first hours of ventilation is a predictor of failure. Patients with COPD and severe respiratory failure, who have already been evaluated with precrisis functional respiratory damage, are more prone to fail NIV, requiring endotracheal intubation, notwithstanding an initial improvement [7,8].

When the case of exacerbation is a community acquired pneumonia the failure rate is higher.

In hypercarbic AECOPD with respiratory failure with a cardiac component, NIV has shown a high success rate with rapid resolution of the lung oedema [9].

One crucial element for the success of NIV is due to the choice of ventilators and interfaces. Air leaks from the mask have significant effects on the triggering of the ventilator and patient–ventilator interaction. The majority of the ventilators conceived for home-use have an efficient internal algorithm for leak compensation. Old ICU ventilators are without these features and, if used for delivering NIV, require a fine-tuned set-up of the trigger sensitivity to avoid auto-triggering phenomena and asynchrony. Recently, the introduction of specific modules, based on sophisticated algorithms for leaks compensation, have resolved this inconvenience

The preferred interfaces for delivering NIV are oro-nasal or face masks. However, lack of tolerance, skin lesions, and leaks can cause a failure requiring endotracheal intubation. Recently, helmets introduced for NIV therapy have reduced discomfort, cutaneous pressure lesions, eye irritation, and gastric distension. The main limitations of this interface are, however, determined by a quote of

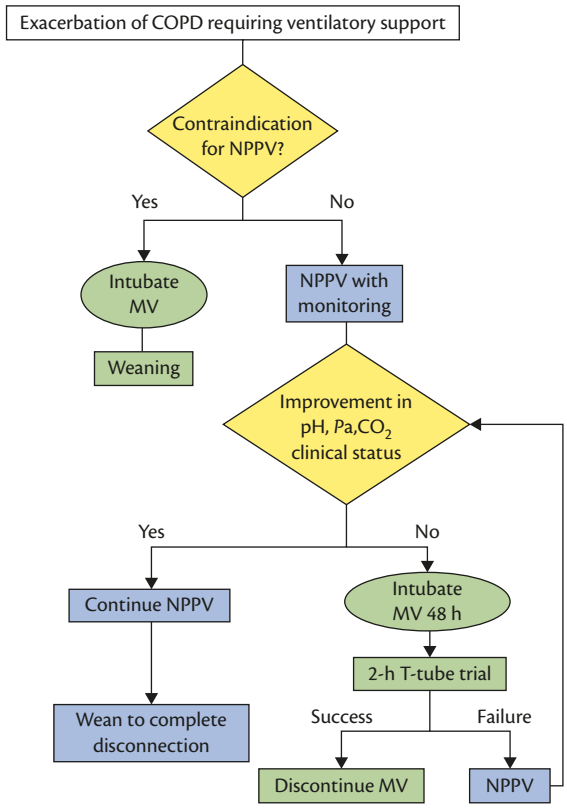


Fig. 112.2 ATS/ ERS TASK FORCE: Standards for the diagnosis and treatment of patients with COPD.
Reproduced with permission of the European Respiratory Society: *Eur Respir J* June 2004 **23**, 932–46; doi:10.1183/09031936.04.00014304.

potential rebreathing and the possibility of dyssynchrony that need specific settings [10].

Several ventilation modes can be used. The ones most frequently used are pressometric techniques.

PSV is the most common mode applied for NIV. It allows the patient to determine the respiratory frequency and tidal volume (V_T). The main limitation of this modality is the possible decrease in volume occurring as a result of an increase of resistance of the respiratory apparatus and the need for proper synchronization between patient and machine, more difficult in case of leaks. Pressure support is given to reduce the work of breathing and prevent barotrauma. In general, the level of pressure support are tuned between 10 and 20 cmH_2O according to clinical response, the relief of the accessory muscles of respiration and the reduction of respiratory frequency. PEEP is set between 4 and 6 cmH_2O to compensate the intrinsic PEEP and ineffective respiratory efforts.

Pressure assisted and controlled modes can be also used. They allow a better control of the effective volume, but are preferred substitute at least in part for spontaneous respiratory activity.

Controlled volume modes are rarely used, in the absence of leakage ensure respiratory frequency and a determined current volume, but invariably cause discomfort with possible asynchrony, and increase ineffective respiratory efforts and work. This ventilator mode is more commonly adopted in the early phases of invasive mechanical ventilation of the most severe patients, after intubation, to assure adequate ventilation and control hyperinflation.

The careful monitoring of the patient and the response to NIV are indispensable elements for therapeutic success. Peripheral oxygen saturation monitoring, blood gas analyses, evaluation of arterial pressure, respiratory and cardiac frequency are aimed to constantly adapting ventilation parameters to the changing needs of the patient. The therapeutic response will therefore establish the assistance needs and the duration of ventilation support.

NIV weaning can be achieved by reducing the duration of ventilation periods during the day and keeping patient on nocturnal sessions to lighten the work of respiratory muscles and improve sleep quality [11].

The resolution of the causes of exacerbation, the adequate oxygen saturation with a PaO_2/FIO_2 above 120, a PEEP level below 5 cmH_2O, a pH above 7.35 with a stable haemodynamic condition without sign of cardiac ischaemia, dyspnoea, or tachypnoea suggest the suspension of ventilation support.

Invasive mechanical ventilation

The failure of non-invasive treatments, the need to protect airways, shock, and changes in the state of consciousness, serious arrhythmias or severe cardiac failure require endotracheal intubation and mechanical ventilation.

The initial regulation of the ventilator is usually adjusted in Volume controlled mode with great attention to minimize the effects of auto-PEEP. In order to reduce the risk of volutrauma, low current volumes are used in the order of 6-8 ml/kg with low respiratory frequencies and with an I/E ratio adequate to allow a longer expiration time to avoid hyperinflation. In general, high respiratory flows should be used, usually greater than 60 litres/minute in order to reduce the length of insufflations.

The improvement of clinical conditions with low level or absent sedation are crucial to start weaning from invasive mechanical ventilation. The preferred techniques of weaning are the progressive decrease to Pressure Support and PEEP up to value respectively of 8 cmH2O Pressure support and 3–5 cmH_2O PEEP, or T piece trials [12].

The weaning failure in chronic patients is high. The stability of vital parameters, a respiratory rate lower than 35 breath/min and the capacity to maintain adequate peripheral O_2 saturation for at least 2 hours are predictors of success.

In AECOPD patients with previous negative weaning trials, NIV can be applied immediately after extubation to improve the chances of success and prevent re-intubation.

Acknowledgements

The authors gratefully acknowledge the input of Luca Montini.

References

1. Rabbat A, Guetta A, Lorut C, Lefebvre A, Roche N, and Huchon G. (2010). Management of acute exacerbations of COPD. *La Revue des Maladies Respiratoires*, **27**(8), 939–53. [Review; French.]
2. Celli BR, MacNee W, and ATS/ERS TASK FORCE. (2004). Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper . *European Respiratory Journal*, **23**, 932–46.
3. Walters JA, Wang W, Morley C, Soltani A, and Wood-Baker R. (2011). Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*, **10**, CD006897. [Review.]

4. Martinez FJ, Han MK, Flaherty K, and Curtis J. (2006). Role of infection and antimicrobial therapy in acute exacerbations of chronic obstructive pulmonary disease. *Expert Review of Anti-Infective Therapy*, **4**(1), 101–24.
5. Ram FS, Picot J, Lightowler J, and Wedzicha JA. (2004). Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*, **3**, CD004104. [Review.]
6. Squadrone E, Frigerio P, Fogliati C, et al. (2004). Noninvasive vs invasive ventilation in COPD patients with severe acute respiratory failure deemed to require ventilatory assistance. *Intensive Care Medicine*, **30**(7), 1303–10.
7. Antón A, Güell R, Gómez J, et al. (2000). Predicting the result of noninvasive ventilation in severe acute exacerbations of patients with chronic airflow limitation. *Chest*, **117**(3), 828–33.
8. Ambrosino N, Foglio K, Rubini F, Clini E, Nava S, and Vitacca M. (1995). Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. *Thorax*, **50**(7), 755–7.
9. Nava S, Carbone G, Dibattista N, et al. (2003). Noninvasive ventilation in cardiogenic pulmonary edema: a multicenter, randomized trial. *American Journal of Respiratory and Critical Care Medicine*, **168**, 1432–7.
10. Costa R, Navalesi P, Spinazzola G, et al. (2008). Comparative evaluation of different helmets on patient-ventilator interaction during noninvasive ventilation. *Intensive Care Medicine*, **34**(6), 1102–8.
11. Nava S, Navalesi P, and Conti G. (2006). Time of non-invasive ventilation. *Intensive Care Medicine*, **32**(3), 361–70. [Review.]
12. Girard TD, Kress JP, Fuchs BD, et al. (2008). Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): a randomised controlled trial. *Lancet*, **371**(9607), 126–34.

PART 4.12

Respiratory acidosis and alkalosis

CHAPTER 113

Pathophysiology and therapeutic strategy of respiratory acidosis

Luciano Gattinoni and Alfredo Lissoni

Key points

- Respiratory acidosis is a process in which the low pH is primarily due to a rise in PCO_2. In critically-ill patients the CO_2 load may be greatly increased due to hypermetabolism, excessive parenteral nutrition, or titration of HCO_3^- by fixed acids.
- CO_2 buffering in vivo leads to an increase in HCO_3^- of 1 mmol/L for every increase of 10 mmHg (1.33 kPa) in PCO_2 above 40 mmHg (5.33 kPa). In chronic conditions the kidney-related increase of strong ion difference (reduction in plasma chloride) leads to a plasma HCO_3^- increase of approximately 3.5 mmol/L for every increase of 10 mmHg (1.33 kPa) in PCO_2 above 40 mmHg (5.33 kPa).
- If respiratory acidosis is present, identifying the precipitating factors and assessing whether the associated signs (hypoxaemia, hypercapnia, and acidosis) are themselves life-threatening is fundamental. Assessment of the precipitating factors and the time required for their correction is of paramount importance in planning therapeutic strategy.
- Since hyperinflation of the lung, with its cardiovascular consequences, is the most harmful complication of mechanical ventilation in chronic respiratory acidosis, it is essential to set a small tidal volume associated with an adequate expiratory time. Non-invasive ventilation appears to be a promising treatment of chronic respiratory acidosis.
- The artificial lungs to remove CO_2 extracorporeally and are increasingly employed during bridge to lung transplantation, acute respiratory distress syndrome, and the hyperinflation states of COPD re-exacerbation or status asthmaticus.

Pathophysiology

Introduction

Although carbon dioxide (CO_2) is not an acid *per se*, it becomes a proton (H^+) donor when it is combined with water:

$$CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^- \quad \text{[eqn 1]}$$

When PCO_2 increases above its physiological levels (i.e. above 40–45 mmHg (5.33–6 kPa), corresponding to 1.2–1.35 mmol/L), acidaemia usually develops. Thus, respiratory acidosis can be defined as a process in which the tendency for the arterial pH to decrease is primarily due to an increase in PCO_2.

The CO_2 load

In normal man, the amount of CO_2 produced metabolically is approximately 200–250 mL/min, corresponding to an acid load of 13,000–16,000 mmol/day. This amount may be increased by 30–100% because of increased metabolism, burns, infection, and an excessive calorific intake, particularly during parenteral nutrition [1]. An additional source of CO_2, not metabolically produced, is the titration of HCO_3^- by fixed acid, as lactic acid (LAH), particularly relevant in critically-ill patients.

Excretion of CO_2

The acid load expired by the lungs can be expressed as:

$$VCO_2 = K \times PaCO_2 \times V_A \quad \text{[eqn 2]}$$

where VCO_2 is the expired CO_2, V_A is alveolar ventilation, $PaCO_2$ is the partial pressure of CO_2 in arterial blood, and K is a factor converting pressure to volume fraction. Of note, we will refer always to the alveolar ventilation, which is the fraction of the minute ventilation, which actually reaches the perfused alveoli. The difference between the total ventilation and the alveolar ventilation is modelled as physiological dead space, in part anatomical (ventilation of regions not designed for gas exchange) and in part alveolar, i.e. the fraction of alveolar ventilation ventilating unperfused alveoli.

VCO_2 can also be expressed according to Fick's law as:

$$VCO_2 = Q(CvCO_2 - CaCO_2) \quad \text{[eqn 3]}$$

where Q is the cardiac output, and $CvCO_2$ and $CaCO_2$ are, respectively, the CO_2 contents of mixed venous and arterial blood. Assuming, for simplicity, that the relationship between CO_2 content and partial pressure is linear in the range of physiological interest, and combining and rearranging equations 2 and 3, it follows that:

$$PaCO_2 \propto (Q / (V_A + Q))PvCO_2 \quad \text{[eqn 4]}$$

This equation shows that $PaCO_2$, for a given acid load (which increases the $PvCO_2$) is directly proportional to cardiac output and inversely proportional to alveolar ventilation.

Body response to respiratory acidosis

Buffer system (minutes)

Of the 15,000 to 30,000 mmol of protons delivered daily to the extracellular fluid, only 40–60 nmol/L (i.e. only 1 mmol of H^+ out of 1 million) are found free in the blood. The remainder are bound

by the buffer system. Buffers that are present in extracellular and intracellular fluids, are substances characterized by pK values (i.e. $-\log_{10} K$, where K is the acid dissociation constant) close to the pH value and which are able to bind or release H^+, thus preventing large changes in free H^+ concentration. In general, buffers are weak acids, which may be present electrically neutral (AH) or electrically charged (A^-). At a given pH their electrical status is defined by the Henderson–Hasselbalch equation:

$$pH = pK + (A^- / AH) \quad \text{[eqn 5]}$$

where $[A^-]$ and [AH] are the concentrations of dissociated base and undissociated acid, respectively. The pK values and the concentrations of the various extracellular buffers are listed in Table 113.1.

Of note, only proteins and phosphates are available to buffer the CO_2 load. It is important to note that the buffer mechanism described remains entirely in the 'buffer base dominion,' this means that the total amount of dissociated buffers does not change as the free H^+ deriving from CO_2 load hydration are buffered by A^-, forming AH, while CO_2 becomes HCO_3^-. In vivo, this immediate buffering mechanism produces ≈ 1 mmol/L HCO_3^- increase every ≈10 mmHg of increased PCO_2.

Kidneys response (days)

The normal kidneys compensate the low pH by increasing plasma strong ion difference (SID). To perform this variation the kidneys must excrete the appropriate amount of strong ions. In the urine the electrolyte equilibrium can be written as:

$$Na^+ + K^+ + UI^+ = Cl^- \quad \text{[eqn 6]}$$

where UI^+ and UI^- are the unmeasured positive or negative strong urinary ions. The most important unmeasured positive strong ion is NH_4^+, the most important unmeasured negative ions is SO_4^{2-}, which derives from sulphur acid metabolism. To manipulate the difference of strong ions that are relevant in generating the plasma SID (and pH) it follows that:

$$Na^+ + K^+ + CI^- = UI^- - UI^+ \quad \text{[eqn 7]}$$

To increase plasma SID (traditionally called compensatory metabolic alkalosis), urinary SID must decrease, and this occurs by increasing Cl^- excretion. To maintain electroneutrality, the difference $UI^- - UI^+$ must decrease and this occurs by rising NH_4^+ excretion, which is the best way to excrete an increased amount of Cl^- while retaining Na^+ [2,3]. Therefore, immediately after the PCO_2 rise and the pH decrease, the kidneys start to increase the ammonium production, thus increasing the chloride excretion. Indeed, during respiratory acidosis, plasma chloride decreases (increasing plasma SID), while urine chloride and the ammonium increase (with associated reduction in urinary pH). It takes approximately 2–3 days to excrete a sufficient amount of chloride in order to significantly affect the plasma SID. When plasma SID is increased the buffer base ($HCO_3^- + A^-$) increases equally. In vivo this process leads to an increase of ≈3.5 mmol/L of HCO_3^- every ≈10 mmHg of PCO_2 chronically increased.

Acid–base regulation in critically-ill patients

Every step of acid–base regulation may be affected in critically-ill patients:

- The acid load may be altered by both the underlying disease (hypoperfusion, shock, increased metabolism, etc.) and therapeutic intervention (excessive parenteral feeding).
- The buffer system is frequently abnormal in critically-ill patients; decreased levels of albumin, the most important component of the A^-–AH buffer pair, are not unusual. A decreased concentration of both A^-–AH and HCO_3^-–CO_2 buffer pairs implies a greater change in pH for a given acid load.
- Transport of blood from the venous to the arterial side may also be affected (low-flow states). In these conditions, the CO_2 clearance may be altered, resulting in a large difference between the acid–base status of the venous and arterial blood, with increases in the PCO_2 and pH gradients.
- The physiological response to increased PCO_2 and decreased pH, i.e. increased ventilation, is usually impaired in critically-ill patients for two main reasons. The underlying disease may affect the lung, thus preventing increased ventilation (due to reduced minute ventilation or increased dead space), and these patients are usually on mechanical ventilation. If volume-controlled ventilation is used, PCO_2 will rise as the patient (usually sedated and sometimes paralyzed) cannot change either the tidal volume or the respiratory rate. If pressure-support ventilation is used, the patient may respond to the increase in PCO_2 by triggering mechanical breathing more frequently. However, the depth of breath (i.e. the tidal volume) is often out of the patient's control. Thus it is obvious that mechanical ventilation has a deleterious effect on the physiological response to changes in acid–base status.

Table 113.1 The blood buffers

Buffer pairs	Normal concentration (dissociated + undissociated)	pK	Base-to-acid ratio at pH 7.4 (dissociated/undissociated)
Bicarbonate–carbonic acid (mmol/L)	25	6.1	$[HCO_3^-]/[CO_2]$ = 20/1
Dibasic–monobasic phosphate (mmol/L)	2	6.8	$[HPO_4^{2-}]/H_2PO_4^-$ = 4/1
Proteins (mmol/L)	14 (7 g/dL)	6.8	Pr–/HP = 4/1
Haemoglobin (mmol/L)	90 (15 g/dL)	6.8	Hb–/HHb = 4/1

- The physiological response to decreased pH in the renal tubular cells, in which HCO_3^- losses are replaced, may also be impaired in the critically ill, whose renal function is often affected. It is also important to realize that some forms of renal support, as haemofiltration, may lead to HCO_3^- losses, with consequent additional derangement of the acid–base balance.

To summarize, it is important to remember that the physiological control of the acid–base equilibrium is often impaired in critically-ill patients, and physicians must understand which mechanisms are altered so that an adequate substitute can be provided for the physiological control which has been lost.

Therapeutic strategies

Approach to respiratory acidosis

In patients presenting with hypercapnia, acidosis, and hypoxaemia, two lines of action are required:

- Identification of the causes of respiratory acidosis, with particular focus on the correction of precipitating factors which may be reversible.
- Treatment of the symptoms and signs if they are themselves a possible cause of unfavourable outcome.

These two actions should be pursued together, as correction of the precipitating factors may lead to almost immediate resolution of the respiratory acidosis. However, the first goal in intensive care is the maintenance of homeostasis, and correction of life-threatening conditions is the priority. Thus, the indications for symptomatic treatment will be discussed first.

Hypoxaemia, hypercapnia, and acidosis

Hypoxaemia

Hypoxemia unavoidably occurs during CO_2 retention when the patient breathes room air ($F_IO_2 = 21\%$) since:

$$F_AO_2 = F_IO_2 - F_ACO_2 \qquad \text{[eqn 8]}$$

where F_AO_2 is the alveolar fraction of oxygen, F_IO_2 is the inspired fraction of oxygen, and F_ACO_2 is the alveolar fraction of CO_2. This type of hypoxaemia can easily be corrected by increasing F_IO_2. For example, when $P_ACO_2 = 80$ mmHg (10.66 kPa) ($F_ACO_2 = 11.2\%$), F_AO_2 can be restored to its normal values by increasing F_IO_2 from 21 to 26.6%. Therefore, the hypoxaemia due to hypercapnia is easily corrected by increasing the inspired oxygen fraction, differently from the hypoxaemia due to the right to left shunt. The pathophysiological meaning of different PO_2/PCO_2 combinations are listed in Table 113.2 (conditions of high altitude or inhalation of hypoxic gas mixtures are excluded).

Hypercapnia and acidosis

Similarly to PO_2, there is no threshold value of PCO_2 or pH which is 'harmful' per se. Many factors may influence the response to increased CO_2, such as the rate of increase in PCO_2 (acute or chronic), age, and cardiovascular conditions. If associated with normoxia, near-normal pH, consciousness, and haemodynamic stability, a high PCO_2 does not need any therapeutic intervention. The indications for mechanical assistance should be based on a global clinical assessment, considering the three main consequences of increased PCO_2, i.e. tissue acidosis, impairment of the central nervous system, and the cardiovascular response [4].

Tissue acidosis

As molecular CO_2 enters the cell membrane faster than HCO_3^-, it is generally believed that intracellular pH decreases more than extracellular pH. However, there is increasing evidence that the intracellular buffers limit tissue acidosis and hypercapnia is well tolerated. If cellular acidosis develops, cell function and viability are impaired.

Effects on the central nervous system

Increasing PCO_2 may have a severe effect on central nervous system activity. Experimentally, the brain excitability first decreases, then increases, with associated seizures, and finally decreases to anaesthesia and coma. CO_2 is one of the major determinants of the cerebral vascular reactivity, both directly and indirectly (through pH changes), and acute hypercapnia may result in an increased cerebral blood flow and intracranial pressure.

Circulatory response to hypercapnia

The effect of hypercapnia on the cardiovascular system depends on the balance between the direct depressant effects of PCO_2 on heart and peripheral vascular smooth muscles, and the increased plasma levels of epinephrine and norepinephrine due to activation of the sympathetic nervous system. In normal conditions, the net result is an increase in cardiac output and a slight decrease in peripheral resistance. The arterial pressure tends to rise and the pulmonary artery pressure may increase substantially. It is important to remember that these reactions are observed in intact subjects. In patients given β-blockers, for example, hypotension and decreased cardiac output may be observed.

Table 113.2 Relationship between PO_2 and PCO_2

	Normal PCO_2	**Low PCO_2**	**High PCO_2**
Normal PO_2	Normal	Pure hyperventilation if $F_IO_2 = 21\%$ (stress + anxiety, metabolic acidosis); if $F_IO_2 > 21\%$, the above conditions plus shunt	Ventilatory impairment while inhaling $F_IO_2 > 21\%$
Low PO_2	Oxygenation impairment due to shunt plus relative ventilatory impairment	Oxygenation impairment due to shunt with physiological ventilatory response	Ventilatory impairment if $F_IO_2 = 21\%$; oxygenation impairment due to shunt if $F_IO_2 > 21\%$ associated with ventilatory impairment
High PO_2	$F_IO_2 > 21\%$ without ventilatory impairment	Hyperventilation during inhalation of $F_IO_2 > 21\%$	Ventilatory impairment while inhaling $F_IO_2 > 21\%$

Causes of respiratory acidosis and precipitating factors

The most common causes of respiratory acidosis and the time required for their correction are summarized in Table 113.3. They can be classified into three groups:

- In this group the cause of hypercapnia can be removed easily. If hypoxaemia can be corrected by supplemental oxygen administration, it is better, after removal of the precipitating factors, to wait for a spontaneous increase in alveolar ventilation. Hypercapnia does not require any treatment if associated with a stable pH, high HCO_3^-, and haemodynamic stability in a conscious patient.
- In this group, the correction of the precipitating factors will probably require hours or days. The need for mechanical ventilation should be determined on the basis of a global clinical assessment. In patients in whom hypercapnia is associated with clinical signs of severely increased work of the respiratory muscles, mechanical support should be introduced before the development of respiratory fatigue, which may lead to a sudden deterioration of PCO_2 and pH.
- In the final group the cause cannot be corrected (e.g. late-stage neuromuscular disease). In most cases, the issue is more ethical than medical, and the therapeutic plan should be discussed with the patients and relatives (e.g. planning for home ventilation).

Assessment and correction of hypercapnia

Knowledge of the previous respiratory status is of paramount importance in determining the goal of respiratory support. A reasonable goal in a previous healthy subject could be normal blood gases ($PaCO_2$ = 40 mmHg (5.33 kPa), PaO_2 > 80 mmHg (10.66 kPa)). In a subject with previous chronic respiratory impairment, the goal should be the blood gas values present before the superimposed acute derangement (e.g. PaO_2 = 60 mmHg (8 kPa), $PaCO_2$ = 50 mmHg (6.66 kPa)). An accurate history is essential for differentiating chronic and acute respiratory impairment (i.e. to define the target blood gases). Measurement of the blood gases alone may be misleading. In fact, the normal increase in HCO_3^- of ≈1 mmol/L (acute conditions) or ≈3.5 mmol/L (chronic condition) for every increase of 10 mmHg (1.33 kPa) in $PaCO_2$ may be offset by the concurrent presence of metabolic acidosis, which 'consumes' the HCO_3^-. Under these conditions the HCO_3^- level does not discriminate between acute and chronic respiratory acidosis.

In typical chronic respiratory acidosis, hypoxaemia is usually corrected by increasing FIO_2. The risk of high PaO_2 in chronic patients breathing spontaneously (coma) has probably been overestimated [5], and reasonable oxygenation is a mandatory target.

Since $PaCO_2 \propto VCO_2/VA$, it is evident that it can be decreased by either decreasing VCO_2 or increasing the alveolar ventilation VA. Methods of decreasing VCO_2 include withdrawal of the excessive load of glucides delivered by parenteral nutrition, control of temperature in a hyperthermic patient, and artificial removal of part of VCO_2 by extracorporeal methods such as dialysis or artificial lungs. However, the usual way of correcting hypercapnia is to increase alveolar ventilation, and this is usually achieved by mechanical ventilation. When the causes of hypercapnia are extrapulmonary, such as central nervous system or neuromuscular diseases, and the lung parenchyma is normal, mechanical ventilation causes no more problems than during general anaesthesia in a normal patient.

Major problems may occur in patients in whom hypercapnia is due to dysfunction of the small airways (e.g. bronchospasm or asthma), parenchymal lesions (e.g. emphysema), or diseases involving both airways and parenchyma (e.g. severe chronic obstructive pulmonary disease (COPD)). If mechanical support of these patients is unavoidable, it is essential to avoid worsening hyperinflation, which may lead to devastating haemodynamic consequences including cardiac tamponade. Small tidal volumes and prolonged expiratory time must be maintained when ventilating these patients, even at the cost of a relatively high PCO_2. The

Table 113.3 Causes of respiratory acidosis

	Immediate reversibility	Reversibility within hours/days	Irreversible
Respiratory drive	Drugs (antidotes available) Nutritional insufficiency	Chronic loading Metabolic alkalosis Endocrine disturbances	Congenital
Airways	Secretions Foreign bodies Bronchospasm Airways apparatus	Asthma Bronchial stenosis	Terminal COPD
Muscles	Drugs (antidotes available)	Neuromyopathies Endocrine/electrolyte disorders Abdominal distension Hyperinflation	Quadriplegia Terminal neuromuscular Disease
Chest wall		Flail chest	Kyphoscoliosis Thoracoplasty
Lung parenchyma	Pneumothorax Pleural effusion	Pulmonary oedema Pulmonary embolism	Terminal obstructive and restrictive lung disease

advantages of this setting have been shown in asthmatic patients [6] and suggested in other patient populations [7]. As a general rule, non-invasive ventilation is preferable to mechanical ventilation with intubation in the hypercapnic patient [8]. If the patient is hypercapnic, hyperinflated, and performing excessive respiratory work, the use of continuous positive airway pressure may decrease respiratory work and enable the patient to maintain spontaneous breathing. It must be noted, however, that when mechanical ventilation is per se harmful to correct hypercapnia, the artificial lungs are the appropriate solution. This form of support is increasingly used worldwide as it allows to remove varying amounts of VCO_2, up to removal of all the metabolically-produced CO_2, therefore abolishing the need for mechanical ventilation [9,10]. The main indications are, to date, bridge to lung transplant, acute respiratory distress syndrome and COPD re-exacerbation.

References

1. Covelli HD, Black JW, Olsen MS, and Beekman JF (1981). Respiratory failure precipitated by high carbohydrate loads. *Annals of Internal Medicine*, **95**(5), 579–81.
2. Kellum JA. (2000). Determinants of blood pH in health and disease. *Critical Care*, **4**(1), 6–14.
3. Ring T, Frische S, and Nielsen S. (2005). Clinical review: renal tubular acidosis—a physicochemical approach. *Critical Care*, **9**(6), 573–80.
4. Bidani A, Tzouanakis AE, Cardenas VJ, Jr, and Zwischenberger JB. (1994). Permissive hypercapnia in acute respiratory failure. *Journal of the American Medical Association*, **272**(12), 957–62.
5. Aubier M and Dombret MC. (1993). Acute exacerbation of chronic airflow obstruction. In: Pinsky MR and Dhainaut JFA. (eds) *Pathophysiology: Foundations of Critical Care*, pp. 427–46. Baltimore, MD: Williams & Wilkins.
6. Darioli R and Perret C. (1984). Mechanical controlled hypoventilation in status asthmaticus. *American Reviews in Respiration Diseases*, **129**(3), 385–7.
7. Hickling KG, Henderson SJ, and Jackson R. (1990). Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Medicine*, **16**(6), 372–7.
8. Brochard L, Mancebo J, Wysocki M, et al. (1995). Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *New England Journal of Medicine*, **333**(13), 817–22.
9. Gattinoni L, Carlesso E, and Langer T (2011). Clinical review: Extracorporeal membrane oxygenation. *Critical Care*, **15**(6), 243.
10. Gattinoni L, Carlesso E, and Langer T. (2012). Towards ultraprotective mechanical ventilation. *Current Opinions in Anaesthesiology*, **25**(2), 141–7.

CHAPTER 114

Pathophysiology and therapeutic strategy of respiratory alkalosis

Thomas Langer and Pietro Caironi

Key points

- Respiratory alkalosis is an increase in arterial pH due to an imbalance between metabolic CO_2 production and CO_2 removal, in favour of the latter.
- Respiratory alkalosis is usually a sign of an underlying pulmonary or central nervous system disease.
- An excessive CO_2 removal during controlled mechanical ventilation or extracorporeal CO_2 removal can also cause hypocapnia and, therefore, result in respiratory alkalosis.
- The metabolic compensation (mainly renal) restores pH values close to normality in 24–48 hours, through the reduction in plasma strong ion difference (increase in plasma chloride concentration).
- Respiratory alkalosis per se is rarely dangerous, and the clinical approach is directed towards diagnosis and treatment of the underlying disorder.

Definition

Respiratory alkalosis is a condition characterized by low partial pressure of carbon dioxide (PCO_2) and an associated elevation in arterial pH caused by an imbalance between CO_2 production and removal, in favour of the latter. The increase in CO_2 removal usually occurs because of increased alveolar ventilation. Respiratory alkalosis is a primary acid–base derangement, i.e. the increased CO_2 elimination is the manifestation of a clinical condition and not a compensatory response to metabolic acidosis.

Pathophysiology of the control of breathing

In physiological conditions, alveolar ventilation is finely tuned by the activity of two groups of sensors—central chemoreceptors (located at the ventral surface of the medulla, within the central nervous system) and peripheral chemoreceptors (type 1 glomus cells of carotid and aortic arch bodies) [1]. These receptors are mainly stimulated by changes in PCO_2 and pH, i.e. an increase in PCO_2 and/or a reduction in pH will activate the receptors and thus increase the signal strength (input) to the central controller, causing an increased output signal to the effectors (respiratory muscles), and a consequent increase in alveolar ventilation. This mechanism will eventually reduce PCO_2, normalize arterial pH and thereby reduce the input to the central controller. In addition to increases in PCO_2/reductions in pH, also very low values of PO_2 (less than 50 mmHg) can activate peripheral chemoreceptors and have a similar effect on alveolar ventilation [2]. In the case of hypocapnia and slight alkalosis, however, this hypoxic respiratory response is abolished [3]. Finally, besides central and peripheral chemoreceptors, lung receptors (Table 114.1) might also play a role in the pattern of respiration. These receptors are usually not active in physiological conditions.

Pathophysiology of hypocapnia

Conditions that cause increased alveolar ventilation, without having as input stimulus a reduction in pH, will cause hypocapnia associated with a variable degree of alkalosis. These conditions can be schematically divided into three categories (Table 114.2).

Table 114.1 Schematic representation of lung receptors' types and evoked reflexes

Receptor type	Type	Stimuli	Respiratory reflex/effect
Slowly adapting receptor	Mechanosensitive	Lung inflation	Termination of inspiration (Breuer–Hering reflex), expiratory facilitation, bronchodilation
Rapidly adapting receptor	Mechanosensitive and chemosensitive	Lung inflation and deflation, and chemical irritants	Augmented breath/gasp, irregular inspiration, and shortened expiration
C-fibre receptor, former J-receptors	Chemosensitive	Irritants, inflammation, congestion, pulmonary oedema, micro-embolism	Rapid, shallow breathing, apnoea (simultaneous chemical stimulation)

Table 114.2 Causes of respiratory alkalosis

Central	Condition
Voluntary hyperventilation	
Psychogenic	Pain, panic attack, hysteria
Central neurogenic hyperventilation	Brainstem injuries, invasive brain tumours, brain infarcts
Hormonal	Increased progesterone levels in pregnancy and liver cirrhosis
Infectious	Meningitis, encephalitis
Thermal hyperpnoea	Fever, hyperthermia
Intoxication	Salicylate, topiramate
Peripheral	
Chemoreceptors	Hypoxic pulmonary disease, high altitude
Lung receptors	Pulmonary oedema, pneumonia, acute respiratory distress syndrome, asthma, pulmonary embolism, interstitial fibrosis
Iatrogenic	
Mechanical ventilation	Excessive mechanical ventilation (accidental or therapeutic for traumatic brain injury)
Extracorporeal CO_2 removal	Excessive extracorporeal CO_2 removal

Increased activity of the 'central controller'

Conditions characterized by an increased activity of the 'central controller', dissociated from input arising from peripheral sensors, result in an increased activity of the respiratory muscles, which in turn cause an augmented alveolar ventilation [4,5]. In theory, this might be due to an increased activity of the central controller per se (such as voluntary hyperventilation and central neurogenic hyperventilation) or by an increased activity of central chemoreceptors, as hypothesized in salicylate and topiramate intoxications [6,7].

Increased input from the peripheral chemoreceptors and lung receptors

In case of severe hypoxaemia, the peripheral chemoreceptors (mainly carotid bodies) will increase their signalling activity and cause increased alveolar ventilation [2,3]. Of note, peripheral chemoreceptors respond to PO_2, and not to oxygen content or oxygen delivery. Moreover, respiratory alkalosis due to an increased signalling from lung receptors (Table 114.1) is a common finding in several pulmonary diseases, including pneumonia, pulmonary oedema, pulmonary embolism, and fibrosis [8,9]. In fact, in pathological conditions, also vagal afferents, i.e. signals arising from lung receptors, can trigger pulmonary reflexes and might have a role in the control of breathing [10].

Excessive CO_2 removal through controlled mechanical ventilation and/or extracorporeal CO_2 removal

In case of mechanical ventilation in sedated and paralysed patients, the 'effectors', i.e. the respiratory muscles, are no longer regulated by the 'central controller'. Indeed, it is the attending physician deciding the rate of alveolar ventilation through the settings of the ventilator. The lack of feedback mechanisms can therefore ensue in an excessive CO_2 removal, leading to respiratory alkalosis, as often occurring during general anaesthesia in operating rooms. A similar scenario is the result of excessive ventilation of the membrane lung in mechanically-ventilated patients treated with extracorporeal respiratory supports.

Effects of respiratory alkalosis

The major effect of hyperventilation is the increase in pH and the consequent shift of electrolytes that occurs in relation to it. As a general law, anions (chloride) will increase (mainly exiting from erythrocytes), while cations (sodium and potassium) will decrease, as they enter in erythrocytes and other cells. Moreover, the acute reduction in ionized calcium due to the change in extracellular pH may cause neuromuscular symptoms ranging from paraesthesias, up to tetany and seizures. Finally, acute respiratory alkalosis causes a constriction of cerebral arteries that can lead to a reduction of cerebral blood flow [11]. This phenomenon is of particular importance for patients with traumatic brain injury.

Metabolic compensation

The kidneys respond to respiratory alkalosis by uncoupling sodium from chloride excretion. Indeed, sodium is excreted with a weak anion (mainly bicarbonate), while chloride is retained. The effect on urine is an increase in urinary strong ion difference (SID)/urinary anion gap and a consequent increase in urinary pH [12,13]. This, in turn, causes an increase in plasma chloride concentration, and a reduction in plasma SID, which tend to bring back plasma pH towards normal values. The renal compensation restores pH values close to normality within 24–48 hours. Another, quantitatively less important mechanism of compensation, is the electrolyte shift, mainly chloride, from red blood cells to plasma.

Therapeutic strategies

The clinical approach to respiratory alkalosis is usually directed toward the diagnosis and treatment of the underlying clinical disorder. To reduce hypocapnia, especially in pathological activation of the central controller, both physical (increase in dead space) and pharmacological means (opiates and benzodiazepines) have been described [14].

References

1. Caruana-Montaldo B, Gleeson K, and Zwillich CW. (2000). The control of breathing in clinical practice. *Chest*, **117**, 205–25.
2. Duffin J. (2010). The role of the central chemoreceptors: a modeling perspective. *Respiratory Physiology & Neurobiology*, **173**, 230–43.
3. Duffin J. (2007). Measuring the ventilatory response to hypoxia. *Journal of Physiology*, **584**, 285–93.
4. Gaviani P, Gonzalez RG, Zhu JJ, Batchelor TT, and Henson JW. (2005). Central neurogenic hyperventilation and lactate production in brainstem glioma. *Neurology*, **64**, 166–7.
5. Johnston SC, Singh V, Ralston HJ, III, and Gold WM. (2001). Chronic dyspnea and hyperventilation in an awake patient with small subcortical infarcts. *Neurology*, **57**, 2131–3.
6. Mascheroni D, Kolobow T, Fumagalli R, Moretti MP, Chen V, and Buckhold D. (1988). Acute respiratory failure following

pharmacologically induced hyperventilation: an experimental animal study. *Intensive Care Medicine*, **5**, 8–14.
7. Montcriol A, Meaudre E, Kenane N, Asencio Y, Bordes J, and Palmier B (2008). Hyperventilation and cerebrospinal fluid acidosis caused by topiramate. *Annals of Pharmacotherapy*, **42**, 584–7.
8. Elliott CG. (1992). Pulmonary physiology during pulmonary embolism. *Chest*, **101**, 163S–71S.
9. Trenchard D, Gardner D, and Guz A. (1972). Role of pulmonary vagal afferent nerve fibres in the development of rapid shallow breathing in lung inflammation. *Clinical Science*, **42**, 251–63.
10. Widdicombe J. (2006). Reflexes from the lungs and airways: historical perspective. *Journal of Applied Physiology*, **101**, 628–34.
11. Wasserman AJ and Patterson JL. (1961). The cerebral vascular response to reduction in arterial carbon dioxide tension. *Journal of Clinical Investigation*, **40**, 1297–303.
12. Gattinoni L, Carlesso E, Cadringher P, and Caironi P. (2006). Strong ion difference in urine: new perspectives in acid-base assessment. *Critical Care*, **10**, 137.
13. Langer T, Valenza F, and Caironi P. (2012). Urine electrolytes and acid base. In: J. L. Vincent and J. B. Hall (eds) *Encyclopedia of Intensive Care Medicine*, pp. 2368–70. Springer Berlin Heidelberg.
14. Chang CH, Kuo PH, Hsu CH, and Yang PC. (2000). Persistent severe hypocapnia and alkalemia in a 40-year-old woman. *Chest*, **118**, 242–5.

PART 4.13

Pneumonia

CHAPTER 115

Pathophysiology of pneumonia

Jordi Rello and Bárbara Borgatta

Key points

- Hypoxaemia is a key element in pathogenesis, diagnosis, and prognosis of ventilator-associated pneumonia (VAP).
- Aspiration of secretions from the airway is the main source of infection for VAP in mechanically-ventilated (MV) patients, and infection develops when bacteria overwhelms the host's defences.
- Prevention care bundles reduce the incidence of VAP, as well as MV duration and intensive care unit (ICU) length of stay.
- Early antibiotic therapy is responsible for decrease in VAP incidence, but facilitates selection of multidrug-resistant organism.
- Mortality is low, but VAP is an important cause of morbidity, with prolonged MV, ICU length of stay, and excessively high estimated costs.

Introduction

Hospital-acquired pneumonia (HAP) is defined as pneumonia developing 48 hours or more after hospital admission. Ventilator-associated pneumonia (VAP) is a type of HAP that occurs after 48–72 hours of endotracheal intubation and is responsible for approximately 80% of HAP, and so, is the most frequent form of infection in the intensive care unit (ICU). New definitions include worsening of oxygenation as a major criteria for differentiating VAP from other respiratory tract infections.

Epidemiology

VAP occurs with an incidence of 5–20 cases per 1000 ventilator days. Improving preventive measures have dramatically decreased its incidence over the last decade. Cumulative risk for developing VAP is 1–3% per day of MV, condensed within the first week following intubation. Rates are usually higher in surgical than medical ICUs. More than half of prescribed antibiotics in the ICU are for VAP treatment. It is an important cause of morbidity, with prolonged MV, ICU/hospital length of stay, and estimated costs as high as $40,000 per patient. ICU mortality ranges from 24 to 76%, with overall attributable mortality lower than 10%, focusing on surgical patients (in contrast with medical or trauma) [3]. Furthermore, infections caused by multiresistant pathogens, such as methillicin-resistant *Staphyloccocus aureus* (MRSA), *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Stenotrophomonas maltophilia,* have substantially higher mortality. VAP is a prognostic marker in chronic obstructive pulmonary disease (COPD) patients who undergo cardiac surgery and are MV.

Pathogens

Bacteria are the almost exclusively responsible for HAP and VAP in immunocompetent patients, fungal and viral micro-organism are exceptionally isolated in this group of patients. Aetiological agents differ widely between populations since they are determined by the type of ICU, hospital or ICU length of stay, prior antimicrobial therapy, and diagnostic method used. Considering this, the most frequently isolated micro-organisms in VAP are *Pseudomonas aeruginosa, Staphylococcus aureus*, and Enterobacteriaceae. On the other hand, *Candida* and *Enterococcus* species should be considered as colonizers since there is not histological prove of them causing pneumonia.

Classification

Early-onset HAP or VAP is the one occurring during the first 4 days of hospitalization (ward or ICU respectively), whereas when it develops at the 5th day or afterwards is referred as late-onset HAP/VAP. Each one presents with a specific profile.

Early VAP

Usually due to aspiration of normal oropharynx flora in comatose patients or during intubation [1–6]. Caused by community-acquired pathogens (*Streptococcus pneumoniae, Haemophilus influenza*, or meticillin-susceptible *S. aureus*), where antimicrobial resistances are rare.

Late VAP

This is caused by micro-organisms that colonize the upper airway, biofilm, and respiratory tract [1–6], often by pathogens with strong intrinsic or acquired antimicrobial resistance. Risk factors for late-onset VAP include tracheobronchial colonization with enteric Gram negative bacilli (GNB) or *P. aeruginosa*, duration of MV, prolonged antibiotic treatment, and prior use of antibiotics within the preceding 30 days. Late VAP is independently associated with higher mortality. Caused mainly by GNB, 30–70% of cases are due to *P. aeruginosa, Acinetobacter*, or MRSA. Very late VAP in tracheostomized patients is associated with non-fermentative GNB.

Colonization of the lower respiratory tract

Patterns of colonization differ within ICU depending on infectious diseases protocols, hand hygiene, and airway management. Classically, four routes have been described; nevertheless, micro-aspiration of secretions from upper airways remains as the most important source, representing almost 90% of all cases.

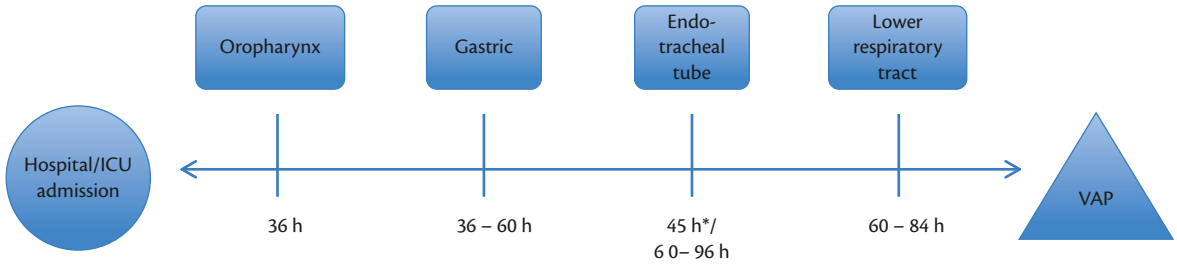


Fig. 115.1 Organ colonization time-evolution during ICU stay.
*At 48 hours 80% of ETT are colonized, but heavy colonization occurs at 60–96 hours.

During hospitalization there's a shift of flora colonizing the airway; initially, there's a reduction of the normal flora, which facilitates the adhesion, and growth of enteric GNB and *S. aureus*. See Fig. 115.1 for the colonization's evolution in MV patients.

Endogenous

Oropharyngeal colonization

More than half of healthy patients can be chronically colonized by normal flora, with COPD patients being especially prone. In MV patient's teeth, a composite of bacteria, mucus and detritus is formed—an adherent matrix called biofilm, which is a source for further bacterial colonization in addition to inflammation of periodontal tissue that can shed bacteria and inflammatory products into the lower respiratory tract.

Aspiration from the upper respiratory tract

- **The main route by which the bacteria invade lower respiratory tract:** favoured by impaired or abolished cough reflex by sedatives and muscle paralysers.
- **Facilitated by the endotracheal tube (ETT) as a result of various mechanisms:**
  - First, it keeps the vocal chords open.
  - Secondly, above ETT a pool of secretion is formed that by capillary leak goes down longitudinal channels formed by the folds of the cuff, even when correctly positioned and inflated at standard pressure. Subglottic secretion drainage reduces the risk for developing VAP.
  - Gross leakage occurs with tracheal suctioning, absence of positive end-expiratory pressure (PEEP), low pressure of the cuff, and disconnection from MV.
  - Furthermore, at the ETT's inner surface biofilm forms, serving as a reservoir for infection and protection from antibiotic effects. This biofilm is reduced with a silver-coated ETT; on the other hand, it can be embolized into lung parenchyma with manipulation of the inner surface of the ETT.

Gastric: macro-aspiration

A nasogastric tube causes oesophageal sphincter incompetence resulting in oesophageal reflux [2,4,6,7] and the possibility of aspiration, especially in patients receiving enteral nutrition. Nonetheless, it is a secondary source of aspiration.

Contiguous and haematogenous spread

Both routes have been described, but are unusual sources of colonization.

Exogenous

Exogenous ways of colonization represent approximately <5% of all routs [2,4,6,7]. It refers to direct inoculation of the microorganism through the ETT by health care workers that manipulates the patient's airway. Inadequate hand washing may contribute to cross-infection with resistant species. The ventilator circuit is often highly colonized (80% of condensate after 24 hours by enteric gram-negative bacteria (EGNB)); however, when it is routinely changed, there's no impact on VAP incidence. Potential bacterial aerosolization can occur from precipitate of the condensate from warm humidifiers, which justifies the use of cascade humidifiers, which do not generate micro-aerosols.

Box 115.1 Risk factors for HAP

- Artificial airway.
- Sedation.
- Massive aspiration.
- ICU/ hospital length of stay.
- Primary disease:
  - Trauma.
  - Burns.
  - Central nervous system disease.
  - Cardiac disease.
- Age > 70 years.
- Chronic lung disease.
- Severity of underlying illness.
- Depressed consciousness.
- Acute respiratory distress syndrome.
- Prior antibiotic treatment:
  - Protective against early-VAP.
  - Increases risk for late-VAP.
- Reintubation.
- H2 blockers/antacids.
- Nasogastric tube.
- Intracranial pressure monitor.

Risk factors and prevention

Artificial airway is the most important risk factor for developing HAP, increasing the risk from 6 to 21-fold. Indeed, many authors use HAP and VAP interchangeably. Antibiotic exposure has a protective effect in early VAP, but increases risk for late VAP, since it selects multiresistant species. Risk factors for HAP are summarized in Box 115.1. Prevention [8,9] of VAP can be achieved with implementing care bundles, which include hand hygiene before airway manipulation, oral care with chlorhexidine, maintenance of intracuff pressure above 20 cmH_2O to reduce leakage of oropharyngeal secretions to the lower airways tract, and sedation control protocols. Minimizing sedation is a strategy to be enhanced to prevent VAP. Furthermore, full bundles compliance reduces duration of MV and ICU length of stay.

Host response

VAP develops when micro-organisms present in distal lung tissue (alveoli) overwhelm host defences with its virulence and burden. Pneumonia in ventilated patients is a multifocal process disseminated within each pulmonary lobe. These foci of pneumonia are predominantly distributed in lower lobes and dependent zones of the lungs. Histological lesions are always located within large zones of altered lung parenchyma, which correspond to an inflammatory exudate with fibrin and some capillary congestion, ensuing at the 3rd to 7th day of pneumonia. Because of this multifocal and patchy distribution, quantitative biopsy cultures cannot reliably discriminate between patients with or without evidence of histological pneumonia [7].

In patients who develop VAP, altered innate and adaptive immune responses have been reported. Decreased T-helper lymphocytes (CD^{3+} and CD^{4+}) due to accelerated apoptosis, increased monocyte apoptosis, and both peripheral and lung neutrophil dysfunction, all resulting in decreased clearing of pathogens.

Additionally, there is also a genetic component influencing the host's response to the infection, polymorphism of the complement pathway (specifically C2 E318D) is associated with increased risk for VAP and higher mortality. Micro-arrays have demonstrated specific different immunological signatures for VAP and VAT.

References

1. Rello J, Lisboa T, and Koulenti D. (2014). Respiratory infections in patients undergoing mechanical ventilation. *Lancet Respiratory Medicine*, **2**, 764–74.
2. Chastre J and Fagon JY. (2002). Ventilator-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine*, **165**, 867–903.
3. Rello J, Ollendorf DA, Oster G, et al. (2002). Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest*, **122**, 2115–21.
4. Rello J and Diaz E. (2003). Pneumonia in the intensive care unit. *Critical Care Medicine*, **31**, 2544–51.
5. Vincent JL, Rello J, Marshall J, et al. (2009). International study of the prevalence and outcomes of infection in intensive care units. *Journal of the American Medical Association*, **302**, 2323–9.
6. Diaz E, Lorente L, Valles J, et al. (2010). Mechanical ventilation associated pneumonia. *Medicina Intensiva*, **34**, 318–24.
7. American Thoracic Society and Infectious Diseases Society of America. (2005). Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine*, **171**, 388–416.
8. Blot S, Rello J, and Vogelaers D. (2011). What is new in the prevention of ventilator-associated pneumonia? *Current Opinions in Pulmonary Medicine*, **17**, 155–9.
9. Rello J, Afonso E, Lisboa T, et al. (2012). A care bundle approach for prevention of ventilator-associated pneumonia. *Clinical Microbiology and Infection*, **19**(4), 363–9.
10. Gallego M and Rello J. (1999). Diagnostic testing for ventilator-associated pneumonia. *Clinics in Chest Medicine*, **20**, 671–9.
11. Fàbregas N, Torres A, El-Ebiary M, et al. (1996). Histopathologic and microbiologic aspects of ventilator-associated pneumonia. *Anesthesiology*, **84**, 760–71.

CHAPTER 116

Diagnosis and management of community-acquired pneumonia

Antoni Torres and Adamantia Liapikou

Key points

- The microbial pattern of the severe community-acquired pneumonia (SCAP) has changed, with *Streptococcus. pneumoniae* still the leading pathogen, but a decrease in atypical pathogens, especially *Legionella*, and an increase in viral and polymicrobial pneumonias.
- At least two blood samples should be drawn for culture and urinary antigen tests for *Legionella pneumophila* and *S. pneumoniae* performed. For intubated patients, an endotracheal aspirate and bronchoscopic samples should be obtained. Polymerase chain reaction (PCR) techniques in respiratory samples and in blood is a promising new method for the detection of viruses and atypical pathogens.
- New variables, such as hypoglycaemia and thrombocytosis, and a biomarker-procalcitonin will be useful for predicting ICU admission in patients with CAP.
- Combination treatment offers an advantage over monotherapy by expanding the antimicrobial coverage and improving survival among critically-ill patients with bacteraemic pneumococcal illness. The recommended antibiotic regimen in depends of the presence of *Pseudomonas aeruginosa* infection.
- In unresponsive patients, careful re-evaluation of treatment, particularly the initial choice of antibacterials, and further extensive and invasive diagnostic efforts are warranted.

Introduction

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality, and the most common infectious cause of death in the developed world [1]. In general, the mortality of patients with CAP who require admission to the intensive care unit (ICU) increases to 20–50%. Nearly all patients who die as a consequence of severe CAP develop severe sepsis or septic shock. Approximately 50% of CAP admissions to Spanish ICUs are associated with septic shock.

Aetiology

The spectrum of causal pathogens in severe pneumonia is broader than that in non-severe cases. *S. pneumoniae* is still the leading pathogen, followed by *H. influenzae, S. aureus, L. pneumophila, Enterobacteriaceae*, especially *Escherichia coli, Klebsiella species*, and *P. aeruginosa* [2]. Bacteraemia is more common than CAP and up to 20% of severe CAP episodes are caused by polymicrobial infection.

Viruses are the most common aetiological agents after *S. pneumoniae.* Easily transmissible viruses such as influenza, metapneumovirus (hMPV), respiratory syncytial virus (RSV) and adenovirus are most common.

In 2009, a new H1N1 strain of influenza A virus emerged, causing a pandemic. Rapidly progressive viral pneumonia, affecting mainly young, obese patients represented the primary cause of ICU admission with mortality ranging from 17.3% to 46% among different sites [3].

In patients admitted in the ICU the most common aetiologies were *S. pneumoniae* (62%), atypical pathogens (14%) and polymicrobial aetiologies (11%). The most frequent polymicrobial pattern was *S. pneumoniae* and viral infection, particularly influenza virus [4].

There is a classical correlation of influenza virus infection and pneumonia due to *S. aureus* and *S. pneumoniae*.

The microbial pattern of the severe CAP has changed over the years, with the decrease of atypical pathogens, especially *Legionella* and the increase of viral pneumonia [5]. This may be due to improvement in diagnostic tools, such as PCR techniques. A large number of micro-organisms other than *S. pneumoniae* must be considered, especially *Pseudomonas aeruginosa,* and CA—MRSA.

- The risk factors for *Pseudomonas* pneumonia [6] include:
- Recent hospitalization.
- Frequent (>4 courses per year) or recent administration of antibiotics (last 3 months).
- Severe disease (FEV1 < 30%) and oral steroid use (>10 mg of prednisolone daily in the last 2 weeks).

Accordingly, the risk factors for community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), an emerging problem, are participating in contact sport, living in crowded or unsanitary conditions, intravenous drug abuse, and male homosexuality.

Diagnosis

Clinical presentation

Severe CAP is characterized as an acute febrile illness with severe respiratory failure (PO_2/FIO_2 < 250) requiring invasive or non-invasive ventilation. The patient with sepsis or septic shock

from CAP presents with mental confusion, hypotension with the need for vasopressors, tachypnoea, tachycardia, or organ dysfunction as renal failure.

Often the severity reflects a progressive pneumonia with complicated pleural effusion or empyema, or metastatic infection as pericarditis, endocarditis.

Often severe CAP presents with decomposition of an underlying comorbidity such as chronic obstructive pulmonary disorders (COPD), diabetes, congestive heart failure, chronic liver, or renal insufficiency.

Radiographic evaluation

A chest radiograph is required to establish the diagnosis, suggest the aetiological agent, extent, or complications of CAP, prognosis, and to aid in differentiating CAP from other common causes of cough and fever, such as acute bronchitis.

The radiograph of severe CAP consists more often of multilobar infiltrates or a rapid increase in the size of infiltrates>50% during the first day of treatment. Moreover, the chest X-ray may show complications of pneumonia as pleural effusion or abscess formation.

Microbiological diagnosis

Diagnostic efforts to isolate a defined pathogen are necessary, as the results may influence both initial treatment and secondary therapy after initial treatment failure. However, the responsible pathogen is not isolated in up to 50% to 60% of patients with severe CAP [1].

The recommendations of IDSA/ATS for microbiological diagnosis are summarized in Table 116.1.

Sputum samples

A culture from a purulent sputum specimen of a bacterial species compatible with the morphotype observed in the Gram stain should be considered for confirmation of the species identification and antibiotic susceptibility testing. The sensitivity of sputum Gram stain was 82% for pneumococcal pneumonia, 76% for staphylococcal pneumonia and 79% for *Haemophilus influenzae* pneumonia, with specificities ranging from 93 to 96% [7].

In addition to routine cultures, a specific request for culture of respiratory secretions on buffered charcoal yeast extract agar to isolate *Legionella* species may be useful in areas where *Legionella* is endemic, as well as in patients with a recent travel history [1]. Sputum cultures for *Legionella* spp. should always be attempted for patients who are *Legionella* urine antigen positive in order to provide isolates for epidemiological typing and comparison with isolates from putative environmental sources.

During bronchoscopy in severe CAP, bronchoalveolar lavage (BAL) quantitative culture (cut-off 10^4 cfu) is a sensitive method for aetiological diagnosis (resistant microorganism, polymicrobial, unusual pathogen). In mechanical ventilation a BAL or protected sheath brush (PSB)/BAL have to be taken from the very beginning and may be useful in guiding therapy even performed during antibiotic treatment.

PCR techniques increased the total viral yield five-fold compared with direct fluorescence antibody assay in the respiratory samples of critically-ill patients [8]. This rapid tool minimizes the proportion of undiagnosed severe CAP, especially in immunocompromised patients, and guides treatment towards a more specific antibiotic regimen.

Blood cultures

Although the overall yield of blood cultures is probably less than 20% in patients hospitalized for SCAP, the positivity of the results and the likelihood of changes in treatment based on the results, increases with severity.

Immunological methods

The *S. pneumoniae* urinary antigen test in adults has a sensitivity of 65–100% and a specificity of 94%. This test should also be considered whenever a pleural fluid sample is obtained in the setting of a parapneumonic effusion [6]. In the diagnosis of CAP caused by *L. pneumophila* urinary antigen detection for serotype 1 has a sensitivity of almost 80% and a specificity approaching 100% [1].

Paired serology for infections caused by *M. pneumoniae*, *C. pneumonia*, and *Legionella* sp. is more useful in epidemiological studies than clinical practice.

Real-time PCR (rt-PCR) assay detected *S. pneumoniae* DNA in 85.3% of patients with positive blood culture findings, whereas blood culture findings were positive in only 50% of the patients with detectable *S. pneumoniae* DNA [9]. This study confirms the superior sensitivity of PCR in blood and the association between a high quantitative bacterial genomic load of *S. pneumoniae* in blood samples and increased risk of death.

A Finish study [10] proved that sputum is clearly superior to both nasopharyngeal aspirates and throat swabs for reliable detection of *M. pneumoniae* by PCR.

Table 116.1 Recommendations IDSA/ATS and ERS for microbiological diagnosis of SCAP

1. Pre-treatment Gram stain and culture of expectorated sputum should be performed only if a good-quality specimen can be obtained and quality performance measures for collection, transport, and processing of samples can be met.	Moderate recommendation; level II evidence.
2. Patients with severe CAP, should have at least two blood samples drawn for culture, urinary antigen tests for *Legionella pneumophila* and *S. pneumoniae* performed, and expectorated sputum samples collected for culture. For intubated patients, an endotracheal aspirate sample should be obtained.	Moderate recommendation; level II evidence.
3. Diagnostic thoracentesis should be performed in hospitalized patients with CAP when a significant (as judged by the admitting physician) pleural effusion is present.	A3; consistent evidence, level 3.
4. Bronchoscopic sampling of the lower respiratory tract can be considered in intubated patients and selected non-intubated patients, where gas exchange status allows.	A3; consistent evidence, level 3.

Reproduced from Mandell LA et al., 'Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults', *Clinical Infectious Diseases*, 2007, **44**(Suppl. 2), pp. S27–72, by permission of Oxford University Press. Data from Woodhead M et al., 'Guidelines for the management of adult lower respiratory tract infections', *Clinical Microbiological Infections*, 2011, **17**(Suppl. 6), pp. E1–59.

Definition of severity

Many studies of the epidemiology of patients with CAP have demonstrated the importance of assessing severity of illness and stratifying patients on the basis of their risk of mortality.

The pneumonia severity index (PSI) and CURB-65 have low sensitivity and specificity for predicting ICU admission compared with the predictive power of mortality in patients with CAP [11].

Furthermore, in comparison with PSI, the CURB-65 has been shown to outperform generic sepsis and early warning scores [12].

IDSA/ATS issued guidelines on the management of CAP include specific criteria (Box 116.1) to identify patients for ICU admission [1]. Other models specific to severe CAP have been developed.

There is considerable clinical and research interest in the use of novel biomarkers to diagnose and classify CAP. Of the novel biomarkers, most attention has been focused on procalcitonin. Ramirez et al. [13], in a recent study of 685 patients with CAP, assessed biomarkers for the prediction of ICU admission and the IDSA/ATS guidelines minor criteria for severe CAP. Inflammatory biomarkers (C-reactive protein (CRP), tumour necrosis factor-a, procalcitonin and interleukin-6) identified patients needing ICU admission. Patients with severe CAP by minor criteria and low levels of procalcitonin may be safely admitted to wards.

Available simple biomarkers also have prognostic significance. Hypoglycaemia on admission is associated with nearly three-fold greater inpatient mortality, unaffected by the presence of diabetes [14]. Thrombocytosis may also be a risk factor for 30-day mortality. Hypoglycaemia and thrombocytosis are not presently in the list of IDSA/ATS minor criteria for severe CAP, but may need to be considered.

Box 116.1 Criteria for ICU admission. One of the major or three or more of the minor criteria would indicate ICU admission

Major criteria

- Invasive mechanical ventilation.
- Septic Shock with the need for vasopressors.

Minor criteria

- Respiratory rate ≥30 breaths/min.
- PaO_2/FIO_2 ≤250.
- Multilobar infiltrates.
- Confusion disorientation.
- Uraemia (blood urea nitrogen (BUN) level ≥20 mg/dL).
- Leucopenia (white blood cell count $<4 \times 10^9$/L).
- Thrombocytopenia (platelet count $<100 \times 10^9$/L).
- Hypothermia (core temperature <36°C).
- Hypotension (SBP <90 mmHg) requiring aggressive fluid resuscitation.

Reproduced from Mandell LA et al., 'Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults', *Clinical Infectious Diseases*, 2007, 44(Suppl. 2), pp. S27–72, by permission of Oxford University Press.

Empirical treatment: algorithms

Recommendations for antibiotic treatment for severe CAP are based on illness severity, frequency of specific pathogens, local microbial resistance patterns, and drug safety profiles.

In patients with CAP and septic shock, delay must not be more than 1 hour after diagnosis [6].

Empirical recommended therapy for severe CAP is listed in Box 116.2.

Combination treatment offers an advantage over monotherapy by expanding the antimicrobial coverage and by improving survival among critically-ill patients with bacteraemic pneumococcal illness [15]. The recommended antibiotic regimen consists of a β-lactam (preferably intravenously) with a macrolide or with a respiratory fluoroquinilones, especially ciprofloxacin or levofloxacin.

If the patient has risk factors for *Pseudomonas* infection the combination of an antipseudomonal β-lactam with macrolide+ aminoglycoside or an antipseudomonal β-lactam with ciprofloxacin is the favourable treatment [6].

The role of glucocorticoids in severe CAP is still controversial with positive [16] and negative [17] studies. Melvis et al. [18] reported dexamethasone added to antibiotic treatment can reduce length of hospital stay, but not mortality in a population of CAP hospitalized patients.

Low molecular heparin should be given in patients with acute respiratory failure [A3, recommendation].

Several studies indicate that non-invasive ventilation (NIV) may also work in patients with pneumonia, particularly in patients with COPD. NIV has been shown to reduce intubation in patients with ARDS in 54% of treated cases [6].

Box 116.2 Therapy of CAP admitted to ICU

No risk factors for *P. aeruginosa*

- Non antipseudomonal cefalosporin III + macrolide.

  or

- Non-antipseudomonal cefalosporin III +/– moxifloxacin or levofloxacin.

Risk factors for *P. aeruginosa*

- Antipseudomonal cefalosporin[a] or acylureidopenicillin/β-lactamase inhibitor or carbepenem (meropenem preferred, up to 6 g possible, (2 g every 8 hours, three doses) in 3-hour infusion

  plus

- Ciprofloxacin[b]

  or

- Macrolide + aminoglycoside (gentamicin, tobramycin, amikacin).

[a]Ceftazidime + penicillin G coverage for *S. pneumonia*.
[b]Levofloxacin 750 mg/24 hours or 500 mg bd is an alternative.
Reproduced with permission from Woodhead M et al., 'Guidelines for the management of adult lower respiratory tract infections', *Clinical Microbiology and Infection*, 2011, **17**(Suppl. 6), pp. E1–59 © 2011 Woodhead et al. *Clinical Microbiology and Infection* © 2011 European Society of Clinical Microbiology and Infectious Diseases.

Definitive adjusted treatment

Table 116.2 lists the recommended antibiotic therapies for the most important pathogens in severe CAP, according to ERS/ESCMID guidelines [6]. Panton–Valentine leukocidin-producing *Staphylococcus aureus* (PVL-SA) or CA-MRSA cause severe pneumonia with rapid lung cavitation and multi-organ failure. The recommended antibiotic treatment for this necrotizing pneumonia includes the combination of intravenous linezolid, clindamycin, and rifampicin [1,6]. Antibiotic resistance among *S. pneumoniae* is the main concern owing to the dominance of this organism as a cause of severe CAP, and because penicillin and macrolide resistance are frequently linked. The prevalence of *S. pneumoniae* strains resistant to penicillin dropped to 10% or lower in most reports. In patients with pneumococcal pneumonia resistant (low-level) to penicillin a new formulation of co-amoxiclav acid (2000/125 instead of 875–1000/125), offers the advantage of higher penicillin dosing [19].

In pneumococci, erythromycin MICs >0.5 mg/L predict clinical failure. The prevalence of resistance in many countries compromises the efficacy of macrolides in the treatment of pneumococcal infection [1,6]. In patients with risk factors for *P. aeruginosa*, meropenem offers advantages over imipenem because of the option to increase the dose significantly up to 3.2 g. Patients at risk of CAP through *P. aeruginosa* should always be treated by two antipseudomonal drugs in order to reduce the chance of inadequate treatment.

The emergence of new influenza virus subtypes has rekindled the interest in the clinical course and outcome of patients with influenza-associated pneumonia. The implementation of early (<2 days) antiviral therapy was associated with lower mortality in ventilated patients with 2009 H1N1. Apart from neuraminidase inhibitors such as oseltamivir and zanamivir for pneumonia caused by influenza viruses, antibacterial agents targeting *S. pneumoniae* and *S. aureus* are necessary.

Table 116.2 Therapy of specific microorganisms in CAP

Pathogen	Recommended treatment
Highly resistant *S. pneumoniae* (MIC > 8 mg/dL)	Levofloxacin, moxifloxacin, vancomycin, teicoplanin, linezolid
MSSA	Flucloxacillin, cephalosporin ii, clindamycin, levofloxacin, moxifloxacin
MRSA	Vancomycin, teicoplanin +/– rifampicin linezolid, clindamycin(if sensitive)
Ampicillin-resistant *Haemophilus influenzae*	Aminopenicillin plus B-lactamase inhibitor levofloxacin, moxifloxacin
Mycoplasma, *Chlamidophila pneumoniae*	Doxycycline, macrolide, levofloxacin, moxifloxacin
Legionella pn.	Macrolide (azithromycin preferred), levofloxacin, moxifloxacin +/– rifampicin
Coxiella burnetti	Doxycycline, levofloxacin, moxifloxacin
Acinetobacter baumanii	Cefalosporin III + aminoglycoside, ampicilin-sulbactam

Reproduced with permission from Woodhead M et al., 'Guidelines for the management of adult lower respiratory tract infections', *Clinical Microbiology and Infection*, 2011, 17(Suppl. 6), pp. E1–59 © 2011 Woodhead et al. *Clinical Microbiology and Infection* © 2011 European Society of Clinical Microbiology and Infectious Diseases.

Response to treatment

For patients initially admitted to the ICU, the risk of failure to respond to therapy is already high. As many as 40% will experience deterioration even after initial stabilization in the ICU. The inadequate response depends on factors related to initial severity, with the causative organism and host characteristics [1].

Non-responding pneumonia occurring in the first 72 hours of admission is usually due to antimicrobial resistance or an unusually virulent organism or a host defence defect. Non-responsiveness after 72 hours is usually due to a complication (empyema, endocarditis, acute respiratory distress syndrome). The evaluation of non-responding pneumonia depends on the clinical condition.

The percentage of treatment failure in severe CAP is 6–15%. The causes of non-responding pneumonia are classified according to the aetiology as infectious, non-infectious, and of unknown origin.

In hospitalized CAP, infections are responsible for 40% of non-responding CAP. The most frequent micro-organisms found are *S. pneumoniae, Legionella, P. aeruginosa* and *S. aureus*. Micro-organisms may show resistance against antibiotics prescribed or may develop resistance during therapy. Unusual micro-organisms requiring specific antibiotic treatment other than that recommended in the guidelines include *Mycobacteria, Nocardia* spp., anaerobes, fungi, *Pneumocystis jirovecii*, and others [20]. Non-infectious diseases include neoplasms (especially alveolar cell cancer), pulmonary haemorrhages, bronchiolitis obliterans, and organizing pneumonia, eosinophilic pneumonia, hypersensitivity pneumonitis, and drug-induced lung disease.

Careful re-evaluation of treatment, particularly the initial choice of antibacterials, and further diagnostic efforts are warranted. New microbiological and imaging studies (CT of the chest) must be performed to rule out other alternative diagnoses. If simpler procedures do not provide a rapid diagnosis, invasive techniques (i.e. bronchoscopy) are recommended in most cases of non-responding pneumonia. Both PSB and BAL sampling should be done during the same procedure.

Changing of the initial empiric antibiotic regimen with a broader spectrum antibacterial coverage is the optimal management.

References

1. Mandell LA, Wunderink RG, Anzueto A, et al. (2007). Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical Infectious Diseases*, **44**(Suppl. 2), S27–72.
2. Falguera M, Carratalà J, Ruiz-Gonzalez A, et al. (2009). Risk factors and outcome of community-acquired pneumonia due to Gram-negative bacilli. *Respirology*, **14**(1), 105–11.
3. Martin-Loeches I, Rodriguez A, Bonastre J, and the H1N1 SEMICYUC Working Group. (2011). Severe pandemic (H1N1)v influenza A infection: report on the first deaths in Spain. *Respirology*, **16**(1), 78–85.
4. Cillóniz C, Ewig S, Ferrer M, et al. (2011). Community-acquired polymicrobial pneumonia in the intensive care unit: aetiology and prognosis. *Critical Care*, **15**(5), R209.
5. Choi SH, Hong SB, Ko GB, et al. (2012). Viral infection in patients with severe pneumonia requiring intensive care unit admission. *American Journal of Respiratory and Critical Care Medicine*, **186**(4), 325–32.

6. Woodhead M, Blasi F, Ewig S, et al. (2011). Guidelines for the management of adult lower respiratory tract infections. *Clinical Microbiological Infections*, **17**(Suppl. 6), E1–59.
7. Anevlavis S, Petroglou N, Tzavaras A, et al. (2009). A prospective study of the diagnostic utility of Sputum Gram stain in pneumonia. *Journal of Infection*, **59**, 83–9.
8. Aramburo A, van Schaik S, Louie J, et al. (2011). Role of real-time reverse transcription polymerase chain reaction for detection of respiratory viruses in critically ill children with respiratory disease: Is it time for a change in algorithm? *Pediatric Critical Care Medicine*, **12**(4), e160–5.
9. Rello J, Lisboa T, Lujan M, et al. (2009). Severity of pneumococcal pneumonia associated with genomic bacterial load. *Chest*, **136**(3), 832–40.
10. Templeton KE, Scheltinga SA, Graffelman AW, et al. (2003). Comparison and evaluation of real-time PCR, real-time nucleic acid sequence-based amplification, conventional PCR, and serology for diagnosis of Mycoplasma pneumoniae. *Journal of Clinical Microbiology*, **41**(9), 4366–71.
11. Chalmers JD, Mandal P, Singanayagam A, et al. Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. *Intensive Care Medicine*, **37**(9), 1409–20. [Review.]
12. Barlow G, Nathwani D, and Davey P. (2007). The CURB65 pneumonia severity score outperforms generic sepsis and early warning scores in predicting mortality in community-acquired pneumonia. *Thorax*, **62**, 253–9.
13. Ramírez P, Ferrer M, Martí V, et al. (2011). Inflammatory biomarkers and prediction for intensive care unit admission in severe community-acquired pneumonia. *Critical Care Medicine*, **39**, 2211–17.
14. Gamble JM, Eurich DT, Marrie TJ, and Majumdar SR. Admission hypoglycemia and increased mortality in patients hospitalized with pneumonia. *American Journal of Medicine*, **123**, **556**, e11–16.
15. Martínez JA, Horcajada JP, Almela M, et al. (2003). Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clinical Infectious Diseases*, **36**, 389–95.
16. Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *American Journal of Respiratory and Critical Care Medicine*, **171**(3), 242–8.
17. Snijders D, Daniels JM, de Graaff CS, et al. (2010). Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. *American Journal of Respiratory and Critical Care Medicine*, **181**, 975–82.
18. Meijvis SC, Hardeman H, Remmelts HH, et al. (2011). Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet*, **377**(9782), 2023–30.
19. File TM, Garau J, Jacobs MR, et al. (2005). Efficacy of a new pharmacokinetically enhanced formulation of amoxicillin/clavulanate (2000/125 mg) in adults with community acquired pneumonia caused by Streptococcus pneumoniae, including penicillin-resistant strains. *International Journal of Antimicrobial Agents*, **25**, 110–19.
20. Menendez R and Torres A. (2007). Treatment failure in community-acquired pneumonia. *Chest*, **132**(4), 1348–55.

CHAPTER 117

Diagnosis and management of nosocomial pneumonia

Jean Chastre

Key points

- Although appropriate antibiotics may improve survival in patients with pneumonia, the use of empirical broad-spectrum antibiotics in patients without infection is potentially harmful, facilitating colonization and superinfection with multiresistant micro-organisms. Any strategy designed to evaluate patients suspected of having developed nosocomial pneumonia (NP) should be able to withhold antimicrobial treatment in patients without pneumonia.
- Because even a few doses of a new antimicrobial agent can negate results of microbiological cultures, pulmonary secretions in patients suspected of having developed NP always should be obtained before new antibiotics are administered.
- Empirical treatment of patients with NP should be selected based on available epidemiological characteristics, information provided by direct examination of pulmonary secretions, intrinsic antibacterial activities of antimicrobial agents, and their pharmacokinetic characteristics.
- Altered pharmacokinetics secondary to increase in volume of distribution in critically-ill patients can result in insufficient serum β-lactam concentrations when standard dosages are administered, emphasizing the need to carefully monitor peak and trough levels of antibiotics when treating resistant pathogens.
- Once the microbiological data become available, antimicrobial therapy should be re-evaluated in order to avoid prolonged use of a broader spectrum of antibiotic therapy than is justified by the available information. For many patients, including those with late-onset infection, the culture data will not show the presence of highly resistant pathogens, and in these individuals, therapy can be narrowed or even reduced to a single agent in light of the susceptibility pattern of the causative pathogens without risking inappropriate treatment.

Introduction

Nosocomial pneumonia (NP) is the most frequent ICU-acquired infection among patients who are treated with mechanical ventilation (MV) [1,2]. Because several studies have shown that appropriate antimicrobial treatment of patients with NP significantly improves outcome, rapid identification of infected patients and accurate selection of antimicrobial agents are important clinical goals [1].

Diagnosis

NP is typically suspected when a patient has new or progressive radiographic infiltrates and clinical findings suggesting infection, such as the new onset of fever, purulent sputum, leukocytosis, increased minute ventilation, and/or a decline in arterial oxygenation. Because interpretation of chest radiographs is difficult, particularly in patients with prior abnormalities, it is also mandatory to consider the diagnosis of NP in ventilated patients who deteriorate clinically, and/or in whom vasopressors need to be increased in order to maintain blood pressure, even in the absence of a clear-cut progression of the radiographic abnormalities.

Two diagnostic algorithms can be used when NP is suspected. The first option is to treat every patient with new antibiotics, even when the likelihood of infection is low, arguing that several studies showed that the immediate initiation of appropriate antibiotics was associated with reduced mortality. The second option is to use an invasive diagnostic strategy based on quantitative cultures of distal respiratory specimens obtained using bronchoscopic or non-bronchoscopic techniques, such as bronchoalveolar lavage (BAL), in order to improve the identification of patients with true NP and facilitate decisions about whether or not to treat with antibiotics [3]. Although using different diagnostic techniques, these two algorithms share the same goals, i.e. early, appropriate treatment of patients with true pneumonia, while avoiding antibiotics in patients without NP [1,2].

The clinical strategy

Using this strategy, antimicrobial therapy is started just after having obtained a specimen of the proximal airway secretions for qualitative microbiological testing. Initial therapy is then adjusted according to culture results and/or clinical response. Antibiotics are discontinued if and only if the following three criteria are fulfilled on day 3:

- Clinical diagnosis of NP is unlikely (there are no definite infiltrates found on chest radiography at follow-up and no more than one of the three following findings are present: temperature > 38.3°C, leukocytosis (>12,000/mm^3) or leukopenia (<4000/mm^3), and purulent tracheobronchial secretions) or an alternative non-infectious diagnosis is confirmed.
- Tracheobronchial aspirate culture results are non-significant.
- Severe sepsis or shock are not present [4].

While the simple qualitative culture of endotracheal aspirates (EA) is a technique with a high percentage of false-positive results due

to bacterial colonization of the proximal airways in many ICU patients, recent studies using quantitative or semi-quantitative culture techniques suggest that the diagnostic accuracy of EA cultures is similar to the accuracy of more invasive techniques [1]. The inherent advantages of these techniques are that they are also available to non-bronchoscopists, they are less expensive than bronchoscopy, and they can be performed safely in patients not receiving MV. Disadvantages include misclassification of some patients, either because the diagnosis of pneumonia is missed when EA quantitative culture results grows below the threshold defining a positive result (10^5–10^6 CFU/mL), or because a false diagnosis of pneumonia is established in patients with only airway colonization.

The invasive strategy

This strategy uses quantitative cultures of lower respiratory secretions collected by BAL, with or without a bronchoscope to define both the presence of pneumonia and the aetiological pathogen(s). Using this strategy, therapeutic decisions are tightly protocolized, using the results of direct examination of distal pulmonary samples and of quantitative cultures in deciding whether to start antibiotic therapy, which pathogens are responsible for infection, which antimicrobial agents to use, and whether to continue therapy (using a cut-off of 10^4 CFU/mL) [2].

Quantitative cultures of BAL specimens consistently yield fewer micro-organisms growing above the diagnostic threshold than are present in qualitative cultures of tracheal aspirates [2]. Thus, when therapeutic decisions have been based on these data, fewer patients have been treated with antibiotics, and a potentially narrower spectrum of therapy was used, compared with the clinical approach, thereby limiting the emergence and dissemination of drug-resistant strains and minimizing antibiotic-related toxicity [3]. Another compelling argument in favour of the invasive strategy is that this approach directs attention away from the lungs as the source of fever when BAL quantitative culture results are negative. Many ICU patients with negative bronchoscopic cultures have other potential sites of infection that need to be identified in order to avoid delays in initiating appropriate treatment.

The accuracy of bronchoscopic techniques is questionable in patients who have received prior antibiotics, particularly when new antibiotics have been introduced after the onset of the symptoms suggestive of NP and before pulmonary secretions were collected. However, several investigators have found that cultures of respiratory secretions are not modified in a major way when pneumonia develops in patients who have been receiving systemic antibiotics for several days before the appearance of the new pulmonary infiltrates. The reason for this appears to be that the bacteria responsible for the new infection are likely to be resistant to the antibiotics that have been used [5].

One major technical problem with all bronchoscopic techniques is correct selection of the sampling area in the tracheobronchial tree. The sampling area is usually selected based on the location of the radiographic infiltrate, or the bronchoscopic identification of a pulmonary segment that has purulent secretions. In patients with diffuse pulmonary infiltrates or minimal new changes in a previously abnormal chest radiograph, determining the correct segment to sample can be difficult. In such cases, sampling should be directed to the area where endobronchial abnormalities are maximal. Because autopsy studies indicate that NP frequently involves the posterior portion of the right lower lobe, this area should probably be given priority for sampling [2].

Summary of the evidence

Besides decision-analysis studies and a single retrospective study, five trials have used a randomized scheme to assess the effect of a diagnostic strategy on antibiotic use and outcome in patients suspected of having ventilator-associated pneumonia (VAP) [6]. In a French study in which 413 patients were randomized, those receiving bacteriological management using BAL had a lower mortality rate on day 14, lower sepsis-related organ failure assessment scores on days 3 and 7, and less antibiotic use [3]. Pertinently, 22 non-pulmonary infections were diagnosed in the bacteriological strategy group and only five in the clinical strategy group, suggesting that over-diagnosis of VAP can lead to errors in identifying non-pulmonary infections. More recently, a randomized trial conducted in Canada investigated the effect of different diagnostic approaches on outcomes of 740 patients suspected of having VAP [7]. There was no difference in the 28-day mortality rate in patients in whom BAL was used, versus those in whom EA was used as the diagnostic strategy. The BAL and the EA groups also had similar rates of targeted antibiotic therapy on day 6, days alive without antibiotics, and maximum organ dysfunction scores. Unfortunately, information about how the decision algorithms were followed in the two diagnostic arms once cultures were available was not provided, raising uncertainties about how de-escalation of antibiotic therapy was pursued in patients with negative BAL cultures. Obviously, the potential benefit of using a diagnostic tool such as BAL for safely restricting unnecessary antimicrobial therapy in such a setting can only be obtained when decisions regarding antibiotics are closely linked to bacteriological results, including both direct examination and cultures of respiratory specimens.

Treatment

Initial therapy

Failure to initiate prompt appropriate and adequate therapy (the aetiological organism is sensitive to the therapeutic agent, the dose is optimal, and the correct route of administration is used) has been a consistent factor associated with increased mortality [1]. Because pathogens associated with inappropriate initial empirical antimicrobial therapy mostly include antibiotic-resistant micro-organisms, such as *Pseudomonas aeruginosa, Acinetobacter* spp., *Klebsiella pneumoniae, Enterobacter* spp., and methicillin-resistant *Staphylococcus aureus* (MRSA), patients at risk for infection with these organisms should initially receive a combination of agents that can provide a very broad spectrum of coverage (see Table 117.1) [1]. Several observational studies have now confirmed that the use of a regimen that initially combines a broad-spectrum β-lactam with an aminoglycoside increases the proportion of patients appropriately treated compared with monotherapy or to a regimen combining a β-lactam with a fluoroquinolone [8,9]. Only patients with early-onset infection, mild or moderate disease severity, and no specific risk factors for multiresistant strains, such as prolonged duration of hospitalization (>5 days), admission from a health care-related facility, recent prolonged antibiotic therapy, and specific local epidemiological data, can be treated with a narrow-spectrum drug, such as a non-pseudomonal third-generation cephalosporin [1,2].

Table 117.1 Initial antimicrobial therapy in patients with VAP

	Micro-organisms usually responsible	Initial antimicrobial therapy
Early-onset VAP: (<5–7 days of MV) and no risk factors for drug-resistant pathogens (admission from a health care-related facility, recent prolonged antibiotic therapy, and specific local epidemiological data)	Streptococci, methicillin-sensitive *S. aureus*, *H. influenzae*, *Moraxella catarrhalis*, enteric Gram-negative (non-pseudomonal)	Non-pseudomonal 3rd-generation cephalosporin or β-lactam–β-lactamase inhibitor combination, plus one dose of an aminoglycoside in case of severe sepsis or septic shock
Late-onset and/or risk factors for drug-resistant pathogens	Difficult-to-treat Gram-negative bacilli, such as Enterobacter, *Citrobacter freundii*, *Serratia*, indole + *Proteus*, *Morganella*, *Providencia*, extended spectrum beta lactamase (ESBL)-producing Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter baumannii*, MRSA	Aminoglycoside (amikacin), plus one of the following: ◆ Antipseudomonal penicillin: ◆ Piperacillin+tazobactam ◆ Ceftazidime ◆ Carbapenem (imipenem, meropenem, doripenem) ◆ Cefepime Consider adding vancomycin or linezolid when the patient is colonized by MRSA and/or local prevalence of infection caused by MRSA is high, particularly when Gram staining of respiratory secretions shows Gram-positive cocci

Optimizing antimicrobial therapy

Several published reports have demonstrated the need to adjust the target dose of antimicrobial agents used in treating severe NP to individual patient's pharmacokinetics and putative bacterial pathogens' susceptibilities. Most investigators distinguish between antimicrobial agents that kill by a concentration-dependent mechanism (e.g. aminoglycosides and fluoroquinolones) from those that kill by a time-dependent mechanism (e.g. β-lactams and vancomycin). Altered pharmacokinetics secondary to an increase in volume of distribution in critically-ill patients can result in insufficient serum β-lactam concentrations when standard dosages are administered, emphasizing the need to carefully monitor peak and trough levels of antibiotics when treating resistant pathogens [10]. Higher dosing regimens than those usually recommended and/or prolonged duration of infusion are frequently needed in such circumstances [11]. Development of *a priori* dosing algorithms based on minimal inhibitory concentrations (MIC), patient creatinine clearance and weight, and the clinician-specified area under the inhibitory curve (AUIC) target might be a valid way to improve treatment of these patients, leading to a more precise approach than current guidelines for use of antimicrobial agents [11].

Focusing therapy once the agent of infection is identified

Once the results of respiratory tract and blood cultures become available, therapy can often be focused or narrowed, based on the identity of pathogens and their susceptibility to specific antibiotics, in order to avoid prolonged use of a broader spectrum of antibiotic therapy than is justified by the available information [1]. For example, vancomycin and linezolid should be stopped if no MRSA is identified, unless the patient is allergic to β-lactams and has developed an infection caused by a Gram-positive micro-organism. Very broad-spectrum agents, such as carbapenems, piperacillin–tazobactam, and/or cefepime should also be restricted to patients with infection caused by pathogens only susceptible to these agents. Unfortunately, several studies have shown that, although de-escalation was not associated with any adverse outcomes, it was not consistently performed in many ICUs [12,13].

Switching to monotherapy at days 3–5

The two most commonly cited reasons to use combination therapy for all the antibiotic-treatment duration are to achieve synergy and prevent the emergence of resistant strains. Synergy, however, has only been clearly documented to be valuable in the therapy of *P. aeruginosa* or other difficult-to-treat Gram-negative bacilli (GNB) and in patients with neutropenia or bacteraemic infection, which is uncommon in NP. When combination therapy was evaluated in randomized controlled studies, its benefit was inconsistent or null, even when the results were pooled in meta-analyses or the analysis was restricted to patients infected by *P. aeruginosa* [14,15]. Based on these data, therapy could be safely switched to monotherapy in most patients after 3–5 days, provided that initial therapy was appropriate, clinical course appears favourable, and that microbiological data do not suggest a very difficult-to-treat micro-organism, with a very high in vitro MIC, as it can be observed with some non-fermenting-GNB.

Shortening duration of therapy

Based on data obtained from several randomized trials, an 8-day regimen can probably be standard for most patients with NP [16]. Possible exceptions to this recommendation include immunosuppressed patients, those whose initial antimicrobial treatment was not appropriate for the causative micro-organism(s), and patients whose infection was caused by non-fermenting GNB and had no improvement in clinical signs of infection.

Many clinicians, however, remain hesitant about prescribing fewer fixed days of antibiotics for patients with NP, and would prefer to customize antibiotic duration based on the clinical course of the disease and/or using serial determinations of a biological marker of infection, such as procalcitonin (PCT). The rationale for using a biomarker to tailor antibiotic-treatment duration relies on the fact that the inflammatory response is most often proportional to infection severity. When that response is absent or low, it might be logical to discontinue antibiotics earlier. Thus, adapting antimicrobial-treatment duration to PCT kinetics seems reasonable, and has been demonstrated to be useful in several randomized trials targeting patients with acute

respiratory infection, including five trials conducted in the ICU [17,18].

Conclusion

Nosocomial pneumonia is associated with mortality in excess of that caused by the underlying disease alone, particularly in case of infection caused by high-risk pathogens, such as *P. aeruginosa* and MRSA. The high level of bacterial resistance observed in patients who develop NP limits the treatment options available to clinicians and encourages the use of antibiotic regimens combining several broad-spectrum drugs, even if the pretest probability of the disease is low, because initial inappropriate antimicrobial therapy has been linked to poor prognosis. Besides its economic impact, this practice of 'spiralling empiricism' increasingly leads to the unnecessary administration of antibiotics in many ICU patients without true infection, paradoxically resulting in the emergence of infections caused by more antibiotic-resistant micro-organisms that are, in turn, associated with increased rates of patient mortality and morbidity. Every possible effort should therefore be made to obtain reliable pulmonary specimens for direct microscopic examination and cultures from each patient clinically suspected of having developed NP in order to be able to de-escalate treatment every time it is possible.

References

1. American Thoracic Society and Infectious Diseases Society of America. (2005). Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine*, **171**, 388–416.
2. Chastre J and Fagon JY. (2002). Ventilator-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine*, **165**, 867–903.
3. Fagon JY, Chastre J, Wolff M, et al. (2000). Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Annals of Internal Medicine*, **132**, 621–30.
4. Torres A and Ewig S. (2004). Diagnosing ventilator-associated pneumonia. *New England Journal of Medicine*, **350**, 433–5.
5. Souweine B, Mom T, Traore O, et al. (2000). Ventilator-associated sinusitis: microbiological results of sinus aspirates in patients on antibiotics. *Anesthesiology*, **93**, 1255–60.
6. Shorr AF, Sherner JH, Jackson WL, and Kollef MH. (2005). Invasive approaches to the diagnosis of ventilator-associated pneumonia: A meta-analysis. *Critical Care Medicine*, **33**, 46–53.
7. Heyland D, Dodek P, Muscedere J, and Day A. (2006). A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *New England Journal of Medicine*, **355**, 2619–30.
8. Micek ST, Welch EC, Khan J, et al. (2010). Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to Gram-negative bacteria: a retrospective analysis. *Antimicrobial Agents and Chemotherapy*, **54**, 1742–8.
9. Martinez JA, Cobos-Trigueros N, Soriano A, et al. (2010). Influence of empiric therapy with a beta-lactam alone or combined with an aminoglycoside on prognosis of bacteremia due to Gram-negative microorganisms. *Antimicrobial Agents and Chemotherapy*, **54**, 3590–6.
10. Taccone FS, Laterre PF, Dugernier T, et al. (2010). Insufficient beta-lactam concentrations in the early phase of severe sepsis and septic shock. *Critical Care*, **14**, R126.
11. Lodise TP and Drusano GL. (2011). Pharmacokinetics and pharmacodynamics: optimal antimicrobial therapy in the intensive care unit. *Critical Care Clinic*, **27**, 1–18.
12. Rello J, Vidaur L, Sandiumenge A, et al. (2004). De-escalation therapy in ventilator-associated pneumonia. *Critical Care Clinic*, **32**, 2183–90.
13. Giantsou E, Liratzopoulos N, Efraimidou E, et al. (2007) De-escalation therapy rates are significantly higher by bronchoalveolar lavage than by tracheal aspirate. *Intensive Care Medicine*, **33**, 1533–40.
14. Marcus R, Paul M, Elphick H, and Leibovici L. (2011). Clinical implications of beta-lactam-aminoglycoside synergism: systematic review of randomised trials. *International Journal of Antimicrobial Agents*, **37**, 491–503.
15. Brunkhorst FM, Oppert M, Marx G, et al. (2012). Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial treatment for sepsis-related organ dysfunction. *Journal of the American Medical Association*, **307**, 2390–9.
16. Chastre J, Wolff M, Fagon JY, et al. (2003). Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *Journal of the American Medical Association*, **290**, 2588–98.
17. Bouadma L, Luyt CE, Tubach F, et al. (2010). Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet*, **375**, 463–74.
18. Schuetz P, Briel M, Christ-Crain M, et al. (2012). Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. *Clinical Infectious Diseases*, **55**, 651–62.

CHAPTER 118

Diagnosis and management of atypical pneumonia

Martin Langer and Edoardo Carretto

Key points

- 'Atypical pneumonia' is not rare in the critically-ill patient and 'atypical micro-organisms' are intrinsically resistant to β-lactams. Specific empiric antimicrobial treatment (macrolides, newer fluorquinolones) is mandatory.
- 'Atypical' pneumonia belongs mainly to the community-acquired pneumonia (CAP) and consequently CAP-guidelines include diagnosis and treatment of the 'atypical' pneumoniae.
- Hospital-acquired 'atypical' pneumonia are almost exclusively caused by *L. pneumophila* and may occur in immunocompromised patients with cancer, organ transplant, or undergoing immunosuppressive treatment, who are exposed to contaminated water in the hospital.
- For *L. pneumophila* infections, the **urinary antigen test** is a rapid assay, easy to perform, and widely available. Its major limitation is the specificity only for serogroup 1 (>70%, but <100%). Since the isolation of *L. pneumophila* from respiratory tract is still considered the diagnostic gold standard in microbiology, an attempt to culture the micro-organism should be made whenever is possible.
- Evaluation of serological response (IgM and IgG) in both, acute, and convalescent (3–4 weeks) sera, permit the diagnosis of *M. pneumoniae* and *C. pneumoniae*. In the near future, it is expected that Nucleic Acid Amplification tests (NAAT) techniques will represent the future key points for the diagnosis.

Introduction

The term 'atypical pneumonia' is probably obsolete and also questionable [1], but still widely used, and this chapter refers to pneumonia caused by *Legionella pneumophila, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae* [2]. 'Atypical' pneumonia belongs mainly to the type community-acquired pneumonia (CAP) occurring both in immunocompromised and in immunocompetent patients, and consequently all CAP-guidelines extensively discuss clinical features, diagnosis, and treatment of the so-called atypical pneumoniae. Hospital-acquired (mainly not intensive care unit (ICU)-acquired) 'atypical' pneumonia are almost exclusively caused by *L. pneumophila* and may occur in immunocompromised patients with cancer, organ transplant, or undergoing immunosuppressive treatment, who are exposed to contaminated water in the hospital [3].

As shown in Table 118.1 and Fig. 118.1 the definition of 'atypical pneumonia' is not inclusive of viral pneumonia, and attempts to identify viruses that are of particular importance for epidemiological purposes [4–6].

The British Thoracic Society reports prevalence data for patients admitted to the ICUs with CAP: 17.8% of infections are due to *Legionella pneumophila*, and 2.7% and 2.2% to *Mycoplasma* and *Chlamydophila*, respectively [7]. In the Italian GiViTI—ICU surveillance project from 2009, *Legionella pneumophila* was identified in 4.6% of patients admitted for severe CAP. Legionellosis must therefore be considered in all patients admitted to the ICU with severe CAP. *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* causes infrequently severe illness in immunocompetent adults, but are more often diagnosed in children, the elderly, or immunocompromised hosts.

Clinical diagnosis

The clinical diagnosis of 'atypical pneumonia' in patients admitted to the ICU because of severe sepsis or respiratory failure is difficult and there are no specific clinical or radiological findings. 'Atypical pneumonia,' more than just a pneumonia, is a syndrome with pulmonary and extrapulmonary manifestations. Pneumonia with concomitant non-specific central nervous system (CNS) abnormalities, such as headache, mental confusion, lethargy, renal, and hepatic involvement (microscopic haematuria, increased creatinine, transaminases, and increased lactate dehydrogenase), cardiac abnormalities (relative bradycardia), diarrhoea, electrolyte abnormalities (hyponatraemia, hypophosphataemia), but also absence of sputum production and 'no growth' from standard cultures may suggest 'atypical' micro-organisms, and request adequate and urgent empirical treatment and diagnostic work-up. In an observational study, legionellosis, probably because not suspected/treated in a timely manner, was independently associated with early treatment failure and this increases the risk of death [8].

Radiology, albeit not specific, is a cornerstone of the diagnosis of 'atypical pneumonia' in patients admitted to the ICU. Severe CAP due to *Legionella* spp. usually cause patchy, localized infiltrates in the lower lobes, being frequently multilobar and even bilateral. In rare instances, legionellosis is associated with cavitations, more frequently in patients treated with steroids. Clinical history and evidence of contact with animals are important elements that support the suspicion of 'atypical' pneumonia due to infrequent diseases

Table 118.1 The most frequently isolated 'typical' and 'atypical' micro-organisms in CAP patients with increasing severity

	Micro-organisms		
	'Typical' pathogens	**'Atypical' pathogens**	**Other pathogens**
Outpatient	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella* spp.	*Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophila*	**Respiratory viruses:** influenza A-B, adenovirus, respiratory syncytial, para-influenza, H1N1
Inpatient: non-ICU	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella* spp., Gram-negative bacilli	*Legionella pneumophila, Mycoplasma pneumoniae, Chlamydophila pneumoniae*	**Respiratory viruses:** influenza A-B, adenovirus, respiratory syncytial, para-influenza, H1N1 Aspiration
Inpatient: ICU	*Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae,* Gram-negative bacilli	*Legionella pneumophila* (*Mycoplasma pneumoniae*)	**Respiratory viruses (H1N1):** *Aspergillus* spp., *Pneumocistis jiroveci* Aspiration

Adapted from Mandell LA et al., 'Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults', *Clinical Infectious Diseases*, 2007, **44**(Suppl. 2), pp. S27–72, by permission of Infectious Diseases Society of America. Data from File TM, 'Community-acquired pneumonia', *Lancet*, 2003, **362**, pp. 1991–2001.

such as Q fever, psittacosis, and tularaemia, which are hardly ever aetiologies seen outside a specific context.

Knowledge of the diseases and clinical suspicion are important, but not sufficient for diagnosis. Only specific microbiological investigations allow a reliable diagnosis, which is useful for the obligatory reporting and of great value for epidemiological purposes. A reliable microbiological diagnosis permit the tailoring of the type and duration of the treatment, even in cases where an adequate empiric, guideline-orientated treatment had been prescribed.

Microbiological diagnosis

Legionella infections

From the microbiological point of view, to date more than 50 *Legionella* species have been classified. *Legionella pneumophila* was the first species described and it causes 80–90% of reported cases of legionellosis. *L. pneumophila* is divided into 16 different serogroups, but serogroup 1 accounts for more than 70% of all of the legionellosis [9,10].

The diagnostic tools of *Legionella* infections have been focused on culture and serological investigation. A significant improvement was achieved using methods able to detect the urinary antigens of the micro-organism. Recently, nucleic acid amplification tests (NAATs) revealing the DNA of *Legionella* strains from environmental and clinical samples have been made available.

The urinary antigen test is based on the qualitative detection of a soluble antigen specific for *Legionella pneumophila* serogroup 1 [11], revealed through a rapid immunochromatographic assay. This antigen has been detected in urine as early as 3 days after the onset of symptoms and it may persist for months [12]. These tests

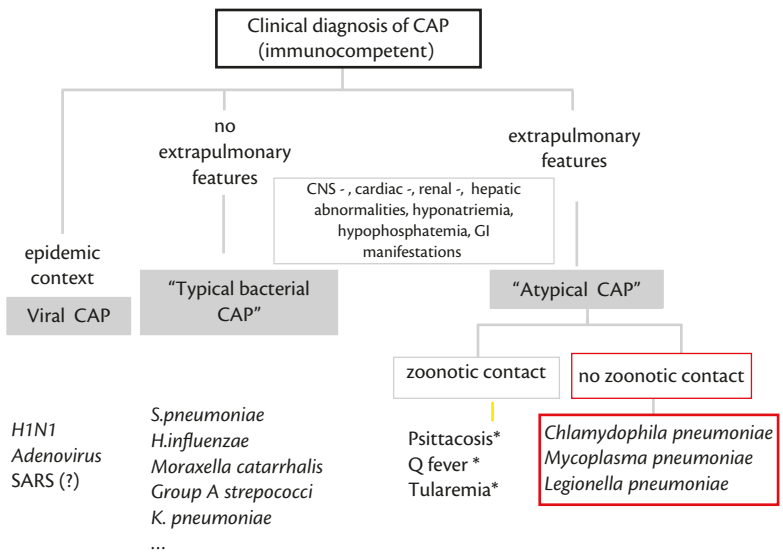


Fig. 118.1 Flow chart—'atypical pneumonia'—data from [5] and [6]. B. A. Cunha extensively investigated 'atypical pneumonia', and his work is helpful to understand similarities and differences with respect to 'typical' CAP.

*For psittacosis, Q fever, and tularaemia see specific literature.

Data from Cunha BA, 'Clinical features of legionnaires' disease', *Seminars in Respiratory Infections*, 1998, **13**, pp. 116–27; and Cunha BA, 'The atypical pneumonias: clinical diagnosis and importance', *Clinical Microbiology and Infection*, 2006, **12**(Suppl. 3), pp. 12–24.

provide quick results (15 minutes) using a common urine sample, and detect the antigen in early, as well as later, stages of disease, and antimicrobial treatment does not influence the result of the test. In infections due to *L. pneumophila* serogroup 1 the sensitivity of the method varies from 60 to 100%, with a specificity of more than 99% [13]. The major disadvantage of this test is its inability to diagnose infections caused by serogroups 2–16. Furthermore, the prolonged persistence of the antigen in the urinary samples may mislead the diagnosis if the patient had an asymptomatic *Legionella* infection, or a Pontiac fever, in the months before the episode of pneumonia that is to be investigated.

Isolation of *L. pneumophila* from respiratory specimens (e.g. sputum, tracheal aspirate, broncho-alveolar lavage, etc.) using selective media is considered to be the diagnostic gold standard. However, this kind of culture has to be specifically requested by the laboratory, since specific media are necessary, which are not routinely used. The culture is also time-consuming, because *Legionella* spp. take 3–7 days to grow. However, although the sensitivity of this method varies from laboratory to laboratory, an attempt to culture the micro-organism should be made whenever is possible. Through cultural methods it is possible to diagnose infections caused by *Legionella pneumophila* (serogroups different from 1) or by *Legionella* spp. different from *Legionella pneumophila* (most frequently involving *Legionella micdadei*, now reclassified as *Tatlockia micdadei*). Moreover, the isolation of the strain will allow epidemiological studies or could be required for comparison, with molecular techniques, of the isolate to environmental strains if necessary. If a patient is positive to the urinary antigen, allowing epidemiological studies, the clinician should immediately collect a respiratory sample, trying to isolate and identify the micro-organism. Even if there are no data about the decreased sensitivity of the culture in patients treated with effective antibiotics, it can be postulated that every day of effective therapy decreases the likelihood of isolating the micro-organism.

As far as serological analysis is concerned, different techniques are available and should be performed on paired sera (acute and convalescent). The most commonly used techniques are enzyme immunoassays (EIAs), even if detection of antibodies with indirect fluorescence has better performances, but they are time-consuming and require skilled personnel. The main disadvantage of serology is that the host response is typically slow, and sometimes specific antibodies can be detected only months after the onset of symptoms. Thus, serological testing is useful for epidemiological purposes, but has little or no impact for the diagnosis and treatment of the early stage of the disease [14].

Recently, nucleic acid-based methods have been applied to the detection of *Legionella* species, both in clinical and in environmental samples. The polymerase chain reaction (PCR) techniques, if used in combination with the urinary-antigen test, increase the diagnostic chances in the early stage of the disease compared with the use of each test alone [15]. These tests have been successfully used in reference and research laboratories, although most of these experiences were with 'home-made' techniques. At the time of writing, only one out of the three commercial available assays is FDA-cleared. Although these methods have high capability for the future, they should be used only in reference settings and in selected cases, such as suspected infections in patients exposed to *L. pneumophila* strains different from serogroup 1 (e.g. for environmental exposure).

Mycoplasma pneumoniae and *Chlamydophila pneumoniae*

The aetiological diagnosis of these two entities implies common problems. The diagnosis of both pathogens is based on serological tests and on NAATs. Culture is very difficult and time-consuming, and can be performed only in reference laboratories.

For *Mycoplasma* infections, serological tests should be performed on paired sera (acute and convalescent), using complement fixation test and EIAs. However, this approach is useful only for epidemiological purposes. The diagnosis of acute infections can be achieved by evaluating the IgM antibodies even if they are lacking in children under 6 months of age, in some cases of primary infections and during re-infections. For *M. pneumoniae,* IgMs are produced 3–4 days or later after the onset of symptoms, and sometimes persist for several weeks to months.

Regarding serological tests for *C. pneumoniae,* determined in paired sera, the micro-immunofluorescence (MIF) test is able to document infections and is useful for epidemiological purposes and is currently considered the gold standard.

Both for *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, PCR systems have been developed and used for diagnosis. For these micro-organisms, comparison of NAATs with culture and/or serology is difficult, since there are problems in defining a reliable gold standard. To date, there are no commercial FDA-cleared assays, although a wide variety of PCR-based protocols, using different target genes, have been developed in research laboratories. These techniques, and in particular real-time PCR, will represent the future key points for the diagnosis [16].

What should clinicians do for the diagnosis?

If an 'atypical pneumonia' is suspected, clinicians should:

- Collect a urinary sample for detection of *Legionella pneumophila* serogroup 1 antigen.
- If legionellosis is strongly suspected, or if the urinary antigen is positive, appropriate respiratory samples should be collected as soon as possible and sent to the laboratory, with a previous communication to the microbiologist.
- Collect acute and convalescent (3–4 weeks) sera for IgM and IgG serology for *L. pneumophila, M. pneumoniae*, and *C. pneumoniae.*
- Contact the laboratory to discover whether NAATs are available for the diagnosis and also to find the correct way to collect samples to be used with these techniques.

Transmission within the ICU and isolation practice

While hospital acquisition of legionellosis from contaminated water in hospital is of great concern, and may present in clusters or outbreaks, a person-to-person transmission has never been reported [17]. Isolation of *Legionella*-infected patients is therefore unnecessary.

Treatment

Starting from the well-known unresponsiveness of 'atypical' bacteria to β-lactam antibiotics and the impossibility to perform 'standard'

sensitivity testing, the cornerstone of treatment is empirical therapy with macrolides or newer fluorquinolones. In the absence of adequate clinical studies, all available guidelines are based on in vitro investigations, observational studies and expert opinions.

Every CAP-guideline includes 'anti-atypical' drugs as their first line CAP treatment, mainly a combination of a respiratory fluorquinolone or a macrolide (with a β-lactam). In many severe and poorly responsive cases diagnosed as legionellosis, combination therapy, adding rifampicin to the fluorquinolone has been tried, but the efficacy is still controversial [3,18]. From 2 to 3 weeks of treatment are usually considered adequate, but this information too is not 'evidence based.'

Once the microbiological diagnosis becomes available, the treatment of 'atypical' pneumonia may also be targeted according to the pathogen [19]:

- ***Mycoplasma pneumoniae*:** doxycycline, macrolide, newer fluoroquinolones (most data available for levofloxacin).
- ***Chlamydophila pneumoniae*:** doxycycline, macrolide, fluoroquinolones.
- ***Legionella* spp.:** newer fluoroquinolones (most data available for levofloxacin), macrolide (azitromycine preferred) +/– rifampicin.

References

1. Murdoch DR and Chambers ST. (2009). Atypical pneumonia—time to breathe new life into a useful term? *Lancet—Infectious Diseases*, **9**, 512–19.
2. Plouffe JF. (2000). Importance of atypical pathogens of community-acquired pneumonia. *Clinical Infectious Diseases*, **31**(Suppl. 2), S35–9.
3. Carratala J and Garcia-Vidal C. (2010). An update on *Legionella*. *Current Opinions in Infectious Diseases*, **23**, 152–7.
4. Mandell LA, Wunderink RG, Anzueto A, et al. (2007). Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical Infectious Diseases*, **44**(Suppl. 2), S27–72.
5. Cunha BA. (1998). Clinical features of legionnaires' disease. *Seminars in Respiratory Infections*, **13**, 116–27.
6. Cunha BA. (2006). The atypical pneumonias: clinical diagnosis and importance. *Clinical Microbiology and Infection*, **12**(Suppl. 3), 12–24.
7. Lim WS, Baudouin SV, George RC, et al. (2009). British Thoracic Society guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax*, **64**(Suppl III), iii1–iii55.
8. Roson B, Carratala J, Fernandez-Sabe N, Tubau F, Manresa F, and Gudiol F. (2004). Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. *Archives of Internal Medicine*, **164**, 502–8.
9. Yu VL, Plouffe JF, Pastoris MC, et al. (2002). Distribution of *Legionella* species and serogroups isolated by culture in patients with sporadic community-acquired legionellosis: an international collaborative survey. *Journal of Infectious Diseases*, **186**, 127–8.
10. Stout JE and Yu VL. (1997). Legionellosis. *New England Journal of Medicine*, **337**, 682–7.
11. Berdal BP, Farshy CE, and Feeley JC. (1979). Detection of *Legionella pneumophila* antigen in urine by enzyme-linked immunospecific assay. *Journal of Clinical Microbiology*, **9**, 575–8.
12. Kohler RB, Winn WC, Jr, and Wheat LJ. (1984). Onset and duration of urinary antigen excretion in Legionnaires disease. *Journal of Clinical Microbiology*, **20**, 605–7.
13. Tronel H and Hartemann P. (2009). Overview of diagnostic and detection methods for legionellosis and *Legionella* spp. *Letters in Applied Microbiology*, **48**, 653–6.
14. Den Boer JW and Yzerman EP. (2004). Diagnosis of *Legionella* infection in Legionnaires' disease. *European Journal of Clinical Microbiology & Infectious Diseases*, **23**, 871–8.
15. Diederen BM. (2008). *Legionella* spp. and Legionnaires' disease. *Journal of Infection*, **56**, 1–12.
16. Diaz MH and Winchell JM. (2012). Detection of *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* directly from respiratory clinical specimens using a rapid real-time polymerase chain reaction assay. *Diagnostic Microbiology and Infectious Disease*, **73**, 278–80.
17. Newton HJ, Ang DK, van Driel IR, and Hartland EL. (2010). Molecular pathogenesis of infections caused by *Legionella pneumophila*. *Clinical Microbiology Reviews*, **23**, 274–98.
18. Pedro-Botet ML, Garcia-Cruz A, Tural C, et al. (2006). Severe Legionnaires' disease successfully treated with levofloxacin and azithromycin. *Journal of Chemotherapy*, **18**, 559–61.
19. Woodhead M, Blasi F, Ewig S, et al. (2011). Guidelines for the management of adult lower respiratory tract infections—full version. *Clinical Microbiology and Infection*, **17**(Suppl. 6), E1–59.

PART 4.14

Atelectasis and sputum retention

CHAPTER 119

Pathophysiology and prevention of sputum retention

John J. Marini and Paolo Formenti

Key points

- Common predispositions to secretion retention are airway intubation, prolonged sedation, muscular weakness, aspiration of oral secretions, coughing discomfort, restricted breathing after surgery, bronchitis due to smoking, and advanced age.
- Effective removal of secretions from the respiratory tract depends on two key factors—integrity of the mucociliary transport system and the ability to cough productively.
- Mucus retained within the airway lumen impairs effective delivery of aerosol therapies, while predisposing to lung collapse, inflammation, and infection.
- Intubation for mechanical ventilation impairs cough, interrupts mucociliary clearance, and encourages formation of a tube-lining biofilm that is isolated from blood flow and body defences.
- Respiratory and coughing muscle strength, body position, lung volume, airway secretion viscosity and location, depth of sedation, and suctioning effectiveness are some of the important variables that determine the impact of secretion retention on ventilation, gas exchange, and patient outcome.

Introduction

A thin lining of tracheobronchial secretions contributes importantly to normal respiratory system defence, whereas retained airway mucus complicates the care of the critically-ill ventilated patient. Excessive secretions that must be cleared from the airways by coughing, huffing, or catheter aspiration, are defined as **sputum**. They may arise acutely or be present chronically, but they are always abnormal. Retained secretions in the acute care setting may impair gas exchange, increase the breathing workload, predispose to infection, or contribute to atelectasis. Prevention and reversal of the latter phenomenon is a fundamental goal of effective intensive care.

Pathogenic mechanisms of secretion retention and atelectasis

Sputum retention may either cause or result from atelectasis. Once established, parenchymal collapse impairs clearance of mucus from the central airways. Among the most common predispositions to secretion retention are airway intubation, prolonged sedation, muscular weakness, aspiration of oral secretions, coughing discomfort, restricted breathing after surgery, bronchitis due to smoking, and advanced age [1]. Obstructive atelectasis involves narrowing or occlusion of the bronchial tree by foreign bodies or mucus, tumours, or lymph nodes. In some cases, a lack of surfactant increases the surface tension of alveoli, encouraging their collapse [2]. Whatever the setting, strong measures must be taken to reduce the prevalence of these ubiquitous disorders.

The following mechanisms may contribute to the development of atelectasis:

- Compression atelectasis occurs when the transmural pressure distending the alveolus is reduced sufficiently to allow alveolar collapse. Common causes include loss of muscular tone, as during the induction of anaesthesia, pleural effusion, abdominal distention, supine positioning, and lung oedema.
- Obstructive atelectasis, a common cause for the generation of atelectasis or a contributor to its persistence, results from reabsorption of gas from the alveoli when communication between the gas exchange interface and the trachea is interrupted by foreign bodies, tumours, or mucus plugs. Gas uptake by the blood then continues while replenishing gas inflow is prevented (Fig. 119.1).
- Adhesive atelectasis results from surfactant deficiency. Increased alveolar surface tension cannot be counterbalanced by tidal transalveolar pressures, leading to alveolar instability and collapse. This mechanism probably makes an important contribution to the maintenance of established collapse, but is less central to its generation, given normal surfactant reserve and high rate of surfactant turnover.

Bronchial secretions

Effective removal of secretions from the respiratory tract depends on two key factors—integrity of the mucociliary transport system and the ability to cough productively. Airway mucus traps inhaled particulate toxins and transports them out of the lungs by means of ciliary beating and cough. A deficient mucous barrier leaves the lungs vulnerable to injury, and excessive mucus or impaired clearance contributes to all common airway diseases.

Mucus is continuously swept from distal to proximal airways, propelled in a proximal direction by ciliary beating. This action clears inhaled particles, pathogens, and dissolved chemicals that might otherwise threaten the lungs [3]. While the small airways produce a thin mucus gel layer, a thicker layer (up to 50 μm) accumulates

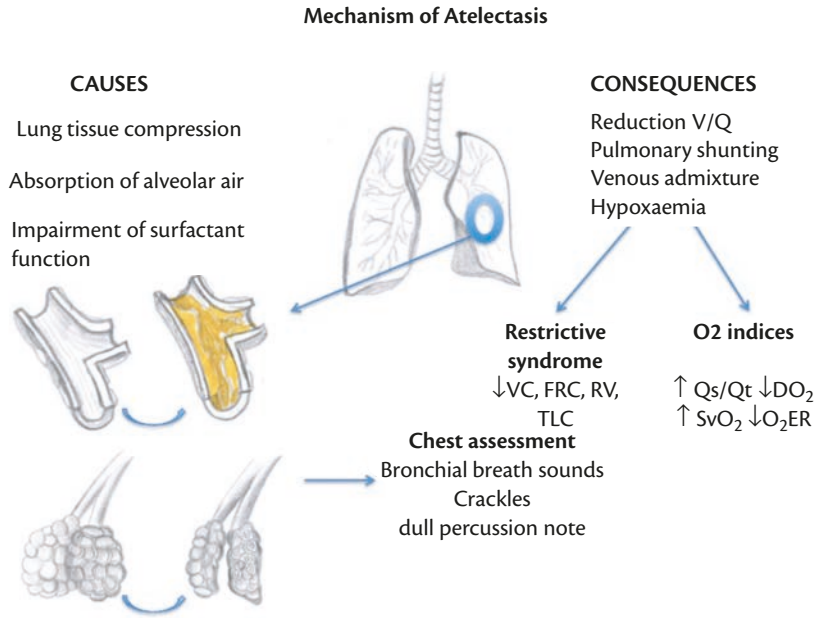


Fig. 119.1 Schematic figure to explain mechanism of atelectasis and physiological/clinical implication.
VC, vital capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; DO_2, oxygen delivery.

in the larger airways from accumulated mucus transported from distal airways and any drying that may result from suboptimally conditioned inspired gas. After mucus ascends the trachea, it is normally transported mouthward past the vocal cords by ciliary epithelium in the posterior commissure of the larynx. It then enters the pharynx and is swallowed, with approximately 30 mL of airway mucus eliminated via the gastrointestinal tract daily [4]. The rate of mucociliary clearance increases with greater hydration [5], and the rate of ciliary beating can be increased by purinergic, adrenergic, cholinergic, and adenosine-receptor agonists, as well as by irritant chemicals. Sputum retention occurs when patients are unable to clear secretions by themselves or with assistance. Retention of airway secretions may lead to obstruction of major bronchopulmonary units and lobar atelectasis.

A second mechanism of fundamental importance for the expulsion of pathological mucus from the airways is cough clearance. Coughing is a complex phenomenon that is usually triggered by local 'irritation' caused by the stimulation of vagal afferents in the intrapulmonary airways or in the larynx and pharynx. Reflex activation of the expulsive abdominal and intrathoracic muscles makes it possible to quickly evacuate accumulated secretions from the central bronchi. Assuming that the airway is not intubated, the glottis can temporarily close during forceful contraction of the abdominal and internal intercostal muscles [6]. After airway pressure rapidly elevates, sudden opening of the glottis allows compression of the central airway and sufficiently high flow to shear the debris from its mucosal attachments.

During invasive mechanical ventilation, cough efficiency is impaired because the glottis cannot close, even though increased resistance of the upper airways (intubation tube, ventilatory circuit) may predispose to an increase in tracheal pressure during forceful exhalation. Coughing is suppressed during general anaesthesia and can be significantly reduced by the administration of opioids. In patients who are *not* intubated, neuromuscular weakness(phrenic paralysis, myasthenia, Guillain–Barré syndrome, etc.), pain, or impaired consciousness are often responsible for 'ineffective' cough. In others, peripheral obstruction of the airways chokes off maximal expiratory flow, detrimentally affecting cough.

Dyspnoea often results when mucus obstructs airflow by narrowing the 'effective' airway lumens within the collective airway system. Physical signs of impaired mucus clearance include persistent cough, bronchial breath sounds, rhonchi, and wheezes. Retained mucus and inflammatory exudates may appear as localized haze, atelectasis, or linear or branched opacities on plain radiographs of the chest. Not only is it important to recognize the role of mucus in clinical presentations of increased effort and impaired oxygenation, but also to understand that mucus must be cleared from the airway lumen to facilitate effective delivery of aerosol therapies and, in many cases, to address patient–ventilator asynchrony. In addition, the presence of retained mucus may predispose to or be a sign of inflammation or infection that warrants additional treatment.

Factors modulating the formation of atelectasis

Several important clinical circumstances influence the formation of atelectasis. Atelectasis develops both during intravenous and inhalational anaesthesia. Ventilatory effects of regional anaesthesia depend on the type and extent of motor blockade. The maximum decreases of functional residual capacity (FRC) seem to occur within the first few minutes of general anaesthesia and as a consequence of changing positions. Transition from the upright to the supine position causes FRC to decrease 0.5 L to 1.2 L, even in the awake state, with a further reduction of 0.5–0.7 L in FRC occurring during general anaesthesia. High inspired oxygen concentrations are associated with 'absorption' atelectasis. Absorptive collapse is prevalent, as the use of high FIO_2 (i.e. approaching 1.0) is standard practice among many anaesthesiologists. Obesity worsens arterial oxygenation through multiple mechanisms, of which development of atelectasis is an important contributor [7]. Markedly reduced

FRC limits expiratory reserve and promotes airway closure to a greater extent in obese patients than in patients of normal weight. Two practical points are important regarding ventilator settings during deep sedation. In contrast to volume-controlled ventilation, pressure-controlled ventilation delivers smaller tidal volumes when respiratory system compliance declines (e.g. during surgical retraction or after placement of abdominal packs). Smaller tidal volumes may then lead to atelectasis (unless volume alarms are appropriately set) and may go undiagnosed because there is no tell-tale change in the peak airway pressure [8].

Risk factors

There are several risk factors associated with the development of atelectasis caused by obstruction of the major airways and bronchioles, or by pressure originating outside the lung, e.g. from fluid or air in the pleural space (Box 119.1). Some predispositions are directly linked with the sputum retention that tends to occur commonly as a complication in the post-operative period.

It is clear that low V/Q areas in dependent lung regions (i.e. areas of relative underventilation) are inclined to develop progressive atelectasis. Any influence that enhances such underventilation will increase this tendency. Apart from inhibition of diaphragmatic action, the most important of these risk factors is airways disease, particularly chronic bronchitis and/or emphysema. In chronic airways disease, inspired gas is unevenly distributed, both temporally and spatially. Reduced peak expiratory flow impedes expulsion of accumulated secretions.

Another common factor augmenting the tendency toward collapse is a rapid shallow pattern of ventilation, commonly seen in patients with obesity and in those with post-operative pain, when the discomfort of an abdominal or thoracic incision inhibits normal depth of inspiration. The latter problem may be partially alleviated or, conversely, compounded by the use of sedative and narcotic analgesics, which relieve pain, but depress ventilation, suppress coughing and retard sputum clearance. Depressed central respiratory drive due to chronic obstructive lung disease, neurological disease, or hypoventilation syndromes also aggravates the atelectatic tendency. Reduced inspiratory reserve due to peripheral nerves (Guillain–Barré syndrome or spinal cord injury), neuromuscular (myasthenia gravis, post-anaesthetic persistent curarization syndrome), muscular (muscular dystrophies), and musculoskeletal disorders (ankylosing spondylitis, thoracoplasty, kyphoscoliosis) may also be associated with a shallow breathing pattern, increased hypoventilation of dependent lung regions, and an enhanced tendency to atelectasis.

Box 119.1 Atelectasis risks factor associated with airways obstruction

- Impaired swallowing function, particularly in older adults—aspirating secretions into the lungs is a major source of infections.
- Any condition that interferes with spontaneous coughing, yawning, and sighing.
- Lung disease, such as asthma, bronchiectasis, or cystic fibrosis.
- Confinement to bed, with infrequent change of position.
- Abdominal or chest surgery.
- Recent general anaesthesia.
- *Shallow breathing:* a result of abdominal pain or rib fracture.
- Respiratory muscle weakness, due to muscular dystrophy, spinal cord injury, or another neuromuscular condition.
- *Obesity:* fat in the abdomen can elevate the diaphragm and hamper the ability to inhale fully.
- Age.

Ventilation patterns and airway secretion clearance

Intubation for mechanical ventilation impairs cough, interrupts mucociliary clearance, and encourages formation of a tube-lining biofilm that is isolated from blood flow and body defences. These factors lead to sputum retention, airway occlusion, atelectasis, and ventilator-associated pneumonia. Respiratory muscle strength, position, lung volume, viscosity, and location of airway secretions, depth of sedation, and 'coughing strength' (expiratory flow generated spontaneously or in response to suction) are some of the variables that may determine the impact of secretion retention on ventilation, gas exchange, and patient outcome [8]. The minimum standard of airway management requires adequate gas humidification and airway suctioning [9]. Open suctioning, higher suction pressures, wide-bore suction catheters, and the release of positive end-expiratory pressure (PEEP)—a manoeuvre that encourages mouthward migration of secretions retained in the periphery of the PEEP-distended lung can improve secretion clearance, but may compromise gas exchange in the short term. Closed suctioning can minimize potential adverse physiological effects of airway suctioning, but may not be as effective for secretion clearance [10].

It has been demonstrated that airway clearance can be augmented by imposing an expiratory flow bias or by manual lung hyperinflation, which transiently improves airway resistance, recoil force, and dynamic lung/thorax compliance. Chest wall vibration, with or without manual lung hyperinflation and suctioning, can improve expiratory flow, airway resistance, and dynamic lung/thorax compliance, but has not been demonstrated to improve secretion clearance [11].

Consequences of atelectasis

Atelectasis decreases pulmonary compliance and is associated with a worsening in systemic oxygenation associated with a reduction in FRC [12]. In the presence of increased airway resistance or decreased lung compliance, increased transpulmonary pressure is required to achieve a given tidal volume, with consequent increase in the work of breathing. Most often, this volume reduction impairs the efficiency of systemic oxygenation, and prompts hyperoxic gas inhalation with subsequent reabsorption. In the hyperoxic range, such effects are better detected by arterial blood gas analysis, rather than simply observing oxygen saturation.

High tidal ventilating pressures when the lung is not fully recruited may inflict lung damage. Yet, use of 'lung protective' low tidal volumes may not be sufficient to avert lung inflammation. It has been demonstrated that in the absence of PEEP, impaired lung compliance is accompanied by increased cytokine production. Pulling together all recent findings it seems reasonable to suggest

that using low tidal volume without preventing atelectasis by adequate PEEP may be a misguided ventilation strategy [13].

Prevention of sputum retention and atelectasis

Invasive mechanical ventilation via endotracheal intubation or tracheostomy bypasses the upper airways, and its normal heat and moisture exchanging process. Humidification is necessary to prevent hypothermia, disruption of the airway epithelium, bronchospasm, atelectasis, and airway obstruction [14]. Moreover, a continuous loss of moisture and heat occurs during prolonged mechanical ventilation with poorly-conditioned inspired gas and predisposes to airway damage. Inadequate humidification and heating of the inspired gas mixture promotes mucosal damage (destruction of cilia and mucous glands). During normal respiration, humidity in the trachea can range from 36 to 40 mg/L, and the optimal moisture concentration beyond the carina approximates 44 mg/L (100% relative humidity (RH) at 37°C). When providing active humidification to patients who are invasively ventilated, it is suggested that the device provides a humidity level between 33 mgH_2O/L and 44 mgH_2O/L, and a gas temperature between 34°C and 41°C with a RH of 100% in order to prevent the drying of secretions in the artificial airway.

Active humidification through a heated humidifier (HH) and passive humidification through a heat and moisture exchanger (HME, 'artificial nose'), are available for warming and humidifying gases delivered to mechanically-ventilated patients. HMEs operate passively by storing heat and moisture from the patient's exhaled gas and releasing it to the inhalation gas stream.

Very recently, recommendations regarding gas humidification have been published that follow the grading of recommendations assessment, development, and evaluation (GRADE) system for scoring evidence quality [15].

- Humidification is recommended for every patient receiving invasive mechanical ventilation.
- Active humidification is suggested for non-invasive mechanical ventilation, as it may improve secretion mobility and comfort.
- When providing active humidification to patients who are invasively ventilated, it is suggested that the device provides a humidity level between 33 mgH_2O/L and 44 mgH_2O/L, and gas temperature between 34°C and 41°C at the circuit Y-piece, with a relative humidity of 100%.
- When providing passive humidification to patients undergoing invasive mechanical ventilation, it is suggested that the HME provide a minimum of 30 mgH_2O/L.
- Passive humidification is not recommended for non-invasive mechanical ventilation.
- When providing humidification to patients with low tidal volumes, such as when lung-protective ventilation strategies are used, HMEs are not recommended because they provide additional dead space, which can increase the ventilation requirement and $PaCO_2$.
- It is suggested that HMEs are not useful as a prevention strategy for ventilator-associated pneumonia.

Box 119.2 Prevention of sputum retention and atelectasis

- *Active humidification:* humidity level between 33 mgH_2O/L and 44 mgH_2O/L, and gas temperature between 34°C and 41°C.
- Adequate hydration to thin the secretions.
- Oxygen has a drying effect.
- Adequate analgesia.
- *Physiotherapy:* active cycle of breathing, body positioning and manual techniques (i.e. percussion, shaking and vibrations).

Supplemental strategies to prevent sputum retention include hydration, dry mouth prevention, oxygen modulation, adequate pain relief, and timely airway suctioning [16]. Adequate **hydration** helps to thin and lubricate secretions, making them easier for the patient to expectorate. Damage to the cilia can be prevented by **humidification** of the respiratory tract via humidifiers and nebulizers.

Because **oxygen** has a drying effect, sufficient humidification of high inspired concentrations of oxygen is important, especially if there is an existing lung disease. Nebulized β-2-adrenoceptor agonists, such as salbutamol, and mucolytics, such as recombinant human deoxyribonuclease (Dornase alfa) have been shown to increase mucociliary clearance. It is well known that **smokers** with a history of ischaemic heart disease and inadequate pain control are at high risk of developing sputum retention. There is also a strong risk of sputum retention in an individual with a history of chronic obstructive pulmonary disease and/or cerebrovascular accident. Adequate **analgesia** is usually needed to facilitate effective coughing during the post-operative period. Other post-operative pain factors that may limit a patient's ability to cough effectively include decreased levels of consciousness, narcotic analgesics, abnormal chest wall compliance, vocal cord dysfunction, expiratory muscle weakness, and obstructed airflow,

Physiotherapy can help patients to remove excess secretions by using active exercise to enhance mucociliary clearance. Apart from cough encouragement, active breathing, body positioning, and vibration techniques (i.e. manual percussion, chest wall shaking, and high frequency airway vibration with asymmetrical flow patterns) can be used to loosen secretions and, thus, facilitate expectoration. Other devices that manipulate the airway with positive pressure, including the positive expiratory pressure masks, intermittent positive pressure breathing, and insufflation-exsufflation (assisted coughing) can also be used [17] (Box 119.2). Manual hyperinflation techniques may be required with some intubated patients.

Airway suctioning is usually necessary to clear secretions from patients with an endotracheal tube or tracheostomy. However, a suctioning manoeuvre should only be used when other efforts to clear secretions have failed. It is an unpleasant procedure for the patient and can cause damage to the tracheal epithelium. Deleterious effects can be minimized by using an appropriate suction catheter and suction technique. Unless unavoidable, suctioning should not be performed on patients with stridor, severe bronchospasm, clotting disorders, pulmonary oedema, and recent pneumonectomy or oesophagectomy [18]. In theory, coughing stimulated by suctioning may promote propagation of mobile inflammatory biofluids from diseased zones into previously unaffected sectors of the lung [19].

References

1. Magnusson L and Spahn DR. (2003). New concepts of atelectasis during general anaesthesia. *British Journal of Anaesthesia*, **91**, 61–72.

2. Stangel P. (1989). Sputum retention. *Chest*, **95**, 939–40.
3. Fahy JV and Dickey BF. (2010). Airway mucus function and dysfunction. *New England Journal of Medicine*, **363**, 2233–47.
4. Knowles MR and Boucher RC. (2002). Mucus clearance as a primary innate defense mechanism for mammalian airways. *Journal of Clinical Investigations*, **109**, 571–7.
5. Salathe M. (2007). Regulation of mammalian ciliary beating. *Annual Reviews of Physiology*, **69**, 401–22.
6. Canning BJ. (2006). Anatomy and neurophysiology of the cough reflex: ACCP evidence-based clinical practice guidelines. *Chest*, **129**(Suppl.), 33S–47S.
7. Talab HF. (2009). Intraoperative ventilatory strategies for prevention of pulmonary atelectasis in obese patients undergoing laparoscopic bariatric surgery. *Anesthesia and Analgesia*, **109**(5), 1511–16.
8. Pelosi P and Gattinoni L. (1998). The effects of body mass on lung volumes, respiratory mechanics, and gas exchange during general anesthesia. *Anesthesia and Analgesia*, **87**, 654–60.
9. Branson RD. (2007). Secretion management in the mechanically ventilated patient. *Respiratory Care*, **52**(10), 1328–42.
10. Fernandez M. (2004). Changes in lung volume with three systems of endotracheal suction with and without pre-oxygenation in patients with mild-to-moderate lung failure. *Intensive Care Medicine*, **30**(12), 2210–15.
11. Hess D. (2001). The evidence for secretion clearance techniques. *Respiratory Care*, **46**(10), 1276–93.
12. Stiller K. (2000). Physiotherapy in intensive care: towards and evidence based practice. *Chest*, **118**(6), 1801–13.
13. Tusman G. (2012). Atelectasis and perioperative pulmonary complications in high-risk patients. *Current Opinions in Anaesthesiology*, **25**(1), 1–10. [Review.]
14. Volpe MS and Marini JJ. (2008). Ventilation patterns influence airway secretion movement *Respiratory Care*, **53**(10), 1287–94.
15. Branson RD. (2006). Humidification of respired gases during mechanical ventilation: mechanical considerations. *Respiratory Care Clinics of North America*, **12**(2), 253–61.
16. Restrepo RD and Walsh BK. (2012). Humidification during invasive and noninvasive mechanical ventilation: 2012. *Respiratory Care*, **57**(5), 782–8.
17. Pryor JA. (1999). Physiotherapy for airway clearance in adults. *European Respiratory Journal*, **14**(6), 1418–24.
18. Jaber S, Amraoui J, Lefrant JY, et al. (2006). Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Critical Care Medicine*, **34**(9), 2355–61.
19. Marini JJ and Gattinoni L. (2008). Propagation prevention: a complementary mechanism for 'lung protective' ventilation in ARDS. *Critical Care Medicine*, **36**(12), 3252–8.

CHAPTER 120

Lung recruitment techniques in the ICU

Thomas Kiss and Paolo Pelosi

Key points

- 'Recruitment manoeuvre' stands for a process of intentional transient increase of transpulmonary pressure above values used during regular mechanical ventilation, whose main objective is to open unstable distal airways and/or airless alveoli.
- The effectiveness of recruitment manoeuvres is probably related to the nature, phase, and/or extent of the lung injury, as well as the recruitment technique itself.
- Recruitment manoeuvres can be performed in several different ways. Today, the most relevant recruitment manoeuvres in terms of clinical applicability in the intensive care unit (ICU) are sustained inflation manoeuvres, high pressure-controlled ventilation, incremental PEEP, and intermittent sighs.
- Anaesthesiologists commonly perform bag squeezing as a recruitment manoeuvre, as it is simple to perform during surgery. This procedure closely resembles the sustained inflation technique.
- Ventilation with variable tidal volumes, may be a simple and interesting alternative for lung recruitment in the ICU, but clinical evidence has to be demonstrated yet.

Introduction

Protective mechanical ventilation (MV) represents one of the most important interventions in patients suffering from the acute respiratory distress syndrome (ARDS). Albeit MV is not curative, it is useful for reducing the work of breathing and maintaining an adequate gas exchange.

Lung recruitment manoeuvres (RMs) have been suggested as a means of homogenizing the lung structure and distribution of the mechanical stress across the lungs. Such effects of RMs can be achieved provided enough pressure is applied for sufficient time at the airways, and maintained if adequate levels of positive end expiratory pressure (PEEP) are used. When RMs effectively open atelectatic tissue, shear stress and cyclic collapse/reopening are reduced. Also, if an increased end-expiratory lung volume is achieved after RMs, the applied tidal volume (V_T) will be distributed across a larger lung surface, resulting in reduced regional dynamic stress and strain.

Results from clinical trials have suggested that RMs are useful to revert life-threatening hypoxaemia and derecruitment resulting from suctioning procedures of the airways, as well as disconnection from the mechanical ventilator. Nevertheless, no study has shown that RMs reduce mortality or the duration of mechanical ventilation in patients with ARDS. In contrast, there is increasing clinical evidence that low V_T in combination with RMs and adequate levels of PEEP are useful for reducing the incidence of post-operative pulmonary complications in patients undergoing open abdominal surgery. However, those beneficial effects cannot be ascribed solely to RMs themselves.

This chapter aims at:

- Defining RMs and describing host-dependent factors that may influence their performance.
- Describing established RMs and their functional and biological impact.
- Presenting experimental data on new promising forms of RMs that may become relevant in clinical practice.

Definition of recruitment manoeuvre

RM stands for a process of intentional transient increase of transpulmonary pressure (P_L) above values used during regular mechanical ventilation, whose main objective is to open unstable distal airways and/or airless alveoli. RM is also often termed *alveolar recruitment manoeuvre*, since opening of collapsed alveolar units is believed to represent the major effect of a RM. It must be kept in mind, however, that the existence of alveoli closure, and obviously also its potential reversal by RMs, in ARDS has been questioned. It has been shown in dogs with experimental ARDS induced by intravenous administration of oleic acid, that the alveoli of dependent zones were not collapsed, but rather filled with exudate. Whereas the end expiratory lung volume did not change after RMs and higher PEEP, the lung function improved importantly. Thus, it is possible that RMs exert part of their effects through redistribution of intra-alveolar fluid across lung units.

While non-supported spontaneous breathing, patient position, and higher levels of PEEP alone can increase the regional P_L and result in opening of lung units, they cannot be termed RMs in a strict sense.

Factors influencing the efficacy of recruitment manoeuvres

The lung response to RMs is determined mainly by host-dependent factors—cause and severity of lung injury and position of the lungs with respect to the gravity gradient.

Origin and severity of lung injury

ARDS is the result of different insults to the lungs. There are two major types of ARDS, namely primary (also known as

direct or pulmonary) and secondary (also known as indirect or extra-pulmonary) ARDS. The structure that is primarily damaged in pulmonary ARDS is the alveolar epithelium, and its typical hallmark is filling of the intra-alveolar space by oedema, fibrin, and neutrophilic aggregates. In extrapulmonary ARDS, distal organs release pro-inflammatory mediators into the bloodstream. Those mediators initiate the damage of the pulmonary capillary endothelium, leading to microvessel congestion and interstitial oedema with comparatively less flooding of intra-alveolar space.

There is a considerable body of evidence showing that the type of lung injury in ARDS importantly influences the performance of RMs. In an investigation on three models of ARDS in dogs, namely saline lung lavage (surfactant depletion), intravenous oleic acid administration and pneumonia, RMs were particularly effective in improving oxygenation and increasing the end-expiratory lung volume after surfactant depletion. In contrast, animals with pneumonia showed almost no improvement in lung function following RMs and high PEEP. Riva et al. compared the effects of a RM in models of pulmonary and extrapulmonary ARDS induced by intratracheal and intraperitoneal instillation of *Escherichia coli* lipopolysaccharide with similar transpulmonary pressures. They found that the RM was more effective for opening collapsed alveoli in extrapulmonary compared with pulmonary ARDS, improving lung mechanics and oxygenation with limited damage to alveolar epithelium. In contrast, Grasso et al. reported that RMs combined with high PEEP levels can lead to hyperinflation due to inhomogeneities in the lung parenchyma, independent from the origin of the injury insult (pulmonary or extrapulmonary).

In patients suffering from ARDS, Gattinoni and colleagues found that RMs are more efficient in severe, compared with non-severe ARDS. Using whole lung computed tomography, those authors showed that the reduction in non-aerated and poorly aerated lung tissue was more pronounced in those patients showing the most severe gas exchange and lung tissue abnormalities.

Positioning

Prone positioning may not only contribute to the success of RMs, but can be considered itself to be a RM. During prone position, the transpulmonary pressure in dorsal lung areas increases, opening alveoli and improving gas exchange. Some authors reported that in healthy, as well as lung-injured animals, mechanical ventilation leading to lung over distension and cyclic collapse/reopening is associated with less extensive histological change in dorsal regions when animals are in prone, as compared with supine position. It is still unclear if body position affects the distribution of lung injury, but the development of ventilator-induced lung injury (VILI) due to excessively high V_T seems to be delayed during prone compared with supine position.

In 2013, Guerin et al. demonstrated in a multicentre trial that the early application of prone-positioning sessions of at least 16 hours significantly decreased 90-day mortality in patients with severe ARDS.

Types of recruitment manoeuvre

Intensive care unit setting

RMs can be performed in several different ways. Today, the most relevant RMs in terms of clinical applicability are sustained inflation (SI) manoeuvres, high pressure-controlled ventilation, incremental PEEP, and intermittent sighs. However, the best way to perform RMs has not been established and, in fact, it may vary according to specific circumstances.

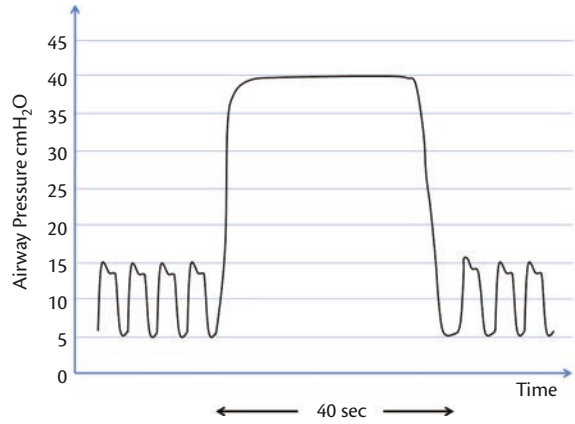


Fig. 120.1 Sustained inflation manoeuvre, with respiratory system plateau pressure of 40 cmH_2O for 40 seconds.

The SI is by far the most frequently used RM. Commonly, it is performed by application of a continuous pressure of ≈40 cmH_2O for up to 60 seconds at the airways [1], as illustrated in Fig. 120.1. The SI is effective in decreasing lung atelectasis, improving lung functional variables of oxygenation and respiratory mechanics, and also counteracting endotracheal suctioning-induced alveolar derecruitment [2]. However, the efficacy of SI has been questioned and other studies showed that SI may be ineffective [3], short-lived, associated with circulatory impairment [4], increased risk of baro-/volutrauma, reduced net alveolar fluid clearance, and even worsened oxygenation [5].

Due to those side effects, researchers developed other types of RMs, among which the most important are:

- Incrementally increased driving pressure at a fixed level of PEEP (Fig. 120.2) [6].

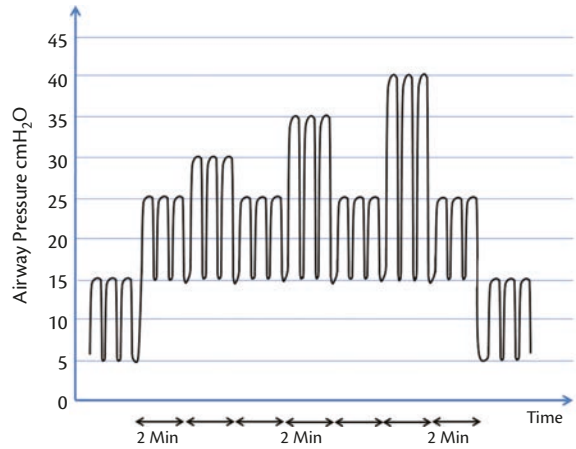


Fig. 120.2 Prolonged recruitment manoeuvre (PRM) consisting of progressively increase of driving pressure levels in 2-minute steps of 5 cmH_2O, with a fixed PEEP of 15 cmH_2O in pressure-controlled mode (frequency 10/min).
Adapted from *Respiratory Physiology and Neurobiology*, **169**(3), Rzezinski AF et al., 'Prolonged recruitment manoeuvre improves lung function with less ultrastructural damage in experimental mild acute lung injury', pp. 271–81, Copyright 2009, with permission from Elsevier.

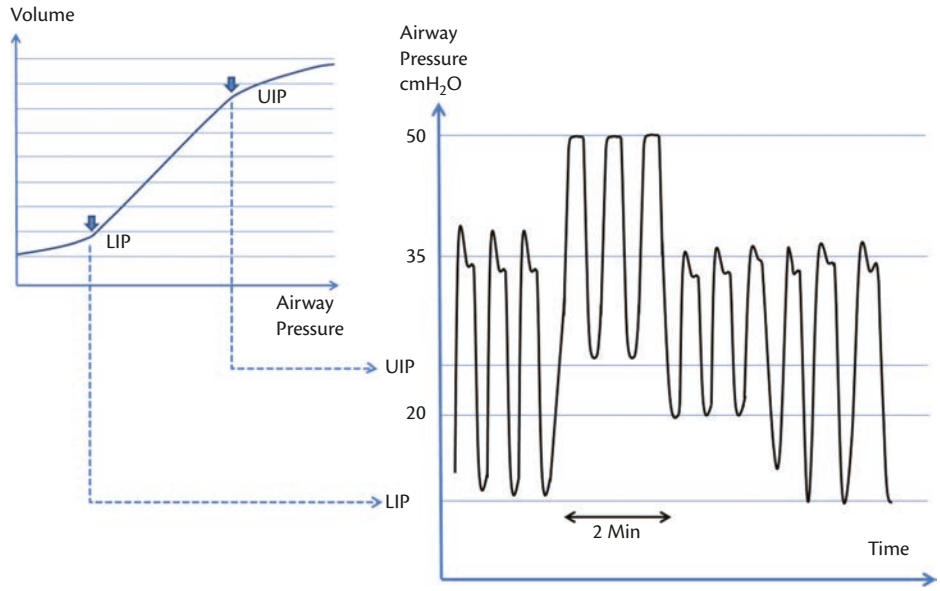


Fig. 120.3 Recruitment manoeuvre (RM) according to pressure-volume (P–V) curve of the respiratory system [3]. P–V curve, lower and upper inflection point (lower inflection point (LIP) and upper inflection point (UIP), respectively) are obtained at zero end-expiratory pressure. Patients are ventilated in volume control mode with tidal volume 8 mL/kg (predicted body weight) and positive end-expiratory pressure (PEEP) 3–4 cmH_2O higher than the LIP. This RM is performed in pressure control ventilation with a peak pressure of 50 cmH_2O and a PEEP level 3 cmH_2O higher than the UIP for 2 minutes. Peak pressure and PEEP are then gradually decreased to 35 and 20 cmH_2O, respectively. Following that, the ventilation mode is switched from pressure–volume controlled ventilation mode, and the PEEP is decreased in 2-cmH_2O steps until the PEEP level before RM is reached. After the RM, tidal volume and PEEP are equal to the values set before RM.

- PCV applied with PEEP above the upper inflection point of the pressure–volume curve of the respiratory system, followed by change to VCV with stepwise decrease of PEEP and inspiratory plateau pressure below the upper inflection point (Fig. 120.3) [3].
- Prolonged lower pressure recruitment manoeuvre with PEEP elevation up to 15 cmH_2O and end-inspiratory pauses for 7 seconds twice per minute over a 15-minute session (Fig. 120.4) [7].
- Intermittent sighs to reach a specific plateau pressure in volume or pressure control mode (Fig. 120.5) [8].
- Long slow increase in inspiratory pressure up to 40 cmH_2O (so-called 'RAMP' manoeuvre) (Fig. 120.6) [9].
- 'Maximum recruitment strategy' (MRS) according to Borges et al. [10], and adapted by Matos et al. (Fig. 120.7) [11].

Among those manoeuvres, the MRS is probably the one with the highest clinical impact. This manoeuvre was described in detail by Borges et al. [10], who treated 26 patients with sequential increments in PEEP at constant driving pressure until PaO_2 + $PaCO_2$ ≥ 400 mmHg. During the MRS, PEEP values of 45 cmH_2O and inspiratory peak pressures as high as 60 cmH_2O can be achieved. The major side effects of the MRS are transient haemodynamic depression and hypercapnia, major clinical consequences, e.g.

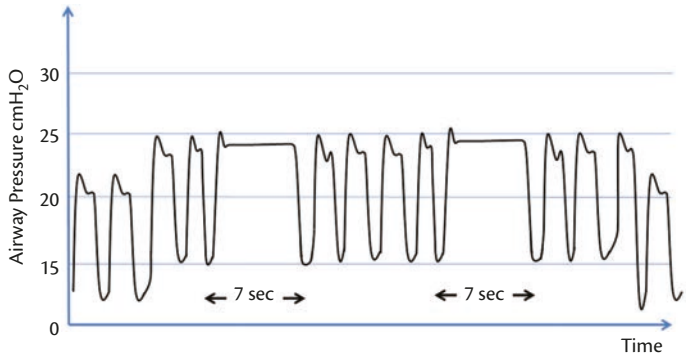


Fig. 120.4 Recruitment manoeuvre (RM) according to Odenstedt [7]. Basal ventilation (BV) during the recruitment protocol is delivered with volume controlled ventilation (tidal volume of 10 mL/kg, respiratory rate of 20/min, inspiratory to expiratory ratio (I:E) of 1:2 and inspiratory oxygen fraction of 0.5). The RM consists of PEEP increase to 15 cmH_2O, while maintaining the other ventilator settings, and end-inspiratory pauses of 7 seconds at a rate of 2/min, over a period of 15 minutes.

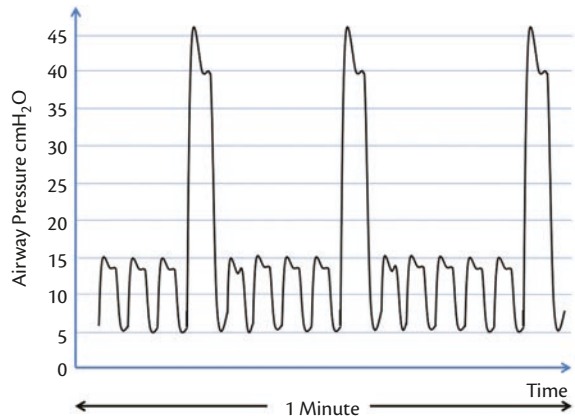


Fig. 120.5 Recruitment manoeuvres according to Steimback [8]. Baseline ventilation is delivered with volume controlled ventilation (tidal volume of 4 mL/kg, positive end-expiratory pressure of 5 cmH_2O). Sighs with inspiratory plateau pressure of 40 cmH_2O are delivered in the volume control mode, 3 times per minute.

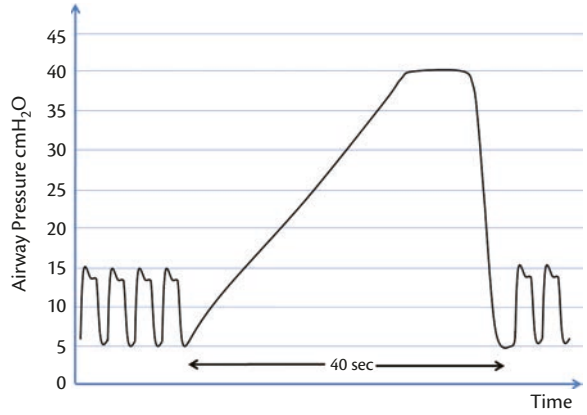


Fig. 120.6 Recruitment manoeuvre 'RAMP' consisting of slow and continuous increase of the airway pressure up to 40 cmH_2O, over a period of 40 seconds, according to Riva [9].
Data from Riva DR et al., 'Recruitment maneuver: RAMP versus CPAP pressure profile in a model of acute lung injury', *Respiratory Physiology and Neurobiology*, 2009, **169**(1), pp. 62–8.

pneumothorax, have not been observed. Recently, de Matos et al. [11] enhanced MRS by combining Borges' recruitment phase with a PEEP titration phase consisting of decremental PEEP steps from 25 to 10 cmH_2O. They concluded that MRS successfully recruited non-aerated lung areas for extended periods of time. These authors also did not observe barotrauma, nor significant clinical complications despite peak airway pressures of up to 60 cmH_2O during the MRS, mean titrated PEEP of 25 cmH_2O, and resulting inspiratory plateau pressures as high as 40 cmH_2O in the first day following the MRS.

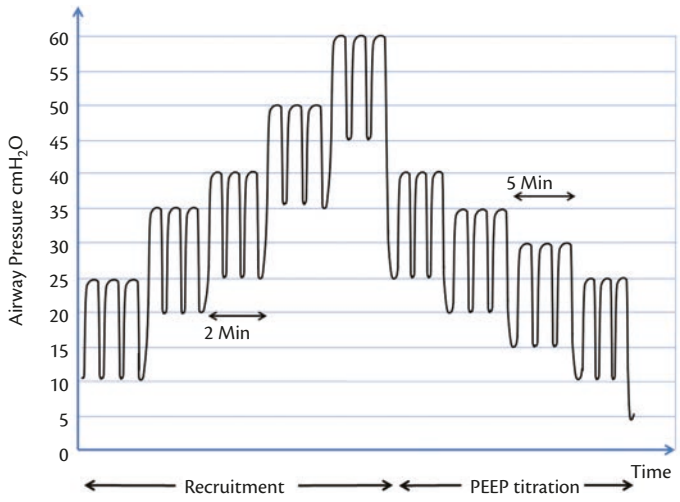


Fig. 120.7 Two-phase maximum recruitment strategy (MRS) according to Borges et al. [10] and modified from Matos et al. [11]). The first phase (recruitment phase) consists of 2-minute steps of tidal ventilation with pressure-controlled ventilation, fixed driving pressure of 15 cmH_2O, respiratory rate of 10–15/min, inspiratory: expiratory ratio of 1:1 and increments in PEEP levels of 5 cmH_2O up to 45 cmH_2O. During the second phase (PEEP titration phase), the PEEP is decreased to 25 cmH_2O and then in steps of 5 cmH_2O, whereby each step lasts 5 minutes.
Adapted from de Matos GF et al., 'How large is the lung recruitability in early acute respiratory distress syndrome: a prospective case series of patients monitored by computed tomography', Critical Care, 2012, 16, 1, p. R4. This material is reproduced under the Creative Commons Attribution Licence https://creativecommons.org/licenses/by/2.0/uk/. Data from Borges JB et al., 'Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome', *American Journal of Respiratory Critical Care ! Medicine*, 2006, 174, 3, pp. 268–278.

Operation room setting

There is a robust physiological rationale supporting the use of RMs for reversing lung collapse during general anaesthesia. Loss of lung aeration in dorsal lung zones is well documented in general anaesthesia, and invariably related to the development of atelectasis [12].

Anaesthesiologists more commonly perform RMs by squeezing the anaesthesia bag, in a procedure that closely resembles SI. Bag squeezing is relatively easy and simple to perform, but keeping the airway pressure, while fresh gas flows from the anaesthesia machine is tricky, even using pressure-release valves. Furthermore, when switching from manual to controlled ventilation the pressure in the anaesthesia circuit may drop to zero, leading to derecruitment. Certainly, SI can be applied by using continuous airway pressure (CPAP), but this mode is not present in most anaesthesia ventilators. Thus, during general anaesthesia, RMs are more easily conducted under tidal ventilation, mainly during volume controlled ventilation (VCV).

Fig. 120.8 illustrates two strategies for recruiting the lungs in the VCV mode. In the first variant, the PEEP is increased stepwise until the desired PEEP and inspiratory plateau pressure levels are achieved. Following that, the PEEP is reduced in steps of 2–5 cmH_2O to determine which PEEP value is associated with the lowest static elastance of the respiratory system (decremental PEEP trial). In the second variant, the PEEP is increased to 10–15 cmH_2O and maintained constant thereafter. The respiratory rate is reduced to 6–10/min, while V_T is increased stepwise by 2–4 mL/kg until an inspiratory plateau pressure of 30–40 cmH_2O is achieved. Finally, an adequate and protective V_T is set at the ventilator. This manoeuvre has been used successfully in a multicentre randomized clinical trial on the intra-operative use of PEEP [13]. Furthermore, using a similar RM and higher PEEP levels in patients undergoing open abdominal surgery, Severgnini et al. reported an improved lung function as long as 5 days after surgery, compared with a ventilation strategy without RMs and low PEEP.

Shall the anaesthesia ventilator not be able to provide higher PEEP values, the V_T or the driving pressure can be titrated to achieve the desired opening pressure target during a few breaths. The appropriate target must take into account the elastance of the chest wall, which will reduce the effective transpulmonary pressure. In patients with non-injured lungs and normal chest wall elastance, airway pressures of 40 cmH_2O are enough to recruit the lungs (14), but morbidly obese patients may require up to 60 cmH_2O (15).

Impact of recruitment manoeuvres on ventilator-induced lung injury

While much is known about the impact of RMs on lung mechanics and gas exchange, only a few studies addressed their effects on VILI. Steimback et al. [8] evaluated the effects of frequency and inspiratory plateau pressure (P_{plat}) during RMs on lung and distal organs in rats with acute lung injury (ALI) induced by paraquat. They observed that, although a RM with standard sigh (180 sighs/hour and P_{plat} = 40 cmH_2O) improved oxygenation, and decreased $PaCO_2$, lung elastance, as well as alveolar collapse, it resulted in hyperinflation, ultrastructural changes in alveolar capillary membrane, and increased lung and kidney epithelial cell apoptosis.

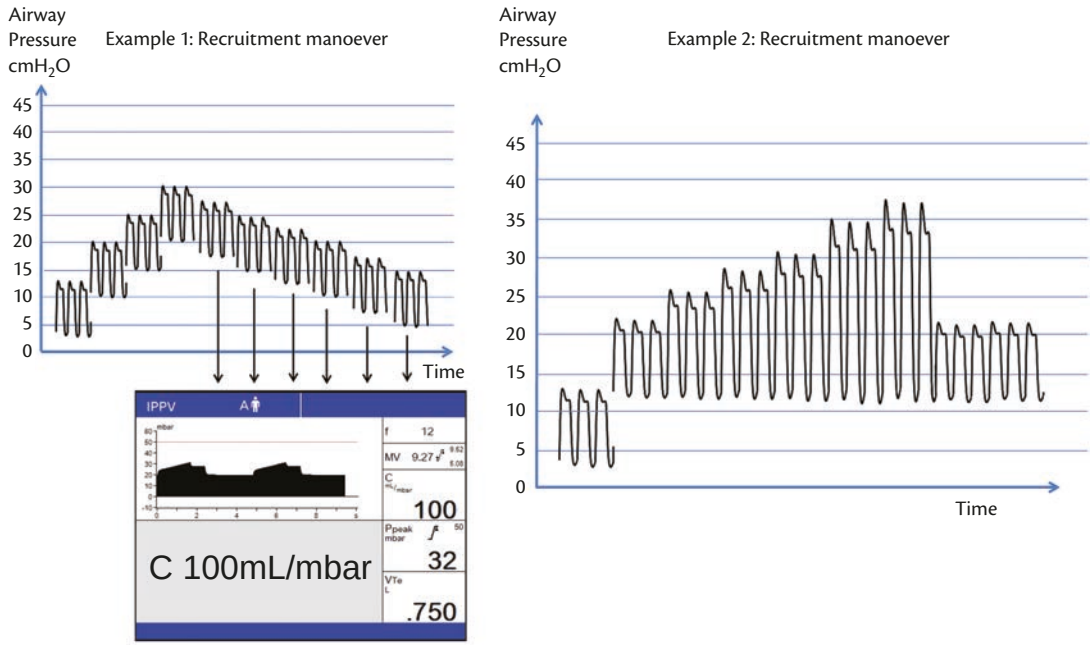


Fig. 120.8 Recruitment manoeuvres that can be performed with the anaesthesia ventilator. The manoeuvres are performed under volume controlled ventilation and FiO_2 of 1.0. The tidal volume is set at 10 mL/kg and the inspiratory to expiratory ratio (I:E) ratio at 1:1. In the first variant (left panel) the positive end-expiratory pressure (PEEP) is increased by 5 cmH_2O every 3–5 breaths, up to 20 cmH_2O. Following that, the PEEP is decreased in steps of 2–3 cmH_2O and the respiratory system compliance is measured at each step (decremental PEEP trial). The lungs are re-expanded in the same way and the PEEP of highest respiratory system compliance set at the ventilator. In the second variant (right panel), the PEEP is increased to 10–15 cmH_2O and maintained constant. The tidal volume is increased in steps of 2–4 mL/kg until an inspiratory plateau pressure of 30–40 cmH_2O is achieved. Finally, the tidal volume is set again at the initial value.
Data from Hemmes SN et al., 'Rationale and study design of PROVHILO - a worldwide multicenter randomized controlled trial on protective ventilation during general anesthesia for open abdominal surgery', *Trials*, 2011, 12, p. 111.

On the other hand, the reduction of the sigh frequency from 180 to 10 sighs/hour at the same P_{plat} (40 cmH_2O) diminished lung elastance and improved oxygenation, with a marked decrease in alveolar hyperinflation, and apoptosis in lung and kidney epithelial cells. The association of this sigh frequency with a lower P_{plat} of 20 cmH_2O worsened lung elastance, histology and oxygenation and increased $PaCO_2$. We speculate that there is a sigh frequency threshold beyond which the intrinsic reparative properties of the lung epithelium are overwhelmed. Although the optimal sigh frequency may be different in healthy and ALI animals/patients, our results suggest that RMs with high frequency or low plateau pressure should be avoided. Theoretically, a RM using gradual inflation of the lungs might yield a more homogeneous distribution of pressure throughout the lung parenchyma, avoiding repeated manoeuvres and reducing lung stretch while allowing effective gas exchange.

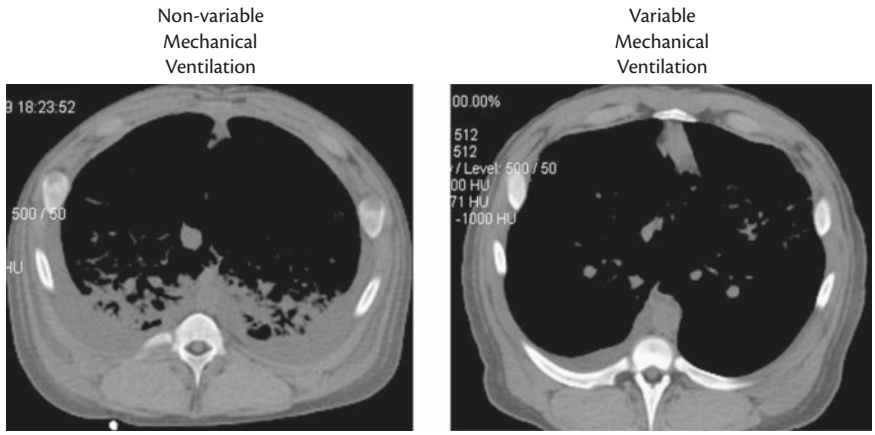


Fig. 120.9 Computed tomography scans of two pigs with lung injury induced by saline lung lavage and higher tidal volumes. Left: after approximately 7 hours of protective non-variable mechanical ventilation according to the ARDS Network protocol. Right: after approximately 7 hours of protective variable mechanical ventilation with higher levels of PEEP. Note that the animal treated with non-variable mechanical ventilation presented large areas of non-aeration in dependent dorsal zones, whereas the animal treated with variable mechanical ventilation did not, suggesting full and stable lung recruitment through variable tidal volumes combined with higher PEEP.
Courtesy of João B. Borges, Göran Hedenstierna and Marcelo Gama de Abreu, Hedenstierna Lab, University of Uppsala, Sweden.

Riva et al. [9] compared the effects of SI using rapid high recruitment pressure at 40 cmH_2O for 40 s with the so-called RAMP manoeuvre, a slow increase in airway pressure up to 40 cmH_2O during 40 seconds in paraquat-induced ALI. They reported that the RAMP manoeuvre improved lung mechanics with less alveolar stress. Among other RMs proposed as alternatives to SI, RAMP may differ according to the time of application and mean airway pressure.

Variable mechanical ventilation as recruitment manoeuvre

Variable mechanical ventilation is characterized by breath-by-breath changes in airway pressures and V_T. Variable mechanical ventilation has been shown to improve oxygenation, respiratory mechanics, and reduce diffuse alveolar damage in experimental models of ARDS [16]. Among the possible mechanisms of variable mechanical ventilation, lung recruitment is likely the most important one.

The use of variable V_T during volume controlled ventilation significantly improved lung function in experimental models of atelectasis [17]. In patients during surgery for repair of abdominal aorta aneurysms, variable mechanical ventilation improved arterial oxygenation and compliance of the respiratory system, as compared with non-variable mechanical ventilation [18].

Experimental evidence suggests that variable mechanical ventilation is superior to conventional RMs regarding the efficiency of opening and keeping lung units open. Variable ventilation improved recruitment in both normal and injured lungs in mice [19]. Fig. 120.9 illustrates the effects of variable mechanical ventilation on lung aeration in a model of experimental ARDS.

Despite the large evidence regarding the potential of variable ventilation to promote lung recruitment, this mechanism is less probable during assisted ventilation. In experimental ALI, it has been shown that variable pressure support ventilation improved oxygenation [20], but this effect was mainly related to lower mean airway pressures and redistribution of pulmonary blood flow towards better ventilated lung zones.

Conclusion

The use of RMs in patients suffering from ARDS, as well as in patients undergoing surgery under general anaesthesia, remains controversial. The effectiveness of such manoeuvres is likely related to the nature, phase, and/or extent of the lung injury, as well as the recruitment technique itself. The SI represents the most commonly used RM, but it may lead to a paradoxical impairment of oxygenation due to redistribution of pulmonary blood flow and also to circulatory depression. With the purpose of reducing such side-effects, several RMs have been suggested. In order to be effective, RMs must take different aspects into account, namely the level of the recruiting pressure, the time, as well as the pattern/frequency with which this pressure is applied to achieve recruitment. Besides the SI, a couple of RMs that seem particularly interesting for use in clinical practice on the ICU are:

- Incrementally increased driving pressure at a fixed level of PEEP.
- PCV applied with PEEP above the upper inflection point of the pressure-volume curve of the respiratory system, followed by change to VCV with stepwise decrease of PEEP and inspiratory plateau pressure below the upper inflection point.
- Prolonged lower pressure recruitment manoeuvre with PEEP elevation up to 15 cmH_2O and end-inspiratory pauses for 7 seconds twice per minute during a 15-minute period.
- Intermittent sighs to reach a specific plateau pressure in volume or pressure control mode.
- Long slow increase in inspiratory pressure up to 40 cmH_2O.
- 'Maximum recruitment strategy'.

In the operation room, the RM that can be performed with all anaesthesia ventilators consists of a PEEP increase to 10–15 cmH_2O, a reduction of the respiratory rate to 6–10/min, and a stepwise increase of V_T by 2–4 mL/kg until an inspiratory plateau pressure of 30–40 cmH_2O is achieved. The use of variable ventilation, i.e. application of random variable tidal volumes, may also prove a simple and interesting alternative for lung recruitment in the clinical scenario, mainly on the ICU. Clinical evidence suggests that the use of RMs is useful as a rescue strategy for hypoxaemia, but studies on the impact of RMs on morbidity and mortality in intensive care, as well as surgical patients are warranted.

Acknowledgements

We thank Marcelo Gama de Abreu (Department of Anesthesiology and Intensive Care Therapy, University Hospital Carl Gustav Carus, Dresden, Germany) who helped draft the manuscript.

References

1. Fan E, Wilcox ME, Brower RG, et al. (2008). Recruitment maneuvers for acute lung injury: a systematic review. *American Journal of Respiratory and Critical Care Medicine*, **178**(11), 1156–63.
2. Maggiore SM, Lellouche F, Pigeot J, et al. Prevention of endotracheal suctioning-induced alveolar derecruitment in acute lung injury. *American Journal of Respiratory and Critical Care Medicine*, **167**(9), 1215–24.
3. Villagra A, Ochagavia A, Vatua S, et al. (2002). Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **165**(2), 165–70.
4. Odenstedt H, Aneman A, Karason S, Stenqvist O, and Lundin S. (2005). Acute hemodynamic changes during lung recruitment in lavage and endotoxin-induced ALI. *Intensive Care Medicine*, **31**(1), 112–20.
5. Musch G, Harris RS, Vidal Melo MF, et al. (2004). Mechanism by which a sustained inflation can worsen oxygenation in acute lung injury. *Anesthesiology*, **100**(2), 323–30.
6. Rzezinski AF, Oliveira GP, Santiago VR, et al. (2009). Prolonged recruitment manoeuvre improves lung function with less ultrastructural damage in experimental mild acute lung injury. *Respiratory Physiology & Neurobiology*, **169**(3), 271–81.
7. Odenstedt H, Lindgren S, Olegard C, et al. (2005). Slow moderate pressure recruitment maneuver minimizes negative circulatory and lung mechanic side effects: evaluation of recruitment maneuvers using electric impedance tomography. *Intensive Care Medicine*, **31**(12), 1706–14.
8. Steimback PW, Oliveira GP, Rzezinski AF, et al. (2009). Effects of frequency and inspiratory plateau pressure during recruitment manoeuvres on lung and distal organs in acute lung injury. *Intensive Care Medicine*, **35**(6), 1120–8.
9. Riva DR, Contador RS, Baez-Garcia CS, et al. (2009). Recruitment maneuver: RAMP versus CPAP pressure profile in a model of acute lung injury. *Respiratory Physiology & Neurobiology*, **169**(1), 62–8.
10. Borges JB, Okamoto VN, Matos GF, et al. (2006). Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **174**(3), 268–78.

11. de Matos GF, Stanzani F, Passos RH, et al. (2012). How large is the lung recruitability in early acute respiratory distress syndrome: a prospective case series of patients monitored by computed tomography. *Critical Care*, **16**(1), R4.
12. Rothen HU, Sporre B, Engberg G, Wegenius G, and Hedenstierna G. (1993). Re-expansion of atelectasis during general anaesthesia: a computed tomography study. *British Journal of Anaesthesia*, **71**(6), 788–95.
13. Hemmes SN, Severgnini P, Jaber S, et al. (2011). Rationale and study design of PROVHILO—a worldwide multicenter randomized controlled trial on protective ventilation during general anesthesia for open abdominal surgery. *Trials*, **12**, 111.
14. Tusman G, Bohm SH, Vazquez de Anda GF, do Campo JL, and Lachmann B. (1999). 'Alveolar recruitment strategy' improves arterial oxygenation during general anaesthesia. *British Journal of Anaesthesia*, **82**(1), 8–13.
15. Reinius H, Jonsson L, Gustafsson S, et al. (2009). Prevention of atelectasis in morbidly obese patients during general anesthesia and paralysis: a computerized tomography study. *Anesthesiology*, **111**(5), 979–87.
16. Spieth PM, Carvalho AR, Pelosi P, et al. (2009). Variable tidal volumes improve lung protective ventilation strategies in experimental lung injury. *American Journal of Respiratory and Critical Care Medicine*, **179**(8), 684–93.
17. Mutch WA, Harms S, Ruth Graham M, Kowalski SE, Girling LG, and Lefevre GR. (2000). Biologically variable or naturally noisy mechanical ventilation recruits atelectatic lung. *American Journal of Respiratory and Critical Care Medicine*, **162**(1), 319–23.
18. Boker A, Haberman CJ, Girling L, et al. (2004). Variable ventilation improves perioperative lung function in patients undergoing abdominal aortic aneurysmectomy. *Anesthesiology*, **100**(3), 608–16.
19. Thammanomai A, Hueser LE, Majumdar A, Bartolak-Suki E, and Suki B. (2008). Design of a new variable-ventilation method optimized for lung recruitment in mice. *Journal of Applied Physiology*, **104**(5), 1329–40.
20. Gama de Abreu M, Spieth PM, Pelosi P, et al. (2008). Noisy pressure support ventilation: a pilot study on a new assisted ventilation mode in experimental lung injury. *Critical Care Medicine*, **36**(3), 818–27.

CHAPTER 121

Chest physiotherapy and tracheobronchial suction in the ICU

Gianluigi Li Bassi and J. D. Marti

Key points

- Ventilated patients often retain respiratory secretions because of hypersecretion, impaired clearance, and immobilization.
- Several clinical studies that evaluated the role of chest physiotherapy in the intensive care unit have been limited by inappropriate outcomes, accurate definitions of complications, and diversity in the applied methods. Thus, well-designed clinical studies are warranted to substantiate benefits associated with routine use of chest physiotherapy techniques.
- Posture change, chest percussion, incentive spirometry, and manual hyperinflation are the most common techniques applied in the intensive care unit to improve mucus clearance and prevent pulmonary complications.
- In intubated or tracheostomized patients, endotracheal suctioning is essential to remove accumulated mucus within the large airways.
- Endotracheal suctioning should be performed by qualified personnel with extensive training in recognizing indications, properly perform the procedure, and promptly respond to any potential complication.

Introduction

In mechanically-ventilated patients, chest physiotherapy and tracheobronchial suction are essential procedures to maintain airway patency and prevent pulmonary complications. Patients on invasive mechanical ventilation commonly present retention of airway secretions, which constitutes a daily challenge for respiratory therapists, nurses, and physicians.

Mucus clearance

The airway lining fluid is a biphasic layer, with antimicrobial and immunomodulatory properties, formed by a gel-phase (mucus), and a low-viscosity inner layer (sol-phase), which mainly provides lubrication for ciliary beating. Mucus production in healthy subjects is approximately 10–100 mL/day.

Mucociliary clearance

Mucociliary clearance is a primary defence mechanisms of the respiratory system [1]. Each ciliated cell has approximately 200 cilia on its surface, which move within the periciliary liquid layer at 8–15 Hz. Mucus overlying the periciliary fluid is transported by the outermost parts of the cilia [2]. Mucociliary clearance rates range between 4 and 20 mm/min.

Mucus clearance via two-phase gas–liquid mechanism

During mechanical ventilation, inspiratory and expiratory airflows interact with mucus. As a result, mucus is propelled in the direction of the highest airflow via the two-phase gas–liquid flow mechanism [3,4]. The majority of chest physiotherapy techniques rely on this mechanism to clear mucus. The critical factors necessary to move mucus through airflows are:

- The shear stress exerted by the airflow on the liquid layer.
- The ratio between thickness of the mucus layer and the airway diameter.
- The rheological properties of secretions.
- Gravity [3,4].

Inspiratory and expiratory airflows exert opposite shear forces on the mucus layer [5]. The difference between inspiratory and expiratory flow rate can be modulated by adjusting ventilator parameters that affect the inspiratory flow, i.e. duty cycle [6,7]. Additionally, in patients, positioned in the semirecumbent position, mucus transport mainly depends on a balance between the airflow shear forces on the liquid layer and gravitational force.

Mucus clearance in critically-ill patients

Mucus retention is highly prevalent in mechanically ventilated patients because mucociliary velocity is drastically reduced [8], and the inflated endotracheal tube cuff averts mucus clearance. Therefore, mucus accrues [7], unless it is aspirated through suctioning. Contributing factors to mucus retention are hypersecretion of mucus, immobilization, weak cough, and muscle weakness.

Chest physiotherapy

Several chest physiotherapy techniques are routinely applied in critically-ill patients [9] (Table 121.1). The role of chest physiotherapy in the intensive care unit (ICU) to mobilize secretions and improve patient's outcomes lacks of compelling evidence [10,11]. Additionally, bedside techniques to routinely monitor mucus

Table 121.1 Indications for different physiotherapy regimes

	Specific indications	Absolute contraindications	Relative contraindications	Scientific evidence to support the routine use in ICU*	Frequency of treatment	Duration of treatment
Posture change	Deep sedation Neuromuscular disease Pharmacological paralysis	Unstabilized spine Fractures	Rib fractures Spine fractures	Sufficient	Every 1–2 hours	NA
Postural drainage	Lung atelectasis Unilateral lung injury	Increased intracranial pressure Unstabilized spine Fractures	Spine fractures Haemodynamic instability Respiratory instability Obesity	Insufficient	Every 4–6 hours	30 minutes to 12 hours
Percussion	Lung atelectasis Presence of thick mucus Deep sedation Neuromuscular disease Pharmacological paralysis	Bone diseases associated with extremely fragile bones	Bronchospasm (consider bronchodilators before and following the intervention) Rib fractures Subcutaneous emphysema Recent thoracic surgery Coagulopathy or thrombocytopenia	Insufficient	Every 4–6 hours	15–30 minutes
Assisted high-frequency airway clearance techniques	Cystic fibrosis Chronic obstructive pulmonary disease Bronchiectasis	NA	Bronchospasm Rib fractures Subcutaneous emphysema Recent thoracic surgery	Insufficient	Every 6 hours	20–30 minutes
Forced expiratory technique	Neuromuscular disease Slight sedation	Untreated pneumothorax	Recent abdominal surgery Recent thoracic surgery Deep sedation Increased intracranial pressure Active tuberculosis Pneumothorax Bullous emphysema Coagulopathy or thrombocytopenia	Insufficient	Every 2–4 h	5–10 minutes
Cough-assist device	Neuromuscular disease	Untreated pneumothorax	Pneumothorax Bullous emphysema. Recent thoracic surgery Increased intracranial pressure Coagulopathy or thrombocytopenia	Insufficient	Every 6 h	10 minutes
Incentive spirometry	Abdominal surgery Thoracic surgery Conscious patient	NA	Uncooperative patient Vital capacity less than 10 ml/kg	Insufficient	10 times every h	1 breath
Manual hyperinflation	Lung atelectasis Deep sedation Excessive mucus production Inefficient cough	Untreated pneumothorax	Haemodynamic instability Pneumothorax Bullous emphysema. Increased intracranial pressure	Insufficient	Every 6 hours	2–4 minutes
Manual ribcage compression	Lung atelectasis Inefficient cough	NA	Haemodynamic instability Pneumothorax Bullous emphysema. Increased intracranial pressure	Insufficient	Every 6 hours	15 minutes

*Although there is insufficient evidence to support routine clinical use of chest physiotherapy techniques in the intensive care unit, it is pivotal to identify patients at greater risk of pulmonary complications and to prescribe treatments on an individual basis.

ICU, intensive care unit; NA, not available.

clearance are not available. Thus, surrogate end points have been used in research, all of which increase the odds for negative studies and produce controversy in the field. Only qualified personnel with appropriate training should perform chest physiotherapy. Appropriate analgesia is essential throughout the interventions in order to ensure patient's comfort and efficacy of the intervention.

Posture change and postural mucus drainage

The deleterious effects of prolonged immobility have been extensively studied [12]. As a general rule, in ICU patients, changes in posture should be performed every 1 or 2 hours.

Postural mucus drainage therapy consists of placing atelectatic pulmonary segments in a position that allows drainage of mucus through gravity and redistribution of pulmonary ventilation. Postural drainage can be associated with other physiotherapy techniques to enhance benefits. The therapeutic indications must be carefully reviewed, due to the associated potential complications [13].

Percussion and high-frequency airway clearance techniques

Chest percussion and high-frequency airway clearance techniques cause a change in airways diameter and airflow, ultimately resulting in mobilization of secretions adherent to the bronchial walls. Preventive or curative percussion can be applied in intubated or tracheostomized patients [14]. Assisted high-frequency airway clearance techniques, through external devices such as the Percussionaire®, the Vest Airway Clearance System®, and the Hayek Oscillator System®, develop small airflow pulses that alter the rheological properties of mucus and enhance the expiratory-inspiratory flow bias [15]. Following extubation, their use can be indicated on a case-by-case basis in patients who regularly use these devices in out-of-hospital settings.

Directed cough and cough-assist devices

In patients with neuromuscular weakness, who present paradoxical abdominal outward motion during coughing, it is beneficial to compress the lower thorax and upper abdomen to improve peak cough expiratory airflow. Forced expiratory technique (FET), also called 'huffing', is indicated for patients, who present with compliant central airways that collapse during cough. FET consists of coughing efforts with an open glottis at mid- to low lung volume followed by ample ventilation. Huffing can also be applied in tracheally-intubated patients, exerting manual pressure to the thorax and epigastric zone during exhalation.

The mechanical insufflation–exsufflation is a technique applied through the CoughAssist In-Exsufflator (Respironics, Murrysville, Pennsylvania) to simulate cough. The device delivers a pressure-targeted lung insufflation. This is immediately followed by a forced exsufflation, applying negative pressure.

Incentive spirometry

Incentive spirometry (IS) is the most widely applied physiotherapy technique in surgical patients at risk of developing lung atelectasis. The evidence supporting its use is limited by heterogeneous techniques, inconsistent definitions of outcomes, and poor-quality trials. Thus, IS should be used within a well-organized post-surgical physiotherapy programme to accelerate lung recovery and avoid post-operative complications. The technique is best taught prior to surgery. Several volume- or flow-orientated IS are available, aimed at achieving a 1.5 L maximal inspiratory volume and 600–900 mL/sec inspiratory flow. Studies have shown that volume-orientated devices require less inspiratory efforts, generate greater diaphragmatic motion and higher tidal volumes [16]. Cough is essential to mobilize secretions following IS.

Manual hyperinflation

The goals of MH are mobilization of retained secretions, recruitment of atelectatic lung regions and improvement of gas exchange. MH is performed by disconnecting the patient from the ventilator and slowly insufflating a large tidal volume (up to 50% above baseline or up to 40 cmH_2O of inspiratory pressure), via a resuscitator bag. After an inspiratory hold, the circuitry pressure is quickly released in order to assure a high expiratory flow rate. The Mapleson-C circuit generates faster expiratory flow and improved mucus retrieval than do circuits with self-inflating bags [17]. During the procedure, in-line manometers should be used to avoid injurious airway pressures.

Manual rib-cage compression

Manual rib-cage compression (MRCC) technique consists of gentle compression of the rib cage during the expiratory phase and release from the compression at the end of the expiration.

Tracheobronchial suctioning

Box 121.1 details tracheobronchial suctioning indications and methods.

Box 121.1 Tracheobronchial suction

Potential indicators for endotracheal suctioning

- Visible secretions within the artificial airway.
- Dyspnoea or apparent increased work of breathing.
- Pathological sounds (i.e. rhonchi, coarse and gurgling) heard *via* a stethoscope over the trachea.
- Progressive pulse oxymetry desaturation not otherwise explained.
- Increased peak inspiratory pressure in volume controlled MV or decreased V_T in pressure-controlled MV.
- Saw-tooth pattern identified at the real-time flow-volume loop.

Preparation prior endotracheal suctioning

Patient preparation

- In patient on MV, heart rate, pulse oximetry, arterial pressure, and in specific cases, intracranial pressure, should be monitored throughout the procedure.
- If patient is conscious explain the procedure.
- The use of saline to hydrate inspissated secretions and centralize secretions through cough lacks of clear evidence. If secretions appear dehydrated check if humidification of inspired gases is appropriate
- Hyperoxygenate for 120 seconds using in adults FiO_2 of 100 and a 10% increase from baseline in infants. Of note, several ventilators now provide a single working control for suction support.

Operator preparation

- Wash hands.
- Wear disposable apron and protector visor, particularly during open suctioning.
- Wear a sterile glove on the hand manipulating the catheter and a non-sterile glove on the other hand.
- During open suctioning, retrieve the catheter from the sleeve and hold it. In particular, avoid manipulation of the distal catheter tip.
- Connect the catheter to suction tubing.
- During closed or quasi-closed suctioning, the ventilator should be allowed to trigger to provide gas in response to negative pressure.

Equipment

- Consider closed suctioning system (or swivel connector) in patients with severe respiratory disease requiring high level of PEEP and FIO_2.
- Ratio of catheter outer diameter/artificial airway internal diameter should be ≤0.7 in adults and ≤0.5 in children.
- Suction catheter diameter (Fr) = (Artificial airway internal diameter x 3)/2.
- Choose catheters with non-parallel lateral suction holes. In selected cases, a curved tipped catheter may be helpful to suction mucus within bronchi difficult to access.
- Prepare suction tubing.
- The level of vacuum should always be adjusted to the lowest level of vacuum that efficiently removes secretions. In general, vacuum ≤150 mmHg in adults and 80–100 mmHg in infants.

Procedure

- Insert the catheter into the artificial airway and advance its distal tip up to the proximal trachea.
- Intermittent suction should be applied through occlusion of the catheter suction control port.
- Withdraw suction catheter continuously rotating it.
- The procedure should last 15 seconds or less from catheter insertion.
- Check and appropriately treat any potential cardiovascular, pulmonary, and neurological complication throughout the procedure.

Follow-up

- Assess respiratory cardiovascular and neurologic parameters.
- Consider hyperoxygenation.
- Consider recruitment manoeuvre in selected patients with acute respiratory distress syndrome and acute lung injury.
- Rinse suction tubing and, in case of closed suctioning system, suction catheter.
- Dispose of the suction catheter apron and gloves into the proper containers.

Patient preparation

Adequate patient preparation is necessary to avoid complications. Patients commonly remember endotracheal suctioning as one of the most uncomfortable procedures throughout their stay in the ICU; thus, if the patient is conscious, the procedure should be overly explained. Additionally, suctioning should not be performed routinely to minimize the risk of unnecessary complications [18].

Material

Catheter

A larger catheter increases endotracheal tube resistance and facilitates loss of lung volume, because aspirated gas is not rapidly replaced by gas flowing through the endotracheal tube. In patients with thick secretions, catheters with larger and non-parallel side holes should be applied [19].

Closed versus open suctioning

Endotracheal suctioning can be performed either by disconnecting the patient from the ventilator (open suctioning) or through the use of a catheter in-line with the ventilatory circuit (closed suctioning). During closed suctioning, triggered ventilator autocycling should compensate for the loss of pressure. Studies suggest that closed suctioning is beneficial in patients with most severe lung failure [20]. A quasi–closed suctioning system, via a swivel adapter is a potential alternative.

Sterile water

The use of saline, instilled into the endotracheal tube before suctioning remains controversial. The main concern is that saline instillation, may drip into the lungs and cause adverse effects.

References

1. Knowles MR and Boucher RC. (2002). Mucus clearance as a primary innate defense mechanism for mammalian airways. *Journal of Clinical Investigations*, **109**, 571–7.
2. Matsui H, Randell SH, Peretti SW, et al. (1998). Coordinated clearance of periciliary liquid and mucus from airway surfaces. *Journal of Clinical Investigations*, **102**(6), 1125–31.
3. Kim CS, Rodriguez CR, Eldridge MA, et al. (1986). Criteria for mucus transport in the airways by two-phase gas-liquid flow mechanism. *Journal of Applied Physiology*, **60**, 901–7.
4. Kim CS, Greene MA, Sankaran S, et al. (1986). Mucus transport in the airways by two-phase gas-liquid flow mechanism: continuous flow model. *Journal of Applied Physiology*, **60**, 908–17.
5. Kim CS, Iglesias AJ, and Sackner MA (1987). Mucus clearance by two-phase gas-liquid flow mechanism: asymmetric periodic flow model. *Journal of Applied Physiology*, **62**, 959–71.
6. Benjamin R, Chapman G, Kim C, et al. (1989). Removal of bronchial secretions by two-phase gas-liquid transport *Chest*, **95**, 658–63.
7. Li Bassi G, Zanella A, Cressoni M, et al. (2008). Following tracheal intubation, mucus flow is reversed in the semirecumbent position: possible role in the pathogenesis of ventilator-associated pneumonia. *Critical Care Medicine*, **36**, 518–25.
8. Konrad F, Schreiber T, Brecht-Kraus D, et al. (1994). Mucociliary transport in ICU patients. *Chest*, **105**, 237–41.
9. Gosselink R, Bott J, Johnson M, et al. (2008). Physiotherapy for adult patients with critical illness: recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. *Intensive Care Medicine*, **34**, 1188–99.
10. Branson RD (2007). Secretion management in the mechanically ventilated patient. *Respiratory Care*, **52**, 1328–42; discussion 1342–7.

11. Stiller K. (2013). Physiotherapy in intensive care: an updated systematic review. *Chest*, **144**, 825–47.
12. Convertino VA, Bloomfield SA, and Greenleaf JE. (1997). An overview of the issues: physiological effects of bed rest and restricted physical activity. *Medicine & Science in Sports & Exercise*, **29**, 187–90.
13. Hammon WE, Connors AF, and McCaffree DR. (1992). Cardiac arrhythmias during postural drainage and chest percussion of critically ill patients. *Chest*, **102**, 1836–41.
14. Ciesla ND. (1996). Chest physical therapy for patients in the intensive care unit. *Physical Therapy*, **76**, 609–25.
15. Chatburn RL (2007). High-frequency assisted airway clearance. *Respiratory Care*, **52**, 1224–35; discussion 1235–7.
16. Yamaguti WP, Sakamoto ET, Panazzolo D, et al. (2010). Diaphragmatic mobility in healthy subjects during incentive spirometry with a flow-oriented device and with a volume-oriented device. *Jornal Brasileiro de Pneumologia*, **36**, 738–45.
17. Hodgson C, Ntoumenopoulos G, Dawson H, et al. (2007). The Mapleson C circuit clears more secretions than the Laerdal circuit during manual hyperinflation in mechanically-ventilated patients: a randomised cross-over trial. *Australian Journal of Physiotherapy*, **53**, 33–8.
18. American Association for Respiratory Care. (2010). Clinical practice guidelines. Endotracheal suctioning of mechanically ventilated patients with artificial airways 2010. *Respiratory Care*, **55**, 758–64.
19. Shah S, Fung K, Brim S, et al. (2005). An in vitro evaluation of the effectiveness of endotracheal suction catheters. *Chest*, **128**, 3699–704.
20. Cereda M, Villa F, Colombo E, et al. (2001). Closed system endotracheal suctioning maintains lung volume during volume-controlled mechanical ventilation. *Intensive Care Medicine*, **27**, 648–54.

CHAPTER 122

Toilet bronchoscopy in the ICU

Gianluigi Li Bassi and Carles Agusti

Key points

- Toilet bronchoscopy should only be applied when other less invasive methods of secretion removal have failed to dislodge retained mucus and revert to pulmonary atelectasis.
- Toilet bronchoscopy is highly efficient when retained secretions are visible during the procedure, air-bronchograms are not present on the chest radiograph, and when indicated to reverse lobar atelectasis.
- Potential complications associated with toilet bronchoscopy comprise hypoxaemia, cardiac dysrhythmia, haemodynamic instability and pulmonary haemorrhage.
- Overall safety of the intervention is drastically enhanced through proper setting of the mechanical ventilator, adequate sedation and analgesia, and exhaustive monitoring of physiological parameters.
- Specific patient populations on non-invasive mechanical ventilation can also benefit from a bronchoscopic approach to clear retained secretions.

Introduction

Retention of respiratory secretions is common in critically-ill patients [1], and it may interfere with ventilation, impair gas exchange, predispose to respiratory infections, and lead to the development of lung atelectasis. Toilet bronchoscopy is a potentially therapeutic intervention to aspirate retained secretions within the endotracheal tube and airways and revert atelectasis. Aspiration of airway secretions is the most common indication to perform a therapeutic bronchoscopy in the intensive care unit (ICU) [2].

Toilet bronchoscopy efficacy

The reported efficacy of toilet bronchoscopy in removing retained secretions and reversing atelectasis ranges between 19 and 89%, according to the studied ICU population [3]. Toilet bronchoscopy is particularly beneficial when retained secretions are visible during the procedure and when air-bronchograms are not present at the chest radiograph [4]. It is also beneficial when there is an indication to reverse lobar atelectasis [5], rather than simply to remove accumulated mucus. In specific populations, the applied technique may be modified to enhance its efficacy. For instance, in patients with asthma, mucus is highly viscous because of an abnormal concentration of plasma proteins, DNA, cells, and proteoglycans, which results in an inability to remove secretions. In those patients, toilet bronchoscopy with concomitant broncho-alveolar lavage, with or without the use of mucolytics, achieves removal of distal mucus plugs [6]. Finally, some researchers advocate that the sole removal of mucus may not be sufficient to re-expand an atelectatic lobe. Tsao et al. [7] originally reported resolution of lobar atelectasis through selective intrabronchial toilet and air insufflation. A three-way port was connected to the bronchoscope working channel. One port was attached to an ambu bag and the other port was used to monitor insufflation pressure. The bronchoscope was wedged into each subsegment of the collapsed lobe to keep the airway pressure at 30 cmH_2O for 1–2 minutes. These methods were slightly modified later on, through the connection of a standard 15-mm endotracheal tube connector to the bronchoscope working channel port (Fig. 122.1). To date, only one study [4] has compared the effects of chest physiotherapy with toilet bronchoscopy for the treatment of atelectasis in a small ICU population. Chest physiotherapy comprised of deep breathing or manual hyperinflation for 3 minutes, then coughing or tracheal suctioning and finally nebulization of saline, chest percussion, and postural drainage. In both groups, after 24 hours, atelectasis was reversed in 80% of the cases with no indication of advantages in the use of toilet bronchoscopy over less invasive approaches.

Indications

Toilet bronchoscopy is specifically indicated for patients who present with significant retention of airway secretions and pulmonary atelectasis (Fig. 122.2). In critically-ill patients, mucus retention is frequent, because of immobilization, post-operative pain, weak cough, and muscle weakness. Additionally, in intubated ICU patients, mucociliary transport is drastically reduced [8], and outward mucus clearance is not possible because of the endotracheal tube cuff inflated within the trachea. Patients with underlying diseases associated with overproduction of mucus and impairment of its clearance, such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and cystic fibrosis, may benefit from toilet bronchoscopy. In particular, mucus retention and potential benefits of toilet bronchoscopy in asthma should not be underestimated. In these patients, mucus is typically stationary within distal airways, as consistently corroborated in patients who die of status asthmaticus [9], and it is difficult to remove through suctioning. Finally, patients with neuromuscular diseases and ineffective cough seem to benefit from a bronchoscopic approach to clear secretions [10].

Contraindications and adverse effects

Toilet bronchoscopy is generally well tolerated by ICU patients and only a few absolute contraindications exist to its use (Box 122.1). Only personnel experienced in the procedure, who are trained to

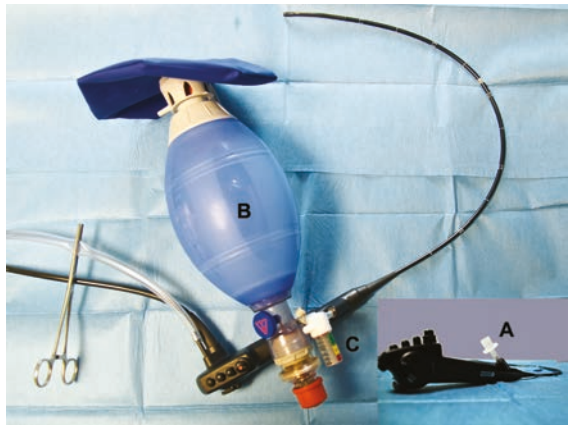


Fig. 122.1 Fibre optic bronchoscopy—ambu bag apparatus for selective segmental bronchial insufflation. Following intrabronchial mucus suctioning, the bronchoscope is wedged into each segment or subsegment of the atelectatic lobe and gas is slowly insufflated through the ambu bag into the bronchoscope working channel to achieve 30 cmH_2O airway pressure for a few minutes. (a) 15-mm endotracheal tube connector; (b) ambu bag; (c) pressure manometer.
Courtesy Hugo Loreiro, MD Hospital Clinic, Barcelona, Spain.

recognize and treat all potential complications, should perform the intervention. The risks associated with the procedure should always be weighed against the potential benefits. In general, toilet bronchoscopy should only be applied when other less invasive methods of secretion removal have failed to remove mucus plugging and revert atelectasis. Nevertheless, toilet bronchoscopy is recommended as a first-line treatment when significant mucus accumulation causes life-threating ventilatory obstruction and standard suctioning fails to promptly clear secretions. In the ICU, bronchoscopic procedures are associated with a 4% incidence of complications [11], most of them minor and transient [2]. However, no studies have specifically evaluated the complication rate of toilet bronchoscopy in ICU patients. The most common complications comprise severe refractory hypoxaemia [12], cardiac arrhythmias and ischaemia [13], haemodynamic instability and pulmonary haemorrhage (Box 122.2) [14].

Monitoring

A chest X-ray should be routinely performed prior to the procedure to identify areas of atelectasis. Strict monitoring is strongly advised during toilet bronchoscopy. Throughout the procedure, heart rate, oxygen saturation, ventilatory parameters, arterial pressure, and, in specific cases, intracranial pressure, and end-tidal carbon dioxide should be assessed.

Equipment

Bronchoscope

In intubated and mechanically-ventilated patients the insertion of the bronchoscope into the artificial airway drastically increases airflow resistance [12] and hinders ventilation. In order to prevent barotrauma and to allow adequate ventilation, it is suggested to use a bronchoscope with a diameter at least 2-mm smaller than the endotracheal tube's internal diameter [15]. Toilet bronchoscopy is an invasive procedure and the use of a sterile bronchoscope is mandatory to avoid iatrogenic respiratory infections.

Additional equipment

Strict hand hygiene is essential prior to and after the procedure. The bronchoscopist should wear protective clothing (gloves, disposable

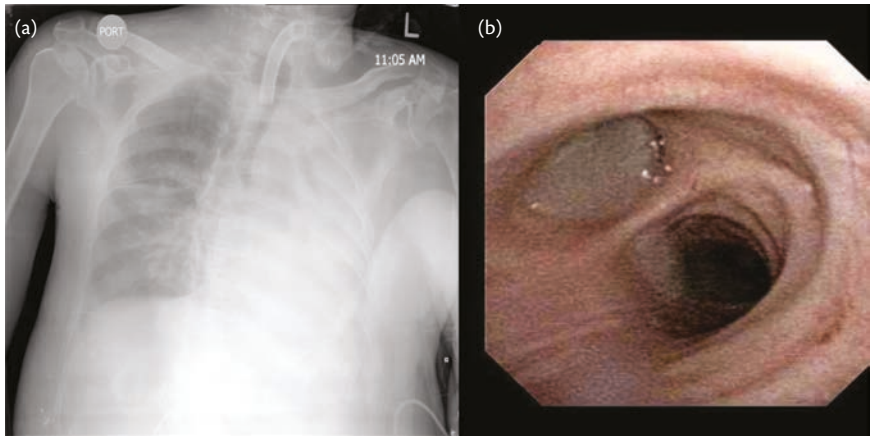


Fig. 122.2 Toilet bronchoscopy indication. (a) Chest radiograph of a tracheostomized critically-ill patient who was admitted for acute exacerbation of chronic obstructive pulmonary disease. The radiograph depicts extensive left lung atelectasis with no evidence of air-bronchograms. (b) Following unsuccessful chest physiotherapy, toilet bronchoscopy showed full obstruction of the left main bronchus by copious airways secretions.

Box 122.1 Toilet bronchoscopy contraindication

Absolute contraindications

- Absence of consent from the patient or his/her representative, unless a medical emergency exists and patient is not competent to give permission.
- Inexperienced bronchoscopist.
- Inadequate facility and/or equipment.
- Inability to adequately oxygenate the patient during the procedure.
- Current myocardial ischaemia.
- Significant haemodynamic instability.
- Life-threatening cardiac arrhythmias.
- Current significant bronchospasm.
- Undrained pneumothorax.

Relative contraindications

- Thrombocytopenia (platelet count ≤50,000 platelets/mm^3).
- INR of 2 or greater, or an elevated PTT.
- BUN >30.
- High-grade tracheal obstruction.
- Recent myocardial ischaemia and/or unstable angina.
- Severe hypoxaemia.
- Intracranial hypertension.
- Poorly-controlled heart failure.
- Recent oral intake.*

INR, International normalized ratio; PTT, partial thromboplastin time, BUN, blood urea nitrogen. *Enteral feeding or oral intake should be discontinued for 4 hours before the procedure.

apron, and protector visor) to minimize potential contamination with colonized respiratory secretions. A swivel adapter should be positioned at the proximal tip of the endotracheal tube to allow insertion of the bronchoscope and mechanical ventilation during toilet bronchoscopy. The outer surface of the bronchoscope should be lightly lubricated with water-soluble lubricant to allow easy passage through the artificial airway. Intrabronchial instillation of sterile saline solution, or mucolytics (10 or 20% acetylcysteine, dornase alfa, 2-mercaptoethane sulphonate), is commonly performed to aspirate inspissated secretions. Sterile saline and mucolitycs are also occasionally used to perform a broncho-alveolar lavage aimed at removing distal mucus plugs [6]. Nevertheless, to date, no studies are available to confirm the additional benefits associated with broncho-alveolar lavage. Finally, a sterile mucus trap may be connected to the working channel to collect and culture aspirated mucus.

Vacuum

It is recommended the level of vacuum be adjusted before performing toilet bronchoscopy to improve the efficacy of suctioning and minimize complications. No studies have comprehensively evaluated the efficacy and safety of toilet bronchoscopy at increasing vacuum levels. When using a 5.2-mm outer diameter bronchoscope the vacuum level is commonly set at −400 mmHg. Nevertheless, in patients with loose secretions, acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), or those intubated with a 7-mm internal diameter endotracheal tube, the vacuum should be decreased to the lowest level that efficiently removes secretions to reduce risks of lungs collapse. Importantly, the primary aim of toilet bronchoscopy is aspiration of secretions; hence, suctioning when the bronchoscope is not close to secretions, or when all the mucus has already been aspirated should be avoided.

Setting the mechanical ventilator

Several ventilatory parameters should be adjusted to safely perform toilet bronchoscopy. However, no international consensus exists on how to set the mechanical ventilator during the procedure. First and foremost, given the significant risk for developing hypoxaemia, the inspiratory fraction of oxygen should be increased to 100%. Secondly, bronchoscopy is usually performed during either flow- or pressure-controlled modes of ventilation. The flow-controlled mode ensures the delivery of the set tidal volume, and the resulting pressure applied to the airway opening can rise to any value according to the impedance to inflation and the pressure limit

Box 122.2 Toilet bronchoscopy potential complications

Respiratory complications

- Hypoxaemia.
- Hypercapnia.
- Atelectasis.
- Bleeding.
- Bronchospasm.
- Pneumothorax.
- Respiratory arrest.

Cardiovascular complications

- Bradycardia.
- Tachycardia.
- Cardiac arrest.
- Hypotension.
- Hypertension.
- Myocardial infarction.

Neurological complications

- Intracranial hypertension.
- Seizures.

Infectious complications

- Fever.
- Pneumonia.
- Bacteraemia.

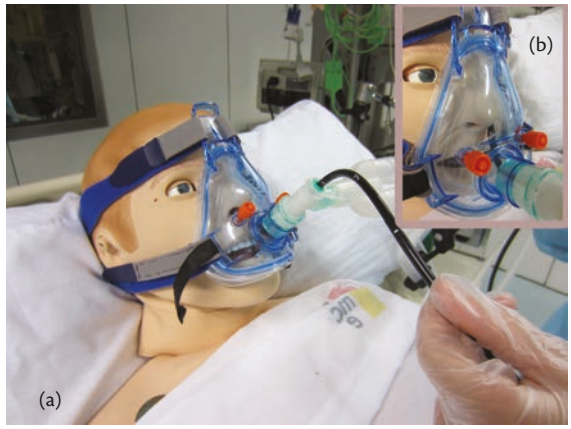


Fig. 122.3 Toilet bronchoscopy during non-invasive ventilation. (a) Transnasally insertion of the flexible bronchoscope during non-invasive ventilation. (b) The T-adapter was attached to the face-mask for the insertion of flexible bronchoscope and its passage through the nose.

alarm. Thus, prior to insertion of the bronchoscope the pressure limit alarm needs to be increased to allow for ventilation. During pressure-controlled ventilation minute ventilation can drastically decrease, unless the set inspiratory pressure is adjusted to overcome the bronchoscope-related airflow resistance. Finally, there is evidence from laboratory [15] and clinical studies [16] that the insertion of a bronchoscope into the artificial airway significantly increases the positive end-expiratory pressure (PEEP), because of the added resistance to passive exhalation and gas trapping. Nevertheless, during toilet bronchoscopy frequent aspirations could ultimately result in lung derecruitment, rather than significant gas trapping [17]. For these reasons the ventilatory mode should be set based on the patient's underlying conditions and associated risks. In patients with significant intrinsic PEEP or at risk for barotrauma, pressure-controlled mode of ventilation should be preferred, whereas in patients with acute lung injury, ARDS, hypercapnic, or who require high levels of PEEP, volume-controlled mode could be a safer choice. Thirdly, the external PEEP should be markedly decreased during the procedure to at least 50% of the baseline values, or even less in patients with underlying bronchoconstriction, emphysema, and auto-PEEP. Finally, the ventilator should be allowed to trigger during suctioning to prevent lung derecruitment, thus flow- or pressure- trigger should be set accordingly.

Sedation, analgesia, and topical anaesthesia

Toilet bronchoscopy is an invasive procedure, which is highly uncomfortable for patients. The use of sedatives, analgesics and topical anaesthetics is mandatory to achieve favourable procedural condition, improve patient tolerance and reduce potential complications [18]. Commonly, in deeply sedated and intubated patients on mechanical ventilation toilet bronchoscopy can be performed by applying topical anaesthetics, administered as needed through the bronchoscope working channel. 1 or 2% lidocaine solution is the most commonly used anaesthetic. Care should be taken with the total administered dose in patients of advanced age, and with impaired liver function and cardiac conditions. In lightly sedated, mechanically-ventilated patients and those on spontaneous ventilation, systemic sedation, analgesia, and topical anaesthetics are recommended. Short-acting sedatives, i.e. midazolam and propofol achieve optimal sedation, anxiolysis, and amnesia, and are highly recommended for toilet bronchoscopy. Fentanyl is the preferred analgesic during toilet bronchoscopy due to its rapid onset of action, short half-life, and efficient suppression of cough. In specific cases, short-acting neuromuscular blocking agents can be used to optimize ventilation during the procedure and to prevent potential complications.

Toilet bronchoscopy during invasive ventilation

The bronchoscope is initially inserted into the artificial airway and secretions accumulated within its lumen are fully aspirated. When lobar atelectasis is detectable at the chest radiograph, the bronchoscope should first be advanced toward the secondary bronchus tributary of the lung consolidation, and mucus plugs fully removed. Next, all lobar bronchi should be comprehensively assessed and built up secretions removed. In patients with disseminated retention of airways secretions, a systematic approach should be undertaken in order to ensure full removal of airway secretions from all secondary bronchi. Follow-up chest radiograph is recommended to demonstrate resolution of the atelectasis.

Toilet bronchoscopy during non-invasive ventilation

Several patients who require non-invasive ventilation are often unable to efficiently clear respiratory secretions. In those patients toilet bronchoscopy may prevent respiratory deterioration and the need of endotracheal intubation. Studies have reported feasibility and safety of fibre optic bronchoscopy in critically-ill patients with acute lung injury [19] and COPD exacerbation [20]. Nevertheless, to date, no randomized controlled studies have been conducted to assess the clinical usefulness of toilet bronchoscopy in patients who require non-invasive ventilation. Topical anaesthesia of the nasopharynx and larynx with lidocaine should be performed prior the procedure. Systemic light sedation and/or analgesia should be considered on a case-by-case basis. It is highly recommended that the inspiratory fraction of oxygen be increased to 100%. Inspiratory and end-expiratory pressures should be adjusted to

achieve optimal ventilation and oxygenation. During the procedure, the bronchoscope can be inserted through a T-adapter attached to a face mask (Fig. 122.3) or a specific connector placed in the plastic ring of a helmet and advanced into the airways via either a nasal or oral route.

References

1. Konrad F, Schreiber T, Grünert A, Clausen M, Ahnefeld FW. (1992). Measurement of mucociliary transport velocity in ventilated patients. Short-term effect of general anesthesia on mucociliary transport. *Chest*, **102**, 1377–83.
2. Lucena CM, Martínez-Olondris P, Badia JR, et al. (2011). Fiberoptic bronchoscopy in a respiratory intensive care unit. *Med Intensiva*, **36**(6), 389–95.
3. Kreider E. (2003). Bronchoscopy for atelectasis in the ICU: a case report and review of the literature. *Chest*, **124**, 344–50.
4. Marini JJ, Pierson DJ, and Hudson LD. (1079). Acute lobar atelectasis: a prospective comparison of fiberoptic bronchoscopy and respiratory therapy. *American Reviews in Respiratory Diseases*, **119**, 971–8.
5. Snow N and Lucas AE. (1984). Bronchoscopy in the critically ill surgical patient. *American Surgery*, **50**, 441–5.
6. Henke CA, Hertz M, and Gustafson P. (1994). Combined bronchoscopy and mucolytic therapy for patients with severe refractory status asthmaticus on mechanical ventilation: a case report and review of the literature. *Critical Care Medicine*, **22**, 1880–3.
7. Tsao TC, Tsai YH, Lan RS, Shieh WB, and Lee CH. (1990). Treatment for collapsed lung in critically ill patients. Selective intrabronchial air insufflation using the fiberoptic bronchoscope. *Chest*, **97**, 435–8.
8. Konrad F, Schreiber T, Brecht-Kraus D, and Georgieff M. (1994). Mucociliary transport in ICU patients. *Chest*, **105**, 237–41.
9. Saetta M, Di Stefano A, Rosina C, Thiene G, and Fabbri LM. (1991). Quantitative structural analysis of peripheral airways and arteries in sudden fatal asthma. *American Reviews in Respiratory Diseases*, **143**, 138–43.
10. Jolliet P and Chevrolet JC. (1992). Bronchoscopy in the intensive care unit. *Intensive Care Medicine*, **18**, 160–9.
11. Turner JS, Willcox PA, Hayhurst MD, and Potgieter PD. (1994). Fiberoptic bronchoscopy in the intensive care unit—a prospective study of 147 procedures in 107 patients. *Critical Care Medicine*, **22**, 259–64.
12. Matsushima Y, Jones RL, King EG, Moysa G, and Alton JD. (1984). Alterations in pulmonary mechanics and gas exchange during routine fiberoptic bronchoscopy. *Chest*, **86**, 184–8.
13. Matot I, Kramer MR, Glantz L, Drenger B, and Cotev S. (1997). Myocardial ischemia in sedated patients undergoing fiberoptic bronchoscopy. *Chest*, **112**, 1454–8.
14. Weiss SM, Hert RC, Gianola FJ, Clark JG, and Crawford SW. (1993). Complications of fiberoptic bronchoscopy in thrombocytopenic patients. *Chest*, **104**, 1025–8.
15. Lawson RW, Peters JI, and Shelledy DC. (2000). Effects of fiberoptic bronchoscopy during mechanical ventilation in a lung model. *Chest*, **118**, 824–31.
16. Nakstad ER, Opdahl H, Skjønsberg OH, and Borchsenius F. (2011). Intrabronchial airway pressures in intubated patients during bronchoscopy under volume controlled and pressure controlled ventilation. *Anaesthesia Intensive Care*, **39**, 431–9.
17. Lindgren S, Odenstedt H, Erlandsson K, Grivans C, Lundin S, and Stenqvist O. (2008). Bronchoscopic suctioning may cause lung collapse: a lung model and clinical evaluation. *Acta Anaesthesiologica Scandinavica*, **52**, 209–18.
18. Wahidi MM, Jain P, Jantz M, et al. (2011). American College of Chest Physicians consensus statement on the use of topical anesthesia, analgesia, and sedation during flexible bronchoscopy in adult patients. *Chest*, **140**, 1342–50.
19. Baumann HJ, Klose H, Simon M, et al. (2011). Fiber optic bronchoscopy in patients with acute hypoxemic respiratory failure requiring noninvasive ventilation—a feasibility study. *Critical Care*, **15**, R179.
20. Scala R, Naldi M, and Maccari U. (2010). Early fiberoptic bronchoscopy during non-invasive ventilation in patients with decompensated chronic obstructive pulmonary disease due to community-acquired-pneumonia. *Critical Care*, **14**, R80.

PART 4.15

Pleural cavity problems

CHAPTER 123

Pathophysiology of pleural cavity disorders

Davide Chiumello and Cristina Mietto

Key points

- The pleural cavity is a virtual space. Negative (subatmospheric) pressure is essential to guarantee the mechanical coupling between the lung and the chest wall.
- The three major determinants of this balance are the Starling forces, the lymphatic drainage, and the active transmembrane transport.
- When fluid or air accumulates inside the pleural cavity, pleural pressure rises to atmospheric level. The consequence is that the lung and chest wall tend to their resting position—the lung collapses, while the chest wall tends to expand. The displacement is not equally distributed between lung and chest wall, because it depends upon the individual compliance.
- Pneumothorax can be defined as primary if it is not associated with any lung disease. Otherwise, pneumothorax is usually referred as secondary and the most common causes are chronic obstructive pulmonary disease, cystic fibrosis, infectious diseases, and cancer. Traumatic pneumothorax can be consequence of chest injury or invasive medical procedures (mechanical ventilation, central venous catheter placement, thoracentesis).
- Pleural effusion is classified as transudates or exudates, mainly based on protein content. Transudates are typically bilateral and the increase in systemic capillary pressure is due to increased filtered fluid in the presence of preserved endothelium. Exudates occur when a protein rich fluid is collected for an altered mesothelial barrier permeability.

Introduction

The pleural cavity is a virtual space delimited by the pleura and contains a thin layer of fluid pivotal for the mechanical coupling of the respiratory system. Collection of air (pneumothorax) and excess fluid (pleural effusion) impair the function of the respiratory system and are common in critically-ill patients, occurring in up to 15 and 60% of patients admitted to intensive care unit, respectively [1,2].

Anatomy

The pleural cavity is a closed space bordered by the pleura, a serous membrane consisting of a parietal leaflet that covers the internal surface of the thoracic cage, the diaphragm and the mediastinum, and a visceral leaflet that coats the external surface of the lung. The upper limit of the pleural space, occupied by the dome of the lung, extends 2–3 cm above the first rib and behind the sternocleidomastoid muscle. The inferior limit follows the border between the diaphragm and the chest wall, corresponding to the sixth rib anteriorly and just below the twelfth rib posteriorly. The visceral pleura is adherent to the lung surface from which it is not separable, ensuring a homogenous transmission of the forces. Both pleura are constituted by a single line of mesothelial cells, that are joined by tight junctions, such as endothelial cells, and have intracellular synthesis capability and active trans-cellular transport [3]. Mesothelial cells are provided with microvilli on the luminal side, a major density characterizes the visceral pleura and caudal lung regions. The parietal pleura is distinguished by the presence of stomata, round holes opening between cells which provide communication between the pleural space and lymphatic vessels of submesothelial tissue [3]. Blood supply is from systemic circulation for both pleura, the visceral one drains into the pulmonary vein system. Regarding innervation, the parietal pleura is provided by the intercostal and phrenic nerves, which entail a mark sensibility to pain, while the visceral pleura has an autonomic innervation and it is insensible to painful stimuli. However, nerve terminals with neurochemical characteristics of mechanosensory/nociceptive terminals could be involved in the pathogenesis of dyspnoea associated to pleural diseases [4].

Pleural cavity and respiratory system mechanics

The two pleural leaflets are separate by a thin layer of liquid that must be kept at the minimum needed to ensure the mechanical coupling between the lung and the chest wall. Lung and chest wall resting positions are different, so that at functional residual capacity (FRC) lung inward recoil is counterbalanced by chest wall outward tendency. These opposite recoil forces, which tend to separate the visceral and parietal pleura, are the major determinants of pleural pressure (P_{pl}). Pleural surface is exposed to a negative (subatmospheric) pressure that prevents lung collapsing and allows the lung and chest wall to move together. In clinical practice the oesophageal pressure (P_{es}) is the only available surrogate of P_{pl} and P_{es} variations are reliable of P_{pl} changes [5]. Moreover, P_{pl} is not equal along the whole lung height, but there is a vertical gradient, roughly 0.25 cmH_2O/cm, due to the lung weight [6]. Gravity exerts a uniform force on the lung, but its visco-elastic

nature and the presence of the supporting chest wall determines an inhomogeneous distribution. Consequently, P_{pl} is more negative at the top and tends to keep the lung open, whereas the bottom is compressed against the chest wall and the resulting P_{pl} is relatively higher. P_{pl} gradient is lower than the hydrostatic (1 cmH_2O/cm) because lung density is just one quarter the density of water. In the literature, two different models have been proposed for the pleural liquid pressure (P_{liq}). A theory proposes that Pliq is more negative than P_{pl} because of the presence of points of contact between the two pleural leaflets [7]. The other model states that lung and chest wall recoils are transmitted hydraulically through the pleural liquid, so that P_{liq} equals P_{pl} [8].

If air is collected into the pleural space, pleural pressure rises to atmospheric level causing the lung to collapse and the chest wall to expand, until a new equilibrium is reached. Pleural cavity has a high compliance, meaning that a large amount of fluid can be accumulated before P_{liq} begins to rise. Pleural effusion collects into the pleural cavity with a gravity distribution, altering P_{pl}. Above the pleural fluid P_{pl} gradient is normal, while below the gradient becomes hydrostatic with the consequence of a greater reduction of the transpulmonary pressure (P_L):

$$P_L = P_{aw} - P_{pl} \qquad \text{[eqn 1]}$$

where P_{aw} is the airway pressure. The consequence is the loss of aeration of the dependent lung zones. The displacement is not equally distributed between lung and chest wall, but it depends upon their own compliance. Thus, the volume of lung and chest wall are different, leading to the uncoupling of the respiratory system—the more compliant the chest wall, the more it accomplishes and the more compliant the lung, the greater the reduction in lung volume. Studies showed that pleural effusion entails a decrease in FRC of about one-third of the added volume, while the remainder is accepted by chest wall displacement. Moreover, regional lung volumes changed accordingly and the reduction of lung volume is mostly accounted for by the dependent regions with minimal changes in the upper lobes [9,10]. This distribution is in accordance with an altered P_{pl} and consequently P_L gradient. In another study, lung recruitment manoeuvres partially reversed the reduction in respiratory system compliance primarily due to the lung component, which can suggest that airway collapse can be an important mechanism involved [11].

Consistently, humans studies showed a small increase in lung volume after pleural effusion drainage compared with the volume removed, but a significant dyspnoea relief and more negative P_{es} [12,13]. A possible explanation is that the chest wall outward displacement determines a decrease in the length of the inspiratory muscles reducing their effectiveness [13]. Thoracentesis can restore the normal length and improve muscles efficacy with dyspnoea relief.

Pleural fluid dynamics

Normal pleural liquid volume is roughly 0.2 mL/kg, with a composition typical of plasma filtrate through a biological sieving membrane—protein content is low, 1–2 g/100 mL, and albumin is the major fraction [14]. The volume of pleural liquid is determined by the equilibrium of fluid turnover between in- and outflow, being equal to 0.2 mL/Kg/hour under physiological conditions [14,15]. Pleural fluid filters through the capillary of the parietal pleura and then is reabsorbed, mainly from stomata lymphatic system of the parietal pleura and, to a less extent, by solute-coupled transport and absorption into the capillaries of the visceral pleura. The three major determinants of this balance are the Starling forces, the lymphatic drainage, and the active transmembrane transport. Starling equation describes filtration across biological barriers (i.e., endothelium, as well as mesothelium):

$$If = Kf\left[\left(P_c - P_{liq}\right) - \sigma\left(\pi_c - \pi_{liq}\right)\right] \qquad \text{[eqn 2]}$$

where If refers to the net fluid movement across the compartments, Kf is the filtration coefficient, P is the hydrostatic pressure, π_c and π_{liq} the colloid–osmotic pressure in the sub-pleural capillaries and pleural liquid, respectively, and σ is the protein reflection coefficient of pleural mesothelium. If we consider as a whole the driving force between brackets, the eqn 2 simplifies to:

$$If = Kf \bullet \Delta Pf \qquad \text{[eqn 3]}$$

the transpleural liquid flow is dependent on the overall driving force (ΔPf) and on the Kf, that is equal to the product of the total surface (S) available for filtration and the water hydraulic permeability (Lp) (Kf = S·Lp). Lp (the coefficient defining water hydraulic permeability) is mostly dependent on the size and distribution of small aqueous channels, called pores, opening on the membrane. Studies suggests that mesothelial cells are also active in a solute-coupled liquid absorption and transcytosis based on morphological evidence of vesicular transport [14]. A similar equation can be written for the lymphatic drainage (Jl):

$$Jf = KI \bullet (P_{labs} = P_{liq}) \qquad \text{[eqn 4]}$$

where Kl is the conductance of the lymphatics, which is proportional to extension and is 10-fold greater than Kf, P_{labs} and P_{liq} are the absorption and the pleural liquid pressures, respectively. P_{labs} is rather negative, thus promoting reabsorption of pleural liquid. Lymphatic drainage is the main pathway limiting liquid accumulation and is essential for removing molecules and cells from the pleural space [14,15]. Pleural liquid turnover is polarized, filtration being greater in the upper regions of the cavity, whereas drainage is predominant at the diaphragmatic and mediastinal side [15]. Lymphatic flow seems the only way for draining cells back to blood circulation. Pleural fluid contains approximately 1500–2500 cells/mm^3, the majority are macrophages with fewer leucocytes, erythrocytes, and mesothelial cells [14].

Pneumothorax

Pneumothorax happens when air is introduced into the pleural cavity, causing chest wall displacement and lung collapse. Air can enter through the lung parenchyma or through chest wall injuries. Normally, air is not present into the pleural cavity, despite the negative pleural pressure, because the total of the partial pressure of gases dissolved in blood is less than one atmosphere (arterial blood 708 mmHg and venous blood 655 mmHg, breathing room air). This is essential for keeping the pleural cavity free of gases and reabsorption of collected air. Pneumothorax is classified in two groups based upon the aetiological mechanism–spontaneous

and traumatic (Table 123.1). Spontaneous pneumothorax can be secondary, i.e. associated to pulmonary diseases (mainly chronic obstructive pulmonary disease (COPD), cystic fibrosis, tuberculosis, cancer, interstitial lung diseases, and others). If no lung disease can be identified as a triggering factor, the pneumothorax is usually referred to as being primarily spontaneous, and is more frequent in young, thin, tall males. The classical theory is that it derives from the rupture of a subpleural bleb or bulla. Evidence to support this theory is derived by CT studies finding that 80% of patients with primary spontaneous pneumothorax show emphysema-like changes of lung parenchyma [16]. These alterations are often bilateral and mainly represented in the upper lobes. Some studies found a correlation with atmospheric pressure changes, loud music, height and smoking that seem to be a major risk factor [17].

A different model has been proposed for those patients without sign of emphysema-like changes or broken bulla during surgery. Visceral pleura show lesions of the mesothelial layer that is replaced by an inflammatory fibrotic tissue, alteration referred as 'pleural porosity,' and that can sustain the air leakage [17]. Both bullae and pleural porosity may be related to airway chronic inflammation, anatomy anomalies, connective tissue diseases, local ischaemia or malnutrition. Another possible scenario is the development of a haemopneumothorax, where the cause of bleeding is often an ectopic vessel enveloped into the pleural bulla.

On the other hand, traumatic pneumothoraxes can result from both penetrating and non-penetrating chest injuries, and can be divided into two major groups—iatrogenic or non-iatrogenic. The latter can be due to air leakage directly through the chest wall or visceral pleura wounds. Instead, alveolar rupture is a consequence of lung contusion or blast injuries. Iatrogenic pneumothorax is common and can be a complication of different medical procedures, such as transthoracic needle aspiration, thoracentesis, and the insertion of central intravenous catheters. Another important iatrogenic cause of pneumothorax in critically-ill patients is mechanical ventilation, referred to as barotrauma, and it is due to ventilation with high positive airway pressure, which determines high transpulmonary pressure (P_L) leading to alveoli over inflation or even rupture. Air leakage can be not only into the pleural cavity, but may even extend to mediastinum and body surface.

Table 123.1 Causes of pneumothorax

Type and causes of pneumothorax		
Spontaneous		
Primary		
Secondary	Emphysema	Lymphangioleiomyomatosis
	Asthma	Rheumatoid arthritis
	Cystic fibrosis	Sclerodermia
	Tuberculosis	Marfan's syndrome
	Pneumocistis carinii pneumonia	Ehlers–Danlos syndrome
	Idiopatic pulmonary fibrosis	Lung cancer
	Histocytosis X	Sarcoma
	Sarcoidosis	
Traumatic		
Non-iatrogenic	Penetrating or non-penetrating chest injury	
Iatrogenic	Transthoracic needle aspiration	Subclavian vein catheter
	Thoracentesis	Internal jugular vein catheter
	Transthoracic pleural biopsy	Mechanical ventilation

Pleural effusion

Pleural effusion is defined as any increase in pleural liquid volume sustained by an altered fluid turnover, depending on an increased filtration rate exceeding absorption compensatory mechanisms or caused by a primarily impaired drainage system. Enhanced filtration can be a consequence of increased filtration pressure, or altered mesothelial and endothelial permeability. The increase in pleural liquid promotes a change in the balance of fluid turnover toward a reduced filtration and enhanced absorption—a decrease in the net hydrostatic filtration pressure, an increase in lymphatic flow, and if the fluid has a low protein content, the oncotic pressure is still in favour of reabsorption. Parietal pleura lymphatic drainage is the main adapting mechanism facing fluid retention and can increase to 20 times its basal value [7]. Pleural effusion is classified as transudates or exudates, mainly based on protein content (Table 123.2). A pleural effusion is defined as exudates when the protein concentration is greater than 30 g/L or when the fluid to serum total protein ratio (C_{liq}/C_p) is higher than 0.5. Relaying only on this parameter, 15% of transudates and 10% of exudates are misclassified, thus Light's criteria can be used to better distinguish between the two types of pleural effusion with a sensibility of almost 100% for exudates [18,19]. Light's criteria take into account liquid and serum lactic dehydrogenases (LDH): pleural fluid to serum LDH ratio (LDH_{liq}/LDH_p) greater than 0.6, LDH_{liq} greater than two-thirds of the upper limit of serum reference and C_{liq}/C_p greater than 0.5 [20]. In the case of pleural effusion with a protein concentration between

Table 123.2 Causes of pleural effusion

Transudate	**Exudate**
Congestive heart failure	Pneumonia
Severe mitral stenosis	Neoplastic disease (lung, mesothelioma, metastatic)
Cirrhosis	Pulmonary thromboembolism
Nephrotic syndrome	Autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus)
Hypoalbuminaemia	Asbestos exposure
Pulmonary thromboembolism	Post-coronary artery bypass
Superior vena cava syndrome	Drug-induced
Peritoneal dialysis	Pancreatitis
Myxoedema	Chylothorax

25 and 35 g/L or in patients in therapy with diuretics, where C_{liq} can be misleading, a difference in serum and liquid protein greater than 31 g/L or an albumin concentration difference higher than 12 g/L suggest transudate [19]. This classification comprises different pathological mechanisms beneath the two kind of pleural effusion. In transudates, that are typically bilateral, the increase in systemic capillary pressure is due to the increased filtered fluid in the presence of preserved endothelium and mesothelium sieving properties, resulting in an acellular and low protein fluid. The most frequent conditions associated are heart diseases, chronic renal failure, hepatic cirrhosis, pleural fibrosis, and atelectasis. Isolated right heart failure rarely causes pleural effusion probably because the increased filtration can be matched by the enhanced lymphatic system. On the contrary, pleural effusion is common in case of biventricular or left ventricular failure where there is an increase in visceral pleura permeability leading to functional communication between the pleural and lung extravascular space (i.e., interstitial lung oedema) causing an excess of fluid filtration overwhelming compensatory mechanism. Systemic venous hypertension can be a rare cause of impaired lymphatic drainage. Then, renal and hepatic diseases may determine a decrease in protein content, with the result of a decreased colloid–osmotic pressure, as well as primary hypo-albuminaemia. Lastly, there may be direct transdiaphragmatic leak of ascitic fluid from the peritoneum. On the other hand, exudates occur when a protein rich fluid is collected for an altered mesothelial barrier permeability with cell and protein leak into the pleural space or for impaired lymphatic removal. The most common cause of exudates is inflammation; other conditions associated can be malignant neoplasms, primary of mesothelial cells or metastatic, tuberculosis, or asbestos-related diseases. The hallmark of pleural involvement in local or systemic inflammatory diseases is increased microvascular and mesothelial permeability, occurring with opening of new transcellular pathways and for direct mesothelial cell damage with loss of barrier selectivity [14,15]. One of the most frequent type of exudates is pleural effusion associated to pulmonary infection, parapneumonic effusion. Evidence shows that mesothelial cells are active elements in the immunity defence process—they can recognize the pathogens, and subsequently initiate and propagate the inflammatory response. Mesothelial cells have phagocytic properties and can release reactive oxygen species as first line defence mechanism. Mesothelial cells release also cytokines that are pivotal in the recruitment of native and acquired immunity cells [20]. Inflammation promotes a fibrin deposition upon damaged tissue and a fine balance between fibrin deposition and removal is essential to avoid the development of pleural fibrosis.

Haemothorax is defined as any pleural effusion with a haematocrit greater than 50% of peripheral blood. It is to remember that a haematic pleural effusion with a haematocrit >5% is visually indistinguishable from blood. Most cases are the result of chest trauma or invasive procedures. Other causes can be vascular rupture (aortic dissection or pulmonary vessel malformation), tumours, inherited or acquired coagulopathy, and anticoagulation therapy.

References

1. Yarmus L and Feller-Kopman D. (2012). Pneumothorax in the critically ill patient. *Chest*, **141**(4), 1098–105.
2. Azoulay E. (2003). Pleural effusions in the intensive care unit. *Current Opinions in Pulmonary Medicine*, **9**(4), 291–7.
3. Wang N-S. (1998). Anatomy of the pleura. *Clinical Chest Medicine*, **19**(2), 229–40.
4. Pintelon I, Brouns I, De Proost I, Van Meir F, Timmermans JP, and Adriaensen D. (2007). Sensory receptors in the visceral pleura: neurochemical coding and live staining in whole mounts. *American Journal of Respiratory Cell and Molecular Biology*, **36**(5), 541–51.
5. Cherniack RM, Farhi LE, Armstrong BW, and Proctor DF. (1955). A comparison of esophageal and intrapleural pressure in man. *Journal of Applied Physiology*, **8**(2), 203–11.
6. Milic-Emili J, Henderson JA, Dolovich MB, Trop D, and Kaneko K. (1966). Regional distribution of inspired gas in the lung. *Journal of Applied Physiology*, **21**(3), 749–59.
7. Agostoni E and Zocchi L. (2007). Pleural liquid and its exchanges. *Respiratory Physiology & Neurobiology*, **159**(3), 311–23.
8. Lai-Fook S. (2004). Pleural mechanics and fluid exchange. *Physiology Reviews*, **84**(2), 385–410.
9. Krell WS and Rodarte JR. (1985). Effects of acute pleural effusion on respiratory system mechanics in dogs. *Journal of Applied Physiology*, **59**(5), 1458–63.
10. Dechman G, Mishima M, and Bates JH. (1994). Assessment of acute pleural effusion in dogs by computed tomography. *Journal of Applied Physiology*. **76**(5), 1993–8.
11. Dechman G, Sato J, and Bates JH. (1993). Effect of pleural effusion on respiratory mechanics, and the influence of deep inflation, in dogs. *European Respiratory Journal*, **6**(2), 219–24.
12. Light RW, Stansbury DW, and Brown SE. (1986). The relationship between pleural pressures and changes in pulmonary function after therapeutic thoracentesis. *American Reviews in Respiratory Diseases*, **133**(4), 658–61.
13. Estenne M, Yernault JC, and De Troyer A. (1983). Mechanism of relief of dyspnea after thoracocentesis in patients with large pleural effusions. *American Journal of Medicine*, **74**(5), 813–19.
14. Miserocchi G. (2009). Mechanisms controlling the volume of pleural fluid and extravascular lung water. *European Respiratory Journal*, **114**(18), 244–52.
15. Zocchi L. (2002). Physiology and pathophysiology of pleural fluid turnover. *European Respiratory Journal*, **20**, 1545–58.
16. Bense L, Lewander R, Eklund G, Hedenstierna G, and Wiman LG. (1993). Nonsmoking, non-alpha 1-antitrypsin deficiency-induced emphysema in nonsmokers with healed spontaneous pneumothorax, identified by computed tomography of the lungs. *Chest*, **103**(2), 433–8.
17. Noppen M and De Keukeleire T. (2008). Pneumothorax. *Respiration*, **76**(2), 121–7.
18. McGrath EE and Anderson PB. (2011). Diagnosis of pleural effusion: a systematic approach. *American Journal of Critical Care*, **20**(2), 119–27.
19. Light RW. (1997). Diagnostic principles in pleural disease. *European Respiratory Journal*, **10**(2), 476–81.
20. Jantz MA and Antony VB. (2008). Pathophysiology of the pleura. *Respiration*, **75**(2), 121–33.

CHAPTER 124

Management of pneumothorax and bronchial fistulae

Wissam Abouzgheib and Raquel Nahra

Key points

- Observation is adequate in small pneumothorax.
- Small bore chest tubes are as effective as large ones and should be used initially.
- Ultrasound plays an important role in ruling out a pneumothorax.
- Suction is not always need in an air leak.
- One-way endobronchial valves may be used to treat prolonged air leaks.

Definition and classification of pneumothorax

Pneumothorax refers to the presence of air in the pleural space. The classification of pneumothorax includes spontaneous, traumatic, or iatrogenic. Spontaneous pneumothorax occurs without obvious cause, either primary without evidence of underlying lung disease or secondary with apparent underlying lung disease, often chronic obstructive pulmonary disease (COPD). Traumatic pneumothorax occurs after a blunt or penetrating trauma to the chest. Iatrogenic pneumothorax occurs after a diagnostic or therapeutic intervention, such as transthoracic lung biopsy, central line placement, or barotrauma due to mechanical ventilation. The incidence of pneumothorax, in patients receiving mechanical ventilation, ranges between 7 and 14% [1]. Patients with acute lung injury or ARDS are at high risk.

The clinical presentation ranges from asymptomatic to respiratory failure and prolonged bronchopleural fistulas (BPFs). Prompt diagnosis and management are crucial, especially in symptomatic and critically-ill patients requiring mechanical ventilation. This chapter discusses the diagnosis and management of pneumothorax and BPFs in general with a focus on critically-ill patients

Diagnosis

Clinical manifestations and presentations of pneumothorax are widely variable. Sometimes found incidentally on routine chest imaging, the presence of a pneumothorax is often clinically suspected with the appropriate clinical setting. Spontaneous pneumothorax is usually sought in patients between 20 and 40 years old presenting with sudden onset of dyspnoea and pleuritic chest pain. Secondary pneumothorax in patients with known underlying chronic lung diseases, presenting with more severe symptoms and iatrogenic or traumatic pneumothorax in patients with diagnostic/therapeutic interventions or preceding trauma. Symptoms vary, a small pneumothorax can be asymptomatic and self-limited, whereas a large pneumothorax can cause hypoventilation, hypoxaemia, and/or haemodynamic instability.

Tension pneumothorax represents a surgical emergency and requires emergent intervention. It may lead to respiratory failure requiring mechanical ventilation. It may also complicate pre-existing respiratory failure on positive pressure ventilation.

In intubated and sedated patients, a pneumothorax should be suspected with sudden and unexplained worsening respiratory failure, increased oxygen requirements, haemodynamic instability, and a sudden rise in peak and plateau pressures. It is ideally diagnosed based on clinical presentation, risk factors, and physical examination, and not by imaging followed by immediate emergent decompression.

The first-line imaging modality used to identify a pneumothorax is chest radiography.

A typical finding is the displacement of the white visceral pleural line from the chest wall on an upright chest X-ray. Contralateral shift of the trachea and mediastinum may also be present in spontaneous pneumothorax, but not necessarily suggestive of tension. The underlying lung parenchyma should be examined for the presence of underlying lung disease that would suggest a secondary spontaneous pneumothorax. In bedridden or ICU patients, care should be exercised in order to differentiate visceral pleural line from skin folds. Skin folds frequently extend beyond the rib cage, while blood vessels and lung parenchyma often extend beyond the skin fold. Their attenuation profile is also different, forming a negative black Mach band instead of the white visceral pleural line (Fig. 124.1)

Computed tomography (CT) is reserved for complicated or unclear situations. However, CT scans are more accurate in determining size of pneumothorax when compared to chest radiography [2].

Some investigators have reported using ultrasound to diagnose or rule out a pneumothorax [3], particularly in patients where it is needed urgently at the bedside, such as in ICU or for a trauma patient. The use of bedside ultrasonography has emerged in the past few years as the modality of choice in intensive care units (ICUs), where ultrasonography trained physicians are available. Bedside ultrasonography offers several advantages over chest radiography or CT scans, including rapid availability, lack of radiation, real time interpretation, and lower cost. It also offers the ability to immediately rule out a pneumothorax after an invasive procedure or in the

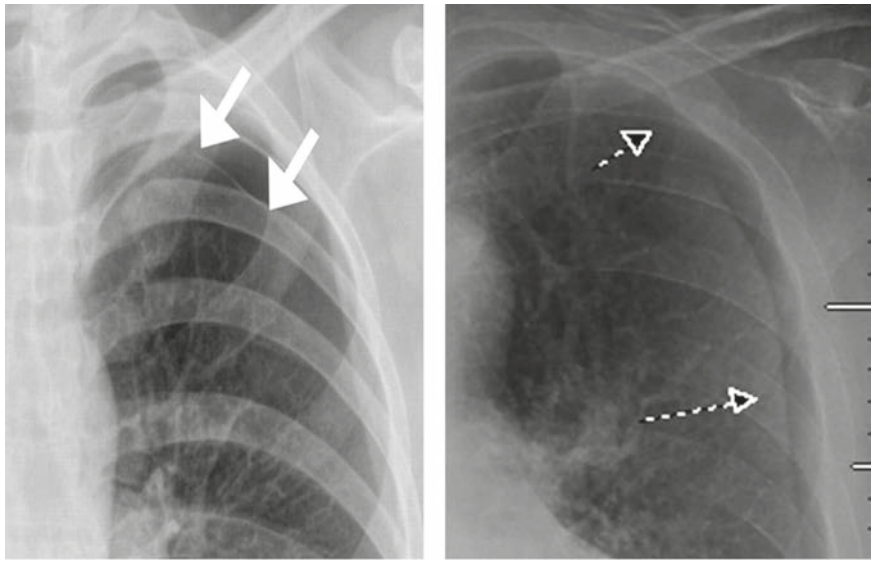


Fig. 124.1 (Left) White visceral pleural line in pneumothorax. (Right) Black Mach band in skin fold.

midst of a clinical deterioration. Two easily identifiable signs are needed to rule out pneumothorax. The sliding lung sign presents as shimmering of the visceral pleura when it moves relative to the parietal pleura during the respiratory cycle. The Comet tail artefacts (also called B-lines) are several echogenic lines that originate at the visceral–parietal pleural interface and extend to the bottom of the sonographic image (Fig. 124.2). The sensitivity and specificity of ultrasound for pneumothorax range from 86 to 98%, which is superior to supine chest radiograph (sensitivity 28 to 75%) [4,5]. Both techniques demonstrated high specificity.

Management of pneumothorax

Several parameters need to be considered in the management of a pneumothorax, such as type, size, severity of symptoms, first episode or recurrence, and patient preference. The British Thoracic Society guidelines define a pneumothorax as small if the distance from chest wall to the visceral pleural line is less than 2 cm or large if the distance is 2 cm or greater [6]. Some clinicians prefer 3 cm laterally and 4 cm apically as the threshold to distinguish small and large pneumothoraces.

Conservative approach: oxygen and observation

The first episode of spontaneous pneumothorax warrants a conservative approach when faced with small size pneumothorax and symptoms are absent or mild. Normal air re-absorption from the pleural space occurs at a rate of 1.25 % and it increases three- to four-fold when high flow (non-intubated patient) or high F_IO_2 (intubated patient) oxygen supplementation is instituted. Patients managed conservatively should be observed in the emergency department for 3–6 hours and discharged home if repeat chest imaging shows no progression.

Manual needle/catheter aspiration

Simple manual aspiration using an intercostal needle or small catheter is indicated in non-complicated patients presenting with a first episode spontaneous pneumothorax, large pneumothorax, or associated with symptoms. It consists of inserting a needle or catheter in the pleural space, and aspirating the pleural air followed by removal of the needle or catheter. The overall resolution

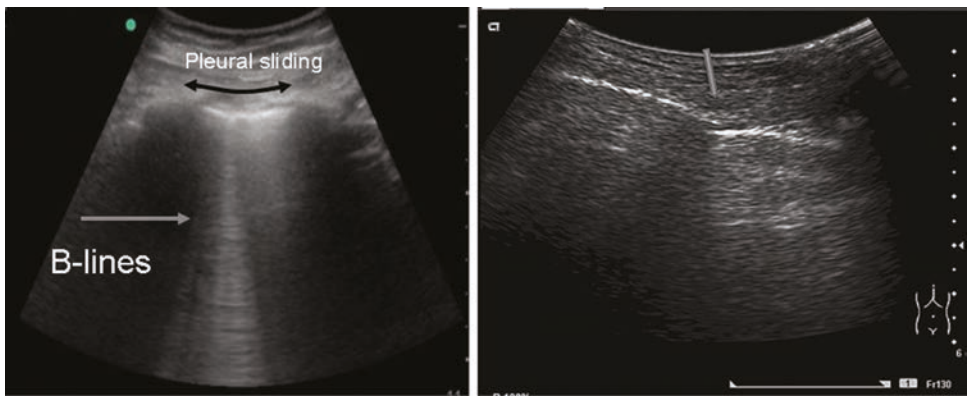


Fig. 124.2 Ultrasound. (Left) No pneumothorax. (Right) Pneumothorax: absence of pleural sliding or B-lines.

rate in spontaneous pneumothorax ranges between 59–83% of patients [7].

Tube thoracostomy: insertion and management

When simple aspiration is unsuccessful to keep the lung inflated, or when air leak is large or persistent, then a tube thoracostomy is indicated. Prior reflection on the magnitude of the underlying air leak, size of the pneumothorax, associated co-morbidities, and concurrent therapies may help when choosing tube thoracostomy size. There is no evidence that large tubes (20–24 F) are any better than small tubes (10–16 F) in the management of pneumothoraces. The initial use of large (20–24 F) intercostal tubes is not recommended, although it may become necessary to replace a small chest tube with a larger one if there is a large air leak preventing complete re-inflation of the lung [6].

The presence and degree of an air leak after chest tube placement, is also important and should be assessed daily to determine whether the tube can be removed. The number of chambers that are bubbling in a wet, suction-controlled, closed drainage provides a semi-quantitative measure of the severity of the leak. It does not indicate flow in any precise manner, but can provide an indication of any day-to-day increases or decreases in the degree of air leak.

Our recommended approach is, for patients who are not at risk for a large air leak, a smaller catheter (8–14 Fr) can be used in combination with a water seal or unidirectional flutter valve (i.e., Heimlich valve), which allows the patient to be mobile. These patients can be followed the next day with chest X-ray after clamping the chest tube for several hours for chest tube removal.

For patients with moderate size pneumothorax or possible moderate air leak, a 16–24 Fr chest tube is usually sufficient to maintain evacuation of the pleural space. The tube may initially be connected to a water seal, but if lung re-expansion does not occur then application of suction (–20 cmH_2O) is needed. Suction helps juxtapose the visceral and parietal pleura, which in theory leads to mechanical pressure on the bronchopleural fistula and potentially promotes healing.

A large surgical chest tube >24 Fr is needed in patients with large air leak, in mechanically-ventilated patients, and when smaller size tubes fail to re-expand the lung.

Small bore drains are as effective for air drainage as large bore drains and are more comfortable for patients. If there is associated blood, a large bore drain will be required. There are no large randomized, controlled trials directly comparing small and large bore drains.

The most common position for chest tube insertion is in the mid-axillary line, through the 'safe triangle'. This position minimizes risk to underlying structures, such as the viscera and internal mammary artery. A more posterior position may be chosen if suggested by the presence of a loculated collection. While this is relatively safe, it is not the preferred site, as it is more uncomfortable for the patient to lie on after insertion and there is more risk of the drain kinking.

For apical and large pneumothoraces extending to the apex, an antero-apical approach is favoured. It requires minimal positioning and rotation of a critically-ill patient. The second intercostal space in the mid-clavicular line is often chosen, two finger breadths from the lateral sternal border. The internal mammary vessels are at risk, but bedside ultrasound may be very helpful in choosing the optimal location, while avoiding vascular structures.

Once the lung has completely expanded and the air leak has resolved, the chest tube removal process begins. Applied suction should be discontinued first [7]. The chest tube should be clamped 6–12 hours after the last evidence of an air leak and a chest radiograph be performed 24 hours after the last evidence of an air leak [7]. If repeat chest X-ray shows resolution of pleural air, then chest tube removal is warranted.

In the case of clinical deterioration, such as worsening dyspnoea, hypoxaemia, subcutaneous emphysema, or signs of tension pneumothorax, the chest tube should be immediately unclamped and connected to suction.

When an air leak persists for more than 3–5 days then air leak management and recurrence prevention should be considered [8].

Bronchopleural fistula

A bronchopleural fistula (BPF) is a communication between the pleural space and the bronchial tree. It represents a significant clinical problem and generally occur after a spontaneous pneumothorax caused by underlying lung diseases, chest trauma, lung resection, or biopsy. The post-operative complication of pulmonary resection is the most common cause. It is also associated with increased costs and high morbidity and mortality [9].

When significant, a BPF may contribute to respiratory failure by increasing work of breathing. However, even when minimal, they can contribute to other complications related to prolonged bed rest or inactivity, such as atelectasis, deconditioning, nosocomial infections, and deep venous thrombosis [10].

The severity of the air leak is generally stratified depending on its frequency (intermittent or continuous) or its occurrence during respiratory cycles (inspiratory, expiratory, or both). Occasionally, it may be severe, leading to detectable differences in the inspired and expired tidal volumes in patients on mechanical ventilation.

When one or more large BPF occurs in a patient with acute respiratory distress syndrome (ARDS), management is extremely challenging. Ventilation is usually not a big problem since air exiting through the BPF has significant CO_2 and has contributed to CO_2 elimination. Oxygenation is the main problem, since it is difficult to maintain adequate positive end expiratory pressure (PEEP). In attempts to minimize leak and facilitate healing of the BPF, high frequency oscillatory ventilation may be useful.

Single lung ventilation may also be considered where large BPF's are present in the mechanically-ventilated patient. The strategy here would be to allow ventilation of the side without the BPF with more conventional ventilator settings, while using settings that minimize tidal volume and airway pressure on the side of the leak.

The initial management of a BPF is conservative for the first 3–5 days with tube thoracostomy, together with treatment of the underlying lung diseases. In patients receiving mechanical ventilation, reducing the air leak through ventilator adjustments to minimize the tidal volume and plateau airway pressure may also help. Ventilator settings should be adjusted to minimize both tidal volume and plateau airway pressure, which may lead to lesser alveolar distension and lower transpulmonary pressure gradient. Applying the least amount of chest tube suction necessary may also be beneficial, as well as weaning and extubating the patient as soon as possible. These strategies are not supported by high quality evidence, but elimination or reduction of contributing factors makes it less likely that a new pneumothorax will develop, or that the existing BPF will worsen and become physiologically significant.

When prolonged, current guidelines recommend early surgical consultation for possible thoracotomy or video-assisted

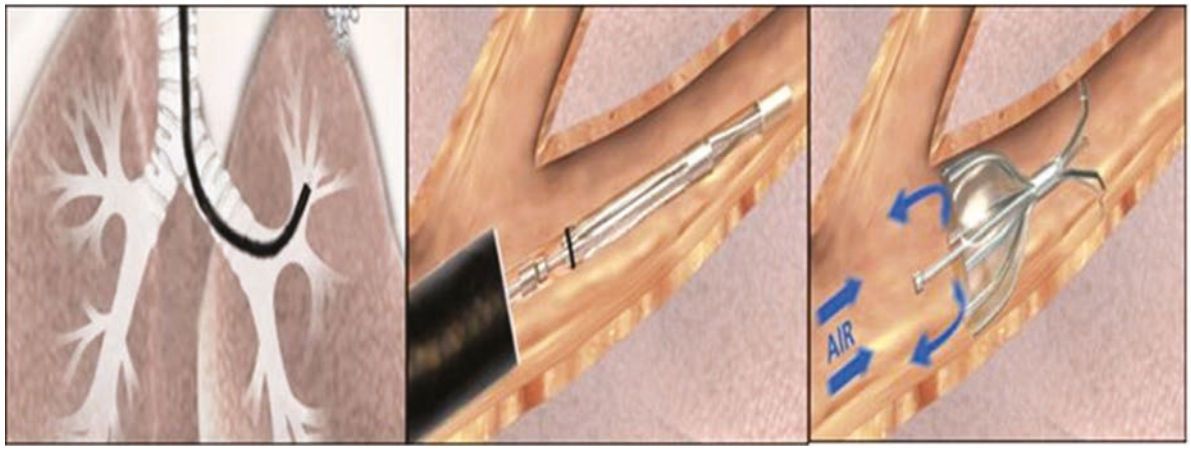


Fig. 124.3 Endobronchial valve. Placement. Left, bronchoscope introduced to culprit airway. Middle, preloaded valve into delivery catheter introduced through the scope channel. Right, deployed valve diverting air going towards broncho-pleural fistula.
Spiration® Valve System images used courtesy of Spiration, Inc.

thoracoscopic surgery [7,8], although the American College of Chest Physicians favours the latter [7].

Surgical correction of BPFs has been associated with high success rate (80–95%) and low mortality rate. However, in critically-ill patients or those with poor performance status, surgical interventions may be too risky. Bronchoscopic management is a less invasive alternative in such situations and may be conducted at the bedside in the ICU. Various devices and sealing compounds have been tried and used with flexible bronchoscopy in the past, but with limited success [11–13], such as instillation of fibrin, acrylic glue, and tissue glue [14]. Also deployment of self-expandable metallic stents or watanabe spigots have been utilized [12].

One-way endobronchial valves, initially developed for bronchoscopic reduction surgery, became available more than a decade ago and have been successfully used in case series for the treatment of prolonged air leaks [15,16]. The airway leading the air leak is initially identified using intermittent balloon occlusion. The valve is then introduced to the desired airway loaded on a delivery catheter through the working channel of the bronchoscope. The valve is umbrella-shaped when deployed in the airway. It fully expands during inspiration and blocks the airflow distally, while it slightly collapses and allows for mucus clearance during expiration (Fig. 124.3). The valve is easily removable bronchoscopically several weeks after resolution of air leak.

Conclusion

Pneumothorax and bronchopleural fistula are frequently encountered in clinical practice. In critically-ill patients, they could represent a serious problem leading to significant co-morbidities. Rapid recognition and intervention are key elements. Bedside ultrasound in the ICU is a new diagnostic tool that facilitates the early diagnosis and treatment.

Surgical correction of BPFs remains the gold standard treatment, but in critically-ill patients, several bronchoscopic interventions may be offered. One-way endobronchial valves placement in the leaky airway is a very promising new strategy in poor surgical candidates.

Acknowledgements

The authors acknowledge R. Phillip Dellinger MD, Camden, USA for his guidance in the preparation of this manuscript.

References

1. de Lassence A, Timsit JF, Tafflet M, et al. (2006). Pneumothorax in the intensive care unit: incidence, risk factors, and outcome. *Anesthesiology*, **104**, 5–13.
2. Engdahl O, Toft T, and Boe J. (1993). Chest radiograph—a poor method for determining the size of a pneumothorax. *Chest*, **103**, 26–9.
3. Mandavia DP and Joseph A. (2004). Bedside echocardiography in chest trauma. *Emergency Medical Clinics of North America*, **22**, 601–19.
4. Wilkerson RG and Stone MB. (2010). Sensitivity of bedside ultrasound and supine anteroposterior chest radiographs for the identification of pneumothorax after blunt trauma. *Academic Emergency Medicine*, **17**, 11–17.
5. Lichtenstein DA. (2009). Ultrasound examination of the lungs in the intensive care unit. *Pediatric Critical Care Medicine*, **10**, 693–8.
6. Henry M, Arnold T, and Harvey J. (2003). BTS guidelines for the management of spontaneous pneumothorax. *Thorax*, **58**(Suppl. 2), ii39–52.
7. Baumann MH, Strange C, Heffner JE, et al. (2001). Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. *Chest*, **119**, 590–602.
8. MacDuff A, Arnold A, and Harvey J. (2010). Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. *Thorax*, **65**(Suppl. 2), ii18–31.
9. Shrager JB, DeCamp MM, and Murthy SC. (2009). Intraoperative and postoperative management of air leaks in patients with emphysema. *Thoracic Surgery Clinics*, **19**, 223–31, ix.
10. Cerfolio RJ. (2002). Advances in thoracostomy tube management. *Surgical Clinics of North America*, **82**, 833–48, vii.
11. Takaoka K, Inoue S, and Ohira S. (2002). Central bronchopleural fistulas closed by bronchoscopic injection of absolute ethanol. *Chest*, **122**, 374–8.
12. Watanabe S, Watanabe T, and Urayama H. (2003). Endobronchial occlusion method of bronchopleural fistula with metallic coils and glue. *Thoracic Cardiovascular Surgery*, **51**, 106–8.
13. Varoli F, Roviaro G, Grignani F, et al. (1998). Endoscopic treatment of bronchopleural fistulas. *Annals of Thoracic Surgery*, **65**, 807–9.
14. Baumann WR, Ulmer JL, Ambrose PG, et al. (1997). Closure of a bronchopleural fistula using decalcified human spongiosa and a fibrin sealant. *Annals of Thoracic Surgery*, **64**, 230–3.
15. Travaline JM, McKenna RJ, Jr, De Giacomo T, et al. (2009). Treatment of persistent pulmonary air leaks using endobronchial valves. *Chest*, **136**, 355–60.
16. Gillespie CT, Sterman DH, Cerfolio RJ, et al. (2001). Endobronchial valve treatment for prolonged air leaks of the lung: a case series. *Annals of Thoracic Surgery*, **91**, 270–3.

CHAPTER 125

Management of pleural effusion and haemothorax

Davide Chiumello and Silvia Coppola

Key points

- The management of pleural effusion depends on type, stage, and underlying diseases.
- Primary treatment of non-malignant pleural effusions is directed to the underlying cause of pleural effusion.
- Parapneumonic effusions should be sampled by thoracentesis. A pleural fluid pH <7.2 is the single most powerful indicator to predict a need for chest tube drainage.
- The rate of re-accumulation of pleural effusion, the patient's prognosis and the severity of symptoms should guide the management of malignant pleural effusions.
- Thoracotomy is the procedure of choice for chest surgical exploration when massive haemothorax or persistent bleeding is present.

Introduction

The goal in the management of pleural effusions is to provide symptomatic relief removing fluid from pleural space and to treat underlying diseases. The management options depend on the type of pleural effusion, stage in the evolution, and underlying disease.

Diagnostic approach

Chest radiography remains the most important technique for the initial diagnosis of pleural effusion.

If an effusion is suspected, ultrasonography (US) should be performed since it is more reliable for detecting small pleural effusions in critical care setting. The major advantage of US over radiography is its ability to differentiate between free and loculated pleural effusion, then it is useful to guide thoracentesis. Computed tomography (CT) can be used to evaluate complex situations, where the anatomy cannot be fully assessed by radiography or US. Although history, physical examination, and radiographic studies may provide important clues to the cause of a pleural effusion diagnostic thoracentesis should be always performed [1–3].

The main step is to determine whether the fluid is a transudate or an exudate, using Light's Criteria [1]. If it is exudative, more diagnostic tests are required to determine the cause of the local disease—differential cell counts, smears and cultures for organisms, measurement of glucose and amylase levels, cytological analysis, and testing for a pleural fluid marker of tuberculosis. Generally, a transudate is considered as uncomplicated effusion that can be managed by conservative treatment or antibiotics alone. An exudative effusion or a large amount of loculated effusion, that is considered complicated effusion, should be managed by drainage. Complicated effusions include empyema, malignant effusion and haemothorax [2,4].

Management

Refractory non-malignant effusions

These effusions can be transudative (congestive heart failure, cirrhosis, nephrosis) or exudative (pancreatitis, connective tissue disease, endocrine dysfunction), uncomplicated or complicated.

Patients who have symptoms due to a pleural effusion that is refractory to primary treatment are candidates for additional therapies. Dyspnoea is the most common symptom that necessitates additional therapy.

Before proceeding with more invasive therapy, trapped lung should be excluded. Trapped lung refers to a fibrous pleural peel that encases the visceral pleura, while the visceral and parietal pleura are widely separated.

Bilateral symmetrical pleural effusions in a patient with congestive heart failure without fever or chest pain should be treated with diuretics before thoracentesis. However, if pleural effusion persists for more than 3 days, thoracentesis should be performed.

Repeated therapeutic thoracentesis are appropriate when the effusion re-accumulates slowly enough that repeated procedures do not become burdensome to the patient.

Additional management options for patients with non-malignant pleural effusions include in-dwelling pleural catheter for intermittent external drainage, pleuroperitoneal shunts for internal drainage, or surgical pleurectomy. These techniques have been applied in patients with non-malignant pleural effusions [3,4].

Parapneumonic effusions

Patients with severe pneumonia often develop parapneumonic effusions, with sometimes progression to empyema.

Parapneumonic pleural effusions are divided in three types:

- An **uncomplicated** effusion occurs when lung interstitial fluid increases and moves across the adjacent visceral pleural membrane.
- **Complicated** effusions occur when there is persistent bacterial invasion of the pleural space.

Table 125.1 Parapneumonic effusion characteristics and outcome

Volume of effusion	Bacteriology	Effusion pH	Outcome
From minimal to moderate free flowing effusion more than 10 mm, but <½ hemithorax	Unknown or negative culture and Gram stain results	Unknown or ≥7.20	Very low or low risk of poor outcome
Large, free flowing (≥½ hemithorax), loculated effusion	Positive culture or Gram stain or pus	<7.20	Moderate–high risk of poor outcome

For the moderate/high risk of poor outcome is sufficient that just only one of the three characteristics is present [7].

Data from Colice GL et al., (2000) 'Medical and Surgical Treatment of Parapneumonic Effusions An Evidence-Based Guideline', *Chest*, **118**, pp. 1158–71.

- An **empyema** is defined as the presence of pus in the pleural space [3].

A positive culture is not required for diagnosis since anaerobic organisms are difficult to culture or sampling is often performed after a patient has received antibiotics. Blood cultures should be performed in all patients with suspected pleural infection, although they are positive in only 14% of these patients. The usual presentation includes fever, cough, dyspnoea, chest pain, purulent sputum, leukocytosis, and new alveolar infiltrate on chest radiograph.

Radiographic and ultrasound imaging play a key role in the evaluation of parapneumonic effusions and empyema.

Optimal evaluation of empyema or loculated effusions requires chest CT scan with intravenous contrast because the pleural microbubbles may suggest that the fluid collection will be more resistant to chest tube drainage. It is clinically impossible to differentiate the presence of a complicated parapneumonic effusion requiring chest tube drainage from a simple effusion that may be resolved with antibiotics alone [5].

Pleural fluid sampling remains the most reliable diagnostic test to guide management and is recommended in all patients with a pleural effusion >10 mm depth associated to pneumonic illness or recent chest trauma or surgery. Small effusions (thickness <10 mm) usually resolve with antibiotics alone.

Pleural fluid pH should be assessed in all non-purulent effusions when pleural infection is suspected. A pleural fluid pH <7.2 is demonstrated as the single most powerful predictor for the need of chest tube drainage. Where pleural fluid pH measurement is not available, glucose and lactic dehydrogenases (LDH) should be measured: a pleural fluid glucose level <50 mg/dL may be used as an alternative marker to indicate a need for chest drain insertion [6,7].

According to the British Thoracic society, the **indications for pleural fluid drainage in pleural infection** are:

- A frankly purulent or turbid/cloudy pleural fluid or a loculated pleural collection
- The presence of organisms identified by Gram stain
- Pleural fluid pH <7.2 in patients with suspected pleural infection
- Poor clinical progress during treatment with antibiotics alone [6].

When the effusion is free-flowing, as demonstrated by lateral decubitus views or US and thoracentesis shows a non-purulent exudate with a glucose level greater than 60 mg/dL, LDH less than 1000 IU/L, and pH >7.20, the patient has a high likelihood of pleural fluid resolution with antibiotics alone over 7–14 days (uncomplicated effusion) [7,8].

Table 125.1 shows the risk of poor outcome in patients with parapneumonic effusions based on the volume of pleural effusion, pleural fluid bacteriology and pleural fluid pH, developed by an expert panel. The panel's consensus opinion suggests drainage for patients with moderate or high risk of poor outcome [7].

The choice of **antibiotic** should be based on the bacteriology. Virtually all antibiotics adequately penetrate the pleural space except aminoglycosides that may be inactivated at low pleural fluid pH. Empiric therapy should cover anaerobic organisms and include clindamycin, beta-lactam plus beta-lactamase inhibitors, and carbapenems. It is recommended that antibiotic therapy be continued until there is radiographic resolution of fluid, generally for 2–4 weeks following defervescence.

In addition to appropriate antibiotic therapy, some complicated parapneumonic effusions and all empyemas require **drainage** for resolution. Failure to improve after tube thoracostomy drainage may indicate that antibiotic coverage is not adequate or that a loculated area of empyema has developed.

Early thoracic **surgical consultation** is appropriate, as many patients require thoracoscopic, or open debridement and drainage. Proper management includes the sterilization of the empyema with appropriate systemic antibiotics (at least 4–6 weeks), the complete pleural fluid drainage, and the obliteration of the empyema cavity by adequate lung expansion.

Options for surgical solutions include open decortication and open thoracostomy. For patients who do not have good drainage of empyema from a well-placed chest tube, an intrapleural administration of fibrinolytic therapy is suggested. Continued failure of adequate pleural drainage should prompt thoracoscopy or thoracotomy to lyse adhesions, to completely drain the pleural space and optimize chest tube placement. The choice between thoracoscopic debridement and decortication depends on several factors; those favouring decortication include more adhesions, greater visceral pleural thickness and larger empyema cavity size [4,7,8].

Malignant effusions

Malignancy is the most common cause of exudative pleural effusions in patients aged >60 years [4].

Malignant pleural effusion implies disseminated disease and median survival depends upon the site and stage of the primary tumour. The decision to treat a malignant effusion depends upon the presence of symptoms and the underlying tumour type. Asymptomatic malignant pleural effusions (up to 25%) do not need to be treated as long as they attain a steady state and remain asymptomatic. Some tumour types may respond to chemotherapy with resolution of the effusion [9].

Symptomatic patients should initially undergo therapeutic thoracentesis to drain the fluid. The rate of re-accumulation of pleural effusion, patient's prognosis, and the severity of patient's symptoms

Table 125.2 Different options of management of malignant pleural effusions

Options	Clinical condition
Observation	Asymptomatic effusions (most will progress and require therapy)
Therapeutic thoracentesis	Relief of dyspnoea (most effusions can recur unless underlying tumour responds to chemo- or radiotherapy)
Chest catheter drainage	Most effusions will recur after catheter removal
Chest catheter drainage with chemical pleurodesis	Uncontrolled and recurrent symptomatic malignant effusions. 90% of patients seem to respond to talc pleurodesis
Thoracoscopy with talc insufflation	Uncontrolled and recurrent symptomatic malignant effusions. In more than 90% of patients effusion seem to be controlled
Pleurectomy	In patients who have failed chemical pleurodesis, but with reasonably long expected survival
Long-term in-dwelling pleural catheter	Symptomatic relief in patients who cannot tolerate a general anaesthesia or are not candidates for video thoracoscopy
Pleuroperitoneal shunt	When other options have failed

should guide the therapy. Patients whose malignant pleural effusion re-accumulates slowly (longer than 1 month) may be managed with therapeutic thoracentesis. Repeat pleural aspiration is recommended for the palliation of breathlessness in patients with a life expectancy <3 months [9,10].

A more aggressive intervention may be required if malignant pleural effusions recur rapidly (less than 1 month). Options include in-dwelling pleural catheter drainage, pleurodesis, pleurectomy, and pleuroperitoneal shunt. Placement of an in-dwelling pleural catheter for drainage is indicated when there is an irremediable lung entrapment or an endobronchial obstruction by tumour. This option is ideal when length of hospitalization has to be kept to a minimum because of the short duration of survival. Pleurodesis is a reasonable alternative for patients with an expected survival of few months. This therapy can be carried out in a single definitive procedure without the potential inconvenience of a long-term drainage catheter. In selected patients with trapped lung and large effusions refractory to chemical pleurodesis, pleuroperitoneal shunting is an acceptable palliative option [9,11].

A summary of the main different approaches to the management of malignant pleural effusions is shown in Table 125.2.

Haemothorax

Haemothorax needs to be differentiated from a haemorrhagic pleural effusion, as the latter can result from only few drops of blood in serous pleural fluid.

The definition of haemothorax is a pleural fluid to blood haematocrit ratio greater than 50%. Routine radiology cannot distinguish blood from other pleural effusions. CT scan helps to identify the precise location of blood. Massive haemothorax is diagnosed when 2 L drain from the chest. Blood removed from a probable haemothorax should be examined to establish its haematocrit and to exclude infection [12].

When a haemothorax is suspected, the essential management, together with appropriate resuscitation, is intercostal drainage. The only exception is the presence of clinical and radiological signs suggestive of aortic dissection or transection, because intercostal drainage can lead to rapid exsanguination.

Intercostal drainage in haemothorax achieves two objectives—to drain the pleural space allowing expansion of the lung and to allow assessment of rates of blood loss. The latter, along with the general clinical state of patient dictates further management.

Chest drains should be large enough to permit some clots to be evacuated (28–30G minimum) and should be placed at the base of the hemithorax. The ideal insertion point is the 6th intercostal space in the mid-axillary line. Lower spaces should be avoided; contraction of the hemithorax is frequently present because of pain and/or pulmonary collapse, and selection of too low space may cause iatrogenic intra-abdominal injury.

Chest tube drainage allows the monitoring of bleeding rate, may potentially tamponade bleeding, and evacuate the pleural space, thus decreasing the risk of developing empyema or a subsequent fibrothorax.

If pleural effusion persists despite tube thoracostomy, a diagnosis of clotted or retained haemothorax is made. The ideal management of clotted haemothorax is a matter of controversy. The placement of additional chest tubes can be ineffective because of the presence of clotted blood and loculations. Although thoracotomy is an effective procedure in the management of clotted haemothorax, video-assisted thoracoscopic surgery (VATS) is currently preferred to open thoracotomy [13].

One easily available and effective alternative to VATS is the use of intrapleural fibrinolysis. Recently, intrapleural streptokinase, has been shown to decrease pleural thickening and adhesion in experimental clotted haemothorax. However, more human trials are needed to confirm this finding [14].

Thoracotomy is the procedure of choice for surgical exploration of the chest when massive haemothorax or persistent bleeding is present.

Generally, indications for emergency or urgent thoracotomy in haemothorax are:

- Haemodynamic instability despite adequate resuscitation.
- Initial drainage >1500 mL.
- Continued bleeding >200 mL/hour for 3 consecutive hours.
- Continued bleeding >1500 mL/day.
- Radiographic evidence of significant retained clot (>1/3 of pleural space) [13,15].

Drainage techniques

Thoracentesis

Thoracentesis is the basic procedure not only to differentiate transudate from exudate, but also to remove the fluid in a patient with a large volume of effusion for symptomatic relief. The most common indication of diagnostic thoracentesis is fluid in the pleural space more than 10 mm in thickness on lateral decubitus chest radiograph with unknown aetiology [1,2,16]

Complications of thoracentesis include pneumothorax, haemothorax, re-expansion pulmonary oedema, and organ laceration. In general, removal of <1500 mL pleural effusion is recommended to avoid the risk of re-expansion pulmonary oedema.

Thoracentesis must be performed with care in mechanically-ventilated patients, because positive pressure ventilation increases the risk of tension pneumothorax. Thoracentesis as therapeutic procedure, may reduce respiratory distress in patients with large effusions [16].

However, Doelken et al. evaluated the effects of thoracentesis on respiratory function in mechanically-ventilated patients and did not find any significant changes in peak or plateau airway pressure or compliance of respiratory system after the procedure [17]. After fluid removal from the pleural space, changes in pulmonary gas volume and size of the thoracic cavity depend on the lung compliance compared with the chest wall compliance—the more compliant the lung is, the greater will be the increase in gas volume [16].

Thoracostomy drainage

Tube thoracostomy allows a continuous and large volume drainage of air or liquid from pleural space.

Specific indications include haemothorax, penetrating chest trauma, complicated parapneumonic effusion or empyema, chylothorax, and pleurodesis of symptomatic pleural effusions. In symptomatic or clinically unstable patients, there is no absolute contraindication to chest tube placement. The need for prophylactic antibiotics depends upon the clinical circumstances. The tube should be removed as soon as it is safe to do so. For the pleural effusions, the indications to remove the tube are when the lung is fully expanded or when the daily fluid output is less than about 100–300 mL/day. Pleurodesis should be considered for patients with uncontrolled and recurrent symptomatic malignant effusions via a tube thoracostomy or during thoracoscopy to produce a chemical serositis and subsequent fibrosis of the pleura. Pleural sclerosis should be attempted only if the lung expands fully after fluid removal. Pleurodesis failure is usually the result of suboptimal technique or inappropriate patient selection [2,4,18].

Surgical therapy

Video-assisted thoracoscopic surgery is very useful in managing incompletely drained parapneumonic effusions and clotted haemothorax. With thoracoscopy, the loculi in the pleura can be disrupted, the pleural space can be completely drained, and the chest tube can be optimally placed [4].

Radical total or subtotal pleurectomy and decortications should be reserved for patients who have failed chemical pleurodesis. Appropriate candidates must be good surgical candidates and have a reasonably long expected survival, as total radical pleurectomy/decortications is a major surgical procedure associated with some mortality [4,18].

Pleuroperitoneal shunts and in-dwelling external catheters

Pleuroperitoneal shunting is a rarely-used option for patients who have lung entrapment, malignant chylothorax, or failed pleurodesis.

In-dwelling catheters provide symptomatic relief in patients with malignant pleural effusions, who either cannot tolerate general anaesthesia or have a trapped lung that is not amenable to video-assisted thoracoscopy. The catheter is placed in the intrapleural space under local anaesthesia and drains externally when effusions are symptomatic. This drainage technique has the disadvantage of ongoing protein losses and increased risk of infection, and because of these side effects it is not used for non-malignant effusions [19].

Acknowledgements

The authors acknowledge R. Phillip Dellinger MD, Camden, USA for his guidance in the preparation of this manuscript.

References

1. Light RW. (2002). Clinical practice. Pleural effusion *New England Journal of Medicine*, **346** (25), 1971–7.
2. Thomsen TW, DeLaPena J, and Setnik GS. (2006). Thoracentesis. *New England Journal of Medicine*, **355**, e16.
3. Rahman NM, Chapman SJ, and Davies RJO. (2004). Pleural effusion: a structured approach to care. *British Medical Bulletin*, **72**, 31–47.
4. Hyeon Yu (2011). Management of pleural effusion, empyema, and lung abscess. *Seminars in Interventional Radiology*, **28**, 75–86.
5. Huggings JT, Sahn SA, Heidecker J, et al. (2007). Characteristic of trapped lung: pleural fluid analysis, manometry, and air contrast chest CT. *Chest*, **131**, 206.
6. Davies HE, Davies RJO, Davies CWH, on behalf of the BTS Pleural Disease Guideline Group (2010). Management of pleural infection in adults: British Thoracic Society pleural disease guidelines 2010. *Thorax*, **65**(Suppl. 2), ii41–ii53.
7. Colice GL, Curtis A, Deslauriers J, et al. (2000). Medical and surgical treatment of parapneumonic effusions. An evidence-based guideline. *Chest*, **118**, 1158–71.
8. Davies CW, Kearney SE, Gleeson FV, et al. (1999). Predictors of outcome and long-term survival in patients with pleural infection. *American Journal of Respiratory and Critical Care Medicine*, **160**, 1682–7.
9. Roberts ME, Neville E, Berrisford RG, et al. (2010). BTS Pleural Disease Guideline Group. *Thorax*, **65**(Suppl. 2). ii32–40.
10. American Thoracic Society. (2000). Management of malignant pleural effusions. *American Journal of Respiratory and Critical Care Medicine*, **162**, 1987–2001.
11. Heffner JE and Klein JS. (2008). Recent advances in the diagnosis and management of malignant pleural effusions. *Mayo Clinic Proceedings*, **83**, 325.
12. Parry GW, Morgan WE, and Salama FD. (1996). Management of haemothorax. *Annals of the Royal College of Surgeons, England*, **78**, 325–6.
13. Mowery NT, Gunter OL, Collier BR, et al. (2011). Practice management guidelines for management of hemothorax and occult pneumothorax *Journal of Trauma Injury, Infection, and Critical Care*, **70**(2), 510–18.
14. Agarwal R, Aggarwal AN, and Gupta D. (2006). Intrapleural fibrinolysis in clotted haemothorax. *Singapore Medical Journal*, **47**(11), 984–6.
15. Hart SR, Willis C, Thorn A, and Barfoot L. (2002). Spontaneous haemopneumothorax: are guidelines overdue? *Emergency Medicine Journal*, **19**, 273–4.
16. Chiumello D, Berto V, and Gallazzi E. (2010). In: Vincent J-L. (ed.) *The Effects of Pleural Effusion: Section IV Yearbook of Intensive Care and Emergency Medicine*, pp. 185–92. Berlin: Springer-Verlag.
17. Doelken P, Abreu R, Sahn SA, and Mayo PH. (2006). Effects of thoracentesis on respiratory mechanics and gas exchange. *Thorax*, **38**, 747–50.
18. Miller KS and Sahn SA. (1987). Chest tubes. Indications, technique, management and complications. *Chest*, **91**, 258–64.
19. Srour N, Amjadi K, Forster AJ, and Aaron SD. (2013). Management of malignant pleural effusions with indwelling pleural catheters or talc pleurodesis. *Canadian Respiratory Journal*, **20**(2), 106–10.

PART 4.16

Haemoptysis

CHAPTER 126

Pathophysiology and causes of haemoptysis

Francesco Blasi and Paolo Tarsia

Key points

- Haemoptysis varies in intensity from a minor event to a life-threatening condition.
- Criteria for the definition of massive/life-threatening haemoptysis should be better defined.
- The epidemiology of haemoptysis has changed over time, particularly in industrialized countries, where bronchiectasis and lung cancer have surpassed tuberculosis as the most frequent causes.
- The lungs are furnished with a dual blood supply, the bronchial arteries and the pulmonary arteries. Although the former account for only about 1% of arterial supply to the lung, bronchial arteries are involved in approximately 90% of haemoptysis cases.
- The mechanisms leading to haemoptysis are being better elucidated, particularly in chronic inflammatory conditions, where release of angiogenic growth factors leads to neovascularization with thin-walled fragile new vessels that are prone to rupture into the airways.

Introduction

Haemoptysis is defined as the expectoration of blood or blood-streaked sputum from the lower respiratory tract. The term derives from the ancient Greek words *haima*, meaning blood, and *ptysis*, meaning spitting. The presence of haemoptysis, even in the case of minor events, is a frightening symptom for the patient. The clinical spectrum may vary from minor blood-stained sputum to major bleeding causing respiratory failure and haemodynamic instability. Underlying causes may vary from benign, self-limiting conditions to severe, potentially lethal diseases.

There is a lack of universal consensus on the quantification and severity of haemoptysis events. Haemoptysis is considered scant when involving <5 mL, mild when <20 mL, and moderate when >20 mL. Massive haemoptysis has been varyingly defined as 100 mL/24 hours to more than 1000 mL/24 hours. Most authors apply the term massive haemoptysis to bleeding >600 mL/24 hours or >25 mL/hour. The term exsanguinating haemoptysis refers to blood loss >1000 mL/24 hours (>150 mL/hour) or >300 mL for a single expectoration event [1]. Given the unreliability in both the patient's and physician's estimates of expectorated volume, and lack of consensus cut-off volume definition, other authors define haemoptysis as massive in the presence of clinical consequences, such as respiratory failure due to airway obstruction or haemodynamic instability [2]. It has been estimated that volumes of blood in the alveoli above 400 mL are sufficient to significantly alter gas exchange. However, it must be considered than, in many situations, haemoptysis arises in patients with underlying cardiorespiratory disease. These subjects may suffer considerable worsening of gaseous exchange even for smaller quantities of blood. It has been proposed that the term 'massive' haemoptysis be substituted with 'life-threatening.' Life-threatening haemoptysis may be defined as any haemoptysis that:

- Is >100 mL in 24 hours.
- Causes abnormal gas exchange/airway obstruction.
- Causes haemodynamic instability.

Independent of its definition, massive/life-threatening haemoptysis involves only a minority of clinical events (generally 5–10%), but related mortality may exceed 50% [1,2]. Mortality is generally more the result of airway compromise with asphyxiation, rather than exsanguination.

Causes

Haemoptysis may derive from a variety of very different conditions, such as infections, pulmonary diseases, neoplastic conditions, cardiovascular alterations, vasculitis, traumatic events, haematological derangements, and iatrogenic or drug-induced events (see Box 126.1). The relative importance of different causes of haemoptysis has changed over time. For centuries, haemoptysis was considered virtually pathognomonic for pulmonary tuberculosis. The following Hippocratic aphorism: 'The spitting of pus follows that spitting of blood, consumption follows the spitting of this and death follows consumption' shows how far rooted in history is the association between haemoptysis and tuberculosis. During the course of the last century, however, effective antimycobacterial treatment and the rise in prevalence of cigarette smoking have changed the epidemiology of haemoptysis. TB continues to be a leading cause of haemoptysis in the developing world, but in industrialized countries bronchial carcinoma and bronchiectasis are more commonly reported [3].

It has been estimated that in bronchogenic carcinoma, haemoptysis presents at some point in the natural history of the disease in up to 20% of patients. Conversely, haemoptysis may be the presenting symptom in only 7% of patients with lung malignancy [4]. Haemoptysis is more likely to occur, and may manifest earlier in

Box 126.1 Causes of haemoptysis

Infection
- Mycobacterial (tuberculosis and atypical mycobacteria).
- Fungal infections (including mycetoma).
- Necrotizing pneumonia.
- Lung abscess.
- Parasitic.
- Septic emboli.

Pulmonary
- Acute bronchitis.
- Chronic obstructive pulmonary disease.
- Bronchiectasis (including cystic fibrosis).
- Alveolar haemorrhage.
- Lymphangioleiomiomatosis.
- Sarcoidosis.
- Lung transplantation.

Neoplastic
- Bronchogenic carcinoma.
- Metastatic lung cancer.
- Endobronchial tumours (bronchial adenoma, carcinoid).

Cardiovascular
- Pulmonary embolism (lung infarct).
- Pulmonary hypertension.
- Pulmonary artery aneurysm.
- Bronchial artery aneurysm.
- Left ventricular heart failure.
- Mitral stenosis.
- Arteriovenous malformations.

Vasculitic
- Wegener's granulomatosis.
- Behçet's disease.
- Goodpasture syndrome.
- Systemic lupus erythematosus.
- Antiphospholipid syndrome.

Traumatic
- Foreign body aspiration.
- Blunt or penetrating chest injury.
- Aortic aneurysm.

Iatrogenic
- Bronchoscopy.
- Endobronchial procedures (brachytherapy, dilation, stent placement, laser).
- Lung biopsy.
- Pulmonary artery catheterization.

Drugs and toxins
- Bevacizumab.
- Solvents.
- Crack cocaine.
- Penicillamine.

Haematological
- Coagulopathy (congenital, acquired, or iatrogenic).
- Thrombocytopenia.
- Platelet dysfunction.

Miscellaneous
- Cryptogenetic.
- Endometriosis.
- Broncholitiasis.

the disease course, when carcinoma originates in a major bronchus compared with more peripheral sites.

Among mycobacteria, haemoptysis is mainly related to *Mycobacterium tuberculosis*, with few reports on the involvement of non-tuberculous mycobacteria. Haemoptysis may be the result of active tuberculosis, generally with small and chronic bouts of blood, although massive haemoptysis has also been described in this context. Inactive mycobacterial disease may be associated with bleeding arising from post-tuberculous thick-walled cavities or bronchiectasis. Rarely, peri-bronchial calcified lymph node may erode into or distort an adjacent bronchus. This condition is known as broncholithiasis and may be associated with symptoms such as cough, recurrent episodes of fever and purulent sputum, and sometimes massive haemoptysis [5].

Aspergilloma is a mycotic colonization of a pre-existing lung cavity or cyst. Post-tuberculous cavities or idiopathic pulmonary fibrosis cavities are examples of pre-existing lung disease conditions that may be prone to fungal colonization. *Aspergillus fumigatus* and *Aspergillus niger* are the most commonly encountered species. The reported incidence of haemoptysis in patients with aspergilloma ranges from 54 to 87.5%. Most patients will experience mild and recurrent episodes of haemoptysis, although roughly 10% may develop massive events [6]. Invasive pulmonary aspergillosis in immunocompromised subjects is also associated with haemoptysis events, although rarely fatal.

Cystic fibrosis, usually in the context of extensive bronchiectasis, has become an increasingly common aetiology of haemoptysis, probably due to the longer survival of affected patients into adulthood. Approximately 40% of patients with cystic fibrosis will develop an episode of haemoptysis during the course of their life, with an average annual incidence of 0.87% [7].

Necrotizing pneumonia, lung abscess, and lung gangrene caused by bacteria, such as *Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae*, other *Streptococcus* spp. and *Actinomyces* spp. may be associated with haemoptysis in up to 15% of cases [8].

Bevacizumab is a monoclonal antibody that targets angiogenic factors and has been shown to be effective in the treatment of various forms of cancer. The use of this drug in patients with lung malignancy may be complicated by a high incidence of pulmonary haemorrhage, mainly in patients with squamous cell histology [9].

The event of pulmonary artery rupture during pulmonary artery catheterization (PAC) is relatively rare with an incidence of 0.01–0.47% [10]. However, when it does happen, associated mortality is considerable, being over 70%. Rupture may be due either to the catheter tip being directed into the vessel wall, or to catheter migration to a smaller calibre branch and subsequent rupturing during balloon inflation.

Pulmonary hypertension is reported as the underlying cause of haemoptysis in 0.2–4% of cases [11]. Conversely, in patients with Eisenmenger syndrome, haemoptysis is a more common finding.

In female patients with thoracic endometriosis haemoptysis represents an early clinical manifestation, occurring at an earlier age, whereas pneumothorax tends to manifest in more advanced disease. In over 80% of cases the right hemithorax is involved [12].

Diffuse alveolar haemorrhage is a rare cause of haemoptysis associated with disruption of the alveolar–capillary barrier. It should be suspected in case of haemoptysis, anaemia and bilateral infiltrates on the chest radiograph. The infiltrates are the result of distal inhalation of blood. Diffuse alveolar haemorrhage may be associated with Goodpasture's syndrome, where antibodies to type IV collagen are deposited along the alveolar and glomerular basement membranes, giving rise to haemoptysis. Diffuse alveolar haemorrhage is also associated with systemic vasculitis, such as Wegener's granulomatosis or microscopic polyangiitis. Less commonly, diffuse alveolar haemorrhage may be associated with other immunological conditions, such as systemic lupus erythematosus, Henoch–Schönlein purpura, IgA nephropathy, rheumatoid arthritis, Behçet's syndrome, and cryoglobulinaemia. Infectious processes, such as leptospirosis, malaria, and cytomegalovirus infection may present alveolar haemorrhage. A number of drugs are also associated with diffuse alveolar haemorrhage, such as propylthiouracil, carbimazole, and crack cocaine [13].

In a sizable number of cases, even after extensive diagnostic work-up, a definitive cause for haemoptosyis is not found. These cases are termed as cryptogentic haemoptysis. The incidence of cryptogenetic haemoptysis varies between different reports, with most being between 15 and 30% [14]. Most of these studies have, however, not systematically used CT evaluation on all patients. Wider availability and technical developments in CT imaging will likely result in reduced prevalence of unknown origin cases of haemoptysis in the future.

Pathophysiology

The lungs are furnished with a dual blood supply, the bronchial arteries and the pulmonary arteries. The former account for only about 1% of arterial supply to the lung and bring nutrients to the lung parenchyma, the bronchi, and vasa vasorum of the pulmonary arteries and veins. The bronchial arteries are a high-pressure circulation system. They have a variable anatomy in terms of origin and branching distribution. They generally originate from the descending thoracic aorta, at the level of the 3rd–8th thoracic vertebral body, more commonly between T5 and T6 (70–83.3% of cases) [15]. The right bronchial artery often arises together with the first aortic intercostal artery to form the intercostobronchial (ICBT) trunk, which usually branches off from the right lateral surface of the descending thoracic aorta. The left bronchial arteries conversely tend to arise from the more anterior surface of the descending thoracic aorta. The four most common bronchial artery branching patterns include type I with one right bronchial artery (rising from the ICBT) and two left bronchial arteries (present in 40.6% of cases), type 2 with one right (rising from the ICBT), and one left bronchial artery (21.3% of cases), type 3 with two right (only one rising from the ICBT), and two left bronchial arteries (20.6%), and type 4 with two right (only one rising from the ICBT), and one left bronchial artery (9.7% of cases) [15]. In approximately 20–30% of cases aberrant bronchial arteries branch off from other systemic arteries, such as the aortic arch, brachiocephalic artery, subclavian artery, internal mammary artery, inferior phrenic artery, or abdominal aorta. In addition, during chronic inflammatory processes collateral blood supply may be recruited from non-bronchial systemic arteries through transpleural vessels. These collateral non-bronchial vessels may derive from ramifications of subclavian, axillary, internal mammary arteries, as well as from subdiaphragmatic arteries. True bronchial arteries (both normal variants and aberrant) can be distinguished from these non-bronchial systemic arteries in that their trajectory into the pulmonary parenchyma parallels the bronchovascular axes. In contrast, non-bronchial systemic collateral vessels do not run parallel to the airways and have a more unpredictable origin from infradiaphragmatic arteries or from the supra-aortic great vessels or their branches, and enter the parenchyma through the inferior pulmonary ligament or through the adherent pleura; their course is not parallel to that of the bronchi.

The pulmonary arteries are a low-pressure circulation system that account for 99% of the arterial supply to the lungs and are responsible for gas exchange. The bronchial and pulmonary systems are in close proximity at the level of the vasa vasorum where they are interconnected by numerous anastomoses. These communications cause a physiological right-to-left shunt that involves approximately 5% of the total cardiac output.

Bleeding in the lungs may originate from bronchial arteries, pulmonary arteries, bronchial capillaries, and alveolar capillaries. Bronchial arteries are the most common site of bleeding causing haemoptysis, being involved in approximately 90% of cases [16]. In only 5% of cases does haemoptysis origin from the pulmonary vessels. In the remaining 5% of cases bleeding arises from ectopic bronchial arteries or other non-bronchial systemic arteries (including the aorta).

Bleeding from the pulmonary artery circulation may be found in disease processes, such as tuberculosis, mycetoma, cavitating lung carcinoma, lymphoma, Behçet disease, pulmonary arteriovenous malformations, and trauma during right heart catheterization. The most common cause of bleeding from the pulmonary circulation is Rasmussens's aneurysm. In the walls of cavitary lesions, bronchial or pulmonary arteries may be subject to deformation causing pear-shaped dilatations, which are, in truth, pseudo-aneurysmatic lesions, which may be eroded due to chronic inflammatory derangement. These aneurysms are traditionally considered responsible for haemoptysis in TB patients. However, the development of hypervascularized, dilated, tortuous bronchial vessels, often anastomotic with the pulmonary circulation, in the absence of true aneurysms, may be equally involved in these patients.

In certain situations, the thin-walled capillary communications between the high-pressure systemic bronchial arterial system, and the lower pressure pulmonary arterial system can vasodilate and enlarge. Conditions causing reduced pulmonary arterial perfusion, such as chronic thromboembolic disease and vasculitic disorders, in which there is a reduction in pulmonary arterial supply distal to the emboli, can lead to a gradual increase in the bronchial arterial contribution [3], thereby increasing the importance of bronchial-to-pulmonary artery anastomoses in regions of the lung that are deprived of their pulmonary arterial blood flow. Experimental studies have suggested that the increased bronchial arterial blood flow is due to neovascularization [3]. The anastomotic vessels, which are subjected to increased systemic arterial pressure, are often thin-walled, and prone to rupture into the alveoli or bronchial airways, giving rise to haemoptysis. During acute or chronic tracheobronchitic events, inflammation of the mucosa with vascular engorgement, desquamation, atrophy, and erosion, may lead to bleeding. Infective agents, such as *Aspergillus* spp. may release fungal endotoxins that exert haemolytic activity. Inflammatory processes release angiogenic growth factors, thus promoting neo-angiogenesis and recruitment of collateral supplies from adjacent vessels and increased anastomoses between bronchial and pulmonary arterial systems [17]. Similar mechanisms are in play in haemoptysis caused by lung cancer. Cancer growth requires new vessel formation derived from pro-angiogenic tumour-secreted cytokines becoming dominant over naturally-occurring angiogenesis inhibitors. Most common factors involved are vascular endothelial growth factor (VEGF), angiopoietin 1, fibroblast growth factor, hepatocyte growth factor, transforming growth factors α and β, platelet-derived growth factor (PDGF), tumour necrosis factor-α, and interleukin-8 [18]. Furthermore, there is evidence that VEGF elevation correlates significantly with the presence of haemoptysis in patients with pulmonary aspergilloma [19]. The hypoxic micro-environment associated with tumour growth causes cellular activation of hypoxia-inducible factor (HIF). HIF up-regulation promotes transcription of pro-angiogenic cytokines [20]. Hypoxaemia-induced angiopoietin 2 release plays an important role in initiating vessel sprouting in concert with VEGF. In contrast with angiopoietin-1, which stabilizes blood vessels, angiopoietin 2 destabilizes blood vessels, thus favouring bleeding. The new vessels associated with chronic inflammatory or tumoural pro-angiogenesis are usually thin-walled and fragile, and thus prone to rupture into the airways, therefore causing haemoptysis.

Other specific mechanisms may be involved in generating haemoptysis, in particular disease conditions. In patients with depressed left ventricular ejection fraction or mitral stenosis elevated pulmonary intravascular pressure may cause rupture of pulmonary veins or capillaries, resulting in blood-stained sputum. In patients with Goodpasture's syndrome, deposition of antibodies directed against the alveolar–capillary basement membrane disrupts capillary integrity leading to bleeding.

References

1. Garzon AA, Cerruti M-M, and Golding ME. (1982). Exsanguinating hemoptysis. *Journal of Thoracic and Cardiovascular Surgery*, **84**, 829–33.
2. Dweik RA and Stoller JK. (1999). Role of bronchoscopy in massive hemoptysis. *Clinical Chest Medicine*, **20**, 89–105.
3. Mal H, Rullon I, Mellot F, et al. (1999). Immediate and long-term results of bronchial artery embolization for life-threatening hemoptysis. *Chest*, **115**, 996–1001.
4. Hirshberg, B., Biran, I., Glazer, M., et al. (1997). Hemoptysis: etiology, evaluation, and outcome in a tertiary referral hospital. *Chest*, **112**, 440–4.
5. Reza B and Ziaollah H. (2007). Surgical management of tuberculous broncholithiasis with hemoptysis: experience with 5 operated cases. *Annals of Thoracic and Cardiovascular Surgery*, **13**, 185–90.
6. Soubani AO and Chandrasekar PH. (2002). The clinical spectrum of pulmonary aspergillosis. *Chest*, **121**, 1988–99.
7. Flume PA, Yankaskas JR, Ebeling M, Hulsey T, and Clark LL. (2005). Massive hemoptysis in cystic fibrosis. *Chest*, **128**, 729–38.
8. Reimel BA, Krishnadasen B, Cuschieri J, et al. (2006). Surgical management of acute necrotizing lung infections. *Canadian Respiratory Journal*, **13**, 369–73.
9. Johnson DH, Fehrenbacher L, Novotny WF, et al. (2004). Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *Journal of Clinical Oncology*, **22**, 2184–91.
10. Bussieres JS. (2007). Iatrogenic pulmonary artery rupture. *Current Opinion in Anaesthesiology*, **20**, 48–52.
11. Reesink HJ, van Delden OM, Kloek JJ, Jansen HM, Reekers JA, and Bresser P. (2007). Embolization for hemoptysis in chronic thromboembolic pulmonary hypertension: report of two cases and a review of the literature. *Cardiovascular Interventional Radiology*, **301**, 136–9.
12. Channabasavaiah AD and Joseph JV. (2010). Thoracic endometriosis: revisiting the association between clinical presentation and thoracic pathology based on thoracoscopic findings in 110 patients. *Medicine (Baltimore)*, **89**, 183–8.
13. Wiik A. (2008). Drug-induced vasculitis. *Current Opinion in Rheumatology*, **20**, 35–9.
14. Set PA, Flower CD, Smith IE, Chan AP, Twentyman OP, and Shneerson JM. (1993). Hemoptysis: comparative study of the role of CT and fiberoptic bronchoscopy. *Radiology*, **189**, 677–80.
15. Cauldwell EW, Siekert RG, Lininger RE, et al. (1948). The bronchial arteries: an anatomic study of 150 human cadavers. *Surgery, Gynecology and Obstetrics*, **86**, 395–412.
16. Yoon W, Kim JK, Kim YH, et al. (2002). Bronchial and nonbronchial systemic artery embolization for life-threatening hemoptysis: a comprehensive review. *Radiographics*, **22**, 1395–409.
17. McDonald DM. (2001). Angiogenesis and remodeling of airway vasculature in chronic inflammation. *American Journal of Respiratory and Critical Care Medicine*, **164**, S39–45.
18. Sun S and Schiller JH. (2007). Angiogenesis inhibitors in the treatment of lung cancer. *Critical Reviews in Oncology Hematology*, **62**, 93–104.
19. Inoue K, Matsuyama W, Hashiguchi T, et al. (2001). Expression of vascular endothelial growth factor in pulmonary aspergilloma. *Internal Medicine*, **40**, 1195–9.
20. Pugh CW and Ratcliffe PJ. (2003). Regulation of angiogenesis by hypoxia: role of the HIF system. *Nature Medicine*, **9**, 677–84.

CHAPTER 127

Therapeutic approach in haemoptysis

Francesco Blasi and Paolo Tarsia

Key points

- The diagnostic work-up involves the complementary use of CT scan, bronchoscopy, and pulmonary angiography.
- Current multidetector CT angiography is currently considered superior and less time-consuming than traditional pulmonary angiography in identifying the artery causing bleeding.
- The priority in management of massive haemoptysis involves prompt resuscitation and airway protection with patient stabilization, followed by medical and endoscopic temporary procedures.
- Super selective bronchial artery embolization (BAE) is now considered the treatment of choice in most patients with massive haemoptysis.
- In cases of recurrent haemoptysis following BAE, particularly in particular conditions such as mycetoma, surgery may still be considered a desirable option, provided the patient is sufficiently fit.

Diagnostic work-up

The aim of diagnostic studies in patients with haemoptysis is two-fold—locate the source of bleeding, and identify the underlying cause. In investigating a patient with haemoptysis, it is important to ascertain that the blood arises from the lower airways and exclude haematemesis from the gastrointestinal tract or epistaxis from the nasopharynx. Alkaline pH (using pH indicator paper), foaminess, and the presence of pus are useful bedside signs that may indicate the lungs are the source of bleeding prior to diagnostic investigation.

Complete past history regarding respiratory and cardiac diseases should be recorded. A history of co-existent haematuria may suggest the presence of diseases such as Wegener's granulomatosis and Goodpasture's syndrome. Current medications, particularly anticoagulant therapy should also be noted. The patient should undergo detailed respiratory and cardiac examination, and nutritional status should be assessed. Additional important signs include finger clubbing, presence of palpable lymph nodes, and signs of skin or mucosal bleeding.

Blood tests should evaluate clotting profile, platelet count, and haemoglobin levels. Repeat testing may be necessary to better quantify the entity of blood loss. Blood gas analysis is essential to assess gas exchange. Sputum testing should be performed for bacteria, mycobacteria and fungi, and malignant cells, particularly in long-term smokers.

Chest X-ray

In most cases, this is the first radiographic investigation performed, and may be informative regarding a number of conditions involving the lung parenchyma, pulmonary vasculature, or the heart. Both a posterior–anterior and a lateral film should be obtained. Pulmonary masses, cavitary lesions, pneumonia, chronic pulmonary disease, or atelectasis may be visualized. Even though the true nature of the disease may not be immediately apparent, a chest radiograph may identify and localize the site of bleeding to one lung or a single lobe in 33–82% of cases [1,2], allowing more focused additional testing. In approximately 20–40% of cases, initial chest X-ray may be normal or non-informative (showing chronic or unchanged abnormalities) [3]. A normal chest radiograph is not sufficient to stop investigations for identifying the condition underlying the haemoptysis, as additional testing such as CT scan may reveal conditions such as pulmonary emboli, pulmonary hypertension, bronchiectasis, or initial interstitial disease, not detectable by a plain chest radiograph. Furthermore, it has been reported that between 5 and 6% of patients with haemoptysis, and a normal chest radiograph, a lung cancer is eventually identified [4].

Chest CT scan

Chest CT scan may allow correct localization of the bleeding site in 65–100% of cases [1,5,6]. Several studies demonstrate that CT is at least equal if not superior to bronchoscopy in identifying the cause of haemoptysis [5,6]. The site of haemorrhage may be localized due to detection of liquefied material within bronchi or ground glass infiltrates in the lung parenchyma. Recently, multidetector computed tomography (MDCT) techniques allow scans of the whole thorax in a single breath hold (little more than 10 seconds), with slice thickness approaching 1 mm. Contrast-enhanced MDCT with both two- and three-dimensional volumetric imaging allow high resolution angiographic studies [7]. MDCT angiography is particularly useful to interventional radiologists prior to planning bronchial arterial embolization.

In a study comparing traditional invasive angiography with CT angiography, the latter allowed more precise demonstration of both bronchial and non-bronchial systemic arteries [8]. Multidetector CT has also proven effective in identifying haemoptysis deriving from the pulmonary artery circulation [9].

CT scans also present some limitations. In severe unstable patients or in cases with active bleeding that requires airway management, shifting the patient to the radiology department may be problematic and bedside bronchoscopy is often preferred in this context.

Bronchoscopy

This procedure may be of help in a number of ways following or during haemoptysis events. It may allow identification of the lung or lobe causing the bleeding, identify the underlying cause, it may help clear the airways from blood clots favouring gas exchange, and finally it may be a means by which therapeutic manoeuvres to stop the bleeding are put in place. It also allows airway sampling, thus obtaining specimens for identification of bacterial, fungal, mycobacterial, or tumoural causes of haemoptysis. Bronchoscopy allows identification of bleeding up to the fifth or sixth generation of bronchi.

Optimal timing for bronchoscopy is still a matter of debate. Bronchoscopy is often performed 'early' (within the first 12–18 hours) due to the fact that bleeding may increase with time rendering later visualization of the airways less effective. This may be more pertinent for clinically stable patients or when bleeding has stopped. On the other hand, in patients with massive haemoptysis it is now possible to perform MDCT angiography or traditional invasive angiography with immediate embolization of culprit bronchial arteries within a very short time span. In these patients, bronchoscopy may be performed 'late' as an aid to identify the underlying cause of haemoptysis, and allowing microbiological and cytological analysis. There is, as yet, no definitive proof that 'early' bronchoscopy is associated with better outcomes.

Rigid bronchoscopy was the procedure of choice in the past. The procedure allows aspiration of large quantities of blood, use of therapeutic manoeuvres, while ensuring adequate ventilation [10]. One drawback of rigid bronchoscopy is the more limited capacity to explore the peripheral bronchial tree and the upper lobes compared with flexible bronchoscopy. Flexible bronchoscopy has now become the most common procedure in patients with haemoptysis, as it may be performed at the patient's bedside and allows visualization of segmental and subsegmental bronchi [11]. Due to the limited size of its operational channel, flexible bronchoscopy has a more limited suctioning capacity compared with rigid bronchoscopy. Fibre optic bronchoscopy identifies the site of bleeding in 73–93% of cases [11], with a lower diagnostic yield recorded in cases of mild-to-moderate haemoptysis.

Within the diagnostic framework of haemoptysis, bronchoscopy, and CT scan should not be considered as alternative procedures, but rather as complementary, each allowing specific information regarding site and cause identification.

Pulmonary angiography

Diagnostic pulmonary angiography was traditionally considered the procedure of choice to identify the source of bleeding. Moreover, it allows bronchial artery embolization during the same procedure. However, given the variability of the bronchial artery supply, complete angiographic investigation of orthoptic and ectopic bronchial arteries to identify the origin of bleeding may be quite time consuming. If CT, bronchoscopy, or both are performed prior to angiography, a better definition of the site of bleeding allows considerable shortening of procedure time. During angiography, signs that may be used to determine the site of bleeding include vessel size, vascular blush, focal hypervascularization, and presence of vascular shunts.

Over the last decade, it has become apparent that diagnostic angiography is less effective than MDCT angiography in detecting the site of bleeding [8].

Therapeutic approach

Treatment of haemoptysis may vary considerably, ranging from outpatient management to intensive care unit admittance. Choice of optimal management depends on the intensity of bleeding, degree of respiratory compromise, and severity of underlying cardiorespiratory status. Mild haemoptysis may be handled on an outpatient basis with antibiotics and symptomatic treatment, such as antitussives. For more severe cases, hospitalization is required for diagnostic and therapeutic work-up. Blood abnormalities must be corrected with corresponding blood products. Tranexamic acid is an antifibrinolytic agent that acts by inhibiting plasminogen activation. Oral or intravenous formulations of this agent have been employed in patients with mild-to-moderate haemoptysis. Intravenous vasopressors do not seem to have a role in the routine management of haemoptysis due to concerns in patients with co-existing coronary artery disease or hypertension. It has been suggested that bronchodilator use may best be limited in patients with haemoptysis as these drugs may exert vasodilator effects, thus facilitating bleeding recurrence [8].

Important steps in the management of patients with massive haemoptysis include:

- Resuscitation, airway protection, and patient stabilization as the priority.
- Subsequent localization of the site of bleeding.
- Specific interventions to stop the bleeding and prevent recurrence.

Intubation may be required with a large bore tube (preferably size 8 or more) to facilitate airway suctioning. A double-lumen endotracheal tube may be used when diseased side isolation is required in order to protect the unaffected lung. The left-sided tube is easier to place compared with the right-sided tube. The latter carries a higher risk of obstructing the right upper lobe bronchus, given that it originates rather proximally along the right main bronchus. Initial management also includes volume resuscitation, and correction of underlying coagulation disorders. If the site of bleeding includes only one lung, the affected side should be kept dependent in lateral decubitus in order to prevent aspiration to the contralateral side. The true clinical validity of this theoretical consideration has not been test in controlled trials.

Bronchoscopic treatment

As discussed earlier, bronchoscopy may be of use in a number of ways in patients with haemoptysis, allowing site of bleeding identification, sampling of the lower airways, airway clearing, and institution of therapeutic manoeuvres. The relative advantages and disadvantages of rigid versus fibre optic bronchoscopy that have been discussed regarding the diagnostic use of bronchoscopy, apply to the therapeutic aspects of the technique also.

Instillation of different types of substances has been used in the treatment of patients with haemoptysis. Cold saline lavage may be performed with 50-mL aliquots of refrigerated (4°C) saline,

instilling roughly 500 mL overall volume. This technique may be effective in stopping bleeding [11]. A rigid bronchoscope is generally preferred due to better suction capacity compared with fibre optic bronchoscopy.

Topical vasoconstrictive agents have been tested, mainly in cases of bronchoscopy-induced airway bleeding. Adrenaline (1:20,000) [11], or antidiuretic hormone derivatives, such as terlipressin (0.5 mg) and ornipressin (5 IU) have been used [12], but their efficacy in massive haemoptysis is debated since the drugs are easily diluted and washed away. Likewise, endoscopic instillation of fibrinogen-thrombin or thrombin has been evaluated, but efficacy has not been convincingly demonstrated [13]. Endobronchial application of tranexamic acid (500–1000 mg) may be used in mild-to-moderate cases. Temporary endobronchial tamponade with a balloon catheter is a commonly employed procedure. 4 Fr 80-cm long Fogarty catheters can be inserted through a flexible bronchoscope and ensure emergency control of bleeding while awaiting bronchial artery embolization or surgery [14]. Alternatively, Freitag et al. [15] developed a 6 Fr 170-cm long double lumen balloon catheter. The second lumen facilitates instillation of cold saline or topical agents. A detachable valve at the proximal end of the catheter allows easy removal of the bronchoscope with minimal risk of balloon displacement. The prolonged use of balloon catheter tamponade is discouraged as ischaemic mucosal injury and post-obstructive pneumonia may ensue.

A number of endobronchial materials or procedures have been used to facilitate temporary bleeding interruption, such as airway stents, silicone spigots, oxidized regenerated cellulose mesh, sealing glues, Nd-YAG laser, cryotherapy, and brachytherapy, particularly in the context of haemoptysis caused by endobronchial carcinoma [11].

Bronchoscopy treatment strategies may allow temporary control of bleeding, buying time while patients' conditions are stabilized. In some instances, the procedures may provide long-lasting haemostatic effects, but in many cases of massive haemoptysis provides temporary relief while awaiting more definitive treatment, such as bronchial artery embolization or surgery.

Bronchial artery embolization

Bronchial artery embolization (BAE) is performed during pulmonary angiography by occluding systemic vessels and blocking arterial blood flow to fragile vessels within diseased tissue. Non-selective BAE was associated with a greater rate of inadvertent occlusion of spinal arteries. More recently, microcatheter superselective bronchial artery catheterization has allowed more stable positioning within the bronchial tree and more distal cannulation avoiding spinal artery embolization.

BAE is now considered the procedure of choice in patients with persistent haemoptysis following medical management, massive haemoptysis, recurrence of haemoptysis, in candidates deemed unfit for surgery, or as an emergency procedure to temporarily control bleeding, while awaiting surgery. Embolizing materials include gelfoam, polyvinyl alcohol (PVA) particles, dextran microspheres, or steel coils. PVA particles, available in a variety of particulate sizes (generally measuring between 350–500 μm in diameter) are the most commonly used agents. These non-absorbable particles prevent recanalization. Metal coils tend to occlude more proximal vessels and render subsequent embolization virtually impossible, but are the material of choice in pulmonary artery aneurysms and in pulmonary arteriovenous malformations. With BAE, immediate control of bleeding may be obtained in 70–95% of patients. Recurrence has been reported in 10–30% of cases [16]. However, the procedure may be repeated safely over time. Recurrence may be due to non-optimal embolization of bronchial arteries, collateral vessel formation, origin of the bleeding from the pulmonary artery circulation, and presence of non-bronchial systemic arteries. Early recurrence (within weeks) of bleeding is generally caused by incomplete embolization, whereas late rebleeding is more likely due to recanalization of embolized vessels or collateral circulation due to progression of the underlying disease condition. Some lung cavitary conditions, such as mycetoma are more prone to recurrence than others and are ultimately best managed by surgery. Persistent recurrence may also be associated with within bleeding arising from the pulmonary artery circulation.

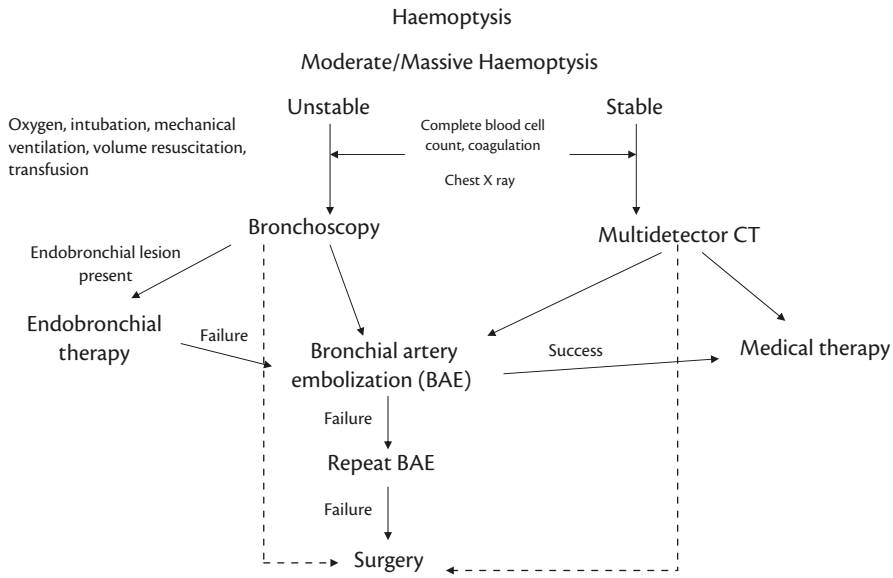


Fig. 127.1 Treatment algorithm for the management of haemoptysis.

Common complications following BAE include fever, dysphagia (present in 1–18% of cases), and chest or back pain (in 24–91% of cases) [17]. These side effects are generally transitory and are probably the result of the occlusion of vessels supplying the oesophagus, and diaphragmatic and pleural visceral pleura. The most feared complication is paraplegia derived from occlusion of spinal arteries that arise from bronchial or intercostal arteries. Use of superselective microcatheters has currently reduce the rate of this complication to <1%. In patients with massive haemoptysis the death rate following BAE is between 7 and 18% [18].

Surgery

Prior to BAE, surgery was considered to be the most effective method of controlling massive haemoptysis. Surgical mortality may be as high as 40% in the emergency setting, with additional morbidity in another 25–50% [19]. Mortality is considerably greater in emergency situations than in elective surgery. Moreover, most case series are now over 20 years old, and mortality has probably dropped considerably over the last decade due to improved surgical techniques and expertise.

Surgery is still considered the strategy of choice in conditions known to exhibit poor response to BAE, such as mycetoma. Additional situations where surgery is still indicated are complex arteriovenous malformations, iatrogenic pulmonary artery rupture, localized bronchiectasis and tuberculosis scars. Radiation therapy is a further option in patients with mycetoma or vascular tumours with massive recurrent haemoptysis [20]. Its effects are mediated through necrosis of feeding blood vessels and vascular thrombosis due to perivascular oedema.

Haemoptysis treatment algorithm

Haemoptysis, particularly massive haemoptysis, may present as a clinical emergency. Prompt patient stabilization, diagnostic testing, and therapeutic management are best obtained through multidisciplinary activation of intensivists, pulmonologists, radiologists, and thoracic surgeons. Fig. 127.1 presents a treatment algorithm that summarizes diagnostic and therapeutic options available for patients with massive haemoptysis.

References

1. Khalil A, Soussan M, Mangiapan G, Fartoukh M, Parrot A, and Carette MF. (2007). Utility of high-resolution chest CT scan in the emergency management of hemoptysis in the intensive care unit: severity, localization and aetiology. *British Journal of Radiology*, **80**, 21–5.
2. Ong TH and Eng P. (2003). Massive hemoptysis requiring intensive care. *Intensive Care Medicine*, 29, 317–20.
3. Flower CDR and Jackson JE. (1996). The role of radiology in the investigation and management of patients with hemoptysis. *Clinical Radiology*, **51**, 391–400.
4. Herth F, Ernst A and Becker HD. (2001). Long-term outcome and lung cancer incidence in patients with hemoptysis of unknown origin. *Chest*, **120**, 1592–4.
5. Revel MP, Fournier LS, Hennebicque AS, et al. (2002). Can CT replace bronchoscopy in the detection of the site and cause of bleeding in patients with large or massive hemoptysis? *American Journal of Roentgenology*, **179**, 1217–24.
6. Hsiao EI, Kirsch CM, Kagawa FT, et al. (2001). Utility of fibreoptic bronchoscopy before bronchial artery embolization for massive hemoptysis. *American Journal of Roentgenology*, **177**, 861–7.
7. Bruzzi JF, Rémy-Jardin M, Delhaye D, et al. (2006). Multi-detector row CT of hemoptysis. *Radiographics*, **26**, 3–22.
8. Remy-Jardin M, Bouaziz N, Dumont P, et al (2004). Bronchial and nonbronchial systemic arteries at multi-detector row CT angiography: comparison with conventional angiography. *Radiology*, **233**,741–9.
9. Khalil A, Parrot A, Nedelcu C, Fartoukh M, Marsault C, and Carette MF. (2008). Severe hemoptysis of pulmonary arterial origin: signs and role of multidetector row CT. *Chest*, **133**, 212–19.
10. Karmy-Jones R, Cuschieri J, and Vallieres E. (2001). Role of bronchoscopy in massive haemoptysis. *Chest Surgery Clinics of North America*, **11**, 873–906.
11. Sakr L and Dutau H. (2010). Massive haemoptysis an update on the role of bronchoscopy in diagnosis and management. *Respiration*, **80**, 38–58.
12. Tüller C, Tüller D, Tamm M, and Brutsche MH. (2004). Hemodynamic effects of endobronchial application of ornipressin versus terlipressin. *Respiration*, **71**, 397–401.
13. De Gracia J, Dela Rosa D, Catalan E, Alvarez A, Bravo C, and Morell F. (2003). Use of endoscopic fibrinogen-thrombin in the treatment of severe hemoptysis. *Respiratory Medicine*, **97**, 790–5.
14. Gottlieb LS and Hillberg R. (1975). Endobronchial tamponade therapy for intractable hemoptysis. *Chest*, **67**, 482–3.
15. Freitag L, Telkolf E, Stamatis G, Montag M, and Greschuchna D. (1994). Three years experience with a new balloon catheter for the management of haemoptysis. *European Respiratory Journal*, **7**, 2033–7.
16. Lee EW, Grant JD, Loh CT, and Kee ST. (2008). Bronchial and pulmonary arterial and venous interventions. *Seminars in Respiratory and Critical Care Medicine*, **29**(4), 395–404.
17. Chun JY, Morgan R, and Belli AM. (2010). Radiological management of hemoptysis: a comprehensive review of diagnostic imaging and bronchial arterial embolization. *Cardiovascular and Interventional Radiology*, **33**, 240–50.
18. Yoon W, Kim JK, Kim YH, Chung TW, and Kang HK. (2002). Bronchial and nonbronchial systemic artery embolization for life-threatening hemoptysis: a comprehensive review. *Radiographics*, **22**, 1395–409.
19. Bussieres JS. (2001). Massive hemoptysis. In: P. Slinger (ed.) *Principles and Practice of Anesthesia for Thoracic Surgery*. New York: Springer Science + Business Media LLC
20. Shneerson JM, Emerson PA, and Philips RH. (1980). Radiotherapy for massive haemoptysis from an aspergilloma. *Thorax*, **35**, 953–4.

SECTION 5

The cardiovascular system

PART 5.1

Physiology

CHAPTER 128

Normal physiology of the cardiovascular system

Hugh Montgomery and Rónan Astin

Key points

- Central venous pressure is not a good guide to preload, or a good predictor of the response to a volume challenge.
- Assessment of the dynamic response of pulse pressure or stroke volume to altered preload identifies fluid responsiveness.
- Afterload is influenced by factors other than simple peripheral vascular resistance.
- Ill-judged peripheral vasoconstriction can lead to decreased cardiac output in the setting of poor left ventricle function and/or hypovolaemia.
- Global cardiac output must be maintained at a level that can support the metabolic demands of the body, but within a range of arterial pressures commensurate with the limits imposed by the autoregulation of individual organ perfusion.

Introduction to the normal physiology of the cardiovascular system

The cardiovascular system (CVS) serves an essential 'delivery' service to every cell. This is not simply restricted to the supply of oxygen from the lung and nutrients from the gut and visceral stores, but of water, hormones and electrolytes. Likewise, it must remove waste products of metabolism such as carbon dioxide, water, and acids, from cells. The CVS also transports heat (e.g. from exercising muscle to the skin), playing a key role in thermoregulation. In performing such roles, the CVS needs to be both redistributive and responsive, being able to change both the scale of its global (macrovascular) and local (microvascular/regional) convective function.

Cardiac performance

Alongside venous compression by skeletal muscle contraction, and respiratory muscle generation of negative intrathoracic pressure (*vis a fronte*), cardiac contraction makes the greatest contribution to the hydraulic work that drives blood flow within the human circulation.

All cardiac chambers are composed of cardiomyocytes, the force (and velocity) generated by which depend upon their size, intrinsic contractile properties, and state of health, response to neurohormonal facilitators (such as tri-iodothyronine) and inotropic stimuli (sympathetic efferent activity, circulating catecholamines), biochemical factors (such as oxygen availability and electrolyte balance) and crucially, loading conditions (stretch or preload). The force generated by any cardiac chamber thus depends upon the same factors that influence the contraction of the myocytes of which the chamber is composed, as well as by the number and orientations of those cells.

Preload

Consider a heart facing constant resistance to efferent flow (afterload), and an unchanging biochemical and neurohormonal milieu. In this state, the force generated by the contracting chamber (the left ventricle (LV), for example) will depend upon the degree to which its constituent cardiomyocytes are stretched. This, in turn, will depend upon the chamber volume (end-diastolic volume (EDV)). This relationship is described by the Frank–Starling curve—with increasing LV preload, stroke volume (SV) rises until a plateau is reached (see Fig. 128.1).

The position of the curve is also affected by ventricular compliance (or distensibility). Because the right ventricle (RV) is generally thinner and more compliant than the LV, its Frank–Starling curve lies upwards and to the left of that for the LV. For any given stroke volume, left ventricular end-diastolic pressure (LVEDP) is thus normally higher than right ventricular EDP (RVEDP).

Compliance is also affected by disease. A left ventricle exposed to lifelong pressure overload may have an increased wall thickness and altered wall composition (with substantial deposits of collagen), meaning that high end-diastolic volumes may yield high intracavity pressures, but have limited capacity to stretch individual myocytes (see Fig. 128.1).

Nonetheless, for any given ventricle at any time, end-diastolic volume is a good measure of preload. In clinical practice, the relationship between EDV and cardiac work is hard to discern, due to difficulties in the direct measurement of hydraulic work and cardiac volume. SV is thus often used erroneously as a surrogate for cardiac work, and end-diastolic pressure (EDP) for cardiac volume.

The flaws with this approach are obvious. First, stroke volume may vary over time quite independently of work, for instance, with changes in afterload or inotropic status. Secondly, EDP depends upon both EDV and ventricular **compliance** ($\Delta EDV/\Delta EDP$), which varies greatly between individuals (as mentioned previously). A high EDP may occur in the presence of a low EDV when compliance is poor. The stretch 'perceived' by the myocyte may be lower still. Furthermore, the relationship between EDV and EDP is not linear, especially at higher volumes, meaning that changes in EDV in response to a fluid challenge become increasingly hard

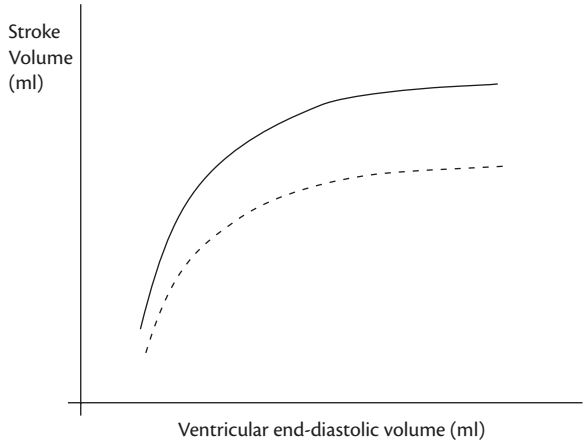


Fig 128.1 The Frank–Starling curve in a healthy ventricle (solid line). As ventricular volume (preload) rises, so too does cardiac work. Under constant conditions of afterload and inotropic drive, this is reflected by a rise in stroke volume towards a plateau. Stroke volume (and ejection fraction) can be increased by a reduction in afterload (such as that induced by vasodilatation), causing the curve to shift upwards and to the left. This does not reflect an inotropic response—the 'stroke work versus EDV' curve is unaffected. The dotted line represents a diseased ventricle. The curve has moved downwards and to the right such that, at any given preload, stroke work (and volume) are reduced. Thus, end-diastolic volume (and with it, pressure) will need to rise if SV is to remain unchanged. The same holds true if ventricular compliance is reduced.

to infer as intravascular volume expands. Compliance may also change over shorter timescales, given that diastolic relaxation is partly an active process.

While left ventricular end-diastolic pressure can be inferred from measurement of pulmonary artery occlusion pressure, pulmonary artery flotation catheters are now infrequently used in routine clinical practice. As a result, central venous pressure (CVP) is taken to infer RV end-diastolic pressure, while changes in RVEDP are also used to infer **left** ventricular EDP. CVP estimates right atrial pressure, and this is often used as an index of right ventricular filling. However, CVP changes in response to alterations in intrathoracic pressure and these changes only influence preload if they are incompletely transmitted across the vessel wall. The degree to which this is true cannot be readily determined. Changes in ventricular compliance and venous tone compound such effects, making CVP a poor guide to RVEDP (and thus LVEDP).

Static measures of CVP (and even of RVEDP) thus provide little insight into the patient's position on the 'Starling curve' and thus their capacity to increase SV in response to a volume challenge ('volume-responsiveness') [1]. This fact is of some importance, given that only half of haemodynamically-unstable intensive care unit patients are responsive in this manner [2]. Instead, dynamic assessment of the SV response to altered preload is required, for which a number of methods are currently used.

Ventricular loading changes during the **positive pressure** ventilatory cycle. The inspiratory phase decreases venous return and thus RV preload, but increases RV afterload. Right ventricular SV thus falls, as does LV filling and, a short while later, SV—usually during expiration [3]. The effects are greatest when both ventricles are operating on the steep portion of the Starling curve. Respiratory cycle-associated changes in SV (or pulse pressure) >12% predict the response to volume loading. Of note, such predictive power is dependent upon the use of tidal volumes of at least 8 mL/kg, and is invalidated by any spontaneous breathing or arrhythmias [4].

Changes in loading can be actively induced to predict volume responsiveness. A 5% increase in SV in response to a 15-second end-expiratory hold is strongly predictive [5]. Lower limb elevation to 45° while rendering of the trunk supine from a 45° position will volume load the RV from the leg and abdominal compartments. This also has value in predicting the response to an exogenous fluid challenge [6].

Afterload

Once ventricular systole has been initiated, the contractile work performed by the heart must be converted into flow. **Afterload**, the contractile tension across the ventricular wall (**wall tension**, T), represents the force to be overcome before the cardiac muscle can shorten and thus start ejecting blood. For a ventricle, Tt = Pr, where the product of contractile wall tension (T) and average wall thickness (t) matches the product of transmural pressure (P) and chamber radius (r) at end-diastole. Thus,

$$T = Pr/t. \qquad \text{[eqn 1]}$$

Increases in afterload reduce the volume of blood expelled for any given amount of cardiac contractile work and can result from various factors. First, afterload varies with wall thickness. More dynamically, chamber radius increases as a function of ventricular filling as EDV rises. Meanwhile, increased impediment (**impedance**) to the flow of ejected blood will also increase afterload. Impedance, in turn, rises if the **resistance** to average flow rises, or if there is limitation to the rate of change of flow through changes in vascular **compliance**—a less stiff vessel will more readily accept ejected blood. In clinical practice, compliance is not monitored, while resistance is derived from measurements of flow and pressure. Ohm's Law relates the constant flow of electric current (I) around an electrical circuit of resistance 'R' to the motive force (voltage, V) driving that flow:

$$V = IR, \text{ or } I = V / R \qquad \text{[eqn 2]}$$

Similarly, continuous flow of blood around a biological circuit (as seen in the microvasculature) is also determined by the ratio of the motive force (the pressure gradient across that vascular bed) and the resistance to flow that the bed offers. Thus, for the systemic circulation:

$$CO = \left(MAP - CVP\right) / SVR \qquad \text{[eqn 3]}$$

where CO represents cardiac output, MAP is mean arterial pressure, CVP is central venous pressure, and SVR systemic vascular resistance.

If pressures are measured in mmHg and flow in mL/sec, resistance can be expressed in mmHg per mL/sec which, when multiplied by 1333, yields the more familiar dynes/sec/cm^5. One dyne represents the force required to accelerate 1 g at a rate of 1 cm/sec^2. Such units are not readily amenable to simple mental calculation at the bedside, where MAP and CVP, and cardiac output, are presented in units of mmHg and L/min, respectively. Using these, SVR can be calculated in Wood's units, where a 'normal range' generally lies between 10 and 20.

In the absence of a substantial shunt, pulmonary blood flow should match systemic cardiac output. If mean pulmonary arterial pressure (PAP) and LVEDP are known, then pulmonary vascular resistance (PVR) can be calculated:

$$PVR = (PAP - LVEDP) / CO \quad \text{[eqn 4]}$$

Finally, one should not forget that afterload is the tension **across** the ventricular wall. As such, it will be influenced by **pleural pressure**. Large negative pleural pressures thus increase afterload and reduce cardiac output. This effect is most readily observed in the asthmatic where cardiac output (and with it, blood pressure (BP)) falls during inspiration, while perhaps being augmented by forceful expiration against resistance. The resultant drop in inspiratory blood pressure is recognized as '***pulsus paradoxus***', an exaggeration of the effect seen during normal breathing.

Vascular flow

As described in 'Afterload' the rate of constant flow through rigid tubes is determined by the ratio of the driving pressure gradient to the resistance (R) to flow. R is, in turn, determined by the radius (r) and length (L) of the tube, and the viscosity of the flowing fluid (η), so that:

$$R = \pi r^4 / (8 \eta L) \quad \text{[eqn 5]}$$

Blood viscosity is influenced most strongly by red cell concentration. A normal haematocrit is associated with a total blood viscosity some three-fold higher than the surrounding plasma alone. However, in critical care, resistance is more generally determined (and modified) by changes in arteriolar cross-sectional area.

As the larger arteries subdivide, the total cross-sectional area of the vasculature increases. The velocity of flow through each vessel thus falls, allowing time for exchange by diffusion. Even small reductions in arteriolar diameter (driven by circulating vasopressor agents such as vasopressin or norepinephrine, or increases in sympathetic efferent output), produces dramatic increases in resistance. If overall cardiac output remains constant, flow velocity through these arterioles rises, while BP (the product of flow and resistance) increases. Alternatively, such increases in afterload may be associated with reductions in flow if cardiac work cannot be augmented sufficiently. In the patient suffering progressive and significant hypovolaemia, a rising resistance initially compensates for a falling cardiac output to maintain the BP. Ultimately, however, such compensation fails and pressures fall. Similarly, the poorly judged use of vasoconstrictor agents in a patient with poor ventricular function (and relatively 'fixed' cardiac work) will 'convert' this work from flow to pressure: a rise in BP will be associated with a reciprocal fall in cardiac output. This is especially true if this scenario occurs in the context of relative hypovolaemia.

Pressure versus flow

For life to be sustained, perfusion must be maintained. While maintenance of adequate global blood flow (cardiac output) can be achieved across a wide range of different pressure/resistance combinations, this is not universally true when specific organs are considered. The phenomenon of **autoregulation** of flow describes the ability of different vascular beds to maintain constant regional flow across a restricted range of different pressures by adjustment of local resistance. Thus, a combination of metabolic and arteriolar myogenic/neurogenic mechanisms maintain constant cerebral blood flow (CBF) across MAP values ranging from approximately 60 to 140 mmHg. This range is influenced by various neuroendocrine and biochemical factors, and by disease states. The same is true of the renal vasculature, where a combination of myogenic mechanisms and tubuloglomerular feedback maintain constant flows until MAP falls below approximately 70 mmHg.

The minimum arterial pressures required for normal global organ function will vary with the individual, and must be judged on that basis. The longstanding hypertensive is likely to have reset their autoregulation to higher ranges, while local (occult) macrovascular stenoses may reduce effective organ perfusion pressure below that which is recorded systemically.

References

1. Marik PE, Baram M, and Vahid B. (2008). Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest*, **134**(1), 172–8.
2. Marik PE, Cavallazzi R, Vasu T, and Hirani A. (2009). Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients. A systematic review of the literature. *Critical Care Medicine*, **37**, 2642–7.
3. Theres H, Binkau J, Laule M, et al. (1999). Phase-related changes in right ventricular cardiac output under volume-controlled mechanical ventilation with positive end-expiratory pressure. *Critical Care Medicine*, **27**, 953–8.
4. De Backer D, Heenen S, Piagnerelli M, Koch M, and Vincent JL. (2005). Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Medicine*, **31**, 517–23.
5. Monnet X, Osman D, Ridel C, Lamia B, Richard C, and Teboul JL. (2009). Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients. *Critical Care Medicine*, **37**, 951–6.
6. Cavallaro F, Sandroni C, Marano C, et al. (2010). Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive Care Medicine*, **36**, 1475–83.

PART 5.2

Cardiovascular monitoring

CHAPTER 129

ECG monitoring in the ICU

Sanjay Gandhi and William R. Lewis

Key points

- Cardiac monitoring with early defibrillation reduces mortality in patients with confirmed myocardial infarction.
- Key goals of monitoring include detection of arrhythmia, identification of myocardial ischaemia and monitoring of the QT interval in the patient at risk for adverse cardiac events.
- Up to 20% of ICU patient develop arrhythmias detectable by ECG monitoring.
- Significant improvements in technology allow for increased automation and improved accuracy of the monitoring equipment.
- Trained personnel are required to interpret, and respond to telemetry alarms and initiate appropriate treatment.

Introduction

Electrocardiographic (ECG) monitoring is routinely used in hospitals for patients with a wide range of cardiac and non-cardiac diagnoses. Besides simple monitoring of heart rate and detection of life-threatening arrhythmias, the goals of ECG monitoring include detection of myocardial ischaemia, diagnosis of complex arrhythmia, and identification of a prolonged QT interval. The ECG remains a cornerstone in diagnosis and management of patients with coronary ischaemia. Over the past decade there has been an increase in the number and complexity of electrophysiological interventions, including complex ablations, biventricular pacing and insertion of implantable defibrillators. ECG monitoring in these patients can serve both a protective and diagnostic purpose—they detect life-threatening arrhythmias and double up as in-patient Holter monitors. Unfortunately, there are no randomized controlled trials of in-hospital cardiac monitoring, expert opinions based on clinical experience and published research in the field of electrocardiography form the basis of current guidelines [1].

Specific indications

Broadly, the indications for ECG monitoring can be categorized into three subgroups, with some degree of overlap—monitoring arrhythmia, detection of myocardial ischaemia, and identification of a prolonged QT interval.

Detection of arrhythmia

Lawrie et al. [2] showed that a 20% reduction in mortality from acute myocardial infarction could be achieved by early detection of ventricular fibrillation in this population. The highest risk of ventricular fibrillation after myocardial infarction is in the first 24 hours [2]. The typical duration of monitoring is 48–72 hours following an uncomplicated myocardial infarction. In the current era, aggressive mechanical and pharmacological interventions have reduced the mortality and incidence of malignant arrhythmia in patients with acute coronary syndromes. However, despite these advances, in a study of 6355 patients with non-ST elevation acute coronary syndrome undergoing Holter monitoring for 7 days, 20% had ventricular tachycardia, 14.7% had myocardial ischaemia, and 5.3% had both [3]. Having both conditions was associated with poor cardiovascular outcomes at 1 year. ECG monitoring is indicated in patients in the early phase of acute coronary syndromes and after complicated percutaneous coronary interventions. ECG monitoring is also used after placement of an intra-aortic balloon pump, both for monitoring for arrhythmia, but also to use the ECG as a trigger for the balloon pump.

ECG monitoring is also recommended in patients resuscitated from in- or outpatient cardiac arrest, due to a high risk for recurrence. Patients with high-grade conduction blocks, long QT interval, syncope, status epilepticus post-implantable cardioverter defibrillator (post-ICD) or pacemaker placement, or complex electrophysiological ablation also benefit from ECG monitoring.

Patients undergoing cardiac surgery are at high risk of ventricular and supraventricular arrhythmias, and an especially high incidence of post-operative atrial fibrillation [4]. These patients are monitored for a minimum of 48–72 hours post-operatively. Atrial epicardial leads can be monitored in these patients for improved accuracy of post-operative tachycardia.

In the intensive care setting, patients with major trauma, respiratory failure, sepsis, acute pulmonary embolism, after non-cardiac surgery, severe electrolyte abnormalities, acute heart failure, acute stroke, and drug overdose are routinely monitored. Twenty per cent of these patients develop significant arrhythmia, most commonly atrial fibrillation and ventricular tachycardia [5].

ST segment ischaemia monitoring

Asymptomatic ischaemic events, as detected by ECG monitoring, occur in 80–90% of patients with unstable angina and are associated with adverse short- and long-term outcomes [1]. However, no randomized clinical trials have demonstrated that addition of computerized ST monitoring improves patient outcomes in these patients. Computerized ST segment monitoring, while available on current generation of ECG monitors, is therefore underutilized [6]. Current guidelines recommend the use of continuous ST segment monitoring for a minimum of 24 hours in patients with acute

coronary syndromes. In addition, continuous ST segment monitoring is also recommended for 8–12 hours, in combination with serial biomarkers, to triage patients who present to the emergency department for evaluation of chest pain syndromes. Baseline ST segment changes should be taken into consideration when interpreting the results of ST segment monitoring for a given patient. Furthermore, in patients with baseline left bundle branch block, a ventricular paced rhythm of other confounding arrhythmia (e.g. atrial flutter), ST segment monitoring is not helpful.

QT interval monitoring

A corrected QT interval (QTc) >500 milliseconds is associated with a higher risk of torsades de pointes and mortality in acutely ill patients [7]. Risk factors for prolonged QT include female sex, electrolyte abnormalities, QT interval prolonging drugs, ischaemia, and acute neurological events. As the T wave is often obscure, most current cardiac monitors do not have algorithms to measure QT interval so manual measurements are required. Serial QT interval measurements should be done in the same lead for comparison. Current guidelines recommend the use of QT interval monitoring in patients who are prescribed anti-arrhythmic and other pro-arrhythmic drugs known to cause torsades de pointes, patients with new onset bradyarrhythmia, severe electrolyte abnormalities, and patients with acute neurological events.

Monitoring system and staffing

Lead systems

Unlike a standard 12-lead ECG, the electrodes for monitoring are placed on the torso to avoid motion artefact. The conventional bipolar three electrode system has the capability to monitor leads I, II, III, or a modified chest lead. This allows for single lead monitoring at any given time. While this may be adequate to monitor heart rate, it is limited in its ability to diagnose complex arrhythmias or to allow ST segment monitoring. More commonly, a five-electrode system, with four limb electrodes and a chest electrode, is used to provide data from six limb leads and any one of the chest leads, typically V1. These monitors also typically provide two channels, usually one limb lead and one chest lead. Multiple lead displays also minimize data loss due to noise. While more elaborate 6–10 electrode systems with the capability to provide a derived 12-lead ECG are available, they are not routinely used. Detection algorithms developed by various manufacturers are tested against standardized rhythm databases according to protocols established by Association for the Advancement of Medical Instrumentation. In post-cardiac surgery patients, an atrial electrocardiogram can be obtained by attaching any one of the electrodes to the atrial epicardial wire.

Attention should be paid to proper lead placement and careful skin preparation to acquire high quality data.

Staffing

The technology for cardiac monitoring has improved significantly since 1967 with increased automation of arrhythmia and ischaemia detection, remote alarms, and the ability to store and display a large amount of digitized data. However, alarms must still be triaged, interpreted, and acted upon to translate the clinical benefit of monitoring. In the National Survey of Continuous Electrocardiographic monitoring, 55% of US hospitals employed a monitor watcher in their 'step down' or telemetry unit [8]. Monitor watchers can immediately review any alarms, may detect subtle changes that do not trigger alarm, assure high quality tracings, and can free nurses for clinical care of the patients. Employing monitor watchers has been shown to increase accuracy of arrhythmia detection and reduce the incidence of sustained ventricular tachycardia [9]. However, as monitoring devices have now improved in their accuracy, in units with a good nurse-to-patient ratio the role of monitor watcher may be somewhat redundant. In a study by Funk et al. there was no difference in mortality, frequency of transfer to the ICU, or life- threatening arrhythmia in 2383 patients on the same cardiac unit with and without a monitor watcher over a period of 9 months [10]. While combined monitoring of several units with a single remote monitor watcher can be considered, it is preferable to have monitoring responsibility at the level of the monitored step-down or telemetry unit.

More importantly, the nursing staff or monitor watcher should be well trained with both didactic and hands-on practice. Physician and nursing leadership should establish staff training standards, define individual roles and responsibilities regarding cardiac monitoring, and establish protocols for documentation and response to monitor alarms. Appropriate life support systems, including defibrillators, temporary pacemakers, and medications, are required to treat serious arrhythmia and should be readily available in these units.

Conclusion

ECG monitoring has become the standard of care in patients at risk for cardiac arrhythmia or ischaemia. There has been a significant improvement in monitoring equipment over the past several decades. Highly-trained personnel are still required to identify serious arrhythmias and carry out appropriate corrective interventions in a timely fashion for better patient outcomes. Finally, in the age of optimum utilization and increased emphasis on cost and efficiency, care patient selection for ICU, and telemetry monitoring units are essential.

References

1. Drew BJ, Califf RM, Funk M, et al. (2004). Practice standards for electrocardiographic monitoring in hospital settings: an American Heart Association scientific statement from the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young: endorsed by the International Society of Computerized Electrocardiology and the American Association of Critical-Care Nurses. *Circulation*, **110**, 2721–46.
2. Lawrie DM, Greenwood TW, Goddard M, et al. (1967). A coronary-care unit in the routine management of acute myocardial infarction. *Lancet*, **ii**, 109–14.
3. Harkness JR, Morrow DA, Braunwald E et al. (2011). Myocardial ischemia and ventricular tachycardia on continuous electrocardiographic monitoring and risk of cardiovascular outcomes after non-ST-segment elevation acute coronary syndrome (from the MERLIN-TIMI 36 Trial). *American Journal of Cardiology*, **108**, 1373–81.
4. Creswell LL, Schuessler RB, Rosenbloom M, and Cox JL. (1993). Hazards of postoperative atrial arrhythmias. *Annals of Thoracic Surgery*, **56**, 539–49.
5. Reinelt P, Karth GD, Geppert A, and Heinz G. (2001). Incidence and type of cardiac arrhythmias in critically ill patients: a single center

experience in a medical-cardiological ICU. *Intensive Care Medicine*, **27**, 1466–73.
6. Sangkachand P, Sarosario B, and Funk M. (2011). Continuous ST-segment monitoring: nurses' attitudes, practices, and quality of patient care. *American Journal of Critical Care*, **20**, 226–37.
7. Pickham D, Helfenbein E, Shinn JA, et al. (2012). High prevalence of corrected QT interval prolongation in acutely ill patients is associated with mortality: results of the QT in Practice (QTIP) Study. *Critical Care Medicine*, **40**, 394–9.
8. Jenkins LS and George, V. (1995). Heart Watch: national survey of continuous electrocardiographic monitoring in U.S. hospitals. *Journal of Nursing Administration*, **25**, 38–44.
9. Stukshis I, Funk M, Johnson CR, and Parkosewich JA. (1997). Accuracy of detection of clinically important dysrhythmias with and without a dedicated monitor watcher. *American Journal of Critical Care*, **6**, 312–17.
10. Funk M, Parkosewich JA, Johnson CR, and Stukshis I. (1997). Effect of dedicated monitor watchers on patients' outcomes. *American Journal of Critical Care*, **6**, 318–23.

CHAPTER 130

Arterial and venous cannulation in the ICU

Ronan O'Leary and Andrew R. Bodenham

Key points

- Vascular access is a core skill and all practitioners should be confident with a variety of techniques. High-quality training is essential.
- Choice of site, techniques, and devices follows careful consideration of the indication, probable duration of therapy, concomitant pathologies, and potential for complications.
- Ultrasound guidance is the standard technique for central venous access, and is also increasingly used for peripheral venous and arterial cannulation.
- All cannulae should be inserted aseptically. Cannulation sites must be regularly inspected for signs of infection and lines removed promptly if indicated.
- Always consider catheter-related complications, especially sepsis, in unexpectedly deteriorating patients.

Introduction

Despite being almost ubiquitous within the critically-ill population, vascular access remains a frequent cause of iatrogenic injury, manifested as both procedural complications, and later events such as infection and thrombosis. Untoward events are minimized by expert tuition and meticulous practical technique. Consensus guidelines on vascular access are shown in Table 130.1. This chapter covers vascular access during in critical illness and discusses the development of more advanced techniques.

Vascular access, particularly central venous catheterization, should not be undertaken lightly. Can a patient be managed without vascular access or can the number of vascular access devices be rationalized? Other routes for drug and fluid administration exist, particularly enterally during the recovery phase.

General principles

These principles apply to all interventions within the ICU and elsewhere in the hospital. Only when life is threatened should vascular access be hurried. Otherwise, practitioners should observe meticulous aseptic technique, and provide adequate anaesthesia and sedation. Central venous access should mimic operative infection control practices.

- **Planning**: consider optimal choice of device, insertion site, duration of therapy, and co-existing pathology. Consider the probable demands on the operator and whether there is sufficient time to complete a complicated task.
- **Explanation and consent**: informed consent should be documented if practicable. If not, the indication with an analysis of risks and benefits should be recorded.
- **Asepsis**: clearly essential for insertion and aftercare, and an area of increasing medico-legal scrutiny. Checklists derived from work at Michigan [1] provide a framework (Fig. 130.1).
- **Anaesthesia and analgesia**: all but the smallest devices should be inserted under local anaesthesia in both awake and sedated patients.
- **Post-insertion**: confirm position by successful aspiration and flushing of the catheter, pressure measurements and waveform display, with X-ray, electrocardiographic, or ultrasound verification. Appropriate anchorage is essential to avoid dislodgement, with conscientious aftercare to reduce infection.

Peripheral venous cannulae

This core skill may be performed poorly, is not risk-free, and the dexterity required in challenging cases is often underestimated. Recently developed aids to visualization, including transillumination tools and infrared devices, although intuitively attractive have yet to demonstrate a clear-cut clinical benefit.

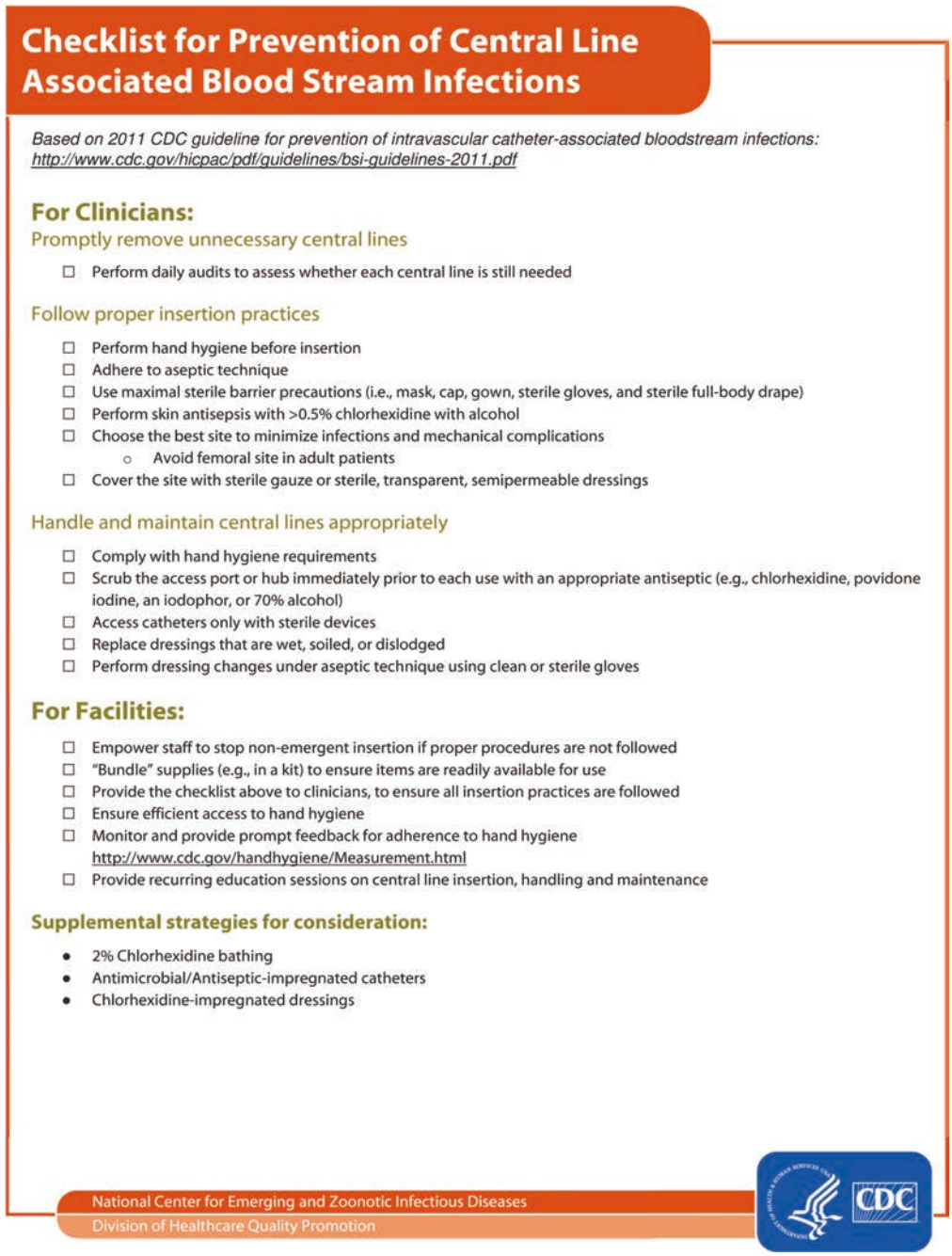
Cannulae of variable sizes and flow rates are available, including longer length devices. Common insertion sites include the dorsum of hand and forearm. The ante-cubital fossa and other joint flexures should be avoided. Less obvious sites include the scalp in infants, upper arm, chest wall in adults, and the external jugular vein. Discomfort may be minimized by using the smallest gauge appropriate device, and local anaesthetic for larger cannulae. Once inserted and secured, vigilance must be maintained for signs of infection and phlebitis.

Ultrasound aids cannulation of larger peripheral veins, particularly in children [2,3]. It allows visualization of the vessel, while the needle/cannula is introduced at a steep angle to the skin until flashback is seen, and then advanced until imaged within the vein. The needle is then flattened and the cannula passed over the needle into the vein. Agitated saline can confirm patency and location, which is otherwise difficult with deeper veins.

Table 130.1 Consensus guidelines on ultrasound-guided vascular access

Organization	Context	Ref.
International consensus of experts	International evidence-based recommendations on ultrasound-guided vascular access	[4]
UK Assoc Anaesthetists	2016 guidance on vascular access	[5]
American Society of Anesthesiologists	All short-term CVCs	[6]
Swedish Society of Anaesthesiology and Intensive Care Medicine	2014 national guidance on all aspects CVCs	[7]

Data from various sources. See references.



Checklist for Prevention of Central Line Associated Blood Stream Infections

Based on 2011 CDC guideline for prevention of intravascular catheter-associated bloodstream infections:
http://www.cdc.gov/hicpac/pdf/guidelines/bsi-guidelines-2011.pdf

For Clinicians:

Promptly remove unnecessary central lines

- ☐ Perform daily audits to assess whether each central line is still needed

Follow proper insertion practices

- ☐ Perform hand hygiene before insertion
- ☐ Adhere to aseptic technique
- ☐ Use maximal sterile barrier precautions (i.e., mask, cap, gown, sterile gloves, and sterile full-body drape)
- ☐ Perform skin antisepsis with >0.5% chlorhexidine with alcohol
- ☐ Choose the best site to minimize infections and mechanical complications
  - Avoid femoral site in adult patients
- ☐ Cover the site with sterile gauze or sterile, transparent, semipermeable dressings

Handle and maintain central lines appropriately

- ☐ Comply with hand hygiene requirements
- ☐ Scrub the access port or hub immediately prior to each use with an appropriate antiseptic (e.g., chlorhexidine, povidone iodine, an iodophor, or 70% alcohol)
- ☐ Access catheters only with sterile devices
- ☐ Replace dressings that are wet, soiled, or dislodged
- ☐ Perform dressing changes under aseptic technique using clean or sterile gloves

For Facilities:

- ☐ Empower staff to stop non-emergent insertion if proper procedures are not followed
- ☐ "Bundle" supplies (e.g., in a kit) to ensure items are readily available for use
- ☐ Provide the checklist above to clinicians, to ensure all insertion practices are followed
- ☐ Ensure efficient access to hand hygiene
- ☐ Monitor and provide prompt feedback for adherence to hand hygiene
  http://www.cdc.gov/handhygiene/Measurement.html
- ☐ Provide recurring education sessions on central line insertion, handling and maintenance

Supplemental strategies for consideration:

- 2% Chlorhexidine bathing
- Antimicrobial/Antiseptic-impregnated catheters
- Chlorhexidine-impregnated dressings

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion

CDC

Fig. 130.1 Michigan checklist for central vascular access.
Reproduced from http://www.cdc.gov/HAI/pdfs/bsi/checklist-for-CLABSI.pdf, © CDC 2014.

Peripherally inserted central venous catheters

A long catheter (with up to three lumens) may be inserted into a peripheral vein, usually in the arm, and passed into central veins where it may remain for prolonged periods. ECG guidance is increasingly used. With practice they are easy and safe to insert, associated with low rates of complications, and are useful for parenteral nutrition or antibiotics during the convalescent phase of illness. Peripherally-inserted central venous catheters (PICCs) can be inserted via antecubital veins or, preferably, using ultrasound to identify deeper upper arm veins away from joint flexures. For ease of passage, the basilic or brachial vein should be used as the cephalic vein runs a more tortuous course. Power-injectable PICC devices allow liquids, e.g. radiological contrast solution, to be injected under high pressure (up to 325 psi). Midlines catheters utilize a similar technique with a shorter catheter whose tip lies in axillary/subclavian vein.

Arterial access

These are typically used for haemodynamic monitoring and sampling, with larger cannulae used for extracorporeal circuits and radiological interventions. Serious complications are uncommon with the former, but not the latter, in particular the femoral cannulae used for extracorporeal membrane oxygenation circuits. Seldinger-type insertion kits are increasingly used for all devices. Ultrasound guidance is useful in the arteriopath, or where oedema and multiple previous cannulations combine to make access difficult, and to access superficial or deeper non-palpable arteries (e.g. mid-forearm) [8].

Site selection is important, even on first cannulation. Consider the risk-benefit ratio of multiple attempts at poor distal vessels, versus a finite risk of successfully cannulating an end-artery more proximally. Peripheral cannulation is typically performed via the radial artery of the non-dominant arm at the wrist. A patent ulnar artery implies the radial is not an end-artery so, if occluded, tissue loss should not occur. Allen's test (compression of radial/ulnar artery, while assessing hand perfusion), while attractive conceptually, does not reliably predict safe cannulation. The brachial artery may be used but, being an end-artery, there is a risk of distal limb occlusion although this has not been demonstrated in retrospective case series [9,10]. Avoid repeated peripheral attempts in hypotensive, vasoconstricted patients, and consider ultrasound early in difficult patients.

The femoral artery is a valuable access site widely used for diagnostic and interventional procedures, but carries increased risks of infection and thrombosis with prolonged catheterization. The superficial femoral artery is often more palpable than the common, but partially overlies the vein and is more likely to be diseased with atheroma. Proximal puncture above the inguinal ligament can lead to occult haemorrhage into the retroperitoneal space which may be life-threatening. Ultrasound should be used to assess patency and guide cannulation (Fig. 130.2).

Catheter removal should be done aseptically. Firm pressure should be applied to the site for at least 10 minutes. Occasionally, persistent bleeding from a superficial artery may require a fine skin suture or tissue glue. Pressure dressings are rarely helpful when a deeper arterial cannulation site continues to bleed. Radiological occlusion devices or surgical closure are required for devices larger than 9 Fr, in the presence of severe coagulopathy, or in areas where pressure cannot be applied. Large, tense haematomas may need surgical drainage, irrespective of vessel closure.

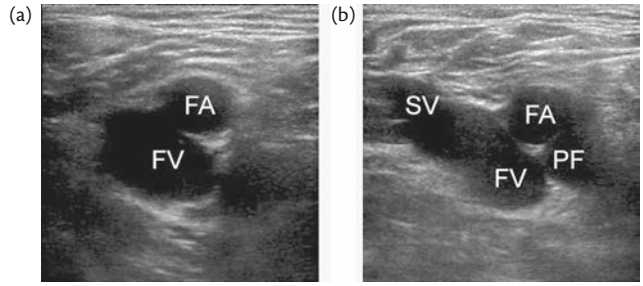


Fig. 130.2 Ultrasound anatomy of the femoral region which may be complex and variable. Left side as viewed from below. (a)Vessels close to the inguinal ligament with common femoral artery (FA) partially overlying the femoral vein. (b) Lower in the groin the superficial artery (SFA) overlaps the FV and profunda femoral artery (PFA). The long saphenous vein (SV) is joining the FV.

Central venous catheters

Central venous access is essential in the management of critically-ill patients and few patients cannot be successfully cannulated centrally, even if only temporarily. Even so, always consider whether peripheral access may be more appropriate, and remove lines inserted under emergency and prehospital conditions as soon as possible. The roles and indications for these devices is widening, while the scrutiny of their complications is increasing [11,12]. Insertion of central venous catheters (CVCs) should closely adhere to institutional or national infection prevention guidance. Infections can be minimized by careful site selection, ultrasound guidance, strict asepsis, insertion packs, and checklists, and frequent monitoring [13].

The internal jugular vein (IJV) is probably the most common site of cannulation. The right IJV approach has the lowest rate of procedural complications and catheter tip misplacement, but an increased risk of infection compared with infraclavicular subclavian routes probably arising from oropharyngeal or tracheostomy contamination. Cannulae sited in the IJV are awkward to dress and awake patients find the site uncomfortable. Many landmark approaches to the IJV have been described. The development of higher-resolution ultrasound equipment has revealed vulnerable and less well appreciated vessels, and other structures near to common insertion sites.

The axillary vein runs from the apex of the axilla, behind the posterior border of the clavicle, and across the first rib to join the subclavian vein and then the IJV forming the brachiocephalic vein behind the sternoclavicular joint. Landmark approaches were traditionally associated with an increased complication rate compared with the IJV, particularly pneumothorax and incorrect tip placement, but recent studies have challenged this (add ref 16 see end). It is, however, a more comfortable site, and easier to dress and keep clean. Ultrasound guidance is associated with safer and more successful techniques for cannulation of the subclavian (via infraclavicular or supraclavicular approaches), or axillary vein (Table 130.2).

Table 130.2 Selected studies employing ultrasound for vascular access

Site	Study population	Comments	Year	Ref.
Internal jugular	Critical care	RCT comparing ultrasound- with landmark-guided cannulation of the IJV Success, time to cannulation and number of attempts all significantly lower in ultrasound group. All complications were lower in ultrasound group, but reported rate of complications higher than expected in a modern critical care setting	2006	[17]
Internal jugular	Elective patients undergoing long-term catheterization	>98% Success on first attempt No cases of pneumothorax No cases of significant haemorrhage	2010	[18]
Subclavian	Critical care	RCT comparing landmark subclavian with ultrasound-guided subclavian/axillary vein. Higher rates of success, reduction in time to cannulation and complications in the ultrasound group	2011	[19]
Infraclavicular axillary vein	1923 Elective patients undergoing long term catheterization	Rate of all major complications >1% in a complex heterogenous group. High rate of success in patients previously cannulated	2012	[20]

Data from various studies. See references.

The femoral vein has the highest rate of infections and thrombosis, and can be associated with occult retroperitoneal haemorrhage. It is uncomfortable for awake and mobile patients (especially with large, stiff catheters), and difficult to keep clean and dress. However, it is often indispensible during life-threatening emergencies, and some extracorporeal circuits are best sited using femoral vessels. The anatomy is more complicated than the side-to-side orientation of vein and artery typically depicted. As with all central sites, ultrasound guidance is recommended.

Tip positioning

The importance of tip position in the superior vena cava (SVC) requires anatomical knowledge. The SVC is a confluence of the two brachiocephalic veins formed behind the first right costal cartilage, is approximately 2 cm wide and 7 cm long with no valves, and descends to the right atrium (RA). Its lateral right border is partially visible on anteroposterior chest X-rays, but it can be difficult to see where the right atrium begins, but this can be estimated from a distance of two vertebral bodies plus discs (verterbral body units) below the carina. Its upper right border bulges into the right pleural space so a tear here risks major haemorrhage into the low-pressure pleural environment.

The catheter tip should lie in the long axis of the SVC or the upper RA, and should not abut the vein wall at an angle. The apparent position of a central venous line on an anteroposterior X-ray may be misleading [15]. Several structures project over an approximate catheter path in the SVC and RA (e.g. ascending aorta, pleura, mediastinum, internal mammary vessels), further difficulties occur if the film is suboptimal or there is distorting pathology.

Catheter misplacement within the venous system is common, either to the neck veins, contralateral side or down an arm—these are generally obvious on X-ray. Catheters outside the venous system are of greater concern so careful assessment is needed before using or removing such catheters. Rare patients have congenital variants e.g. a left sided or a bilateral SVC. Increasing numbers of patients who have had long term CVCs (e.g. for dialysis, cancer, cystic fibrosis) will have central vein narrowing or blockage, with implications for new CVC placement.

Complications

Any anatomical structure adjacent or connected to the vascular tree may be damaged during needle, catheter and guide wire insertion, or later due to thrombosis, perforation and infection. Certain procedural complications are recognized as potentially life-threatening and a cause for high-value legal claims (e.g. haemothorax from great vessel damage, inadvertent carotid cannulation with stroke, and cardiac tamponade [16]).

The most flexible and narrowest gauge catheter possible should be used to reduce insertion trauma and vein irritation. Vessel diameter can be measured ultrasonically and compared with the catheter diameter. A catheter occupying more than one-third of the vein diameter increases the risk of thrombosis. Large-bore cannulae for massive transfusion or dialysis/haemofiltration do not traverse corners easily so the right IJV or femoral veins should be used where possible. The risk of extravasation with peripheral cannulae used for large-volume pressurized fluid infusions should be balanced against those of large-bore central venous catheters, the latter being generally safer if the right expertise and equipment are available.

Guide wires should pass centrally without resistance, but may go astray; without X-ray screening there is no certainty of excluding misplacement. Dilators and catheters passed over a guide wire will enlarge the tract to their diameter, but when inserted over a kinked or excessively angulated guide wire may tear the vein and exit into adjacent structures. The guide wire should be repeatedly checked to ensure free movement to confirm no distortion or false passage.

Poor catheter tip position increases risks of thrombosis, arrhythmias, perforation, and longer-term stenosis. Catheter tips (particularly from the left) can perforate the vein wall and cause a hydrothorax when fluids are infused. The lower half of the SVC is within the fibrous pericardium, where a perforation followed by infusion may cause pericardial tamponade. Ideally, an adequate length of the distal catheter should lie in the SVC long axis with its tip above the pericardial reflection (approximately level with the carina on X-ray). However, this is frequently not achievable, particularly with left-sided catheters; the tip may need to lie within

the pericardial reflection or in the upper right atrium, or as a short-term measure in the left brachiocephalic vein.

Removal

Central catheters should be removed once they are no longer required in a head-down position to avoid air entrainment. Anchorage devices should be removed first, Pressure should be applied for a few minutes and the site covered with an occlusive dressing. Prolonged pressure should be avoided over the carotid artery when removing jugular lines.

Ultrasound-guided central venous access

Ultrasound-guided access allows direct vessel visualization, optimal target site identification, and examination for. thrombosis, valves, dissection, atheroma, or other anatomic abnormalities. Used via the IJV and other routes, it reduces complications, number of attempts and time to successful cannulation, and is recommended by national bodies (Table 130.1). Evidence is accumulating that confirms utility at a variety of sites (Table 130.2). A typical sequence is shown in Fig. 130.3.

Ultrasound is evolving with developments in advanced imaging and needle visualization techniques. These have the potential to advance safety and efficacy in more challenging patients and access sites. For example, compound imaging techniques and the use of multi-modal sensors may accurately identify needle position within a 2D ultrasound image.

Key principles aid successful ultrasound-guided cannulation:

- Position the display opposite to the operator, and orientate the image anatomically as seen from the side of the operator. The display orientation marker is matched to a palpable probe marker.
- Veins are easily compressible. Larger central veins show respiratory fluctuation, and valves may be visible. Arteries are pulsatile, round and not easily compressible. Peripheral arteries typically have characteristic double vena comitantes. Colour Doppler differentiates pulsatile arterial flow from the more continuous venous flow pattern.
- Vessels may be viewed in short axis (out of plane) or long axis (in plane). It is common to use the short axis during needle insertion, but it takes practice to maintain constant needle-tip visualization as the tip may inadvertently pass through the beam and the shaft be mistaken for the tip. Alternatively, the vein may be imaged longitudinally or transversely, and the needle inserted in the long axis. This gives superior needle/wire views, but may not provide concurrent images of surrounding structures and is more challenging to learn.

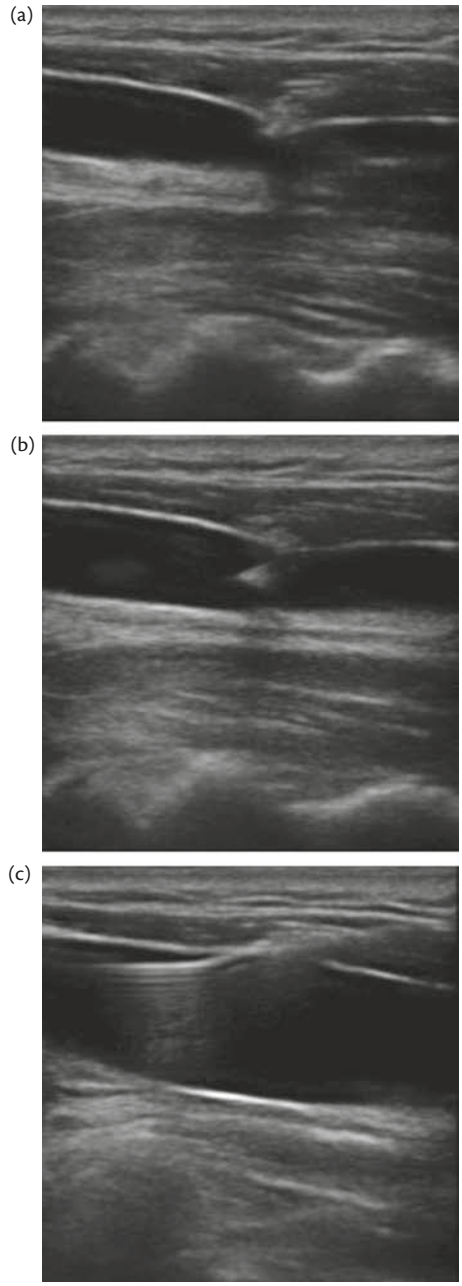


Fig. 130.3 Ultrasound-guided insertion of needle and guide wire to internal jugular vein. The needle tip is identified throughout its path from skin to vein lumen (a). This requires precise positioning as the needle shaft may be confused with the tip. Once the needle tip is visualized within the lumen (b), the guide wire is passed and confirmed to lie within the vein (c).

Conclusion

Vascular access is a key element of critical care and should be practised to an advanced level by all critical care practitioners. It requires comprehensive structured tuition, detailed understanding of anatomy, and thorough post-insertion care. Procedural complications can be reduced by ultrasound and other aids. Vascular catheters act as a potential reservoir and route of transmission for nosocomial infection; this necessitates meticulous attention to insertion technique and monitoring for infection. The future is likely to bring organizational changes to the teaching and assessment of vascular access, including high-fidelity simulation, international guidelines and position statements, standardized advanced equipment and greater scrutiny of complications.

References

1. Pronovost P, Needham D, Berenholtz S, et al. (2006). An intervention to decrease catheter-related bloodstream infections in the ICU. *New England Journal of Medicine*, **355**, 2725–32.

2. Triffterer L, Marhofer P, Willschke H, et al. (2012). Ultrasound-guided cannulation of the great saphenous vein at the ankle in infants. *British Journal of Anaesthesia*, **108**, 290–4.
3. Shiver S, Blaivas M, and Lyon M. (2006). A prospective comparison of ultrasound-guided and blindly placed radial arterial catheters. *Academic Emergency Medicine*, **13**, 1275–9.
4. Lamperti M, Bodenham AR, Pittiruti M, et al. (2012). International evidence-based recommendations on ultrasound-guided vascular access. *Intensive Care Medicine*, **38**, 1105–17.
5. AAGBI working party on vascular access. Safer Vascular access 2016. Available from AAGBI website. http://www.aagbi.org.
6. Rupp SM, Apfelbaum JL, Blitt C, et al. (2012). Practice guidelines for central venous access: a report by the American Society of Anesthesiologists Task Force on Central Venous Access. *Anesthesiology*, **116**, 539–73.
7. Frykholm P, Pikwer A, Hammarskjöld F, et al. (2014). Clinical guidelines on central venous catheterisation. Swedish Society of Anaesthesiology and ICM. *Acta Anaesthesiologica Scandinavica*, **58**, 508–24.
8. Shiloh AL and Eisen LA. (2010). Ultrasound-guided arterial catheterization: a narrative review. *Intensive Care Medicine*, **36**, 214–21.
9. Frezza EE and Mezghebe H. (1998). Indications and complications of arterial catheter use in surgical or medical intensive care units: analysis of 4932 patients. *American Surgery*, **64**, 127–31.
10. Scheer B, Perel A, and Pfeiffer UJ. (2002). Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. *Critical Care*, **6**, 199–204.
11. Bodenham A. (2006). Can you justify not using ultrasound guidance for central venous access? *Critical Care*, R175.
12. Fearnley RA, Bell MD, and Bodenham AR. (2012). Status of national guidelines in dictating individual clinical practice and defining negligence. *British Journal of Anaesthesia*, **108**, 557–61.
13. O'Grady NP, Alexander M, Burns LA, et al. (2011). Guidelines for the Prevention of Intravascular Catheter-related Infections. *Clinical Infectious Diseases*, **52**, E162–93.
14. Parienti J-J, Mongardon N, Mégarbane et al. Intravascular Complications of Central Venous Catheterization by Insertion Site. *N Engl J Med* 2015; **373**, 1220–1229.
15. Gibson F and, Bodenham A. (2013). Misplaced central venous catheters: applied anatomy and practical management. *British Journal of Anaesthesia*, **110**, 333–46.
16. Bodenham A. (2011). Reducing major procedural complications from central venous catheterisation. *Anaesthesia*, **66**, 6–9.
17. Karakitsos D, Labropoulos N, and De Groot E. (2006). Real-time ultrasound-guided catheterisation of the internal jugular vein: a prospective comparison with the landmark technique in critical care patients. *Critical Care*, **10**, R162.
18. Cavanna L, Civardi G, Vallisa D, et al. (2010). Ultrasound-guided central venous catheterization in cancer patients improves the success rate of cannulation and reduces mechanical complications: A prospective observational study of 1,978 consecutive catheterizations. *World Journal of Surgical Oncology*, **8**, 91.
19. Fragou M, Gravvanis A, Dimitriou V, et al. (2011). Real-time ultrasound-guided subclavian vein cannulation versus the landmark method in critical care patients: a prospective randomized study. *Critical Care Medicine*, **39**, 1607–12.
20. O'Leary R, Ahmed SY, McLure H, et al. (2012). Ultrasound-guided infraclavicular axillary vein cannulation: a useful alternative to the internal jugular vein. *British Journal of Anaesthesia*, **109**, 762–8.

CHAPTER 131

Blood pressure monitoring in the ICU

Stefano Romagnoli and Giovanni Zagli

Key points

- The dynamic response of the pressure transducer, which is derived from the relationship between the cardiovascular system and the transducer itself, is dynamic and may change over time when one or more variables alter.
- Satisfactory performance of an arterial pressure transducer can be obtained if the natural frequency and the damping coefficient have suitable values. Both can be measured at the bedside.
- To limit underdamping, the operator should use short, stiff, non-compliant tubing and limit the number of stopcocks. Extra stopcocks and extension lines should be avoided. To avoid overdamping, the cannula and tubing must be kink-free, and clear of clots and air bubbles.
- The clinician must compare his/her own interpretation of the arterial waveform with the systolic and diastolic values delivered by the monitor to confirm the validity of the data. Comparison between invasive and non-invasive BP monitoring is a useful means of artefact detection due to inadequate damping. This should be confirmed with a fast-flush test.
- Considerable haemodynamic information (i.e. preload responsiveness, afterload, vascular tone, and stroke volume) can be obtained from a careful observation and analysis of arterial pressure waves and components. This may help the health care provider to make inferences about the circulation and establish the most appropriate treatment.

Introduction

As a tightly-regulated variable, monitoring of arterial blood pressure (BP) is mandatory in critically-ill patients. The components of BP, such as systolic, diastolic and pulse pressure, and the waveform itself may also help evaluation of the clinical situation. Two systems are mainly used for measuring BP—the indirect cuff method and direct arterial cannulation. The automated intermittent oscillometric technique for non-invasive arterial pressure monitoring is reliable in stable conditions. However, in high-risk situations or in the critically ill, various clinical conditions may contribute to unreliable measurement, e.g. arrhythmias, cardiogenic shock, high-dose vasopressors. Therefore, in conditions of haemodynamic instability resulting from disease and/or surgery in intensive care units (ICUs), operating theatres, emergency departments, and coronary care units, a more accurate beat-to-beat measurement and tracing check of blood pressure is necessary. Faithful reproduction of the arterial waveform then becomes the main purpose of the monitoring device, converting the force into a reliable electrical signal.

Technical aspects, accuracy, and artefacts

The components of an invasive BP monitoring system include an intravascular catheter, a precalibrated pressure transducer, fluid-filled non-compliant tubing to connect the catheter to the transducer, flush devices, stopcocks and, finally, a monitor for amplification, display, and storage of the pressure waveforms. After the system is zeroed at the phlebostatic axis (mid-axillary line at the fourth intercostal space), the pressure waveform of the arterial pulse is transmitted via the column of fluid to the pressure transducer, which converts it into an electrical signal. The signal is then processed, amplified, and converted into a graphic representation by a microprocessor.

Although intra-arterial measurement is considered the gold standard of BP monitoring, accuracy and precision are often invalidated by artefacts that should be recognized and corrected. An understanding of the physical principles involved in pressure transduction is important to recognize the two main artefacts that most frequently compromise accuracy:

- Resonant amplification due to underdamping.
- Overdamping.

Understanding the physical causes of these artefacts is a key factor in avoiding the misinterpretation of arterial pressure and, therefore, inappropriate therapies [1].

BP is a regulated variable integrating various determinants from the cardiovascular system. This system has, in turn, a number of static and dynamic (highly variable over time) characteristics—heart rate, contractility, stroke volume, ejection time, diastolic time, large and small artery stiffness, and vascular tone. All these physical properties interact to generate a pressure wave that is influenced by characteristics such as elasticity, stiffness, length, and calibre. An additional interaction with the transduction system depends on two fundamental characteristics of the transducer:

- Natural frequency (or resonance frequency).
- Damping coefficient.

The natural frequency is the frequency at which a system (e.g. the components of a pressure transducer) naturally vibrates once it

has been set into motion. In other words, it is the number of times (frequency) a system oscillates (moves back and forth) between its original position and its displaced position if there is no outside interference (e.g. frictional forces).

The damping coefficient quantifies the frictional forces that act on the oscillating system and determine how rapidly it comes to rest. Thus, friction reduces the amplitude of oscillations within an oscillatory system.

The relationships between the frequencies delivered by the cardiovascular system (driving force), natural frequency and damping coefficient define the dynamic response, and whether that response is adequate (i.e. without distortion) or not (i.e. distorted due to over- or underdamping).

The frequencies at which the cardiovascular system transfers signals to the transducer can be analysed in detail by breaking down a complex pressure waveform into basic sine waves by means of a Fourier analysis or transformation (see Fig. 131.1) [2]. In a Fourier transformation, each complex pressure wave can be viewed as the sum of fundamental sine waves characterized by its amplitude and period (frequency). The first wave (fundamental frequency or first harmonic) corresponds to the heart rate and is measured in Hertz (cycles per second, Hz). For instance, 60 beats/minute corresponds to 1 cycle/second, equalling 1 Hz. The other waves (second, third harmonic, etc.) are multiples of the fundamental wave, and these contain the 'information' regarding that pressure wave (e.g. dicrotic notch, reflected waves, etc.). At least 6–10 harmonics are required to provide a faithful reproduction of a pressure waveform. For a system to reproduce a distortion-free arterial pressure waveform, with faithful reproduction of detail, when the heart rate is 120 beats/min, the transducer should be able to transmit a frequency of at least 12–20 Hz (120 beats/min = 2 Hz).

If the natural frequency lies close to the frequency of one of the component harmonics, the system oscillates at its maximum amplitude causing resonation. This oscillation produces an amplified pressure wave that, in turn, amplifies the waveform components. In such conditions, the system is underdamped, and the resulting artefact is known as underdamping, resonance, overshoot, or ringing.

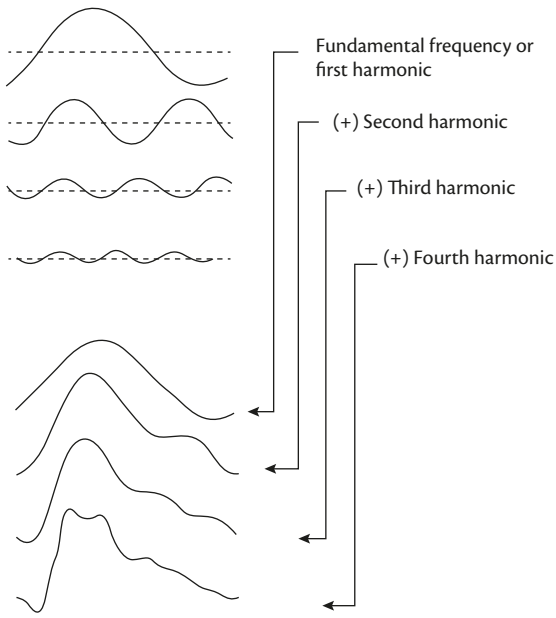


Fig. 131.1 Fourier analysis of an arterial pressure. Three basic sine waves (fundamental, second, and third harmonic) are summed, resulting in the fourth complex wave.

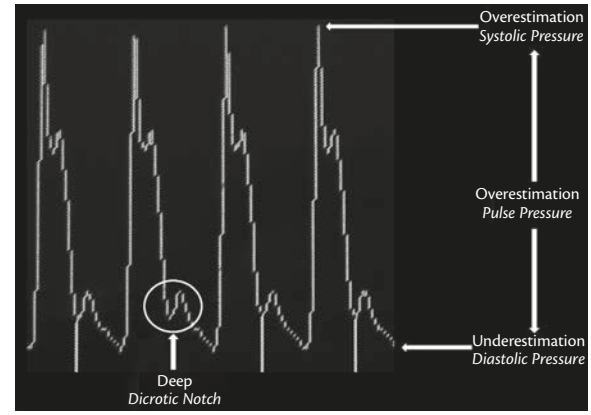


Fig. 131.2 A typical resonant underdamped arterial pressure waveform. All images reproducing arterial pressure traces are from MostCare™, Vygon, Italy, a high fidelity haemodynamic monitoring system.

In the following situations, the resultant waveform will differ from its true counterpart (see Fig. 131.2):

- Systolic BP overestimation (up to 80 mmHg) [3] or systolic pressure overshoot (narrow peak).
- Diastolic BP underestimation.
- Pulse pressure (systolic minus diastolic pressure) overestimation.
- Deep dicrotic notch.
- Non-physiological oscillations during the diastolic phase.

Optimal systems should have a resonant frequency as high as possible to transmit very high frequencies (e.g. high heart rates with steep systolic upstrokes) faithfully without amplification of the signal. The system should also have an adequate damping coefficient low enough to avoid overdamping. Damping is anything that limits the number and amplitude of oscillations in an oscillating system (e.g. friction in the fluid pathway). Some degree of damping is required (see Fig. 131.2), but excessive damping will result in an overdamped signal. Thus, high-frequency sine waves will not be transmitted, resulting in a loss of information. The characteristics of an overdamped wave are as follows (see Fig. 131.3):

- Underestimation of systolic pressure.
- Overestimation of diastolic pressure.
- Underestimation of pulse pressure.
- Slurred upstroke.
- Absent dicrotic notch.
- General loss of detail.

The main reasons for overdamping are air bubbles in the circuit, blood clots, or kinking of the cannula.

In both over- and under-damping, the mean BP approximates to the actual mean BP.

To reduce the likelihood of underdamping, the operator should use short, stiff, non-compliant tubing and limit the number of stopcocks. If these precautions are insufficient, the Accudynamic®

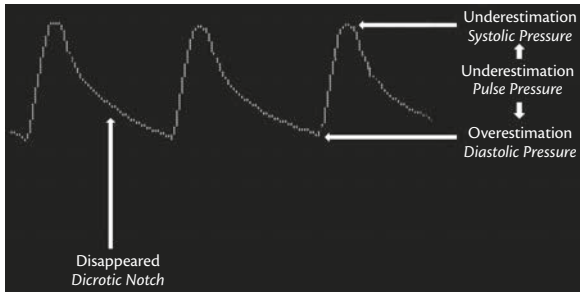


Fig. 131.3 A typical overdamped arterial pressure waveform.

System (ICU Medical, San Clemente, CA, USA), a manufactured tool specifically aimed at increasing the damping coefficient, can be used. To reduce the occurrence of overdamping, the line should always be unkinked and free of air and clot.

When a signal is suspected to be resonating, the operator should perform the following steps:

- Compare the systolic blood pressure measured with the invasive system with that measured by the non-invasive system.
- Perform a fast-flush (square wave) test.

The dynamic response of a transducer can be measured at the bedside using a 'fast-flush' test [4,5], with the BP tracing being recorded onto a paper sheet. The valve of the continuous flush system must be pulled to generate a square wave on the output tracing. By releasing the valve, a variable number of undershoot and overshoot waves can be observed that will decay exponentially in accordance with the damping coefficient. Two measures are necessary (see Fig. 131.4):

- The natural frequency is measured by calculating the distance between successive peaks and applying the following formula:

$$\text{Natural frequency} = \text{Paper speed (mm / sec)} / \text{distance between peaks (mm)} \quad \text{[eqn 1]}$$

e.g. 25 (mm/sec)/1.7 mm = 14.7 Hz

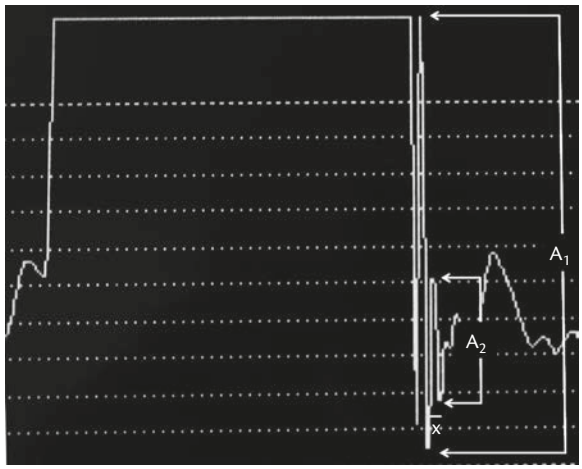


Fig. 131.4 Example of a catheter transducer system response to a fast-flush test. Amplitude ratio is calculated by dividing A2/A1 and resonant frequency by dividing 25 (mm/sec)/x.

- The damping coefficient can be derived by calculating the amplitude ratio (dividing the amplitude of the second oscillation by the first), e.g. 16 mm/22 mm = 0.72.

The calculated values should be plotted onto a graph (see Fig. 131.5), with the interactions between the values allowing the system to be categorized into one of three types—adequate, over- or under-damping.

Haemodynamic information from the waveform

Careful interrogation of the arterial pressure components may assist in analysis of the circulation and to establish the most appropriate therapy. Information regarding preload responsiveness (circulating volume), afterload, vascular tone, and stroke volume can be obtained from understanding the waveform morphology.

The normal components of the arterial pressure waveform are shown in Fig. 131.6 (see also Fig. 131.7).

Changes in the arterial pulse contour are usually due to changes in vascular properties resulting from changes in the amplitude and timing of wave reflections. These are generated by the impact of the pulse against the bifurcations of the arterial tree and against high-resistance arteriolar vessels (the main site of reflection). Changes in arterial pressure with ageing have been widely studied—an increased pulse wave velocity, due to increased stiffness of the arterial system, causes wave reflections to travel very quickly, thus merging the incident early phase of the systolic pressure with its reflective wave (see Fig. 131.7).

Vasoconstriction

The effects of endogenous and external catecholamines are characterized by increases in both systolic (reduced arterial system compliance) and diastolic (reduced peripheral run-off) pressure. Moreover, the dicrotic notch and successive pressure wave rises are progressively earlier (proximal to the systolic peak) as a consequence of rapid equilibrium between aortic and ventricular pressures. The opposite phenomenon—delayed and low dicrotic notch plus reduced systolic and diastolic pressures—is frequently observed in severe vasodilatation (e.g. sepsis, vasovagal reflex, nitrate administration) as a longer time is needed for aortic pressure to exceed ventricular pressure.

Shock

In shock states, except during acute inflammation, diastolic waves are often increased when hypotension is compensated by peripheral vasoconstriction. Thus, arterial waveform observations may help distinguish hypotension due to reduced blood volume from that due to vasodilatation.

Aortic valve stenosis

The duration of ventricular ejection is prolonged, and the systolic upstroke is less steep than in normal left ventricle outflow (*pulsus tardus*) with slow amplitude changes (*pulsus parvus*). The dicrotic notch is usually less evident.

Aortic regurgitation

The waveform is characterized by a steep rise of the systolic upstroke, low diastolic, and wide pulse pressure.

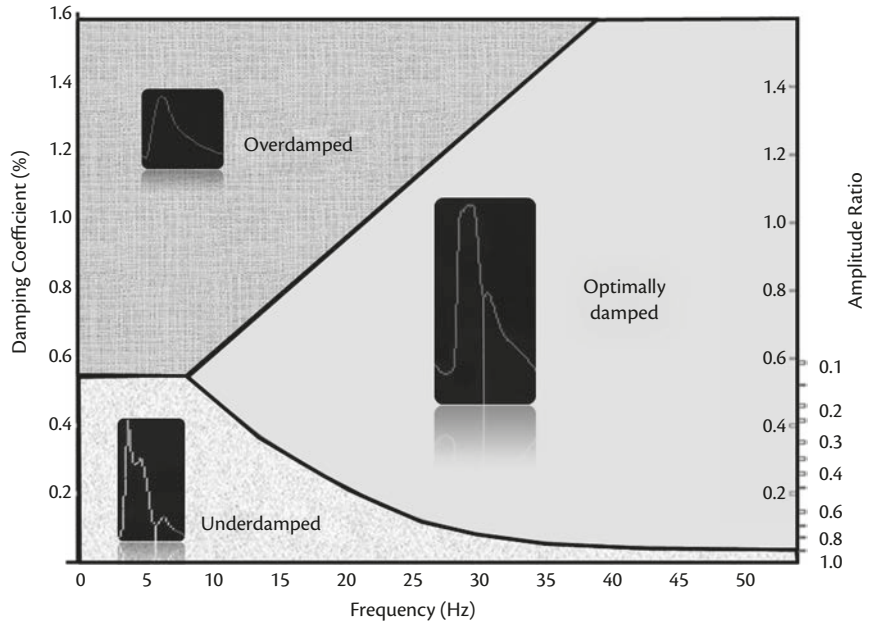


Fig. 131.5 Results from a fast-flush test identify the three main causes of damping. Systolic BP overestimation (up to 80 mmHg) or systolic pressure overshoot (narrow peak).
 Data from Romagnoli S et al., 'Dynamic response of liquid-filled catheter systems for measurement of blood pressure: precision of measurements and reliability of the Pressure Recording Analytical Method with different disposable systems', *Journal of Critical Care*, 2011, **26**, pp. 415–22.

Left ventricular dysfunction (*pulsus alternans*)

This alternation of beats with higher and lower pulse pressures is indicative of severe left ventricular dysfunction. As pulse pressure is proportional to stroke volume, those beats with higher pulse pressures are the result of increased preload remaining from the previous ejection.

Cardiac tamponade (*pulsus paradoxus*)

This is an evident increase and decrease in pulse pressure determined by inspiration and expiration that results from a large dependence of the preload on intrathoracic pressure modifications. *Pulsus paradoxus* is characteristic of cardiac tamponade and all other causes of deep oscillations in thoracic pressure (i.e. bronchospasm, airway obstruction, dyspnoea).

Hypovolaemia: circulating volume and dynamic indices of fluid responsiveness

The effects of positive pressure mechanical ventilation on heart-lung interaction are as follows:

- **During inspiration**:
  - Displacement of pulmonary venous blood into the left heart chambers (increase in left ventricular preload).
  - Decrease in left ventricular afterload (reduction in left ventricular transmural pressure).
  - Increase in left ventricular stroke volume → increase in systolic BP and pulse pressure.
  - Increase in right ventricular afterload (increase in pulmonary vascular resistance).
  - Decrease in the gradient for venous return (mean systemic filling pressure minus right atrial pressure) [6] → decrease in right ventricular stroke volume
- **During expiration**:
  - Pulmonary engorgement of blood → reduction in left ventricular stroke volume.
  - Reduction in stroke volume → reduction in systolic blood pressure.
  - Reduction in pulse pressure.

a) Systolic upstroke
b) Systolic peak
c) Systolic decline
d) Small pulse of reflected pressure wave (frequent)
e) Dicrotic notch (in the central aorta, indicates aortic valve closure (incisura))
f) Diastolic run-off
g) End-diastolic pressure

Fig. 131.6 The normal components of the arterial pressure waveform.

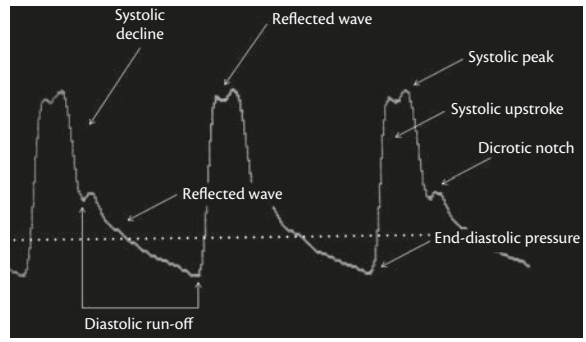


Fig. 131.7 Components of an arterial pressure waveform from an elderly patient undergoing vascular surgery. Note that the peak systolic pressure wave is followed by a small pulse of a reflected pressure wave, suggesting a high grade of arterial stiffness.

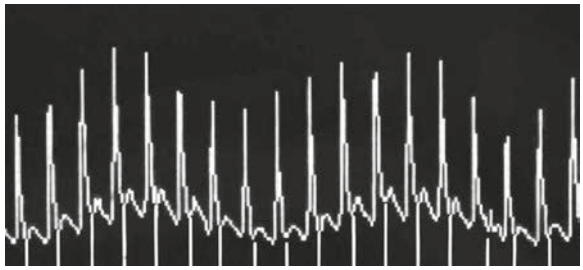


Fig. 131.8 Effect of heart–lung interaction in a hypovolaemic patient.

The greater the variation in BP tracing during the mechanical ventilation respiratory cycle, the greater the reduction in left ventricular preload. Several studies have demonstrated that a systolic pressure variation (SPV) or pulse pressure variation (PPV) >10–15% during the respiratory cycle indicate a high likelihood that patients will be fluid responsive, i.e. increase their stroke volume ≥15% following a fluid challenge (see Fig. 131.8) [7]. In hypovolaemic conditions, the area under the pressure curve appears to be globally reduced with a narrow systolic shape, a lower systolic peak and higher diastolic pressure (in case of vasoconstriction). All are consequences of a smaller left ventricular stroke volume. Moreover, the contribution from reflected waves usually disappears for the same reason.

Conclusion

Invasive arterial pressure is invaluable in diagnostic and therapeutic processes during critical care and major surgery. Pathophysiological mechanisms involved in arterial pressure waveform determination are complex and change rapidly over time. Nonetheless, observation of each component of the arterial wave may provide useful haemodynamic information, but very common artefacts must be recognized and corrected to avoid dangerously inaccurate haemodynamic data interpretation.

References

1. Romagnoli S, Ricci Z, Quattrone D, et al. (2014). Accuracy of invasive arterial pressure monitoring in cardiovascular patients: an observational study. *Critical Care*, **18**, 644.
2. Nichols WW and O'Rourke MF. (2005). Principles of recording and analysis of arterial waveforms. In: Nichols WW and O'Rourke MF (eds) *McDonald's Blood Flow in Arteries*, 5th edn, pp. 215–31. London: Hodder Arnold.
3. Romagnoli S, Romano SM, Bevilacqua S, et al. (2011). Dynamic response of liquid-filled catheter systems for measurement of blood pressure: precision of measurements and reliability of the pressure recording analytical method with different disposable systems. *Journal of Critical Care*, **26**, 415–22.
4. Gardner RM. (1981). Direct blood pressure measurement—dynamic response requirements. *Anesthesiology*, **54**, 227–36.
5. Kleinman B, Powell S, Kumar P, and Gardner RM. (1992). The fast flush test measures the dynamic response of the entire blood pressure monitoring system. *Anesthesiology*, **77**, 1215–20.
6. Gelman S. (2008). Venous function and central venous pressure: a physiologic story. *Anesthesiology*, **108**, 735–48.
7. Montenij LJ, de Waal EE, and Buhre WF. (2011). Arterial waveform analysis in anesthesia and critical care. *Current Opinions in Anaesthesiology*, **24**, 651–6.

CHAPTER 132

Central venous pressure monitoring in the ICU

Sheldon Magder

Key points

- CVP is determined by the interaction of cardiac function and return function.
- The range of clinically important values is small so measurements must be carefully made.
- Pressure measurements with fluid-filled systems are relative to an arbitrary reference value.
- CVP is best used in the negative sense, i.e. a high CVP suggests the subject is unlikely to be fluid responsive.
- CVP is most effective when combined with measurement of cardiac output.

Introduction to central venous pressure monitoring

Although the usefulness of central venous pressure (CVP) monitoring is much maligned, it can be useful in the hands of the astute clinician who understands both measurement pitfalls and the physiology behind its determination. CVP is a low-technology, readily available measure that can be assessed by bedside examination of jugular venous distension above the sternal angle, by using a fluid-filled manometer or, more commonly, an electronic transducer connected to a centrally-placed catheter.

Physiological basis

Two interacting functions determine cardiac output (Fig. 132.1) [1,2]. One is heart function, as indicated by the Starling relationship that relates cardiac output (CO) to preload. Preload is defined as the final tension on a muscle before the onset of contraction. Right heart preload is given by the right atrial pressure (RAP) just before the onset of systole. Each cardiac function curve assumes constant afterload, contractility, and heart rate. The second function that determines CO is venous return, the return of blood to the right heart from the systemic venous circulation. The determinants of return function are mean systemic filling pressure (MSFP), i.e. the pressure in small veins and venules, the downstream RAP, and the resistance between them [3]. MSFP is determined by the volume distending the small veins and venules, and their wall 'stretchiness' (compliance). RAP is common to both functions and provides an indication of their interaction. Under most conditions, flow resistance in the major vessels is trivial so CVP equals RAP. Unless there is tricuspid stenosis, during diastole RAP is equivalent to ventricular diastolic pressure.

CVP does not indicate blood volume and, without consideration of CO, does not indicate heart function. Similarly, it does not indicate the magnitude of left atrial pressure. A single value of CVP does not indicate whether a patient is likely to be fluid-responsive or not. However, CVP measurement can be useful in interpreting responses to fluid boluses, while the pattern of change with a change in CO can indicate whether a falling BP is due to a decrease in cardiac function or in venous return function. Furthermore, the CVP waveform pattern can also be of diagnostic value.

Basis of measurement

Clinically significant values of CVP only occur over a narrow range (~10 mmHg) so small errors in measurement can have a large effect on decisions [4]. It is thus essential to understand the principles behind measurements made with fluid-filled devices. Pressures are measured relative to a reference value. Since the body is surrounded by atmospheric pressure, it is reasonable to set the zero value at atmospheric, and to then determine deviations from this pressure. Thus, a CVP of 0 mmHg is actually ~760 mmHg. However, this creates a problem. The stretch of an elastic structure is determined by the difference in pressure between the inside and outside of the structure (transmural pressure). The heart is within the chest and surrounded by pleural pressure. When chest wall muscles are relaxed, pleural pressure is normally subatmospheric because of inward elastic recoil of the lungs and outward recoil of the chest wall. During the ventilatory cycle, the difference between pleural and atmospheric pressure varies. Pleural pressure falls with spontaneous inspiration and rises with mechanical breaths. When positive pressure is applied to the airways, pleural pressure is always greater than atmospheric pressure. Pleural pressure can also be increased by contraction of chest and abdominal muscles during expiration. During these phases, CVP measured relative to atmospheric pressure does not indicate true transmural pressure of the heart, and thus the force distending intravascular structures and true preload. Ideally, cardiac pressures should be referenced to pleural pressure, but this is generally impractical. To minimize the error produced by not having the correct reference value, cardiac pressures are obtained at end-expiration when pleural pressure is closest to atmospheric.

A second problem with fluid-filled systems is that placement of the measuring device becomes an important factor as the mass of fluid within the device creates a gravitational force, which is then

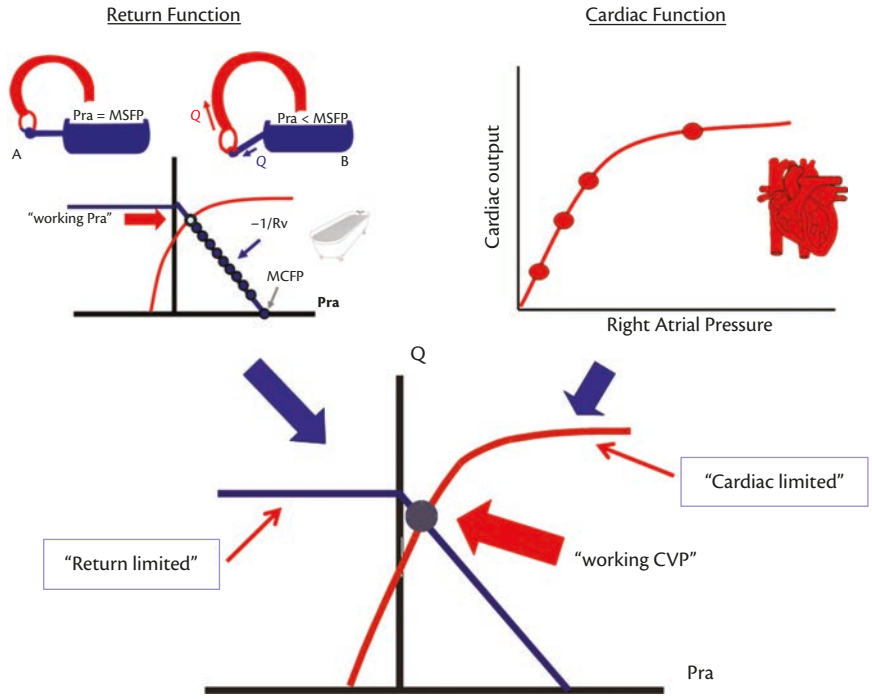


Fig. 132.1 Determinants of cardiac output and the central position of CVP. Cardiac output is determined by the intersection of venous return function, which is a set of venous returns at given right atrial pressures (Pra) (upper left), and cardiac function which is a set of cardiac outputs at a given Pra (upper right). When these two functions are graphed together, their intersection point occurs at the 'working CVP' and working cardiac output, which are the values in the person at that time.
Q, flow (equivalent to cardiac output); MSFP, mean systemic filling pressure; Rv, venous resistance.

included in the measurement. For physiological purposes, the consensus reference level is the right atrial mid-point; this is where blood returns to the heart and is pumped out again. A good approximation of this point is a vertical distance below the sternal angle, where the second rib meets the sternum. This level is valid whether the subject is supine or sitting up at a 60° angle as the right atrium is a round anterior structure; thus its centre remains at a constant distance from the sternal angle. This level is recommended for clinical evaluation of CVP from the jugular distension above this point. When using a transducer, the level is set by siting the stopcock on the transducer set, which opens to air at 5 cm below the sternal angle. More often, the transducer is levelled to the mid-thoracic position as a levelling device is not needed to identify this position. This results in values ~3 mmHg higher than those based on the sternal angle, the precise difference varying with chest size.

If the measuring device has appropriate fidelity, the CVP tracing has three distinguishable upward waves—'a' produced by atrial contraction, 'c' by backward buckling of the tricuspid valve at the onset of systole, and 'v' by atrial filling during ventricular systole (Figs 132.2 and 132.3). There are two downward waves, the 'x' descent due to atrial relaxation, and 'y' due to atrial emptying during the early phase of diastole. The 'a' and 'v' waves are often large. In Fig. 132.2, the bottom of the tracing is 0–1 mmHg, whereas the top is 9–10 mmHg. Fluid therapy is less likely with the latter. Measurement at the base of the 'c' wave gives the final pressure within the ventricle before the onset of systole; in Fig. 132.2 it is 2 mmHg. If the 'c' wave cannot be seen, the base of the 'a' wave usually substitutes adequately. The 'c' position can also be identified by drawing a vertical line from the end of the QRS wave for the ECG; depending on the monitor, some adjustment may be needed for the difference between the ECG electrical signal and the slower fluid signal for pressure through the catheter (Fig. 132.3).

Diagnostic use of CVP

CVP by itself is not a useful guide for fluid management. It must be put in context by measuring CO or, at least, a surrogate of tissue

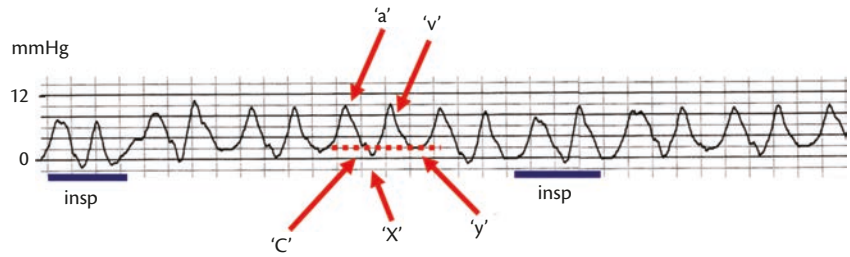


Fig. 132.2 Central venous pressure tracing with labelled individual waves. The dark line and 'insp' indicate inspiration. The dotted line indicates the appropriate place to make the measurement, which is at the bottom of the 'c' wave. The CVP in this example is 2 mmHg.

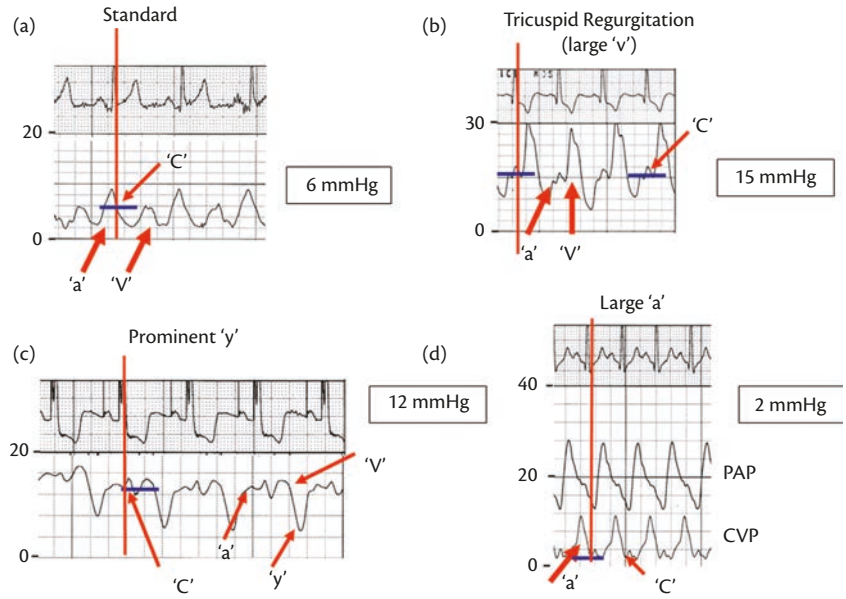


Fig. 132.3 Examples of CVP tracings and appropriate measurements. (a) Normal tracing with the 'a' wave greater than the 'v'. The vertical line indicates the use of the QRS on the ECG to mark the 'c' wave. (b) Example of tricuspid regurgitation with a prominent 'c-v' wave (they run into each other) and prominent 'y' descent. (c) Example of prominent 'y' descent; the 'a' wave is small and the patient has an atrial pacemaker (note the spike in front of the p wave on the ECG). (d) Example of a large 'a' wave; a pulmonary artery tracing (PAP) can also be used to identify the onset of systole.

perfusion [5]. A parallel is trying to interpret PCO_2 without measuring pH. In normal sitting subjects, CVP is sub-atmospheric yet there is no need to give fluid. This similarly applies to a patient with normal sensorium, colour, blood pressure and renal function, and a low CVP.

The utility of CVP measurement arises when fluid is being considered to support BP or oliguria in an unstable clinical situation. If the principal diagnosis is hypovolaemic shock, the CVP will probably be very low so jugular venous pulsations should not be evident with the patient's head raised to 30°. If the diagnosis is right ventricular failure, whether due to right ventricular dysfunction or obstruction (e.g. pulmonary embolism), the CVP should be elevated. These two processes can occur concurrently, e.g. pulmonary embolism and hypovolaemia. If so, fluid should improve the situation or elevate CVP without any restoration of BP.

The value of CVP by itself is most useful in the negative sense. A high CVP indicates that fluid boluses are unlikely to be helpful because the heart is likely functioning on the flat part of the cardiac function curve. Furthermore, even if the person does respond to volume loading, there will be a price to pay for the high CVP, including liver congestion and possible deterioration of renal function. Other treatment approaches might be considered [6].

What is a high CVP? The plateau of the cardiac function curve usually occurs at values <10 mmHg (13–14 mmHg if using mid-thoracic level). Without any measure of CO, it is thus reasonable to target a CVP of 10 mmHg, as recommended in early goal-directed resuscitation protocols. An important limitation is the presence of primarily left ventricular dysfunction (e.g. coronary artery disease or valvular disorders) where left atrial pressure can be markedly elevated without any elevation in CVP. A chest X-ray may provide useful clues.

Blood pressure approximately equals the product of CO and systemic vascular resistance (SVR). A fall in BP may be due to a fall in either. This can be differentiated by examining concurrent changes in CO. If this is maintained or rises, the primary problem is a fall in SVR. Although increasing CO might help, primary treatment should be aimed at the fall in resistance. If both BP and CO fall, the fall in output (due to a decrease in cardiac function or in return function) is the primary problem. If the CVP also falls, the primary problem is a decrease in return function—giving more volume is likely the best treatment choice. However, if CO falls yet CVP rises, treatment should be aimed at improving pump function.

CVP measurements can assist in assessing the response to a fluid challenge. Fluid boluses increase CO by increasing preload. Preload does not have to change much to produce a substantial increase in CO. A measurable rise in CVP and no change in CO implies that the heart is likely functioning on the flat, non-responsive part of the cardiac function curve and further volume loading will not help. This use of the CVP is in the negative sense, i.e. a rise in CVP without a rise in cardiac output means that volume loading will be unlikely to help. The caution here is that some colloid solutions appear to produce a rise in CO without much of a rise in CVP. This suggests they might be actually improving cardiac function in a 'pharmacological' sense, rather than by increasing preload alone. For practical purposes, the increase in CVP should be ≥2 mmHg as this can be readily identified on a monitor.

Respiratory variation in CVP

The heart is surrounded by pleural pressure. Accordingly, pressure measured with a transducer outside the chest and relative to atmospheric pressure, will fluctuate during the ventilatory cycle (Fig. 132.4). Typically, CVP falls with spontaneous inspiration yet right heart volume actually increases. This occurs because the fall in pleural pressure lowers pressure in the heart relative to atmospheric pressure, thereby increasing the gradient for venous

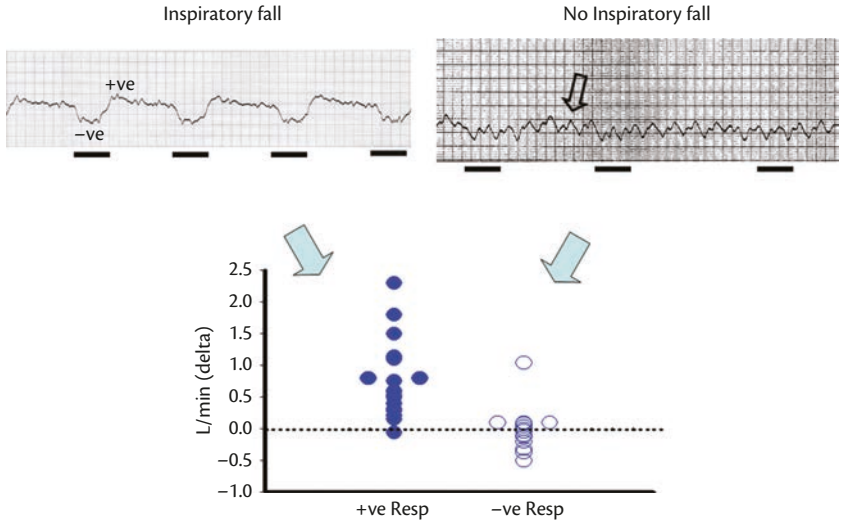


Fig. 132.4 Use of inspiratory variations in CVP to predict fluid responsiveness. In the upper left tracing there is an inspiratory fall in CVP (–ve) indicating the patient would likely respond to fluids. In the upper right tracing, there is no inspiratory fall in CVP, indicating the patient would not be fluid-responsive. The arrow indicates that after the first inspiration there is a small rise in CVP during expiration; the following dip should not be mistaken for an inspiratory fall. The bottom graph shows what happened in 33 patients. +ve indicates an inspiratory fall in CVP and –ve indicates this did not happen. The *y*-axis gives the change in cardiac output with a fluid bolus that was sufficient to raise the CVP by 2 mmHg.

return. Placing the transducer in the pleural space would have seen pressure rise as expected with the increase in right heart volume. However, when the heart is functioning on the flat part of the cardiac function curve, CVP does not fall during inspiration as heart filling is limited. Although transmural pressure increases, end-diastolic volume, and thus stroke volume, does not change. This principle can be used to predict fluid responsiveness. Patients with an inspiratory fall in CVP are likely to increase CO with a volume infusion. However, if the heart is functioning close to the plateau of its function curve, the increase in CO may not be significant. Again, the test is best used in the negative sense. If there is no inspiratory fall in CVP, it is unlikely that the patient will be fluid-responsive. Caveats include a spontaneous inspiratory effort that must be sufficient to decrease pleural pressure enough to affect cardiac filling, even in mechanically-ventilated patients. A fall in CVP during inspiration should be excluded, as this is due to release of active expiratory muscle, rather than a fall in pleural pressure.

Clinical information can also be gained from the magnitude of respiratory swing in CVP. A large inspiratory fall indicates large inspiratory efforts; underlying reasons should be sought, such as increased airway resistance, decreased lung compliance, or increased drive. A large inspiratory rise in CVP in a mechanically-ventilated patient is suggestive of decreased thoracic compliance, which also includes high abdominal pressure. Large expiratory increases in CVP indicate active recruitment of expiratory muscles (Fig. 132.5). These can occur in a pattern in which the CVP rises during expiration; here, the CVP at end-expiration is no longer appropriate for assessing cardiac preload as the measurement includes the rise in pleural pressure. In the second pattern, the CVP can rise at the beginning of expiration and then gradually decrease. Here, the proper place to measure CVP is on a breath with a plateau in the CVP tracing, otherwise the pressure will be overestimated.

Use of CVP waveforms

Clinical information can also be gained from components of the CVP trace (Fig. 132.3). Tall 'v' or 'c-v' waves are suggestive of tricuspid regurgitation. In severe regurgitation, the CVP can even look like a right ventricular pressure tracing. Prominent 'y' descents indicate restriction to cardiac filling, making it is less likely that the

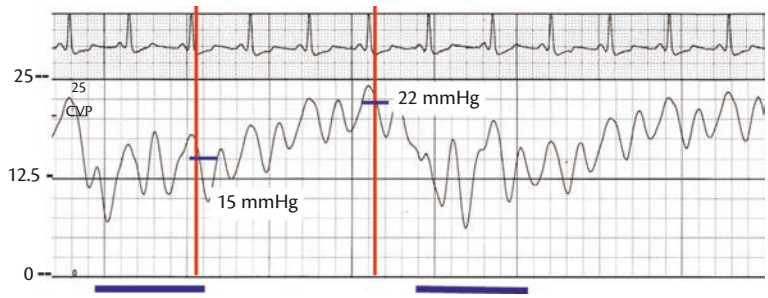


Fig. 132.5 Example of a patient with active use of expiratory muscles. The dark horizontal line indicates inspiration. There is a progressive increase in CVP during expiration that only occurs with recruitment of expiratory muscles. Here, the best measure of CVP is at the beginning rather than the end of expiration, as usually recommended. The appropriate value is 15 mmHg.

patient will be fluid-responsive bolus. The loss of a 'y' descent in a hypotensive patient can be an important indicator that cardiac tamponade is present. A prominent 'a' wave indicates either tricuspid valve stenosis or decreased right ventricular diastolic compliance.

Conclusion

CVP is readily assessable at the bedside. With an understanding of the principles of its measurement and determinants, the CVP can help clinicians distinguish whether a hypotensive state is due to a decrease in SVR or CO. The CVP can then be used to distinguish a decrease in CO due to a decrease in pump function or a problem with the return function, especially when changes in CVP are combined with changes in CO (or a surrogate thereof). CVP and CO measurements also provide a good guide to understanding whether or not further volume boluses will be of use, and thus help avoid excessive volume use. Finally, with experience, the CVP waveform can be used to help predict both cardiac and pulmonary abnormalities.

References

1. Guyton AC. (1955). Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiological Review*, **35**, 123–9.
2. Magder S. (2012). An approach to hemodynamic monitoring: Guyton at the bedside. *Critical Care*, **16**, 236.
3. Coleman TG, Manning RD, Jr, Norman RA, Jr, and Guyton AC. (1974). Control of cardiac output by regional blood flow distribution. *Annals of Biomedical Engineering*, **2**, 149–63.
4. Magder S. (2007). Invasive intravascular hemodynamic monitoring: technical issues. *Critical Care Clinics*, **23**, 401–14.
5. Magder S. (2006). Central venous pressure: a useful but not so simple measurement. *Critical Care Medicine*, **34**, 2224–7.
6. Magder S and Bafaqeeh F. (2007). The clinical role of central venous pressure measurements. *Journal of Intensive Care Medicine*, **22**, 44–51.

CHAPTER 133

Pulmonary artery catheterization in the ICU

Efrat Orenbuch-Harroch and Charles L. Sprung

Key points

- Although there is limited evidence of favourable outcomes from the use of the pulmonary artery catheter, it remains an important diagnostic tool in the management of critically-ill patients, specifically when knowledge of intracardiac pressures and oxygenation parameters is considered to be particularly important.
- The pulmonary artery wedge pressure (PAWP) reflects left atrial pressure, and thus left ventricular end-diastolic pressure (LVEDP), assuming that continuity of the circulation is preserved.
- PAWP should be measured at the end-expiratory phase of ventilation.
- When measuring cardiac output by the manual thermodilution method, at least three measurements should be obtained and averaged to overcome the between-measurement variability.
- Complications occur in 10–15% of pulmonary artery catheter insertion and are related to insertion, passage of the catheter and maintenance of the catheter in the pulmonary artery.

Introduction

Haemodynamic monitoring is a significant component in the management of the critically-ill patient, allowing for evaluation of the aetiology, severity, and response to treatment, and complementing clinical assessment. Flow-directed pulmonary artery catheters (PAC) were introduced in 1970 by Swan and Ganz [1] as a simple and rapid technique for measuring several continuous or intermittent circulatory variables. Initially, the PAC was introduced into clinical practice without substantial supporting evidence; however, subsequent observational trials and more recent randomized controlled trials failed to demonstrate positive outcome benefits [2–4]. As a consequence, the use of the PAC has significantly declined in the last two decades [5]. It remains controversial as to whether an outcome benefit is required prior to using a diagnostic tool. Such a benefit can only be demonstrated when data are interpreted correctly and effective therapy is available after the diagnosis is made. Given its overall safety record, the pulmonary artery catheter still has a valid role in both diagnosing haemodynamic abnormalities and monitoring therapeutic interventions. It should thus be considered for use in appropriate patients for the proper indication.

Indications

The major indications for PAC use are detailed in Box 133.1. The PAC was initially used to guide therapy following complicated acute myocardial infarction where measurements of cardiac output and PAWP could distinguish between cardiogenic and non-cardiogenic mechanisms and guide therapeutic strategy. PAC use also helps to differentiate between cardiogenic and non-cardiogenic pulmonary oedema, and to establish the cause of mechanical complications following myocardial infarction. For example, a >5% rise in right ventricular oxygen saturation over the right atrial value is seen in acute ventricular septal defect. During acute mitral regurgitation a large 'v' wave appears in the PAWP tracing. Cardiac tamponade is characterized by elevation and diastolic equalization of the right atrial (RA), right ventricular end-diastolic (RVEDP) and pulmonary artery wedge (PAWP) pressures, and by the absence of the 'y' descent on the RA tracing. The PAC is also helpful for monitoring the impact of therapeutic interventions in these conditions.

Patients with severe congestive heart failure refractory to aggressive medical management may benefit from PAC-derived information, especially systemic vascular resistance and PAWP, thereby allowing specific therapy to be tailored. The ESCAPE trial [2], however, failed to demonstrate any benefit in mortality or length of hospitalization from PAC use in patients with congestive heart failure.

Traditionally, PACs have been used in high-risk patients undergoing elective or emergent non-cardiac surgery. However, in a large multicentre, randomized controlled trial, no benefit was achieved in either in-hospital mortality or 1-year survival [6]. PACs are believed to benefit cardiac surgery patients with haemodynamic risks, including those with ejection fractions <30%, impaired right ventricular systolic function, left ventricular diastolic dysfunction, acute ventricular septal defects, and patients with left ventricular assist devices [7]. In a randomized trial of patients undergoing elective cardiac surgery, those assigned to receive PAC-directed protocolized therapy to increase their oxygen delivery had shorter ICU and hospital lengths of stay [8]. Although a clinical rationale exists for using the PAC in haemodynamically-unstable patients, several randomized controlled trials in the critically ill have not shown clear outcome benefits [2–4]. One observational study showed a decrease in the mortality rate associated with PAC use in the most severely ill, but an increase in a lower illness severity population [9]. To summarize, there is no absolute indication at present for PAC

Box 133.1 Indications for pulmonary artery catheterization

- **Acute myocardial infarction:**
  - Hypotension.
  - Congestive heart failure.
  - Acute mitral regurgitation.
  - Ventricular septal defect.
  - Right ventricular infarction.
  - Cardiac tamponade.
- **Congestive heart failure:** titrate vasodilator therapy
- **Acute pulmonary embolism.**
- **Shock:**
  - Sepsis.
  - Massive haemorrhage.
- **Respiratory failure:**
  - Non-cardiogenic (acute respiratory distress syndrome).
  - Cardiogenic.
  - Unknown causes.
- **Assess volume status:**
  - Renal failure.
  - Cirrhosis.
- **Surgical patients:**
  - Intra- and post-operative monitoring of high risk surgical patients.
  - Surgical procedures involving massive volume shifts.

Adapted and reproduced with permission from the author: Sprung CL (1993). The Pulmonary artery catheter: Methodology & clinical applications, second edition, pp-33. Critical Care Research Associates, Inc, N.J.

insertion. They should be carefully considered on a patient-by-patient basis, especially in the most severely ill.

Insertion and interpretation of tracing

The most common insertion sites are the internal jugular, subclavian, and femoral veins, but any large vein, including the external jugular and antecubital veins, can be used. Choice of site depends on patient characteristics and operator experience. The right internal jugular and left subclavian veins are favoured because the catheter easily passes through to the pulmonary artery, and have lower rates of infections compared with the femoral vein site.

Puncture is performed with strict adherence to aseptic technique. Access is obtained using a modified Seldinger technique [10]. In brief, the desired vein is located by a needle through which a guide wire is then passed into the vein. The original needle is removed and an introducer sheath is threaded over the guide wire which is then removed The PAC, connected to a calibrated pressure transducer, is then inserted through the introducer sheath and the integral balloon near the tip of the PAC is subsequently inflated with 1.5 ml of air.

The catheter is advanced ('floated') until the right ventricle (RV) tracing is obtained on the monitor and the systolic pressure increases (Fig. 133.1). The catheter is then advanced an additional 5-15 cm, across the pulmonary valve and into the pulmonary artery (PA). Here, the pressure tracing is characterized by a higher diastolic pressure than the RV, and the appearance of a dicrotic notch (Fig. 133.1). Not more than 15 cm of catheter should be introduced into the RV to avoid catheter knotting. Failure to obtain a PA waveform indicates that the catheter is probably curling within the RV. In this situation deflation of the balloon, followed by catheter withdrawal and reinsertion is required.

Finally, the catheter is advanced to the 'wedge' position. The PAWP is identified by a decrease in pressure combined with a characteristic change in the waveform. The balloon should then be deflated and the PA tracing should reappear. If the PAWP tracing persists or there is any uncertainty about whether the tracing is a PAWP or PA tracing, then the catheter should be withdrawn until a definitive PA tracing is identified otherwise the patient is at risk of a pulmonary infarction. The PAWP trace should be obtained on inflation of the balloon with at least 1.25 ml of air. The position of the PAC should always be confirmed with a chest X-ray.

Direct measurements and derived calculations

The pulmonary artery catheter must be appropriately calibrated and zeroed to atmospheric pressure to obtain accurate diagnostic information. Variables that can be measured or derived using the pulmonary artery catheter are detailed in Table 133.1.

Central venous pressure

Central venous pressure (CVP) equals right atrial pressure and right ventricular diastolic pressure. CVP is influenced not only by ventricular function and compliance, but also by intravascular volume, venous return, systemic venous tone, and pulmonary vascular resistance. CVP does not increase until the RVEDP rises. Therefore, left ventricular failure and pulmonary congestion may be present with a normal CVP. CVP is most commonly elevated in the setting of biventricular heart failure, tricuspid regurgitation, or stenosis, pulmonary hypertension, volume overload, constrictive pericarditis, and cardiac tamponade.

Pulmonary artery pressure

Pulmonary artery pressure (PAP) is measured continuously from the distal port of the PAC when the tip of the catheter lies freely in the vascular lumen, beyond the pulmonary valve. PAP is elevated in some high-flow states (hypervolaemia), left ventricular failure, and high-resistance states including pulmonary hypertension, as well as in common conditions that increase pulmonary vascular resistance

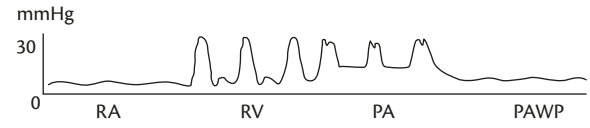


Fig 133.1 Pressure tracings during pulmonary artery catheter insertion.
Adapted and reproduced with permission from Singer M and Webb A, *Oxford Handbook of Critical Care*, Third Edition, 2009, Figure 9.3, p. 175, with permission from Oxford University Press.

Table 133.1 Variables measured or derived using the pulmonary artery catheter

Variable	Formula	Normal range	Units
Measured variables:			
◆ Cardiac output (CO)		4–7	L/min
◆ Mean pulmonary artery pressure (MPAP)		9–16	mmHg
◆ Pulmonary artery wedge pressure (PAWP)		2–12	mmHg
◆ Central venous pressure (CVP)		0–8	mmHg
◆ Mixed venous oxygen saturation		75	%
Derived variables:			
◆ Stroke volume (SV)	CO/HR	60–100	mL/beat
◆ Stroke index (SI)	SV/BSA	30–65	mL/beat/m^2
◆ Cardiac index (CI)	CO/BSA	2.8–4.2	L/min/m^2
◆ Systemic vascular resistance (SVR)	[(MAP-CVP)/CO] × 80	900–1400	dyne/sec/cm^5
◆ Pulmonary vascular resistance (PVR)	[(MPAP-PAWP)/CO] × 80	150–250	dyne/sec/cm^5
◆ Left ventricular stroke work	SI(MAP-PAWP) × 0.0136	43–61	g/m^2
◆ Right ventricular stroke work	SI(MPAP-CVP) × 0.0136	7–12	g/m^2
◆ Oxygen delivery	Cao_2 × CO × 10	640–1400	ml O_2/min
◆ Oxygen consumption	(Cao_2-Cvo_2) × CO × 10	180–280	ml O_2/min
◆ Oxygen extraction utilization ratio	$avDO_2/CaO_2$	0.22–0.3	%

HR, heart rate; BSA, body surface area; Cao_2, arterial oxygen content; Cvo_2, mixed venous oxygen content; $avDO_2$, arteriovenous oxygen content difference ($CaO_2 - CvO_2$).

Adapted and reproduced with permission from the author: Sprung CL (1993). The Pulmonary artery catheter: Methodology & clinical applications, second edition, pp-33. Critical Care Research Associates, Inc, N.J..

in the intensive care unit (ICU) setting (hypoxaemia, thrombosis, fibrosis, sepsis).

Pulmonary artery wedge pressure

The PAWP is obtained by inflating the catheter balloon, encouraging flow-directed movement of the catheter until a branch of the PA is obstructed. Once obstruction occurs, a continuous static column of fluid is created from the catheter tip to the left atrium, provided there is no intervening venous or alveolar obstruction. This fluid column is also continuous with the left ventricle (LV) when the mitral valve is open. Thus, during diastole and in the absence of major mitral valve disease, the PAWP represents the left ventricular end-diastolic pressure (LVEDP) and reflects left ventricular preload. It may not, however, reflect left ventricular end-diastolic volume, since left ventricular distensibility may vary between patients with different clinical situations.

There are several situations in which PAWP and LVEDP are discordant. Reduced left ventricular compliance (due to ischaemia or hypertrophy) and severe aortic insufficiency may cause LVEDP to exceed PAWP due to premature closure of the mitral valve. The LAP also does not reflect LVEDP in mitral stenosis. Furthermore, PAWP exceeds LVEDP if PAWP fails to accurately reflect left atrial pressure (LAP) during pulmonary venous hypertension, respiratory failure, or when the catheter tip sits in either West's Zones I or II (i.e. a non-Zone III position) within the lung where mean alveolar pressure exceeds mean pulmonary venous pressure. In this situation, PAWP is influenced more by alveolar pressure than intravascular pressure. This most commonly occurs during positive pressure ventilation in hypovolaemic patients. Placement of the catheter in a correct zone III position can usually be confirmed by the presence of the catheter tip below the level of the left atrium on a chest X-ray.

Once the PAWP tracing has been obtained, one must ensure that a correct value is recorded. The most common sources of error for PAWP measurement include catheter placement in a non-Zone III lung position, and failure to correctly identify end-expiration when determining PAWP [11]. During positive pressure ventilation, as opposed to spontaneous ventilation, intrathoracic pressures increase during inspiration and decrease during expiration. Such changes affect pulmonary artery pressure and PAWP measurements. Therefore, the proper phase in the ventilatory cycle to judge the PAWP regardless of the mode of ventilation is at end-expiration, when air flow is zero, and intrathoracic and atmospheric pressures are equal. Identification of end-expiration may be particularly difficult with tachypnoea or marked fluctuations in pressure during respiration, and the automated computations of the mean pressure may not accurately reflect pressures at end-expiration. Hence, manual measurement from a graphic recording of the pressure waveform at end-expiration is preferable.

Cardiac output

Cardiac output (CO) is measured with the PAC by thermodilution. This method is based upon conservation of thermal energy over a few consecutive beats. Thermal indicator (cooled fluid) is injected quickly through the central venous port and the change in temperature is registered by a thermistor at the tip of the catheter in the pulmonary artery. The indicator used is a small amount (e.g. 10 mL) of 5% glucose that is cooler than blood, thus slightly lowering its temperature. The degree of change in temperature is inversely proportional to the cardiac output. The thermistor records the temperature change over time and a temperature–time curve is created. The area under the curve is integrated and is inversely proportional to the flow rate or CO, in the absence of an intracardiac shunt or tricuspid regurgitation. The thermodilution method has been

well-validated [12]. It is safe and easily performed at the bedside. However, variations in the amount and rate of injection, or in the phase of the respiratory cycle in which the measurement is taken, may cause large variations in CO measurements. During mechanical ventilation, there may be large swings in intrathoracic pressure caused by many factors, including alterations in venous return, in respiratory pattern or rate. There remains some controversy regarding the optimal time when the thermal indicator should be injected. Therefore, three measurements falling within 10% of each other are obtained and averaged for the estimation of CO [13].

Other sources of error include conditions in which incomplete forward ejection of the indicator exists. Tricuspid regurgitation, a relatively frequent condition among critically ill, will result in under-estimation of CO. Intracardiac shunts, however, cause over-estimation due to dilution of the indicator with left-to-right shunt, or shunting of the indicator to the left heart with a right-to-left shunt. The accuracy of thermodilution is lower with very high or very low values of CO. 'Continuous' thermodilution CO measurement is available in newer catheters. This is based on a warm indicator method, whereby irregular pulses of heat are emitted by a 10-cm thermal filament sited on the catheter at the level of the right ventricle. The resulting thermal signal is measured by a thermistor at the catheter tip at 3-minute intervals, creating a semi-continuous measurement. *In vivo* studies found good accuracy, but with a trend toward overestimation [14]. Doppler-equipped PACs have been developed for continuous measurement of blood flow and cardiac output, but their accuracy depends on correct placement of the Doppler transducers inside the main pulmonary artery. Newer catheter designs incorporate continuous oximetric monitoring of pulmonary artery oxygen saturation by reflectance spectrophotometry, thereby enabling continuous estimation of cardiac output. This technology has acceptable accuracy and correlation compared with mixed venous oxygen saturation [15] and bolus thermodilution cardiac output techniques [16].

Box 133.2 Contraindications to pulmonary artery catheter insertion

Absolute

- Tricuspid or pulmonary valve stenosis.
- Mechanical tricuspid (or pulmonary) valve prosthesis.
- Right atrial or right ventricular mass (tumour or thrombus).
- Tricuspid or pulmonary valve endocarditis.
- Tetralogy of Fallot.

Relative

- Coagulopathy.
- Neutropenia.
- Arrhythmias.
- Left bundle branch block.
- Recent implantation of permanent pacemaker or cardioverter–defibrillator.
- Bioprosthetic tricuspid (or pulmonary) valve.
- Electrolyte abnormalities.
- Digoxin toxicity.

Contraindications

Absolute and relative contraindications for PAC insertion are listed in Box 133.2. The absolute contraindications are rare and include conditions in which catheter advancement may be interrupted or harmful. Coagulopathy should be corrected if possible. In cases of major coagulopathy, which cannot be corrected, the subclavian approach should be avoided. Hypoxaemia, acidosis, electrolyte abnormalities, and digoxin toxicity should also be corrected if possible prior to insertion because of the increased risk of arrhythmias [17].

Complications

Complications occur in about 10–15% of pulmonary artery catheterization, and may rarely be fatal [2–3]. They can be divided to two main categories:

- Complications related to catheter insertion and passage.
- Complications related to catheter use and maintenance.

The first category includes complications of venous access (arterial puncture, haematoma, pneumothorax, and haemothorax), as well as problems associated with trauma to the vessels and heart caused by the passage of the catheter. Various types of arrhythmias related to PAC placement have been described, and include ectopic atrial and ventricular beats, atrial and ventricular tachycardias, and conduction abnormalities. Ventricular arrhythmias during passage of the catheter occur in 13–68% of the patients [18], but mortality related to this complication is low and most of the cases have a benign self-limiting course. Critically-ill patients in the ICU are more prone to developing arrhythmias because of the presence of arrhythmogenic conditions as myocardial ischaemia, electrolyte disturbances, acidosis, hypoxaemia, and elevated endogenous and exogenous catecholamine levels. The development of right-bundle branch block (RBBB) is estimated to occur in 3–6% of catheterizations. In the presence of pre-existing left-bundle branch block, the development of RBBB can lead to complete heart block, but the incidence of this complication is not higher than the incidence of RBBB in patients without underlying conduction defects [19].

Complications associated with the use and maintenance of the catheter include pulmonary artery rupture, pulmonary infarction, thromboembolic events, and catheter-related infections. Pulmonary artery rupture is the most serious complication with a high mortality rate. It should be considered in cases of haemoptysis, dyspnoea, anxiety, and hypotension. Risk factors include age >60 years, pulmonary hypertension, improper balloon inflation, improper catheter positioning, cardiopulmonary bypass, and anticoagulation [18]. In most cases, emergent thoracotomy is needed. The risk of infectious complications increases with duration of catheterization. Most data suggest that the risk of infection increases significantly when catheters remain for more than 3–4 days [20], therefore catheter necessity should be evaluated on a daily basis.

References

1. Swan HJC, Ganz W, Forrester J, Marcus H, Diamond G, and Chonette D. (1970). Catheterization of the heart in man with the use

of a flow-directed balloon-tipped catheter. *New England Journal of Medicine*, **283**, 447–51.
2. Binanay C, Califf RM, Hasselblad V, et al. (2005). Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *Journal of the American Medical Association*, **294**, 1625–33.
3. Harvey S, Harrison DA, Singer M, et al. (2005). Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomized controlled trial. *Lancet*, **366**, 472–7.
4. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network (2006). Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *New England Journal of Medicine*, **354**, 2213–24.
5. Wiener RS and Welch HG. (2007). Trends in the use of the pulmonary artery catheter in the United States, 1993–2004. *Journal of the American Medical Association*, **298**, 423–9.
6. Sandham JD, Hull RD, Brant RF, et al. (2003). A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *New England Journal of Medicine*, **348**, 5–14.
7. Ranucci M. (2006). Which cardiac surgical patients can benefit from placement of a pulmonary artery catheter? *Critical Care*, **10**(Suppl. 3), S6.
8. Pölönen P, Ruokonen E, Hippeläinen M, Pöyhönen M, and Takala J. (2000). A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. *Anesthesia and Analgesia*, **90**, 1052–9.
9. Chittock DR, Dhingra VK, and Ronco JJ. (2004). Severity of illness and risk of death associated with pulmonary catheter use. *Critical Care Medicine*, **32**, 911–15.
10. Seldinger SI. (1953). Catheter replacement of the needle in percutaneous arteriography; a new technique. *Acta Radiologica*, **39**, 368–76.
11. Summerhill EM and Baram M. (2005). Principles of pulmonary artery catheterization in the critically ill. *Lung*, **183**, 209–19.
12. Pepine CJ, Mehta J, Webster WW, Jr, and Nichols WW. (1978). In vivo validation of a thermodilution method to determine regional left ventricular blood flow in patients with coronary disease. *Circulation*, **58**, 795–802.
13. Monnet X, Persichini R, Ktari M, Jozwiak M, Richard C, and Teboul JL. (2011). Precision of the transpulmonary thermodilution measurements. *Critical Care*, **15**, R204.
14. Mihaljevic T, von Segesser LK, Tonz M, et al. (1995). Continuous versus bolus thermodilution cardiac output measurements: a comparative study. *Critical Care Medicine*, **23**, 944–9.
15. Armaganidis A, Dhainaut JF, Billard JL, et al. (1994). Accuracy assessment for three fiberoptic pulmonary artery catheters for SvO_2 monitoring. *Intensive Care Medicine*, **20**, 484–8.
16. Seguin P, Colcanap O, Le Rouzo A, Tanguy M, Guillou YM, and Mallédant Y. (1998). Evaluation of a new semi-continuous cardiac output system in the intensive care unit. *Canadian Journal of Anaesthesia*, **45**, 578–83.
17. Sprung CL, Pozen RG, Rozanski JJ, Pinero JR, Eisler BR, and Castellanos A. (1982). Advanced ventricular arrhythmias during bedside pulmonary artery catheterization. *American Journal of Medicine*, **72**, 203–8.
18. Evans DC, Doraiswamy VA, Prosciak MP, et al. (2009). Complications associated with pulmonary artery catheters: a comprehensive clinical review. *Scandinavian Journal of Surgery*, **98**, 199–208.
19. Sprung CL, Elser B, Schein RM, Marcial EH, and Schrager BR. (1989). Risk of right bundle-branch block and complete heart block during pulmonary artery catheterization. *Critical Care Medicine*, **17**, 1–3.
20. Mueller HS, Chatterjee K, Davis KB, et al. (1988). ACC expert consensus document. Present use of bedside right heart catheterization in patients with cardiac disease. *Journal of the American College of Cardiology*, **32**, 840–64.

CHAPTER 134

Mixed and central venous oxygen saturation monitoring in the ICU

Frank Bloos and Konrad Reinhart

Key points

- Venous oximetry is performed either by blood gas analysis or continuously by fibre optics inserted within the intravascular catheter.
- Mixed venous oxygen saturation (SvO_2) is obtained from the pulmonary artery via a pulmonary artery catheter, while central venous oxygen saturation ($ScvO_2$) is obtained from the superior vena cava via a central venous catheter.
- In critically-ill patients, $ScvO_2$ values <70% are associated with unfavourable outcomes. In septic shock and in peri-operative high-risk patients, a treatment goal of $ScvO_2$ >70% (SvO_2 >65%) should be targeted.
- $ScvO_2$ values >90% indicate reduced O_2 extraction and identifies patients with an increased risk of death.
- Other measures of tissue oxygenation such as serum lactate and organ function need to be monitored in parallel to venous oximetry to increase the sensitivity for detection of a mismatch between O_2 delivery and tissue O_2 need.

Introduction

Extended monitoring techniques, such as pulmonary artery catheterization, pulse wave analysis, or echocardiography are available for assessment of haemodynamic status, particularly in patients with impaired cardiocirculatory function. However, evidence is still lacking as to whether such techniques truly alter outcomes. In this context, achieving fixed targets of haemodynamic parameters, such as supranormal O_2 delivery did not prove beneficial for critically-ill patients. On the other hand, early restoration of a sufficient circulation may prevent the development of multi-organ dysfunction. It therefore seems reasonable that haemodynamic resuscitation should target goals that reflect tissue oxygen needs of an individual patient. Venous oximetry may be such a tool.

Physiological background

The pulmonary artery contains venous blood from the whole body, i.e. a mixture draining from superior and inferior venae cavae. The oxygen saturation of blood in the pulmonary artery is therefore referred to as 'mixed venous oxygen saturation' (SvO_2). This is a marker for whole body oxygen extraction and can be measured with a pulmonary artery catheter. In health, changes in tissue oxygen needs are usually covered by corresponding changes in oxygen delivery. Thus, oxygen extraction and SvO_2 generally remain constant. Oxygen extraction increases and SvO_2 decreases if the cardiovascular system cannot compensate for increased O_2 needs. Thus, a drop in SvO_2 indicates a mismatch between O_2 supply and demand [1].

Changes in SvO_2 result from changes in the relationship between O_2 delivery and need (Table 134.1). A fall in SvO_2 may be due to a decrease in O_2 delivery, such as a drop in arterial O_2 content (i.e. hypoxaemia, anaemia) or cardiac output (i.e. cardiogenic shock). It may also reflect an increase in O_2 need such as fever, shivering, and pain, which would otherwise remain uncovered by a matched increase in O_2 delivery [1].

Insertion of a pulmonary artery catheter is invasive and its clinical utility is a matter of discussion [2]. Central venous catheters (CVC) are frequently used in critically-ill patients. Measurement of oxygen saturation in the blood obtained from a CVC is referred to as 'central venous oxygen saturation' ($ScvO_2$). In general, the physiological principles of SvO_2 can also be applied to $ScvO_2$. However, both values are not identical since a catheter placed within the superior vena cava only represents venous blood draining the upper body. Oxygen extraction by different organs differs according to their varying oxygen needs and deliveries. The corresponding veins therefore hold highly variable oxygen saturations (Fig. 134.1) [4].

Table 134.1 Changes in SvO_2 result from changes in the relationship between O_2 delivery and need

Decrease in SvO_2 or $ScvO_2$	
Increase O_2 consumption	*Decrease O_2 delivery*
Stress Pain Fever Shivering	Drop in arterial oxygen content (i.e. anaemia, hypoxaemia) Drop in cardiac output
Increase in SvO_2 or $ScvO_2$	
Decrease O_2 consumption	*Increase O_2 delivery*
Analgesia Sedation Mechanical ventilation Hypothermia	Increase in arterial oxygen content Increase in cardiac output

Thus, under physiological conditions, $ScvO_2$ is lower than SvO_2 by 2–3%. This relationship is reversed in critically ill patients under analgo-sedation or in shock. While it is not possible in the clinical setting to predict SvO_2 from $ScvO_2$, changes in SvO_2 are adequately mirrored by changes in $ScvO_2$ [3].

Technique of venous oximetry

Oxygen saturation can be measured either discontinuously by blood gas analysis, or by continuous fibre optic monitoring. For blood gas analysis, blood is obtained from the distal lumen of a pulmonary artery catheter for SvO_2, and from the distal lumen of a CVC placed into the superior vena cava for $ScvO_2$. As all clinical studies addressing $ScvO_2$ were undertaken with CVCs in the superior vena cava, therapeutic goals derived from such studies cannot be transferred to femoral vein CVCs since oxygen saturations in the superior and inferior venae cavae differ (Fig. 134.1).

Continuous venous oximetry is achieved using reflection spectrophotometry via fibre optics integrated into the CVC for $ScvO_2$ or the PA catheter for SvO_2. Oxygen saturation is displayed on an external monitor. While continuous venous oximetry is more expensive than blood gas analysis because of the higher costs of the catheters, frequent blood gas analyses may add up to a significant cost and time expenditure.

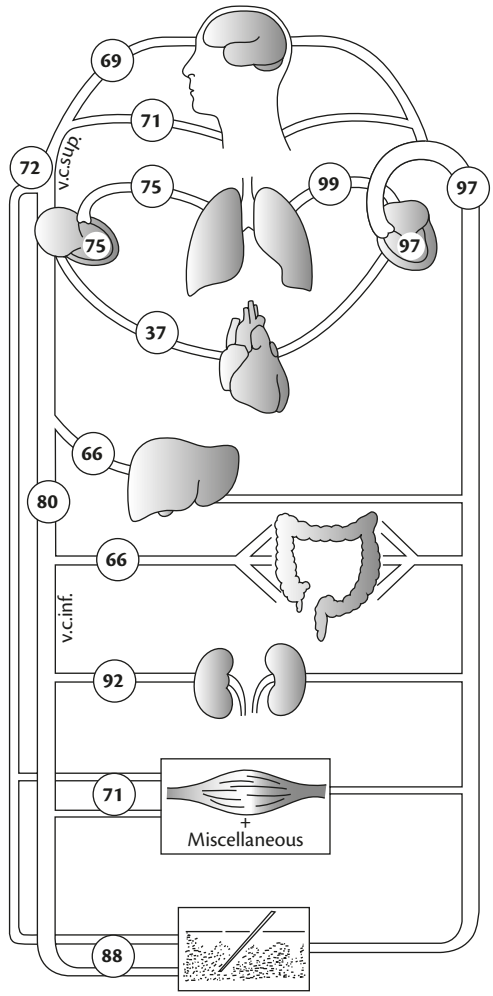


Fig. 134.1 Venous oxygen saturation in different venous systems. Individual oxygen saturations differ according to the different oxygen extraction of specific organs.
Reproduced from *Clinical Aspects of O_2 Transport and Tissue Oxygenation*, 1989, 'Monitoring O_2 transport and tissue oxygenation in critically ill patients', Reinhart K, Eyrich K (eds), with permission from Springer Science and Business Media.

Clinical application

In a large study in critically-ill patients, a treatment goal targeting SvO_2 values >70% did not improve survival rates [5]. However, this treatment goal was only achieved in 66.7% of protocolized patients, the interventions took place late in the course of the disease, and no treatment algorithm was specified for haemodynamically unstable patients. More recent studies in septic shock and in perioperative patients showed that $ScvO_2$-guided treatment algorithms can impact upon outcomes [6,7].

$ScvO_2$ monitoring during surgery

Avoidance or prompt reversal of hypoperfusion during extended surgery may prevent perioperative morbidity and shorten the ICU length of stay. Indeed, patients undergoing intra-abdominal surgery experienced complications more often if a drop in $ScvO_2$ was observed during surgery [8]. A goal-orientated treatment algorithm consisting of hourly $ScvO_2$ measurements reduced the occurrence of organ dysfunction and the duration of hospital stay [6]. This study used O_2 extraction ratio (O_2ER) as a treatment goal, calculated as $(SaO_2 - ScvO_2)/SaO_2$. An intervention was induced if the O_2ER dropped <27%. Fluid was administered when central venous pressures (CVPs) were low, otherwise dobutamine was given until O_2ER was >27%. This goal approximates to $ScvO_2$ values of 70–73% when arterial oxygenation is in the normal range (see Fig. 134.2).

Post-operative $ScvO_2$ monitoring

The occurrence of a low $ScvO_2$ after surgery is associated with increased morbidity [8,9]. Similarly, patients admitted to intensive

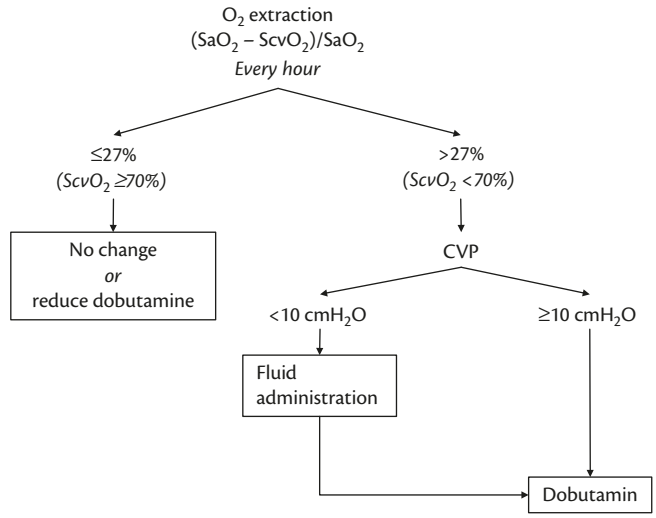


Fig. 134.2 Goal-directed therapy as applied during surgery.
CVP, central venous pressure; SaO_2, arterial oxygen saturation; $ScvO_2$, central venous oxygen saturation.
Data from Donati A et al., 'Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients', *Chest*, 2007, **132**, pp. 1817–24.

care with a low $ScvO_2$ have a higher risk of dying than those with normal $ScvO_2$ values [10]. However, it is unknown for how long a patient should be monitored. Patients after cardiac surgery may also profit from venous oximetry though only data from small studies are available. Low SvO_2 and $ScvO_2$ values are both associated with a higher morbidity in these patients [11]. A small study demonstrated some outcome advantage when haemodynamic stabilization included a $ScvO_2$ target >70% [12]. These data point to the fact that venous oximetry is a rational option in high-risk patients after surgery.

Septic shock

Septic shock is characterized by hypovolemia, arterial hypotension, myocardial depression and microcirculatory dysfunction. A low $ScvO_2$ is associated with an unfavourable prognosis in these patients [13].

Early goal-directed therapy (EGDT) combines several haemodynamic goals into a treatment algorithm (Fig. 134.3) with CVP, mean arterial pressure and $ScvO_2$ targets. Compared with a control group, EGDT resulted in patients being given more fluid, dobutamine and blood transfusions within the first 6 hours following admission to an emergency department [7]. This was associated with an improvement in 28-day mortality from 46.5% to 30.5% ($p = 0.009$). However, three large multicentre trials did not reproduce the beneficial effect of EGDT on outcome [14-16]. Thus, current data do not support the systematic use of this protocolized approach in the haemodynamic resuscitation of patients with septic shock. Whether this limitation also holds true for venous oximetry in unclear since $ScvO_2$ targets in patients with sepsis were always investigated in the frame of EGDT. As in other clinical applications of venous oximetry, $ScvO_2$ and SvO_2 targets should be assessed in the clinical context of the patient.

Currently, international guidelines for the treatment of septic shock have still adopted the concept of EGDT and recommend a $ScvO_2$ >70% [17]. Likewise, a treatment goal >65% is recommended for SvO_2, although EGDT using the pulmonary artery catheter has never been formally tested in septic shock patients.

Importantly, EGDT, and thus the treatment goals for venous oximetry, have been designed for the initial resuscitation of septic shock. Although the treatment goals for SvO_2 or $ScvO_2$ appear reasonable beyond the initial resuscitation phase, this has never been formally studied. Implementation of the Surviving Sepsis Campaign guidelines [17] has been studied in a large Spanish study [18]. Compliance with guidelines was associated with a better survival. Survivors received more fluids and vasopressors, and a $ScvO_2$ >70% was more frequently achieved.

Other clinical applications

Although the pulmonary artery catheter has a recognized role in the management in decompensated heart failure, a venous oximetry value has never been formally studied as a treatment goal. As SvO_2 is tightly correlated with cardiac output, a drop in SvO_2 is a reliable early marker of cardiac deterioration [19]. Patients with congestive heart failure and a low $ScvO_2$ require a more aggressive management approach than those with normal values of $ScvO_2$. Venous oximetry has also been applied in other patient groups in the emergency department, including those sustaining major trauma. However, no study has yet investigated the validity of venous oximetry in aiding haemodynamic stabilization in polytraumatized patients.

Limitations of venous oximetry

Venous oximetry mirrors the adequacy of tissue oxygenation of the whole body. It is not possible using this technique to identify an inadequate oxygen supply in single organs. Thus, a normal value of mixed or central venous oxygen saturation does not always exclude tissue hypoxia. A limitation of the utility of this technique is reached if organ dysfunction progresses or serum lactate increases despite normal, or even increased, venous oximetry [20].

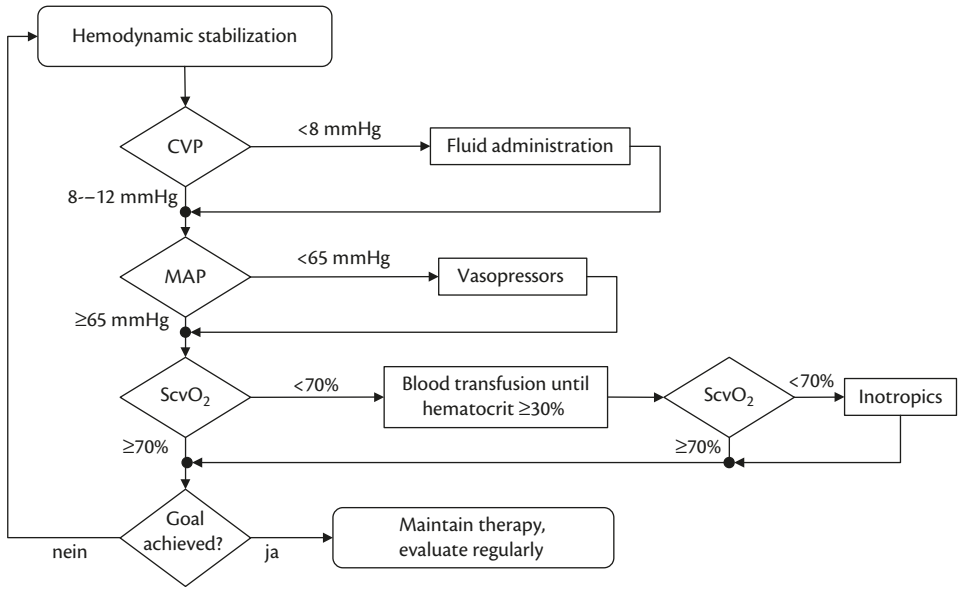


Fig. 134.3 Early goal-directed therapy for patients with septic shock.

CVP, central venous pressure; MAP, mean arterial pressure; $ScvO_2$, central venous oxygen saturation.

Data from Rivers E et al., 'Early goal-directed therapy in the treatment of severe sepsis and septic shock', *New England Journal of Medicine*, 2001, **345**, pp. 1368–77.

This may be related to a decrease in cellular utilization of oxygen due to mitochondrial dysfunction and/or an increase in vascular shunt. Venous oximetry thus only represents the adequacy of tissue oxygenation if the tissues can extract oxygen from the capillary blood. This function may be impaired in severely damaged tissues. Venous hyperoxia is seen under this condition and is associated with an unfavourable outcome. Patients with congestive heart failure frequently have $ScvO_2$ values of approximately 50%, since these patients with low O_2 deliveries need to respond to changes in O_2 need by increasing O_2ER. It is in general unreasonable to attempt to reach a $ScvO_2$ goal of ≥70% in these patients.

References

1. Bloos F and Reinhart K. (2005). Venous oximetry. *Intensive Care Medicine*, **31**, 911–13.
2. Sandham JD, Hull RD, Brant RF, et al. (2003). A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *New England Journal of Medicine*, **348**, 5–14.
3. Dueck MH, Klimek M, Appenrodt S, Weigand C, and Boerner U. (2005). Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions. *Anesthesiology*, **103**, 249–57.
4. Reinhart K. (1989). Monitoring O_2 transport and tissue oxygenation in critically ill patients. In: Reinhart K and Eyrich K (eds) *Clinical Aspects of O_2 Transport and Tissue Oxygenation*, pp. 195–211. Berlin: Springer.
5. Gattinoni L, Brazzi L, Pelosi P, et al. (1995). A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO_2 Collaborative Group. *New England Journal of Medicine*, **333**, 1025–32.
6. Donati A, Loggi S, Preiser JC, et al. (2007). Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients. *Chest*, **132**, 1817–24.
7. Rivers E, Nguyen B, Havstad S, et al. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine*, **345**, 1368–77.
8. Collaborative Study Group on Perioperative $ScvO_2$ Monitoring. (2006). Multicentre study on peri- and postoperative central venous oxygen saturation in high-risk surgical patients. *Critical Care*, **10**, R158.
9. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, and Bennett ED. (2005). Changes in central venous saturation after major surgery, and association with outcome. *Critical Care*, **9**, R694–9.
10. Bracht H, Hanggi M, Jeker B, et al. (2007). Incidence of low central venous oxygen saturation during unplanned admissions in a multidisciplinary intensive care unit: an observational study. *Critical Care*, **11**, R2.
11. Nogueira PM, Mendonca-Filho HT, Campos LA, et al. (2010). Central venous saturation: a prognostic tool in cardiac surgery patients. *Journal of Intensive Care Medicine*, **25**, 111–16.
12. Kapoor PM, Kakani M, Chowdhury U, Choudhury M, Lakshmy, and Kiran U. (2008). Early goal-directed therapy in moderate to high-risk cardiac surgery patients. *Annals of Cardiac Anaesthesia*, **11**, 27–34.
13. Park M, Azevedo LC, Maciel AT, Pizzo VR, Noritomi DT, and da Cruz Neto LM. (2006). Evolutive standard base excess and serum lactate level in severe sepsis and septic shock patients resuscitated with early goal-directed therapy: still outcome markers? *Clinics (Sao Paulo)*, **61**, 47–52.
14. ProCESS Investigators (2014). A randomized trial of protocol-based care for early septic shock. *New England Journal of Medicine*, **370**, 1683–93.
15. ARISE Investigators (2014). Goal-directed resuscitation for patients with early septic shock. *New England Journal of Medicine*, **371**, 1496–506.
16. Mouncey PR, Osborn TM, Power GS, et al. (2015). Trial of Early, Goal-Directed Resuscitation for Septic Shock. *New England Journal of Medicine*, **372**, 1301–11.
17. Dellinger RP, Levy MM, Rhodes A, et al. (2013). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine*, **41**, 580–637.
18. Ferrer R, Artigas A, Levy MM, et al. (2008). Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *Journal of the American Medical Association*, **299**, 2294–303.
19. Muir AL, Kirby BJ, King AJ, and Miller HC. (1970). Mixed venous oxygen saturation in relation to cardiac output in myocardial infarction. *British Medical Journal*, **4**, 276–8.
20. Arnold RC, Shapiro NI, Jones AE, et al. (2009). Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock*, **32**, 35–9.

CHAPTER 135

Right ventricular function in the ICU

Antoine Vieillard-Baron

Key points

- In normal situations, the right ventricle (RV) virtually acts as a passive conduit.
- In the intensive care unit, RV function is key to treatment optimization and prognostic assessment.
- RV function monitoring is strongly recommended in critically-ill patients.
- Echocardiography, by a transthoracic or transoesophageal route, is probably the best technique for this purpose.
- Alterations in respiratory mechanics or in ventilator settings may significantly impact upon RV function.

Introduction

The right ventricle (RV) has long been considered 'useless' because of its intrinsic properties. In normal conditions, it virtually acts as a passive conduit [1]. Unlike the left ventricle, its iso-volumetric contraction pressure is negligible and there is no iso-volumetric relaxation period as it continues to eject blood long after the beginning of its relaxation. Indeed, the pressure within the pulmonary circulation is low in healthy subjects. Thus, the RV is very sensitive to any acute alterations in its afterload, and its ability to adapt acutely is limited. However, in critically-ill patients, there are many clinical situations where there is uncoupling between the RV and the pulmonary circulation, leading to RV systolic dysfunction and, ultimately, failure. Uncoupling means either that pulmonary vascular resistance and RV afterload are too high with respect to RV contractility, as occurs in pulmonary embolism (PE) and the acute respiratory distress syndrome (ARDS), or that RV contractility is too low with respect to slight increases in its afterload, as may occur in patients with septic shock or RV infarction who require mechanical ventilation. Indeed, mechanical ventilation may decrease RV preload, but also significantly increases RV afterload [2].

Uncoupling usually leads to acute cor pulmonale, the reported incidence of which is up to 25% when protective mechanical ventilation is used in ARDS (Table 135.1) [3], and >60% with anatomically massive PE [4]. RV systolic function is key to the patient's haemodynamic profile and in managing their haemodynamic function. There are many important reasons for monitoring RV function in the critically ill. First, right ventricular failure is a major reason for non-responsiveness to fluid [5], in many situations, the right ventricle is preload-unresponsive, whereas the left ventricle

Table 135.1 Recent studies reporting incidence of RV dysfunction when protective ventilation is used in ALI/ARDS patients

	Number of patients	Population characteristics	Tool	Reported parameter of RV dysfunction	Incidence
Vieillard-Baron et al. 2001 [3]	75	ARDS	Ultrasound (TEE)	ACP	25%
Page et al. 2003 [14]	110	ARDS	Ultrasound (TEE)	ACP	24.5%
Osman et al. 2009 [15]	145	ARDS	PAC	CVP > PAOP	27%
Bull et al. 2010 [11]	475	ALI/ARDS	PAC	TPG ≥ 12 mmHg	73%
Brown et al. 2011 [16]	48	ALI/ARDS	Ultrasound (TTE)	ACP	30%
Mekontso-Dessap et al. 2011 [17]	203	ARDS	Ultrasound (TEE)	ACP	22%
Lhéritier G et al. 2013	200	ARDS	Ultrasound (TEE)	ACP	22.5%

PAC, pulmonary artery catheter; TTE, transthoracic echocardiography; TEE, transoesophageal echocardiography; CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure; TPG, transpulmonary gradient; ARDS, acute respiratory distress syndrome; ALI, acute lung injury.

Data from various studies. See references.

remains responsive. Fluid infusion is then always deleterious and exacerbates venous congestion. Secondly, RV dysfunction per se is strongly associated with a poor prognosis in patients with ARDS, PE, and acute myocardial infarction. Finally, RV function also has a pivotal role in the prognosis of chronic disease, as in chronic pulmonary hypertension [6].

RV function monitoring

Table 135.2 summarizes the different devices used at the bedside to monitor RV function. Echocardiography, via transthoracic or transoesophageal routes, is probably the best compromise between clinical effectiveness and invasiveness. Devices based on transpulmonary thermodilution, e.g. the PiCCO system, are inadequate for evaluating RV function [7]. Computerized tomography can offer useful information, e.g. in suspected PE it allows visualization of the thrombus and an evaluation of RV function (Fig. 135.1) [8].

RV function is highly influenced by respiratory mechanics and respiratory settings in mechanically-ventilated patients. Both may impair the pulmonary circulation and so increase RV afterload in certain circumstances. RV function should always be interpreted and re-evaluated in the light of respiratory mechanics and respiratory settings: any change may instantly modify RV function. An example is given in Fig. 135.2.

Pulse pressure variation

In ventilated patients with haemodynamic compromise, blood pressure monitoring by an arterial catheter is strongly recommended. Visualization of a marked respiratory pulse pressure variation usually means that volume resuscitation can (or should) be optimized. However, in other situations, as in severe ARDS, such variations may instead reflect severe RV systolic dysfunction and so may serve as a warning to physicians to pay attention to the right ventricle (Fig. 135.3).

Pulmonary artery catheter

Use of the pulmonary artery catheter (PAC) has declined in recent years because of its limitations, such as its lack of proven impact on prognosis. However, those still using it should understand the parameters of RV dysfunction that should be monitored. Twenty years ago, RV systolic dysfunction was defined in a large series of ARDS patients as central venous pressure (CVP) exceeding the pulmonary artery occlusion pressure (PAOP) (Fig. 135.4) [9]. The pressure gradient between diastolic pulmonary artery pressure (DPAP) and PAOP (Fig. 135.4) [10], or between mean pulmonary artery pressure (MPAP) and PAOP, are likely to be more relevant. The latter gradient, called the transpulmonary gradient, was independently associated with mortality in a large series of ARDS patients [11]. These two pressure gradients do not directly reflect RV function, but rather the status of the pulmonary circulation.

Table 135.2 Main tools available for RV function monitoring

Tool	Parameters of RV dysfunction	Limitations
Arterial catheter	Pulse pressure variations	Non-specific
Pulmonary artery catheter	Central venous pressure >PAOP, elevated DPAP–PAOP gradient or MPAP–PAOP gradient, decreased right ventricular ejection fraction	Invasive, technical errors, transmission of airway pressures
Transpulmonary thermodilution	Inaccurate	Inaccurate
Echocardiography (transthoracic, transoesophageal)	Acute cor pulmonale, RV dilatation, paradoxical septal motion, biphasic pattern of pulmonary blood flow	Discontinuous, semi-invasive (transoesophageal echocardiography)

PAOP, pulmonary artery occlusion pressure; DPAP, diastolic pulmonary artery pressure; MPAP, mean pulmonary artery pressure.

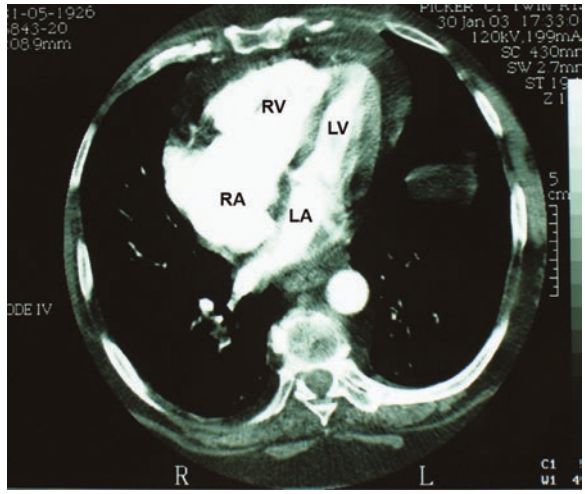


Fig. 135.1 Chest CT scan in a patient hospitalized with massive pulmonary embolism. Note the huge enlargement of the right ventricle.
RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium.

Right ventricle ejection fraction (RVEF) and pulmonary artery pressure (PAP) may be evaluated with a PAC. RVEF can be calculated from RV volume measurements using a fast-response catheter, as proposed many years ago in septic shock [12]. However, a 'low' RVEF may be observed in situations where coupling between the right ventricle and pulmonary circulation is optimal, whereas a 'normal' value may be poorly adapted to a huge increase in RV afterload and then associated with uncoupling. Thus, it is not particularly useful to evaluate RVEF, regardless of any adaptation of the right ventricle to load conditions. The same limitation applies to PAP. A patient may develop acute cor pulmonale, although PAP may be only slightly elevated, yet RV contraction is severely impaired. However, another patient may not do so, despite significant elevations in PAP, as the right ventricle has adapted well to its load conditions.

PAP measurement, if performed, has to be used differently. For instance, it can be used to monitor treatment-related effects (e.g. nitric oxide inhalation should decrease pulmonary hypertension, if beneficial), or to distinguish between acute and chronic RV dysfunction as a systolic PAP remaining below 60 mmHg is highly suggestive of an acute phenomenon (a previously normal RV cannot generate a higher pressure), whereas systolic PAP values >60 mmHg is very suggestive of pre-existing disease with a hypertrophied right ventricle.

Echocardiography

This is probably the best technique for evaluation and monitoring of RV function at the bedside in the critically ill. This objective is served by simple and focused echocardiographic parameters—RV size, interventricular septum movement, and the pattern of RV

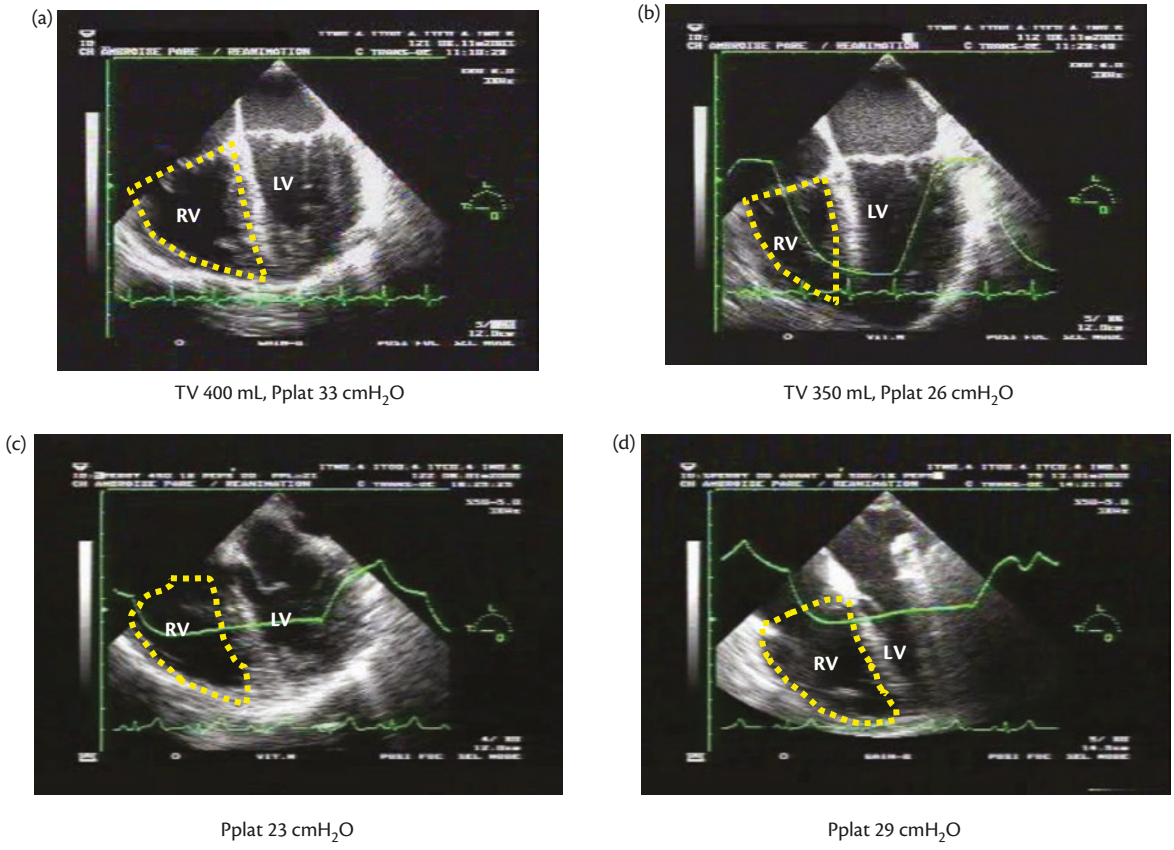


Fig. 135.2 Long-axis view of the left ventricle by transoesophageal echocardiography (TEE) in patients mechanically-ventilated for severe ARDS. (a) Here, TEE demonstrates acute cor pulmonale (note the significant RV dilatation). After reduction of tidal volume and plateau pressure, RV size was normalized (b). In patient 2, note the deterioration of RV function related to the decrease in compliance and increase in plateau pressure from 23 (c) to 29 cmH_2O (d).

TV, tidal volume; Pplat, plateau pressure; RV, right ventricle; LV, left ventricle.

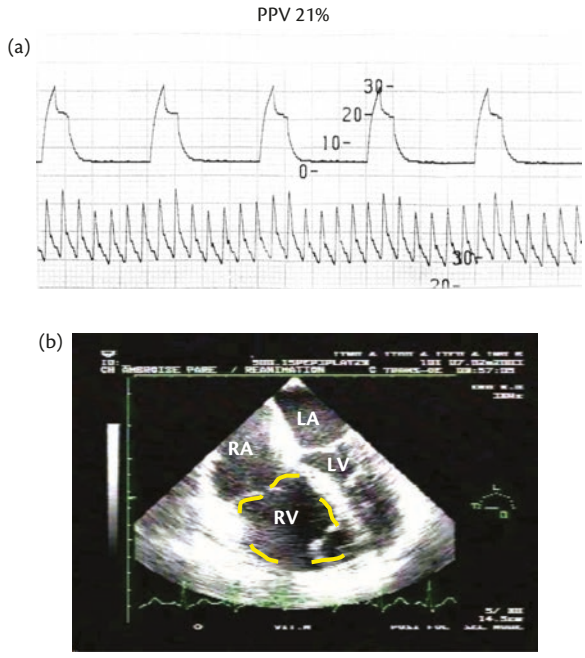


Fig. 135.3 Pulse pressure variations related to acute cor pulmonale in a patient ventilated for ARDS (a). Note the huge increase in RV size with compression of the left ventricle (b).

PPV, pulse pressure variation; RV, right ventricle; LV, left ventricle; RA, right atrium; LA: left atrium.

ejection flow using pulsed Doppler. Acute cor pulmonale is defined by the combination of RV dilatation with paradoxical septal motion during systole (Fig. 135.5) [13]. RV dilatation reflects diastolic overload, whereas paradoxical septal motion in systole indicates systolic overload. A biphasic pattern of ejection flow is highly suggestive of an obstruction in the pulmonary circulation (proximal in PE, distal in ARDS) (Fig. 135.5) [13]. Echocardiography also enables

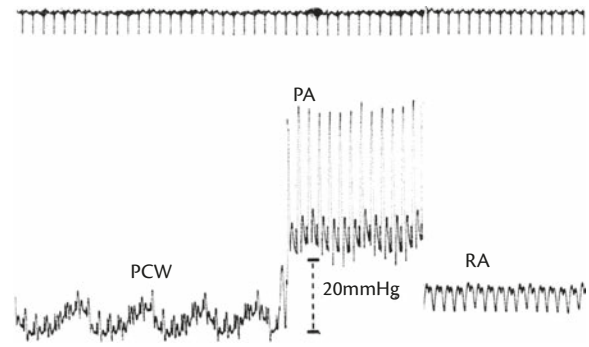


Fig. 135.4 Pulmonary artery catheter in a patient with ARDS. Note that RA pressure was higher than pulmonary capillary wedge (PCW) pressure and, secondly, that the gradient between the diastolic pulmonary artery pressure and the PCW pressure was abnormally elevated.

PA, pulmonary artery pressure; RA, right atrial pressure; PCW, pulmonary capillary wedge pressure.

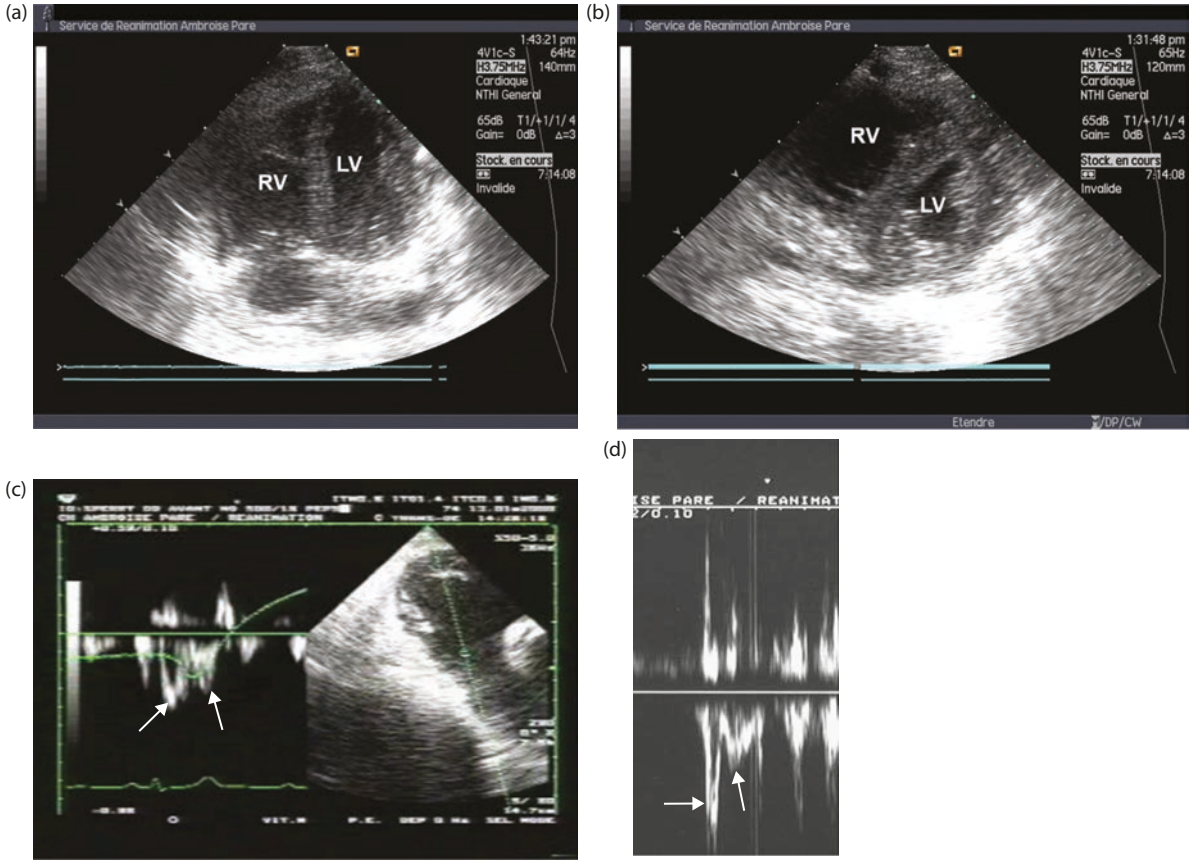


Fig. 135.5 Typical pattern of acute cor pulmonale. (a) and (b) acute cor pulmonale in a patient with ARDS related to influenza. The apical four-chamber view demonstrated RV dilatation (a), whereas the parasternal short-axis view demonstrated paradoxical septal motion (b). In another patient with acute cor pulmonale related to ARDS, note the biphasic pattern of the pulmonary flow (c) (arrows). The same pattern was also seen in a patient with a massive pulmonary embolism (d).
RV, right ventricle; LV,: left ventricle.

an evaluation of RV preload by visualizing the inferior vena cava (IVC). A virtual IVC is suggestive of a preload problem (and the need for fluid in the context of shock), whereas a congested IVC reflects RV diastolic overload.

As reiterated in Table 135.2, a limitation of echocardiography is its inability to monitor haemodynamics continuously, especially RV function. Thus, it should be routinely combined with other systems in the most severely ill patients, such as invasive monitoring of BP.

In conclusion, RV function monitoring is strongly recommended in many situations encountered in the ICU, such as ARDS, septic shock, and PE. Many devices are available, but echocardiography probably constitutes the best compromise between accuracy and invasiveness. Whatever the device used, intensivists must be aware of its limitations, and understand how respiratory mechanics and ventilator settings may impact on RV function.

References

1. Redington AN, Rigby ML, Shinebourne EA, and Oldershaw PJ. (1990). Changes in the pressure volume relation of the right ventricle when its loading conditions are modified. *British Heart Journal*, **63**, 45–9.
2. Scharf SM, Caldini P, and Ingram RH, Jr. (1977). Cardiovascular effects of increasing airway pressure in the dog. *American Journal of Physiology*, **232**, H35–43.
3. Vieillard-Baron A, Schmitt JM, Augarde R, et al. (2001). Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. *Critical Care Medicine*, **29**, 1551–5.
4. Vieillard-Baron A, Page B, Augarde R, et al. (2001). Acute cor pulmonale in massive pulmonary embolism: incidence, echocardiographic pattern, clinical implications and recovery rate. *Intensive Care Medicine*, **27**, 1481–6.
5. Schneider AJ, Teule GJ, Groeneveld AB, et al. (1988). Biventricular performance during volume loading in patients with early septic shock, with emphasis on the right ventricle: a combined hemodynamic and radionuclide study. *American Heart Journal*, **116**, 103–12.
6. Forfia PR, Fisher MR, Mathai SC, et al. (2006). Tricuspid annular displacement predicts survival in pulmonary hypertension. *American Journal of Respiratory and Critical Care Medicine*, **174**, 1034–41.
7. Combes A, Berneau JB, Luyt CE, and Trouillet JL. (2004). Estimation of left ventricular systolic function by single transpulmonary thermodilution. *Intensive Care Medicine*, **30**, 1377–83.
8. Quiroz R, Kucher N, Schoepf UJ, et al. (2004). Right ventricular enlargement on chest computed tomography: prognostic role in acute pulmonary embolism. *Circulation*, **109**, 2401–4.
9. Monchi M, Bellenfant F, Cariou A, et al. (1998). Early predictive factors of survival in the acute respiratory distress syndrome: a multivariate analysis. *American Journal of Respiratory and Critical Care Medicine*, **158**, 1076–81.
10. Marland AM and Glauser FL. (1982). Significance of the pulmonary artery diastolic-pulmonary wedge pressure gradient in sepsis. *Critical Care Medicine*, **10**, 658–61.

11. Bull TM, Clark B, McFann K, Moss M, and National Institutes of Health/National Heart, Lung, and Blood Institute ARDS Network. (2010). Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. *American Journal of Respiratory and Critical Care Medicine*, **182**, 1123–8.
12. Vincent JL, Reuse C, Frank N, Contempré B, and Kahn RJ. (1989). Right ventricular dysfunction in septic shock: assessment by measurements of right ventricular ejection fraction using the thermodilution technique. *Acta Anaesthesiologica Scandinavica*, **33**, 34–8.
13. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, and Jardin F. (2002). Echo-Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. *American Journal of Respiratory and Critical Care Medicine*, **166**, 1310–19.
14. Page B, Vieillard-Baron A, Beauchet A, Aegerter P, Prin S, and Jardin F. (2003). Low stretch ventilation strategy in acute respiratory distress syndrome: eight years of clinical experience in a single center. *Critical Care Medicine*, **31**, 765–9.
15. Osman D, Monnet X, Castelain V, et al. (2009). Incidence and prognostic value of right ventricular failure in acute respiratory distress syndrome. *Intensive Care Medicine*, **35**, 69–76.
16. Brown SM, Pittman J, Miller RR, et al. (2011). Right and left heart failure in severe H1N1 influenza A infection. *European Respiratory Journal*, **37**, 112–18.
17. Mekontso-Dessap A, Boissier F, Leon R, et al. (2010). Prevalence and prognosis of shunting across patent foramen ovale during acute respiratory distress syndrome. *Critical Care Medicine*, **38**, 1786–92.
18. Lhéritier G, Legras A, Caille A, Lherm T, et al. (2013). Prevalence and prognostic value of acute cor pulmonale and patent foramen ovale in ventilated patients with early acute respiratory distress syndrome: a multicenter study. *Intensive care Med*, **39**, 1734–42.

CHAPTER 136

Cardiac output assessment in the ICU

Nishkantha Arulkumaran and Maurizio Cecconi

Key points

- Haemodynamic monitoring itself does not improve patient outcome. This is dependent on the acquisition of accurate data, appropriate interpretation, and suitable management decisions. Any value derived from CO monitoring must be interpreted in the context of other clinical data, in particular, markers of tissue perfusion.
- The best method of CO monitoring depends upon patient's needs, the clinical scenario, and the experience of the treating physician in relation to the monitoring device itself.
- Although many treatment algorithms have 'targets' validated for specific populations of patients, there is no ideal set of values for an individual patient.
- Cardiac output is estimated, not measured. Values of haemodynamic parameters derived from different CO monitoring devices may not, therefore, be directly comparable.
- The trend or change in haemodynamic parameters is at least as important as the absolute values. This is particularly important when any intervention to augment CO is undertaken. Continuous CO monitoring is therefore preferable to intermittent assessment as it allows trends to be more readily determined.

Introduction

Cardiac output (CO) monitoring devices can be used to detect and monitor haemodynamic changes, and guide therapy. In addition to tracking CO, several of these monitors provide additional parameters, such as dynamic indices of preload (including pulse pressure variation (PPV) and stroke volume variation (SVV)), or volumetric indices (including intrathoracic blood volume index (ITBVI) and extravascular lung water index (EVLWI)) (Fig. 136.1). The different methods of CO monitoring each have their own merits and limitations. Here, we will present the rationale for CO monitoring, and describe some of the devices available.

History

CO monitoring was conceived by Adolf Fick in 1870, who suggested cardiac output could be computed from the ratio of oxygen consumption to the difference in arteriovenous oxygen content.

$$CO = VO_2 / [(CaO_2 - CvO_2) \times 10] \quad \text{[eqn 1]}$$

where VO_2 is oxygen consumption, CaO_2 is arterial O_2 content, and CvO_2 is venous O_2 content.

The indicator dilution method involves injection of an indicator dye into the central circulation with its concentration measured downstream. Cardiac output is derived from the area under the dilution curve (a function of the diluted dye over time), as described by the Stewart–Hamilton equation [1]:

$$\text{Cardiac output} = [V(T_B - T_I) \times K_1K_2] / [T_B(t)dt] \quad \text{[eqn 2]}$$

where V is the volume of injectate, T_B is the temperature of blood, T_I is the temperature of injectate, K_1 and K_2 are computational constants, and $T_B(t)dt$ is the integral of blood temperature change.

Following on from earlier work published by Bradley and Branthwaite [2], in 1970 Swan and Ganz reported their flow-directed balloon-tipped, multi-lumen pulmonary artery catheter (PAC) [3]. This enabled clinicians to float the catheter through the right heart into the pulmonary artery and measure cardiac output by transpulmonary indicator dilution at the bedside. The use of cold 5% glucose as the 'indicator' (thermodilution) replaced the use of indocyanine green dye. The PAC has been utilized in various clinical settings, and represents the gold standard against which other CO monitoring devices have been traditionally compared.

Despite numerous clinical trials and validation studies, there are no conclusive data to suggest that one technique is superior to another. Not all devices have been validated against the same set of criteria and in the same clinical settings. There are no reference criteria for acceptance thresholds for the performance of CO monitors, and various reference techniques are used [4]. Clinical data and specific patient issues should be considered when deciding which device to use and how to accurately interpret the data provided. In this chapter, we describe the different options available, features and limitations, and evidence for use in clinical practice.

Methods of cardiac output estimation

Pulmonary artery catheter

Intermittent CO measurement is achieved by injecting a bolus of glucose, preferably cooled to 4°C, into the superior vena cava/right atrium via a proximal port of the catheter and measuring the change in blood temperature at a thermistor sited at the catheter tip 30 cm distally. Cardiac output is calculated from the rate of change in temperature using a modified Stewart–Hamilton equation. The addition of a thermal filament that sends heat pulses into the blood

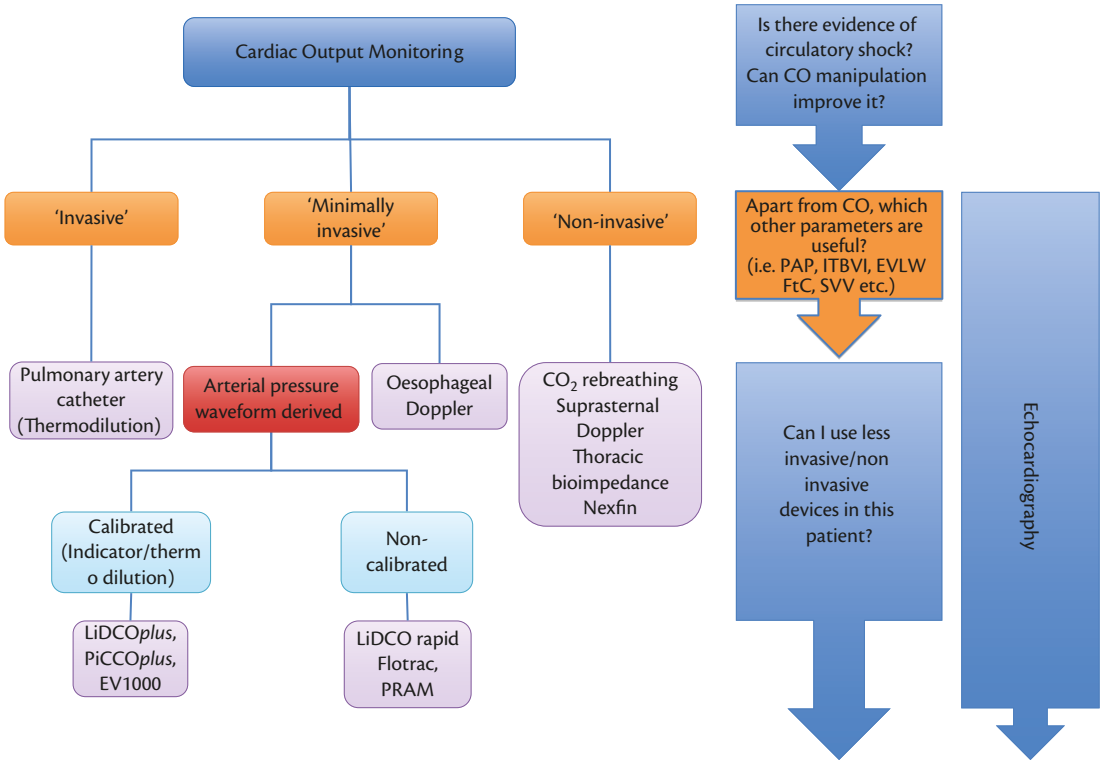


Fig. 136.1 A classification of cardiac output monitors, based on how they work and the level of invasiveness. Several of these monitors provide additional haemodynamic parameters, such as dynamic indices of preload (including pulse pressure variation (PPV) and stroke volume variation (SVV)) or volumetric indices (including intrathoracic blood volume index (ITBVI) and extravascular lung water index (EVLWI)).

within the superior vena cava/right atrium enables estimation of CO averaged over the previous 5–10 minutes. This method is semi-continuous, rather than continuous, and alterations in CO are not detected rapidly.

The main advantage of the PAC over other CO monitoring devices is the ability to directly measure pulmonary artery pressures, right- and left-sided filling pressures, and mixed venous saturations. Measurements derived from thermodilution are relatively accurate, and are comparable with direct Fick and dye dilution methods. As measurements vary with the phase of the respiratory cycle, the average of 3–4 replicate injectates spread over the cycle is usually taken as the CO measurement.

Inaccuracies may arise due to the presence of intracardiac shunts, tricuspid valve pathology, and the simultaneous infusion of cold fluid. As the coefficient of variation for CO measurement is approximately 6–7%, a change of 12–15% in CO between two serial measurements is needed to suggest true clinical significance, other than a chance finding related to the inherent variability of the technique [5].

Observational data suggested PAC use was associated with higher mortality rates and increased use of resources [6]. However, subsequent randomized controlled trials in critically failed to demonstrate either outcome benefit or harm [7,8]. Due to concerns regarding complications related to insertion or use, less invasive CO monitoring devices have superseded the PAC in most clinical scenarios [9].

Pulse pressure analysis monitors

Here, stroke volume is derived from the arterial pressure waveform transduced from an in-dwelling arterial catheter. Such devices use predefined algorithms based on pulse pressure analysis [10]. Each algorithm makes specific assumptions for the estimation of cardiac output and their accuracy depends on the clinical situation. The devices estimate the impedance of the cardiovascular system, based on an assessment of compliance and resistance. This is derived from an online analysis of the arterial pressure waveform, which transforms a pressure over time function into a volume over time function.

There are various clinical situations where the algorithms cannot transform the signal properly, resulting in unreliable CO measurements. These include aortic valve pathology and significant distortions of the arterial waveform (severe arrhythmias, use of vasopressors, multiple ectopics, and the use of intra-aortic balloon counterpulsation) resulting in changes in vascular compliance. Optimization of the input signal is therefore crucial, and calibration may be required prior to use. Patients with atrial fibrillation though with a controlled ventricular rate can have stroke volume (SV) and CO monitored with these devices.

The PiCCO®, LiDCO™, VolumeView™, and COstatus® devices offer cardiac output monitoring from a combination of transpulmonary thermodilution and arterial pressure waveform analysis, e.g. pulse contour (PiCCO) and pulse pressure (e.g. LiDCO). The PiCCO and VolumeView devices require a femoral or brachial arterial catheter in addition to a central venous catheter, whereas the LiDCO requires peripheral arterial and venous access. The PiCCO and VolumeView devices use ice-cold fluid as the indicator, whereas the LiDCO device uses lithium as the indicator 'dye'. The COstatus device requires central venous and peripheral arterial catheters to measure CO and other haemodynamic parameters by measuring changes in blood ultrasound velocity following injection of a warm saline bolus.

The pressure waveform is initially calibrated using the transpulmonary dilution method, allowing data to be monitored

continually. Repeat calibration is required at regular intervals or where any change in vascular system compliance occurs. Although absolute values of haemodynamic parameters cannot be accurately determined without calibration, relative changes in stroke volume in response to a fluid challenge (functional haemodynamic monitoring) are still possible without calibration. These monitors have been used with goal-directed therapy protocols to reduce morbidity in high-risk surgical patients undergoing peri-operative care, based on protocols for fluid and inotrope management.

Some devices, e.g. Vigileo™, MostCare®, and LiDCOrapid® do not use calibration prior to estimation of arterial waveform-derived stroke volume, but these are prone to error with significant changes in vascular compliance. In medical/mixed ICU populations the accuracy of arterial pressure waveform monitoring is highly dependent upon a good calibration [11].

Variations in intrathoracic pressure during mechanical-ventilation result in changes in right atrial pressure, the magnitude of which correlates inversely with intravascular volume. Therefore, mechanically-ventilated patients who are intravascular volume-deficient have a greater variation in pulse pressure and stroke volume. PPV and SVV are thus dynamic indices of preload, with values >10–15% indicative of probable responsiveness to a fluid challenge [12]. Pulse pressure analysis monitors record beat-to-beat variations in PPV and SVV. The PPV to SSV ratio increases with increased vascular tone and can be used to identify vasopressor need in hypotensive patients [13]. The utility of PPV and SVV has limitations in spontaneously ventilating patients, in those with arrhythmias, right heart failure, and those being ventilated with tidal volumes <8 mL/kg. Clinical outcomes associated with the use of PPV and SVV require more rigorous validation, and need to be interpreted within their physiological remits.

Doppler monitoring devices

The oesophageal Doppler monitor uses a disposable flexible 7-mm diameter probe with two D-shaped transducers positioned at the tip. The probe is inserted approximately 35 cm into the oesophagus to the mid-thoracic level at which point aorta and oesophagus run both close and parallel to each other. The probe is orientated to detect blood flow in the centre of the descending thoracic aorta. One transducer emits 4 MHz continuous Doppler, which is reflected off blood corpuscles moving down the descending thoracic aorta resulting in a Doppler frequency shift (f_d) detected by the receiving transducer:

$$f_d = 2(f_o \cdot v \cdot \cos\theta) / c \qquad \text{[eqn 3]}$$

where v is blood flow velocity, f_o is transmitting Doppler ultrasound frequency, and θ is the angle between ultrasound beam and aortic blood flow.

The Doppler frequency shifts undergo fast Fourier transform analysis enabling blood flow velocity within the descending thoracic aorta to be measured in real time. The flow velocity waveforms are displayed on an integral monitor, with the area under the triangular waveform representing the stroke distance, i.e. the distance travelled by a column of blood down the aorta per heartbeat [14]. A nomogram based on the patient's age, height, and weight translates stroke distance into an estimate of total left ventricular stroke volume.

Other measures derived from the oesophageal Doppler include peak velocity (a surrogate of left ventricular contractility) and the corrected flow time (FTc). Peak velocity declines with age, ranging from 90–120 cm/sec in a healthy 20-year-old to 50–80 cm/sec in a 70-year-old. The FTc is the systolic flow time, or the duration of forward flow time, corrected for heart rate by dividing the flow time by the square root of the cardiac cycle time. FTc is inversely related to systemic vascular resistance with a normal range of 330–360 ms in a healthy individual [15]. An increased FTc is seen with a vasodilated circulation, whereas a reduction in FTc is a consequence of any pathology that impairs left ventricular filling or emptying with a resulting vasoconstriction. Such conditions include hypovolaemia, mitral stenosis, pulmonary embolus, or pericardial tamponade, and excessive peripheral vasoconstriction, e.g. due to vasopressors or hypothermia. A rise in FTc with a fluid challenge is used as a dynamic marker of preload and fluid responsiveness.

Accuracy depends on an adequate quality signal from correct placement. This may be difficult to achieve in the ICU patient with minimal or no sedation, or sometimes due to patient positioning. This device has limitations in specific situations. As it measures blood flow in the descending thoracic aorta, which represents 70% of total blood flow in health, this will be affected acutely by aortic cross-clamping. With epidural use, pregnancy and coarctation of the aorta, the proportion of descending aortic to total blood flow to the lower body will alter. Here, absolute values may be inaccurate, although trends can still be followed. Aortic cross-sectional area varies between systole and diastole, especially in younger people with a more elastic aorta, but the area remains relatively fixed through systole. The aortic cross-sectional area in systole is affected by thoracic aneurysms and, to a much lesser extent, by alterations in vascular tone. An intra-aortic balloon pump causes turbulent flow, affecting signal quality. Mindful of the above cautions, cardiac output values correlate reasonably well with the PAC, and can follow trends accurately [16]. Studies have demonstrated reduced morbidity and length of stay in high-risk surgical patients undergoing peri-operative oesophageal Doppler-guided fluid management protocols [17].

The transthoracic Doppler cardiac output monitor (USCOM™, Sydney, Australia) is completely non-invasive. Here, a probe sited in the suprasternal notch is directed towards the ascending aorta. It cannot at present offer continuous monitoring and clinical data demonstrating its utility are awaited.

CO_2 rebreathing/NICO system

The Fick principle has been applied to the NICO system of carbon dioxide (CO_2) rebreathing, where cardiac output is proportional to the difference in arterial and venous CO_2 concentrations. A mainstream infrared sensor for CO_2 measurement is incorporated into the endotracheal tube allowing arterial CO_2 content to be estimated from the end-tidal CO_2 ($ETCO_2$) value and its corresponding dissociation curve. To estimate venous CO_2, a disposable rebreathing circuit is used to allow partial CO_2 rebreathing for a period of time. Every 3 minutes, the rebreathing valve opens to create an additional 150 mL of dead space, thereby increasing $ETCO_2$. CO_2 production is calculated as the product of CO_2 concentration and airflow during this re-breathing cycle. CO_2 produced over a defined period of time is proportional to CO_2 delivery to the lungs.

Alterations in the mode of ventilation, intrapulmonary shunts, increase in dead space, and rapid alterations in haemodynamic variables lead to inaccuracies in measurements and limits its use in critically-ill patients. At present, this technique is at a stage of

infancy and may only be applied in a precisely-defined clinical setting to mechanically-ventilated patients.

Thoracic bioimpedance and thoracic bioreactance

Thoracic bioimpedance (TEB) allows non-invasive and continuous estimation of cardiac output. Impedance is the resistance to a high-frequency, low-amplitude current transmitted between two electrodes. Bioimpedance measures the amplitude of the voltage change across the thorax. TEB works on the principle of the thorax being a cavity containing a volume of fluid (blood) that has a specific resistance. A small current is transmitted between electrodes placed on the neck and the lower thorax, and the voltage is measured. Impedance, which is derived from the voltage, is inversely proportional to the volume of fluid (i.e. aortic blood flow) within the thorax. Thus, an increase in intrathoracic blood volume results in lower impedance. This occurs during systole when aortic blood volume increases. Stroke volume is derived from a formula based on the resistivity of blood, distance between electrodes, ventricular ejection time, and the measured mean thoracic impedance between electrodes.

Various technical and physiological factors affect the accuracy of TEB. Alterations in extravascular lung water and respiratory cycle-dependent alterations in venous blood flow need to be 'filtered' out. Interference from the mechanical ventilator and electrode movement may impair the electrical signal, while increased aortic stiffness also results in decreased accuracy. Data on the validity of TEB in relation to thermodilution-measured CO have been conflicting [18,19]. Serial measurements may be useful to follow trends in CO, although further refinements in this technique are required.

Thoracic bioreactance analyses beat-to-beat changes in electrical currents across the thorax. The size of the phase shifts between electrical currents is proportional to the stroke volume. As its ability to accurately measure phase shifts is less dependent on external noise and electrical interference, thoracic biorectance is more refined than TEB. Early data comparing biorectance (NICOM system, Cheetah) to thermodilution techniques suggest that the methods are comparable [20]. Further studies are required to validate the utility of biorectance and bioimpedance in specific patient populations.

Echocardiography

Transoesophageal echocardiography (TEE) has the clear advantage of providing information on the structure of the heart and proximal aorta in addition to haemodynamic parameters. As such, it has an integral role in the management of the cardiac surgical patient. As an immediate point-of-care assessment of acute haemodynamic change, the role of TEE in the intensive care unit (ICU) is expanding. A miniaturized, disposable biplane TEE probe (ClariTEE®, ImaCor Inc., Garden City, New York, USA) can provide qualitative assessment of cardiac function, although the results from ongoing validation studies are pending. The main disadvantages to TEE are the level of training required to obtain and evaluate images, and the inability to provide continuous cardiac output monitoring.

Conclusion

Novel minimally-invasive monitors that track cardiac output reliably have largely superseded the pulmonary artery catheter. Robust and sensitive methods of validating these devices are required. Selection of the cardiac output monitor and subsequent data interpretation should consider the merits and limitations of the device in respect to the clinical scenario. Ultimately, the best patient outcome can only be achieved with acquisition of accurate data, suitable interpretation of that data, and appropriate management decisions.

References

1. Prys-Roberts C. (1969). The measurement of cardiac output. *British Journal of Anaesthesia*, **41**, 751–60.
2. Branthwaite MA, Bradley RD. (1968). Measurement of cardiac output by thermal dilution in man. *J Appl Physiol*, **124**, 434–8.
3. Swan HJ, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D. (1970). Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *N Engl J Med*, **283**, 447–451.
4. Squara P, Cecconi M, Rhodes A, et al. (2009). Tracking changes in cardiac output: methodological considerations for the validation of monitoring devices: *Intensive Care Medicine*, **35**, 1801–8.
5. Stetz CW, Miller RG, Kelly GE, et al. (1982). Reliability of the thermodilution method in the determination of cardiac output in clinical practice. *American Reviews of Respiratory Diseases*, **126**, 1001–4.
6. Connors AF, Jr, Speroff T, Dawson NV, et al. (1996). The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *Journal of the American Medical Association*, **276**, 889–97.
7. Harvey S, Harrison DA, Singer M, et al. (2005). Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet*, **366**, 472–7.
8. Sandham JD, Hull RD, Brant RF, et al. (2003). A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *New England Journal of Medicine*, **348**, 5–14.
9. Wiener RS and Welch HG. (2007). Trends in the use of the pulmonary artery catheter in the United States, 1993–2004. *Journal of the American Medical Association*, **298**, 423–9.
10. Cecconi M, Wilson J, and Rhodes A. (2006). *Pulse Pressure Analysis: Yearbook of Intensive Care Medicine*. Berlin: Springer.
11. Cecconi M, Dawson D, Casaretti R, et al. (2010). A prospective study of the accuracy and precision of continuous cardiac output monitoring devices as compared to intermittent thermodilution. *Minerva Anestesiologica*, **76**, 1010–17.
12. De Backer D, Heenen S, Piagnerelli M, et al. (2005). Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Medicine*, **31**, 517–23.
13. Hadian M, Severyn DA, and Pinsky MR. (2011). The effects of vasoactive drugs on pulse pressure and stroke volume variation in postoperative ventilated patients. *Journal of Critical Care*, **26**, 328.e1–8.
14. Singer M, Clarke J, and Bennett ED. (1989). Continuous hemodynamic monitoring by esophageal Doppler. *Critical Care Medicine*, **17**, 447–52.
15. Singer M and Bennett ED. (1991). Noninvasive optimization of left ventricular filling using esophageal Doppler. *Critical Care Medicine*, **19**, 1132–7.
16. Dark PM and Singer M. (2004). The validity of trans-esophageal Doppler ultrasonography as a measure of cardiac output in critically ill adults. *Intensive Care Medicine*, **30**, 2060–6.
17. Hamilton MA, Cecconi M, and Rhodes A. (2011). A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesthesia and Analgesia*, **112**, 1392–402.
18. Engoren M and Barbee D. (2005). Comparison of cardiac output determined by bioimpedance, thermodilution, and the Fick method. *American Journal of Critical Care*, **14**, 40–5.
19. Peyton PJ and Chong SW. (2010). Minimally invasive measurement of cardiac output during surgery and critical care: a meta-analysis of accuracy and precision: *Anesthesiology*, **113**, 1220–35.
20 Raval NY, Squara P, Cleman M, et al. (2008). Multicenter evaluation of noninvasive cardiac output measurement by bioreactance technique. *Journal of Clinical Monitoring and Computing*, **22**, 113–19.

CHAPTER 137

Oxygen transport in the critically ill

Stephan M. Jakob and Jukka Takala

Key points

- Tissue oxygen supply cannot be precisely evaluated clinically, since neither systemic blood flow nor arterial oxygen content can be estimated reliably.
- Pulmonary artery catheterization allows measurement of oxygen delivery and demands.
- Mixed venous oxygen saturation is directly correlated with arterial oxygenation, cardiac output, and haemoglobin, and inversely correlated with systemic oxygen consumption.
- Mixed venous oxygen saturation reflects the global adequacy of oxygen delivery, but lower normal limits are individual. Concomitant assessment of blood lactate levels is useful.
- Central venous oxygen saturation and its response to treatment does not necessarily represent mixed venous oxygen saturation and its changes.

Introduction

The cardiovascular system should deliver adequate amounts of oxygen and nutrients to the tissues, and remove their waste products. Measurement of blood pressures, heart rate or cardiac output does not reflect oxygen transport; both oxygen delivery and oxygen demands should be assessed.

Monitoring components of oxygen delivery facilitates early detection of the cause of its deterioration. A sufficient level of oxygen delivery varies widely in individual patients and diseases. Monitoring the adequacy of oxygen transport to the tissues can be particularly important in conditions where blood flow redistribution reduces oxygen delivery inhomogeneously, or when oxygen is used inefficiently. The latter may occur in sepsis [1], in patients with primary mitochondrial diseases, or when drugs affect mitochondrial function [2].

Oxygen in mixed and central venous blood reflects the oxygen reserve, i.e. the amount of oxygen that is delivered, but not extracted. Obviously, arterial oxygen saturation is also a determinant of mixed venous oxygen saturation. The impact of mixed venous oxygen saturation on arterial saturation depends on several factors, the most important being intrapulmonary shunt.

Arterial lactate concentration is an indicator of the adequacy of oxygen delivered in relation to its use for ATP production.

Monitoring oxygen transport within the cardiovascular system

Oxygen delivery to tissues is the product of blood flow and oxygen content:

$$\begin{aligned} DO_2(mL/min/m^2) &= CI(L/min/m^2) \times CaO_2(mL/L) \\ &= CI(L/min/m^2) \times [1.34 \times Hb(g/L) \\ &\quad \times SaO_2 + 0.2325 \times PaO_2(kPa)] \end{aligned} \quad \text{[eqn 1]}$$

Tissue oxygen supply cannot be precisely evaluated clinically, since neither systemic blood flow nor arterial oxygen content can be estimated reliably. Monitoring of global oxygen delivery is, however, possible if cardiac output is monitored. Pulmonary artery catheters (PAC) use thermodilution for cardiac output measurement and monitoring. Measurement of cardiac output using a built-in thermofilament is semi-continuous, but lags several minutes behind the actual changes. Cardiac output can also be monitored with less invasive means, e.g. by ultrasound [3] or pulse contour analysis [4]. Pulse contour analysis needs calibration with an invasive method. Newer uncalibrated devices have been developed, however their performance has been questioned [5]. The advantage of the PAC is the simultaneous monitoring of intravascular pressures and mixed venous oxygen saturation, which helps to evaluate the adequacy of oxygen transport and the causes of insufficient oxygen delivery.

Monitoring oxygen uptake

Oxygen uptake (VO_2) from arterial blood reflects oxygen being consumed by various metabolic processes in the tissues. The fraction of oxygen uptake from oxygen delivery (DO_2) is the oxygen extraction ratio:

$$O_2 \text{ extraction ratio} = VO_2 / DO_2 \quad \text{[eqn 2]}$$

Different tissues have varying oxygen extraction capabilities. When oxygen extraction reaches its maximum (always <100%) during a decrease in DO_2, VO_2 becomes delivery-dependent. As a consequence, a tissue oxygen debt emerges, and anaerobic metabolism with increased lactate production ensues. Tissues may adapt to the low DO_2 by reducing their metabolism and function.

The adequacy of DO_2 may be assessed by instituting a rapid increase and then measuring accompanying changes in VO_2. An

increase in VO_2 >15–20% suggests DO_2 inadequacy. Measuring VO_2 is also useful when evaluating the causes of arterial hypoxemia: in the presence of increased pulmonary shunt (venous admixture), VO_2 can have a substantial impact on arterial oxygenation.

Oxygen consumption can be calculated from data obtained by the PAC using arterial and mixed venous blood samples [6], or can be measured from expiratory gas. Gas exchange monitors, either as stand-alone devices or integrated into patient monitors or ventilators, enable continuous bedside measurement of VO_2. Under conditions of correct calibration and control of measurement conditions, VO_2 can be measured with high accuracy and reproducibility [7,8]. Gas exchange monitors lose their ability to accurately measure VO_2 at FIO_2 >0.60–0.70.

VO_2 can also be calculated using the Fick principle as the product of cardiac output and arterial-mixed venous oxygen content difference:

$$VO_2 = CO \times (CaO_2 - CvO_2) \quad \text{[eqn 3]}$$

However, this approach results in less accuracy and higher variability than VO_2 measurement using gas exchange monitors [6].

Monitoring mixed and central venous oxygenation

Mixed venous oxygen saturation represents the oxygen reserve once blood has passed through the capillaries of the various systemic vascular beds. It is acknowledged as a global indicator of DO_2 adequacy. Because fractions of systemic blood flow delivered to different tissues and their oxygen extraction vary, a normal mixed venous oxygen saturation (SvO_2) does not necessarily guarantee adequate oxygen delivery to all tissues. Nevertheless, in most clinical conditions where tissue hypoxia is present, the mixed venous oxygen content and its changes reflect DO_2 adequacy [9].

Transforming the Fick equation for VO_2 can aid interpretation of mixed venous oxygen saturation:

$$VO_2 = CO \times (CaO_2 - CvO_2) \quad \text{[eqn 4]}$$

$$CvO_2 = CaO_2 - VO_2 / CO \quad \text{[eqn 5]}$$

$$CvO_2 / CaO_2 = 1 - VO_2 / (CaO_2 \times CO) = 1 - VO_2 / DO_2 \quad \text{[eqn 6]}$$

In most clinical conditions, the effect of dissolved oxygen on arterial and venous oxygen content is negligible, and the equations for arterial and mixed venous oxygen content can be simplified as follows:

$$CaO_2\,(mL/L) = 1.34 \times Hb\,(g/L) \times SaO_2 \quad \text{[eqn 7]}$$

$$CvO_2\,(mL/L) = 1.34 \times Hb\,(g/L) \times SvO_2 \quad \text{[eqn 8]}$$

The equations for mixed venous oxygenation can then be simplified further:

$$SvO_2 / SaO_2 = 1 - VO_2 / DO_2 \quad \text{[eqn 9]}$$

$$SvO_2 = SaO_2 - VO_2 / 1.34 \times Hb \times CO \quad \text{[eqn 10]}$$

The last equation demonstrates that SvO_2 will decrease if VO_2 increases and/or if haemoglobin, cardiac output or arterial oxygenation decreases.

The relationship between SvO_2 and CO, VO_2 and haemoglobin is displayed in Fig. 137.1.

Lower limits for 'safe' SvO_2 do not exist. In patients with chronic heart failure, who have adapted to a low cardiac output, SvO_2 saturations <50% are often well tolerated. Conversely, in critically-ill patients, insufficient perfusion with a risk of tissue hypoxia may develop at SvO_2 levels >60% [9]. SvO_2 values <65% should thus be considered as a warning sign of insufficient tissue perfusion in the acutely ill.

Changes in SvO_2, rather than single values, are useful in evaluating responses to therapeutic interventions, since they reflect changes in the oxygen supply/demand relationship [9]. SvO_2 can be monitored on-line using a fibre optic PAC that utilizes reflectance spectrophotometry to measure the mixed venous blood saturation; these have to be first calibrated against co-oximetry [10]. Central venous oxygen saturation ($ScvO_2$) has been used as a surrogate for SvO_2 [11]; however, the two may not necessarily correspond to each other. Changes in $ScvO_2$ in response to treatment may also not correspond to changes in SvO_2 [12].

Relationship between arterial and mixed venous oxygenation

In normal lungs, venous oxygen content has practically no effect on arterial oxygen content, since venous admixture (physiological shunt, Qs/Qt) is negligible. However, the impact of changes in CvO_2 on CaO_2 increases when Qs/Qt becomes larger. In the presence of a large shunt, an increase in VO_2 and/or a reduction

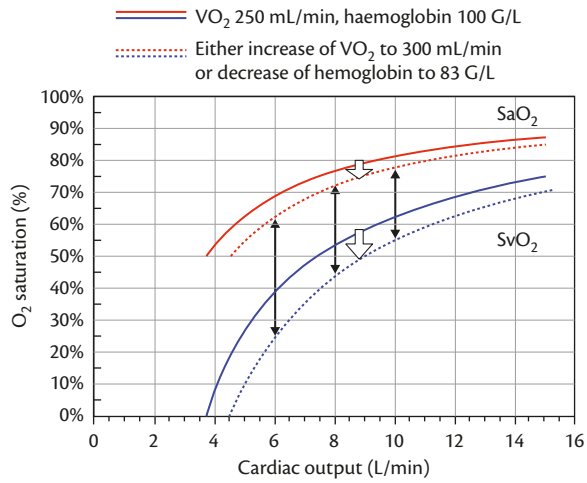


Fig. 137.1 Effect of oxygen consumption and haemoglobin on arterial (red) and mixed venous (blue) oxygenation. A constant physiologic shunt of 50% has been assumed. A similar proportional increase in oxygen consumption and decrease in haemoglobin have identical effects: in both cases the arterial (red dotted line) and mixed venous (blue dotted line) saturation curves shift downwards (open arrows) and the arterial–venous saturation difference widens (solid arrows).

of cardiac output and haemoglobin will cause substantial arterial hypoxaemia. This is evident from the shunt equation:

$$Qs / Qt = (CcO_2 - CaO_2) / (CcO_2 - CvO_2), \quad \text{[eqn 11]}$$

where CcO_2 is the pulmonary venous capillary oxygen content in normally ventilated and perfused alveoli. This can be rearranged as:

$$CaO_2 = CcO_2 \times (1 - Qs / Qt) + CvO_2 \times Qs / Qt \quad \text{[eqn 12]}$$

According to the Fick equation, VO_2 is the product of cardiac output and arterial-mixed venous oxygen content difference. This can be rewritten as:

$$CvO_2 = CaO_2 - VO_2 / CO \quad \text{[eqn 13]}$$

By combining eqns 12 and 13:

$$CaO_2 = CcO_2 - (VO_2 / CO) \times (Qs / Qt) / (1 - Qs / Qt) \quad \text{[eqn 14]}$$

If the dissolved oxygen is ignored, eqn 14 can be written as:

$$SaO_2 = 1 - (VO_2 / CO \times Hb \times 1.34) \times (Qs / Qt) / (1 - Qs / Qt) \quad \text{[eqn 15]}$$

Equation 15 indicates the direct relationship between arterial oxygenation (SaO_2) and cardiac output and haemoglobin, and an inverse relationship with VO_2 (Figs 137.1 and 137.2).

Monitoring the delivery of oxygen to the alveoli

While the amount of oxygen that can be used is dependent on the amount delivered to the tissues, the latter is not only a function of cardiac output and haemoglobin, but also of the amount of oxygen delivered to the blood in the lungs.

Alveolar partial pressure of oxygen (PAO_2) is dependent on barometric pressure (pB), inspired fraction of oxygen (FIO_2), partial pressure of fully saturated water vapour at body temperature (PH_2O; at 37°C, 47 mmHg), alveolar partial pressure of carbon dioxide ($PACO_2$)—estimated as the arterial PCO_2 ($PaCO_2$)—and the respiratory quotient (RQ):

$$PAO_2 = FIO_2 \times (pB - pH_2O) - PaCO_2 \times [1 - FIO_2 \times (1 - RQ)] / RQ. \quad \text{[eqn 16]}$$

Accordingly, oxygen delivery to the alveoli can be monitored using the FIO_2 provided adequate ventilation has been verified either clinically, by monitoring end-tidal CO_2, or by $PaCO_2$ measurement by blood gas analysis. The effect of $PaCO_2$ on PAO_2 becomes smaller when FIO_2 increases. This implies that patients receiving even modest supplementary oxygen can become severely hypercapnic with normal arterial oxygenation.

Monitoring oxygenation of arterial blood

Arterial oxygenation, although most easy to monitor, only partially reflects blood oxygen content. The CaO_2 is a function of haemoglobin (Hb), haemoglobin oxygen saturation (SaO_2), and oxygen dissolved in plasma, which depends on the partial pressure of arterial oxygen (PaO_2):

$$CaO_2 = 1.34 \times Hb \times SaO_2 + 0.2325 \times PaO_2 \quad \text{[eqn 17]}$$

As evident from the equation, haemoglobin concentration and oxygen saturation have the most important impacts on arterial oxygen content.

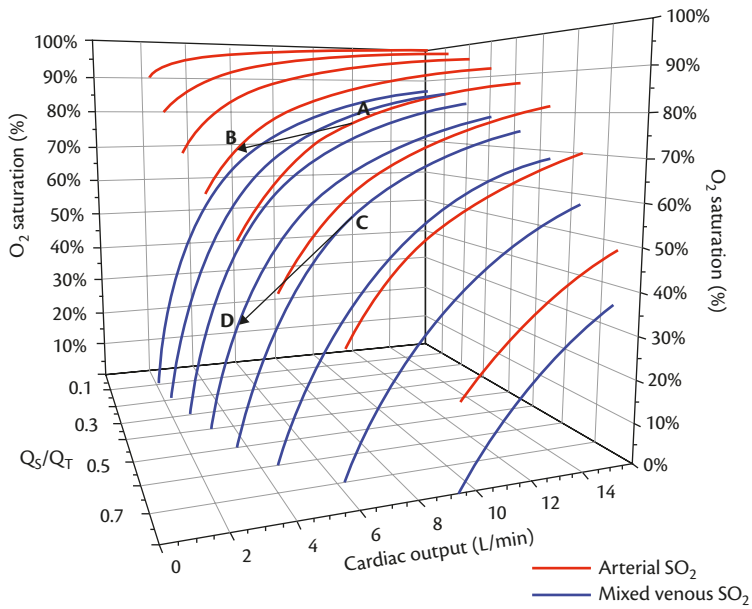


Fig. 137.2 The relationship between venous admixture (Qs/Qt), arterial and mixed venous saturation, and cardiac output. For the calculations, dissolved oxygen has been ignored, and a haemoglobin of 100 g/L and oxygen consumption of 250 mL/min have been assumed. Points A and B represent the effects of cardiac output decreasing from 8 L/min to 4 L/min. The venous admixture is likely to decrease, here from 0.50 to 0.40. Since the decrease in cardiac output is accompanied by increased oxygen extraction, the SvO_2 decreases substantially (points C and D), and the net effect is worsened arterial hypoxaemia.

For monitoring arterial blood oxygenation, blood gas analysis (for PaO_2 and saturation measurement) or pulse oximetry can be used [13]. As detectability of a capillary pulse is a prerequisite for pulse oximetry, monitoring cannot be performed during severe vasoconstriction. Pulse oximetry measures the percentage of oxygenated normal haemoglobin and does not take into account fractions of met- or carboxyhaemoglobin. The percentage of oxyhaemoglobin in total haemoglobin will therefore be overestimated [14].

Tissue oximetry

Oxygen saturation and PO_2 can also be measured directly at the tissue level. Most frequently, these are measured in the brain (PtO_2) and peripheral muscles (StO_2). In the brain, a modified Clark electrode system is most frequently used, with the aim of maintaining brain PO_2 ≥20 mmHg [15]. Brain PO_2 monitoring is mostly used in patients with traumatic brain injury or severe subarachnoid haemorrhage. Low PO_2 values have been associated with increased mortality after traumatic brain injury [16]. Increasing the inspired fraction of oxygen, cerebral perfusion pressure, and/or sedation can help to reverse low PO_2. If they do, survival is improved [17].

Near-infrared spectroscopy has been employed for the assessment of tissue oxygen saturation of the extremities. It correlates with vasoconstriction [18], while low StO_2 and abnormal StO_2-related variables are associated with organ dysfunction and mortality in sepsis [19]. However, the general use of StO_2 monitoring has not yet been established.

Arterial lactate concentration and evaluation of the adequacy of tissue oxygenation

Increased lactate concentrations in tissue hypoxia are due to increased lactate production and/or decreased lactate clearance. Hyperlactataemia is associated with increased morbidity and mortality in various conditions. Mortality can be reduced by therapy guided by lactate levels [20]. Hyperlactataemia can occur secondary to enhanced glucose turnover with increased, rather than decreased oxygen consumption (e.g. during adrenaline treatment), or may be the result of pyruvate dehydrogenase inhibition or isolated reduction of metabolic lactate clearance as a consequence of liver dysfunction. In any case, tissue hypoxia should be excluded when blood lactate is increased. Evaluation of DO_2 adequacy in the critically-ill patient should be based on the combined evaluation of direct and indirect signs of tissue hypoxia. Clinical examination should confirm the absence of hypovolaemia, and circulatory and respiratory failure. Sufficient cardiac output, perfusion pressure, and arterial oxygen content are prerequisites for an adequate DO_2.

References

1. Garrabou G, Morén C, López S, et al. (2012). The effects of sepsis on mitochondria. *Journal of Infectious Diseases*, **205**, 392–400.
2. Delogu G, Moretti S, Antonucci A, et al. (2004). Apoptogenic effect of fentanyl on freshly isolated peripheral blood lymphocytes. *Journal of Trauma*, **57**, 75–81.
3. Wong DH, Tremper KK, Stemmer EA, et al. (1990). Noninvasive cardiac output: simultaneous comparison of two different methods with thermodilution. *Anesthesiology*, **72**, 784–92.
4. Rödig G, Prasser C, Keyl C, Liebold A, and Hobbhahn J. (1999). Continuous cardiac output measurement: pulse contour analysis vs thermodilution technique in cardiac surgical patients. *British Journal of Anaesthesia*, **82**, 525–30.
5. Haenggi M, Barthelmes D, Ulmer H, Takala J, and Jakob SM. (2011). Comparison of non-calibrated pulse-contour analysis with continuous thermodilution for cardiac output assessment in patients with induced hypothermia after cardiac arrest. *Resuscitation*, **82**, 423–6.
6. Brandi LS, Grana M, Mazzanti T, Giunta F, Natali A, and Ferrannini E. (1992). Energy expenditure and gas exchange measurements in postoperative patients: thermodilution versus indirect calorimetry. *Critical Care Medicine*, **20**, 1273–83.
7. Makita K, Nunn JF, and Royston B. (1990). Evaluation of metabolic measuring instruments for use in critically ill patients. *Critical Care Medicine*, **18**, 638–44.
8. Stuart-Andrews CR, Peyton P, Robinson GJ, et al. (2007). In vivo validation of the M-COVX metabolic monitor in patients under anaesthesia. *Anaesthesia and Intensive Care*, **35**, 398–405.
9. Ruokonen E, Takala J, and Uusaro A. (1991). Effect of vasoactive treatment on the relationship between mixed venous and regional oxygen saturation. *Critical Care Medicine*, **19**, 1365–9.
10. Armaganidis A, Dhainaut JF, Billard JL, et al. (1994). Accuracy assessment for three fiberoptic pulmonary artery catheters for SvO_2 monitoring. *Intensive Care Medicine*, **20**, 484–8.
11. Reinhart K, Kuhn HJ, Hartog C, and Bredle DL. (2004). Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. *Intensive Care Medicine*, **30**, 1572–8.
12. Varpula M, Karlsson S, Ruokonen E, and Pettilä V. (2006). Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock. *Intensive Care Medicine*, **32**, 1336–43.
13. Carter BG, Carlin JB, Tibballs J, Mead H, Hochmann M, and Osborne A. (1998). Accuracy of two pulse oximeters at low arterial hemoglobin-oxygen saturation. *Critical Care Medicine*, **26**, 1128–33.
14. Severinghaus JW and Kelleher JF. (1992). Recent developments in pulse oximetry. *Anesthesiology*, **76**, 1018–38.
15. Miller CM. (2012). Update on multimodality monitoring. *Current Neurology and Neuroscience Reports*, **12**, 474–80.
16. Valadka AB, Gopinath SP, Contant CF, Uzura M, and Robertson CS. (1998). Relationship of brain tissue PO_2 to outcome after severe head injury. *Critical Care Medicine*, **26**, 1576–81.
17. Bohman LE, Heuer GG, Macyszyn L, et al. (2011). Medical management of compromised brain oxygen in patients with severe traumatic brain injury. *Neurocritical Care*, **14**, 361–9.
18. Lima A, van Genderen ME, Klijn E, Bakker J, and van Bommel J. (2012). Peripheral vasoconstriction influences thenar oxygen saturation as measured by near-infrared spectroscopy. *Intensive Care Medicine*, **38**, 606–11.
19. Shapiro NI, Arnold R, Sherwin R, et al. (2011). The association of near-infrared spectroscopy-derived tissue oxygenation measurements with sepsis syndromes, organ dysfunction and mortality in emergency department patients with sepsis. *Critical Care*, **15**, R223.
20. Jansen TC, van Bommel J, Schoonderbeek FJ, et al. (2010). Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *American Journal of Respiratory and Critical Care Medicine*, **182**, 752–61.

CHAPTER 138

Tissue perfusion monitoring in the ICU

Eric Kipnis and Benoit Vallet

Key points

- Monitoring the adequate delivery of oxygen relative to demand is essential during resuscitation and for monitoring of vital functions.
- Although tissue oxygenation seems the best endpoint, it can only be directly measured locally in a limited area of a given tissue.
- Assessment of global oxygenation by central ($ScvO_2$) or mixed (SvO_2) venous oxygen saturation is indicative of inadequate oxygen delivery relative to demand when $ScvO_2$ (or SvO_2) is low. However, 'normal' or high values may be truly normal, may 'miss' local perfusion disorders, or may reflect mitochondrial dysfunction in the late stages of sepsis.
- Inadequate tissue oxygenation may also be monitored indirectly through resulting metabolic imbalances that may be either local (increased tissue lactate levels/decreased tissue lactate clearance, increased tissue-to-arterial PCO_2 gradients, or shift in tissue redox state towards a reduced NADH) or global (increased blood lactate/decreased blood lactate clearance, increased veno-arterial PCO_2 difference).
- Blood flow, as well as microcirculatory characteristics, while useful in investigating perfusion, can only be assessed locally in limited areas of accessible tissues.

Introduction

The endpoint of perfusion is an adequate oxygen delivery to mitochondria in order to maintain production of ATP relative to metabolic demand. Any failure in lung, myocardial, or macro/microcirculatory function may lead to inadequate oxygen delivery, eventually compounded by impaired mitochondrial oxygen utilization, ultimately resulting in cell death, organ dysfunction, and failure. This inadequate oxygen delivery relative to demand is the physiological definition of shock regardless of mechanism or aetiology. Therefore, tissue perfusion and oxygenation cannot be dissociated in any approach to resuscitation or monitoring. Throughout this chapter, tissue perfusion monitoring will be considered as monitoring tissue perfusion, ensuring adequate oxygen delivery relative to demand.

Monitoring perfusion through oxygenation

From these considerations, it becomes apparent that routine parameters such as mean arterial pressure (MAP) or central venous pressure (CVP) do not address the question, and that tissue oxygenation seems the best marker of perfusion. It follows that a major issue is the difference between monitoring oxygen locally, in a very limited area of tissue or globally, in blood. To date, there is no means of monitoring oxygen in patients in all or even several tissues simultaneously.

Tissue oxygenation

Tissue oxygenation can be directly monitored. The gold standard is the Clark electrode, which is based upon oxygen reduction of a silver/silver chloride electrode generating a proportional electrical current, as used in blood gas analysers. Other methods have emerged, such as phosphorescence quenching, which measures the oxygen-related decay in phosphorescence of a phosphor after light excitation. All have been developed into microelectrodes that can be transcutaneously inserted into tissues, or incorporated into intravascular in-dwelling catheters for the assessment of either local or global oxygenation.

Indirect, non-invasive spectrophotometric measurements of oxygen saturation are based upon the different red/infrared light absorption characteristics of oxygenated/deoxygenated haemoglobin. The most widespread is routine capillary pulse oximetry, which provides information on oxygenation (SpO_2), but also perfusion through ratios between pulsatile and non-pulsatile signals (perfusion index). Near-infrared spectroscopy (NIRS) also uses haemoglobin saturation to monitor tissue oxygenation (StO_2), most often in the muscle microvasculature, but limb occlusion tests are required to provide perfusion information [1].

Assessment of local tissue oxygenation has found its major clinical use in monitoring oxygenation of the most critical of tissues, the brain, using either microelectrodes small enough to allow insertion into the brain without injury, or NIRS-based non-invasive methods such as StO_2 [2].

Non-invasive techniques such as pulse oximetry or StO_2 are mainly used as routine 'alert' and/or screening for decreased tissue oxygenation in emergency, peri-operative or critical care settings [1].

The main advantage is that tissue oxygenation is a crucial endpoint immediately providing information concerning inadequate oxygen delivery. Aside from the invasive nature of some devices, the main disadvantage is that local tissue oxygenation can only be monitored in a very limited area at any given time.

Global oxygenation

Global tissue oxygenation can only be appraised indirectly through measuring the net result between the oxygen available for delivery

in arterial blood and oxygen uptake by the tissues. Oxygen saturation measured in venous blood downstream from any further uptake, i.e. in the pulmonary artery sampled by a pulmonary artery catheter (SvO_2) or in the superior vena cava sampled by a central venous catheter ($ScvO_2$), should reflect this net balance between global oxygen delivery and uptake. $ScvO_2$ may overestimate SvO_2 by 3–8% leading to accepted thresholds of 70% for $ScvO_2$ and 65% for SvO_2. It seems logical that $ScvO_2$ monitoring would be useful in shock characterized by inadequate delivery relative to demand. Indeed, in a landmark study, Rivers et al. showed that using a $ScvO_2$ endpoint >70% to judge sequential steps for early management of patients with severe sepsis decreased mortality compared with standard therapy [3]. Patients thus managed received more fluids, and were resuscitated to higher mean arterial pressures than patients receiving standard care. $ScvO_2$ has since been incorporated as a resuscitation endpoint in guidelines for the management of severe sepsis and septic shock.

$ScvO_2$ can be obtained either intermittently through blood gas analysis of venous blood obtained from a central venous line inserted in the superior cava, or monitored continuously through central lines that include an oxygen probe. Another advantage is that a 'low' $ScvO_2$ alerts the healthcare practitioner to situations of inadequate oxygen delivery, which may not be apparent using measures such as MAP or CVP. Such alerts must, however, lead to fully exploring and managing all aspects of oxygen delivery, with re-evaluation through the $ScvO_2$ response.

The obvious drawback to $ScvO_2$ measurement is that normal/high values cannot discriminate whether delivery is adequate/in excess of demand, or whether demand is pathologically decreased in injured tissues. In fact, normal/high $ScvO_2$ values are considered a hallmark in persisting or worsening septic shock due to septic mitochondrial dysfunction impeding oxygen extraction and utilization. However, such situations mostly arise in the later stages of critical illness so a normal $ScvO_2$ value remains a reliable target in the early management of sepsis.

A less evident and more problematic limitation stems from how global an indicator it is. Since $ScvO_2$ is measured downstream from tissues, if a given tissue receives inadequate oxygen delivery, the resulting low **local** venous oxygen saturation may be 'masked' by admixture with highly saturated venous blood from tissues with better oxygen delivery/perfusion, resulting overall in normal or perhaps even high $ScvO_2$ values (Fig. 138.1b).

Therefore, while $ScvO_2$ will not miss any global oxygen delivery disorder (Fig. 138.1c), it may remain 'blind' to local perfusion disorders that abound in sepsis due to an impaired microcirculation.

Metabolic markers of adequate tissue perfusion

Metabolic monitoring of tissue perfusion relies on biochemical and enzymatic reactions occurring in cells, and in organelles (mitochondria) that produce the energy needed for organ function. Under adequate oxygenation/perfusion conditions, glucose is the substrate for glycolysis, leading to the formation of pyruvate. This is oxidized into acetyl-CoA, which enters the citric acid (Krebs') cycle inside the mitochondrial matrix, where it is oxidized into CO_2 while reducing NAD^+ to NADH and FAD to $FADH_2$ (Fig. 138.2). NADH and $FADH_2$ are oxidized by the mitochondrial electron transport chain. Their electrons are transferred down the chain to oxygen and, in

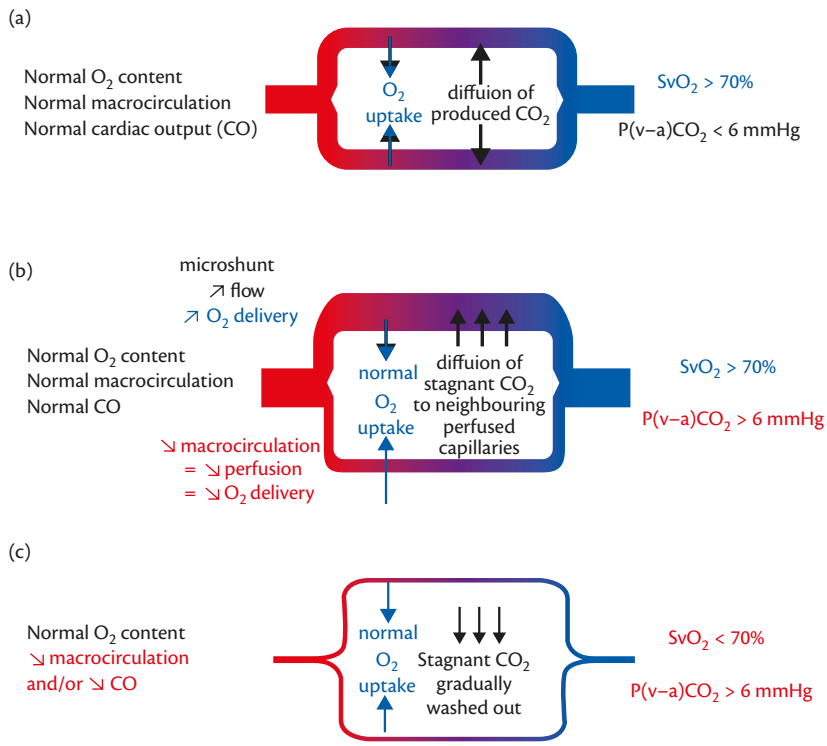


Fig. 138.1 Detection of local or global perfusion disorders with SvO2 or $P(v\text{-}a)CO_2$. (a) Normal. (b) Heterogenous altered microcirculation. (c) Decreased global flow.

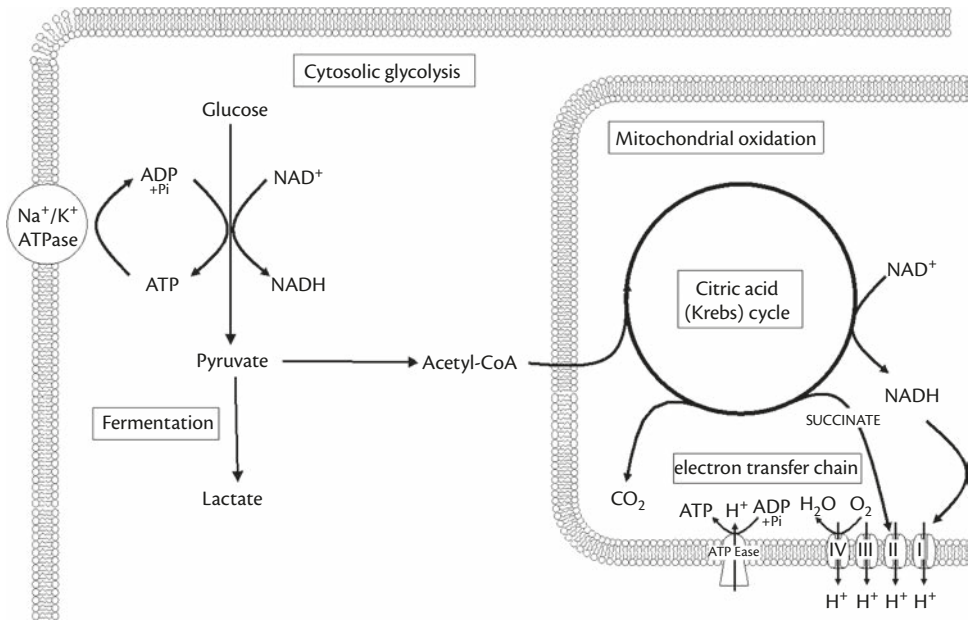


Fig. 138.2 Metabolic parameters of cellular oxygenation/perfusion.

doing so, generates the proton motive force necessary to phosphorylate ADP to the high energy carrier, ATP (Fig. 138.2).

Lactate

Pyruvate can also undergo anaerobic fermentation into lactate. A common misconception is that lactate is only produced in the absence of oxygen. Increased cellular metabolism requiring active Na^+/K^+-ATPase transport uses ATP and may 'drive' glycolysis into producing massive amounts of pyruvate in excess of mitochondrial oxidative capacity (Fig. 138.2). This therefore leads to lactate formation, even in the presence of adequate amounts of oxygen. Such situations may arise from intense physical effort during sport, but has also been demonstrated in sepsis due to endogenous and exogenous catecholamines. This has led to a controversy on the use of lactate as a marker of inadequate cellular oxygenation [4].

However, even given this limitation, lactate has been extensively used and studied in assessing adequate tissue oxygenation/perfusion. Lactate is measured through routine biochemical methods either in blood or using microdialysis probes in tissues. Lactate levels can be considered in terms of its concentration, the lactate-to-pyruvate ratios, or its clearance over time. The body of evidence surrounding lactate has led most guidelines to incorporate increased blood lactate concentrations as diagnostic criteria for impaired perfusion in severe sepsis, septic shock, and severe trauma. As an illustrative example, a multicentre study compared $ScvO_2$ with lactate as resuscitation endpoints, and found that both performed similarly [5]. Furthermore, reaching both $ScvO_2$ and lactate clearance endpoints in septic shock was shown to be superior to $ScvO_2$ alone [6,7]. This suggests that lactate clearance may detect perfusion disorders that $ScvO_2$ cannot.

PCO_2

The production of CO_2, also a by-product of cellular metabolism, is related to oxygen uptake. CO_2 produced by cells is highly diffusible and is 'washed out' from tissues by adequate perfusion, into the pulmonary circulation where its diffusibility allows easy elimination by the lungs. When perfusion is impaired, CO_2 stagnates and increases in tissues. Tonometric methods such as gastric tonometry and sublingual capnography allow CO_2 recovery from accessible mucosal surfaces. These methods allow an approximation of CO_2 production after subtracting the arterial PCO_2 from the tissue partial pressure, i.e. a P(tissue–arterial)CO_2 gradient. Such tissue-to-arterial PCO_2 gradients have been studied as markers of increased tissue CO_2 due to decreased washout through decreased perfusion. Inherently, these local methods only provide information on sublingual and splanchnic perfusion, respectively, and these are variably associated with widespread impaired perfusion. Another drawback is that CO_2 sampling catheters may move and provide inconsistent readings.

Globally-produced CO_2 can be expressed as the difference between the partial pressure of CO_2 downstream from most tissues in the venous system, and CO_2 in arterial blood arriving to the tissues, i.e. the veno-arterial difference or gap: P(v-a)CO_2. Since CO_2 is readily eliminated by the lung, an increase in P(v-a)CO_2 above the normal threshold of 6 mmHg reflects intense CO_2 stagnation in tissues either through local or global perfusion disorders. Indeed, CO_2 is so diffusible that in tissues with decreased or even no perfusion, stagnating CO_2 will diffuse to neighbouring tissues, which remain perfused, increasing venous $PvCO_2$ and, consequently, P(v-a)CO_2 to > 6 mmHg (Fig 138.1b).

Another main determinant of P(v-a)CO_2 is global flow/cardiac output. There must be sufficient cardiac output to wash out CO_2 into the venous, and then pulmonary circulation without it stagnating and increasing. Indeed, in situations of low cardiac output, P(v-a)CO_2 may rise independently of any specific tissue hypoperfusion (Fig. 138.1c). Therefore, P(v-a)CO_2 does not just assess local tissue perfusion but, rather, the adequacy of cardiac output relative to tissue perfusion.

P(v-a)CO_2, like lactate, was compared with $ScvO_2$ in optimization during high-risk surgery; both low $ScvO_2$ and high P(v-a)CO_2

were associated with post-operative complications. However, complications that remained undetected by 'normal' $ScvO_2$ values (>70%) were detected by increases in $P(v\text{-}a)CO_2$ [8]. This suggests that, like lactate, $P(v\text{-}a)CO_2$ may also detect perfusion disorders 'ignored' by the $ScvO_2$.

Redox state

The function of the mitochondrial respiratory chain is to transfer electrons from NADH produced by the citric acid cycle to O_2, driving the ATP production necessary to allow normal cell activity. An increase in cellular activity, provided oxygen delivery remains adequate, will shift the redox state of NADH towards the oxidized form (NAD^+). Inadequate oxygen delivery will result in an increase in NADH. This activity of the respiratory chain *in vivo* can be monitored through this mitochondrial NADH oxidation-reduction (redox) state. The reduced form, NADH, absorbs light and emits fluorescence at different wavelengths, allowing mitochondrial redox state monitoring by measuring UV absorbance or NADH fluorescence. Since absorption is limited by tissue thickness, fluorescence spectrophotometry of NADH has been employed in various in vitro and in vivo models. Devices based upon NADH fluorescence have undergone limited clinical testing [9]. However, the same limitations apply as for other local monitoring systems: they may only detect local disorders and signal quality depends on contact with the explored tissue, which may be inconsistent when, for example, mounted in a Foley catheter.

Blood flow

Rather than assessing metabolic consequences, it is possible to assess blood flow adequacy in surface tissues such as sublingual tissue. Several methods allow either measurement or visualization of erythrocyte movement in tissue capillaries [10].

Laser Doppler flowmetry (LDF) applies the Doppler principle to measuring the velocity shift in refracted light from moving erythrocytes transilluminated by a laser source. Its main advantage is that it provides a quantitative measure of flow (flux). The main disadvantages are the absence of structure visualization, the sampling of a variable area and mix of arterioles–capillaries–venules, and the inability to assess capillary density and/or heterogeneity.

The two major methods of capillary flow visualization are based upon the principles of recovering light from moving erythrocytes in transilluminated tissue, while filtering out light from static structures. In orthogonal polarized spectral (OPS) imaging, this is achieved by light polarization, while sidestream dark field (SDF) imaging uses pulsed lateral transillumination. The main advantage of either approach is visualization, allowing the assessment of capillary density, heterogeneity, and recruitment. However, these parameters can only be assessed qualitatively or semi-quantitatively, and assessment can only be carried out manually off-line.

Flow assessment also has the advantage of being non-invasive, but with the disadvantage of only accessing limited areas of superficial tissue, such as skin or sublingual tissue.

Conclusion

Tissue perfusion monitoring is already part of the routine clinical assessment of critically-ill patients, particularly in sepsis. Several methods described here are recommended in various guidelines. Future use of tissue perfusion monitoring should focus on the hierarchical organization of global tissue oxygenation/perfusion monitoring through sequential use of $ScvO_2$, $P(v\text{-}a)CO_2$, and lactate clearance, and on the development of multimodal local monitoring of flow, oxygenation, and mitochondrial redox status.

References

1. Lipcsey M, Woinarski NC, and Bellomo R. (2012). Near infrared spectroscopy (NIRS) of the thenar eminence in anesthesia and intensive care. *Annals of Intensive Care*, **2**, 11.
2. Rao GS and Durga P. (2011). Changing trends in monitoring brain ischemia: from intracranial pressure to cerebral oximetry. *Current Opinions in Anaesthesiology*, **24**, 487–94.
3. Rivers E, Nguyen B, Havstad S, et al. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine*, **345**, 1368–77.
4. Levy B, Gibot S, Franck P, Cravoisy A, and Bollaert PE. (2005). Relation between muscle Na + K + ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet*, **365**, 871–5.
5. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, and Kline JA. (2010). Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *Journal of the American Medical Association*, **303**, 739–46.
6. Puskarich MA, Trzeciak S, Shapiro NI, et al. (2012). Prognostic value and agreement of achieving lactate clearance or central venous oxygen saturation goals during early sepsis resuscitation. *Academic Emergency Medicine*, **19**, 252–8.
7. Nguyen HB, Kuan WS, Batech M, et al. (2011). Outcome effectiveness of the severe sepsis resuscitation bundle with addition of lactate clearance as a bundle item: a multi-national evaluation. *Critical Care*, **15**, R229.
8. Futier E, Robin E, Jabaudon M, et al. (2010). Central venous O(2) saturation and venous-to-arterial CO_2 difference as complementary tools for goal-directed therapy during high-risk surgery. *Critical Care*, **14**, R193.
9. Mayevsky A, Walden R, Pewzner E, et al. (2011). Mitochondrial function and tissue vitality: bench-to-bedside real-time optical monitoring system. *Journal of Biomedical Optics*, **16**, 067004.
10. Treu CM, Lupi O, Bottino DA, and Bouskela E. (2011). Sidestream dark field imaging: the evolution of real-time visualization of cutaneous microcirculation and its potential application in dermatology. *Archives of Dermatological Research*, **303**, 69–78.

CHAPTER 139

Lactate monitoring in the ICU

Tim C. Jansen and Jan Bakker

Key points

- Hyperlactataemia is common in the intensive care unit and an important prognostic marker for morbidity and mortality.
- Hyperlactataemia is caused by both anaerobic and aerobic mechanisms of production and clearance.
- A number of drugs used in critical care cause hyperlactataemia.
- The use of lactate monitoring in goal-directed therapy has clinical benefit.
- Lactate generally increases the ability to predict non-survival, both in the ED and ICU settings.

Aetiology

Lactic acid is >99% dissociated into lactate anions and protons (H^+) at physiological pH. It has two optical isomers, L- and D-lactate. In the ICU situation there is more interest in L-lactate as D-lactate formation is caused by overgrowth of intestinal flora. L-lactate is produced from pyruvate by lactate dehydrogenase (LDH) (Figure 139.1).

Blood lactate was first measured in human blood by the German physician-chemist Johann Joseph Scherer in 1843, when he described a lethal case of fulminant septic shock due to puerperal fever [1]. Nowadays, lactate is frequently measured in critically-ill patients, usually with the aim of detecting tissue hypoxia. However, this is an oversimplification as aerobic processes can also result in increased lactate levels (Box 139.1).

Anaerobic lactate

If cellular oxygen is lacking, more lactate is produced by anaerobic glycolysis, resulting in hyperlactataemia. The corresponding lactic acidosis is the 'type A' according to the classification of Cohen et al. [2]). Experimental studies have confirmed this by reducing the components of systemic oxygen delivery (haemoglobin level, oxygen saturation, and cardiac output) until oxygen demands could no longer be met. Below this critical level of oxygen delivery, oxygen consumption becomes limited by oxygen delivery and this coincides

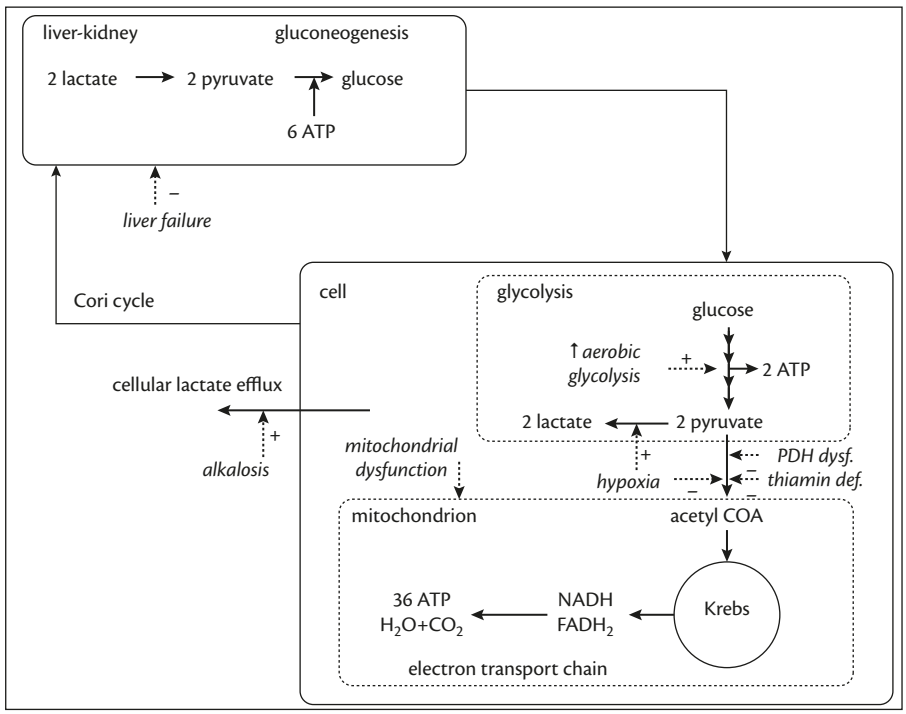


Fig. 139.1 Lactate metabolism: the process of glycolysis, the Krebs' cycle, electron transport chain and gluconeogenesis. Dotted arrows depict the point of action of the various mechanisms causing hyperlactataemia: – inhibitory effect, + excitatory effect.

ATP, adenosine triphosphate; NADH, nicotinamide adenine dinucleotide; $FADH_2$, flavin adenosine dinucleotide; PDH, pyruvate dehydrogenase; dysf, dysfunction; def, deficiency.

with a sharp increase in lactate levels. Similarly, when life support was withdrawn in critically-ill patients in a terminal state of disease, a sharp increase in lactate occurred at the moment that oxygen demands could no longer be met by increased oxygen extraction [3].

In addition to a low **systemic** oxygen delivery, microcirculatory processes that hamper oxygen utilization at the tissue level may also cause lactate levels to rise. Particularly in sepsis, microcirculatory derangements or shunting may lead to insufficient oxygen being delivered to the cell, thereby increasing lactate levels. This is indirectly illustrated by the observation that improving capillary perfusion correlated with a reduction in lactate levels in patients with septic shock, independent of changes in systemic haemodynamic variables [4].

Finally, although hyperlactataemia has often been attributed to intestinal ischaemia, serum lactate is an non-specific marker and probably undergoes significant elevation only after advanced mesenteric damage ([5].

Aerobic lactate

Despite optimal correction of tissue oxygenation, hyperlactataemia may still persist. Thus, cellular hypoxia is not present in 'stress' or 'type B' hyperlactataemia. Other mechanisms account for the production of lactate, namely:

- **Increased aerobic glycolysis**: resulting in elevated concentrations of pyruvate that exceed the capacity of pyruvate dehydrogenase that converts pyruvate into acetyl CoA. Such enhanced glycolysis can be triggered by cytokine-mediated uptake of glucose or catecholamine-stimulated Na^+–K^+-pump activity [6].
- **Mitochondrial dysfunction** [7].
- **Impaired activity of pyruvate dehydrogenase** (PDH): this enzyme is inhibited in septic conditions and increasing its activity with dichloroacetate significantly reduced blood lactate levels [8]. Thiamine deficiency (beriberi disease) also inhibits PDH activity and can cause severe hyperlactataemia .
- **Reduced lactate clearance in liver dysfunction [9] and liver surgery**: decreased clearance has also been reported following cardiac surgery and during sepsis.
- **The lung can be an important source of lactate** [10]: both in pulmonary and extra-pulmonary disease. This probably reflects metabolic adaptations in response to inflammatory mediators rather than tissue hypoxia.
- **Alkalosis** [11]: as an H^+-linked carrier mechanism is involved in transport of lactate across the cell membrane, thereby increasing lactate efflux.
- **The Warburg effect**: with lactate production by malignant cells, even under aerobic conditions [12].
- **Grand mal seizures**.
- **Congenital metabolic diseases**.
- **Drugs and poisons**: epinephrine and $beta_2$ agonists (by increasing glycogenolysis, glycolysis and Na^+–K^+-pump activity), corticosteroids, and a variety of agents causing mitochondrial cytopathy or inhibition of oxidative phosphorylation including metformin (particularly in the presence of renal dysfunction), propofol (propofol infusion syndrome), nucleoside reverse transcriptase inhibitors used in HIV treatment, carbon monoxide poisoning (also reduces the oxygen-carrying capacity of haemoglobin), methanol (through production of formic acid), and cyanide.

A high lactate level found when using a point of care device that is not confirmed using a standard laboratory technique can be used as a diagnostic test for ethylene glycol poisoning. This occurs due to an artefactual reaction with the lactate electrode.

Technique of lactate measurement

Blood lactate levels can be measured by central hospital laboratory machines, point-of-care blood gas analysers or hand-held devices. Generally, all have reported small biases with clinically acceptable limits of agreement. Most investigators report satisfactory agreement

Box 139.1 Aetiology of hyperlactataemia

Anaerobic causes

- Macrocirculatory shock.
- Microcirculatory shunting.
- Carbon monoxide poisoning (carboxyhaemoglobin).

Aerobic causes

- Increased aerobic glycolysis:
  - Catecholamine-stimulated increased Na^+–K^+-pump activity.
  - Cytokine-mediated glucose uptake.
- Mitochondrial dysfunction.
- Pyruvate dehydrogenase dysfunction:
  - Sepsis.
  - Thiamine deficiency.
- Reduced clearance:
  - Liver insufficiency/surgery.
  - Sepsis.
- Alkalosis.
- Malignancy (Warburg effect).
- Epileptic seizure (grand mal).
- Congenital metabolic diseases.
- Drugs and intoxications:
  - Nucleoside reverse transcriptase inhibitors.
  - Epinephrine.
  - Metformin.
  - Propofol (propofol infusion syndrome).
  - Corticosteroids.
  - Cyanide.
  - Ethylene glycol.
  - Methanol.
  - Carbon monoxide poisoning (inhibition of cytochrome oxidase).

comparing capillary, venous, or central/mixed venous levels with arterial levels. Ongoing *in vitro* glycolysis may occur after blood sampling, resulting in erroneous elevation of lactate levels, particularly in cases of leukocytosis or high haematocrit. Analysis within 15 minutes, storage at <4°C, or use of fluoride oxalate tubes are thus recommended. Infusion of Ringer's lactate solution does not hamper measurement accuracy. While renal replacement therapy eliminates only negligible amounts of lactate, the use of lactate-containing buffer solutions can induce transient hyperlactataemia .

Prognosis

In a recent systematic review, all available studies addressing the prognostic value of lactate in the emergency department (ED) or intensive care unit (ICU) were identified [13]. In the ED setting, the area under the receiver operating characteristic curve (AUROC) for mortality varied from 0.67 to 0.98, indicating a moderate to excellent capability to discriminate non-survivors from survivors. In the ICU setting, AUROC varied from 0.53 to 0.86. The positive predictive value or post-test probability for mortality was very low (4–15%) in some studies. However, comparison of pretest probability (population mortality rate) with post-test probability ultimately determines its value in risk stratification. From available studies, lactate generally increases the ability to predict non-survival, both in the ED and ICU settings. The consistency of this finding confirms a role for lactate in the risk stratification of critically-ill patients.

Risk of hyperlactataemia

While hyperlactataemia is associated with worse outcomes, lactate itself is not harmful. It is regularly administered to patients as Ringer's lactate or in lactate-containing buffer solutions for renal

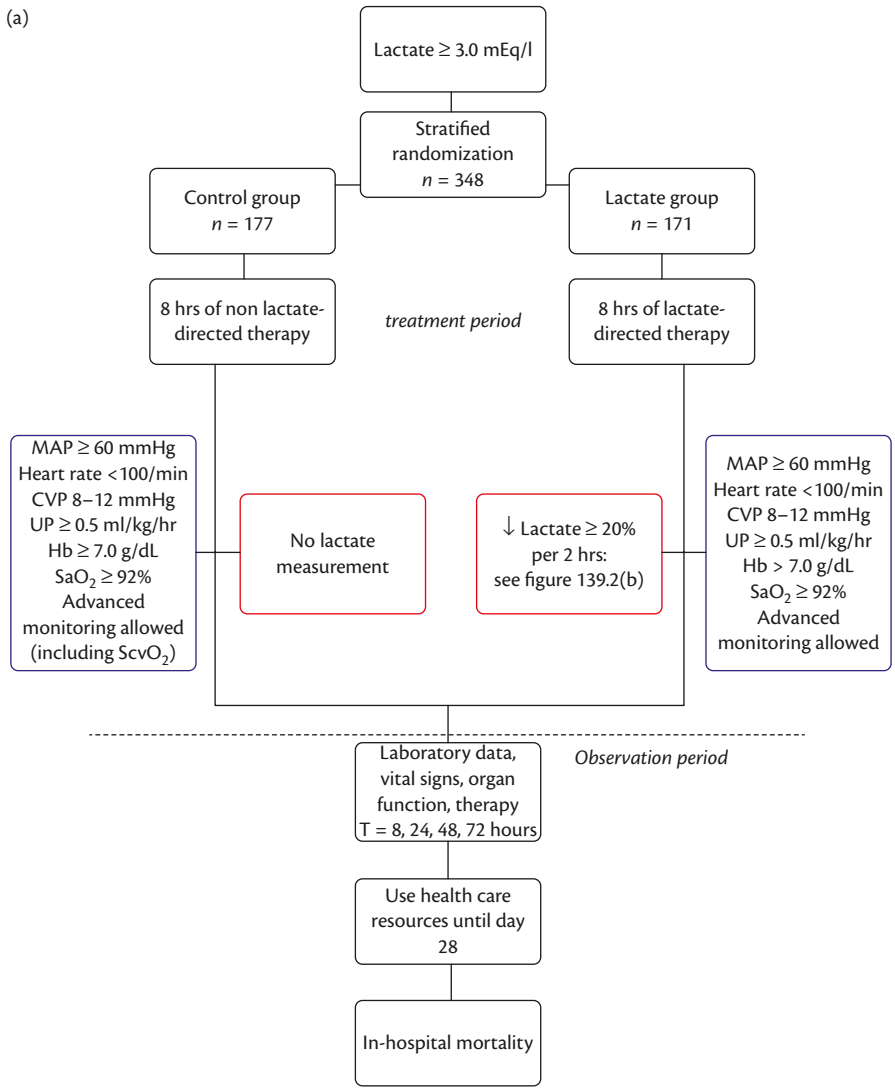


Fig. 139.2 (a) Study of early lactate-guided therapy in ICU patients. Treatment algorithm of control and lactate groups. The CVP target was 12–15 mmHg in mechanically-ventilated patients. CVP was also used as a dynamic safety limit during fluid challenges. The haemoglobin target was 10 g/dL in patients with cardiac ischaemia. (b) Additional treatment algorithm lactate group. If lactate fell ≤2 mmol/L, no further decrease was required. Fluid responsiveness was assessed by 200 mL fluid challenges targeting an increase in MAP, $ScvO_2$ or stroke volume, or a decrease in heart rate.

NTG, nitroglycerine; RBC, red blood cell transfusion.

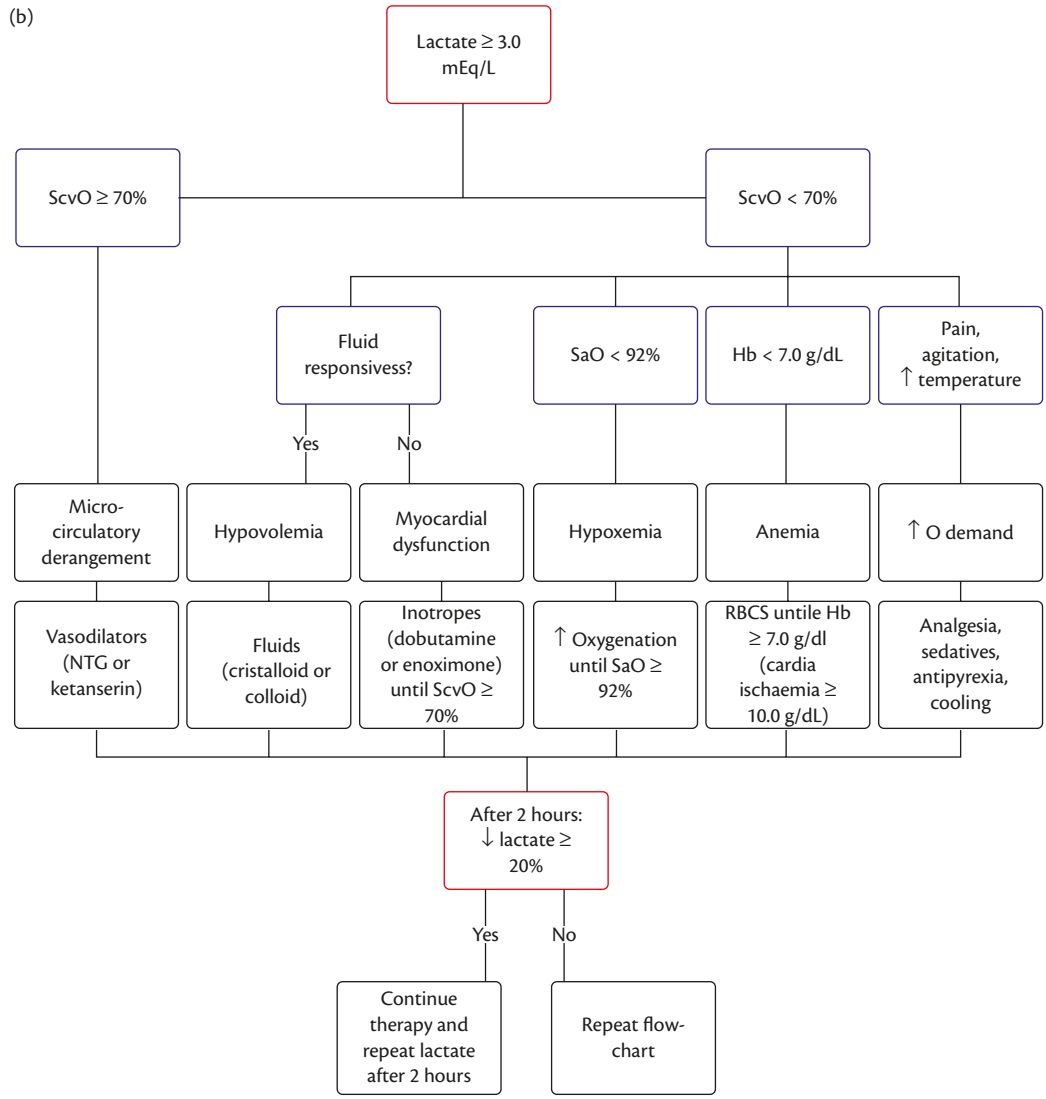


Fig. 139.2 Continued

replacement therapy. Reducing lactate levels by administration of dichloroacetate offered no clinical benefit [8] while lactate is a key metabolite in many tissues [14].

Benefit of lactate monitoring

Lactate monitoring may improve outcomes when hyperlactataemia triggers goal-directed DO_2 therapy. A single-centre trial in post-cardiac surgery patients showed a reduced length of stay [15]. In 2010, a three-centre, open-label US study randomized 300 patients to test non-inferiority between lactate clearance ≥10% and central venous oxygen saturation ($ScvO_2$) ≥70% as goals of early resuscitation in patients presenting to the ED with severe sepsis or septic shock [16]. The intervention lasted until all goals were achieved or for a maximum duration of 6 hours. There were no differences in treatments administered during the first 72 hours and in-hospital mortality rates were similar. This study has some limitations, in particular as $S(c)vO_2$ can be a valuable tool to differentiate anaerobic from aerobic hyperlactataemia, which often requires different treatment. It also seems questionable whether the targeted 10% reduction in lactate levels by 6 hours is sufficient to guarantee adequate resuscitation. Furthermore, only 10% of patients received either dobutamine or a red blood cell transfusion. As fluids and vasopressors were guided by central venous and arterial pressures in both groups, the potential difference in protocol actions directly attributable to either lactate or $ScvO_2$ was small. This complicates interpretation of the study findings as, in retrospect, it seems implausible that a change in resuscitation target could increase mortality by 10%, the non-inferiority margin selected for the trial [17].

A four centre, open-label, randomized controlled trial in the Netherlands [18] randomly allocated 348 patients to either lactate-guided monitoring (lactate group) or a control group during the first eight hours of their ICU stay (Fig 139.2a). In the lactate group, treatment was guided by lactate levels with the objective of decreasing lactate by ≥20% every 2 hours (Fig 139.2b); in the control group the treating clinicians had no knowledge of lactate levels (except for the admission value) over the first 8 hours. This resulted in more fluid and vasodilator administration in the lactate group. A 9.6% absolute mortality reduction was found in the unadjusted primary outcome analysis ($p = 0.067$). This was consistent with a significant mortality reduction in the pre-defined

multivariable analysis (p = 0.006) and with secondary outcome measures. However, despite the outcome benefit, the evolution of lactate levels was similar between groups, suggesting no causal relationship between the resuscitation therapy and hyperlactataemia. Instead, lactate might be an epiphenomenon of disease severity, with clinicians interpreting hyperlactataemia as a warning signal of non-improvement or even deterioration in the presence of stable haemodynamic variables. This could have triggered intensified resuscitation or attention to causes other than inadequate tissue perfusion, e.g. a non-controlled septic focus. Additionally, $ScvO_2$ monitoring, which was mandatory in the lactate group and optional in the control group, may also have had an impact on observed outcomes.

To summarize, these two recent studies show that lactate-directed resuscitation therapy offers clinical benefit for critically-ill patients, although responsible mechanisms remain uncertain. Lactate measurement should probably be accompanied by venous saturation monitoring to guide decision-making and therapy.

Conclusion

Both anaerobic and aerobic mechanisms of lactate production and clearance are important for the correct interpretation of hyperlactataemia . Despite this broad differential diagnosis and acknowledging that the prognostic value of lactate can vary considerably depending on the patient population, a rising lactate generally increases the ability to predict non-survival. Two recent multi-centre trials have confirmed that use of lactate levels in goal-directed therapy improves clinical outcome. These findings suggest that lactate monitoring is beneficial for ICU patients and should be incorporated into early resuscitation strategies.

References

1. Kompanje EJ, Jansen TC, van der Hoven B, and Bakker J. (2007). The first demonstration of lactic acid in human blood in shock by Johann Joseph Scherer (1814-1869) in January 1843. *Intensive Care Medicine*, **33**, 1967–71.
2. Cohen RD and Woods HF. (1976). The clinical presentation and classification of lactic acidosis. In: Cohen RD and Woods HF (eds) *Clinical and Biochemical Aspects of Lactic Acidosis*. Oxford: Blackwell Scientific.
3. Ronco JJ, Fenwick JC, Tweeddale MG, et al. (1993). Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *Journal of American Medical Association*, **270**, 1724–30.
4. De Backer D, Creteur J, Dubois MJ, et al. (2006). The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. *Critical Care Medicine*, **34**, 403–8.
5. Demir IE, Ceyhan GO, and Friess H. (2012). Beyond lactate: is there a role for serum lactate measurement in diagnosing acute mesenteric ischemia? *Digestive Surgery*, **29**, 226–35.
6. Levy B, Gibot S, Franck P, Cravoisy A, and Bollaert PE. (2005). Relation between muscle Na^+K^+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet*, **365**, 871–5.
7. Brealey D, Brand M, Hargreaves I, et al. (2002). Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet*, **360**, 219–23.
8. Stacpoole PW, Wright EC, Baumgartner TG, et al. (1992). A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group. *New England Journal of Medicine*, **327**, 1564–9.
9. Woll PJ and Record CO. (1979). Lactate elimination in man: effects of lactate concentration and hepatic dysfunction. *European Journal of Clinical Investigations*, **9**, 397–404.
10. De Backer D, Creteur J, Zhang H, Norrenberg M, and Vincent JL. (1997). Lactate production by the lungs in acute lung injury. *American Journal of Respiratory and Critical Care Medicine*, **156**, 1099–104.
11. Druml W, Grimm G, Laggner AN, Lenz K, and Schneeweiss B. (1991). Lactic acid kinetics in respiratory alkalosis. *Critical Care Medicine*, **19**, 1120–4.
12. Warburg O. (1956). On respiratory impairment in cancer cells. *Science*, **124**(3215), 269–70.
13. Jansen TC, van Bommel J, and Bakker J. (2009). Blood lactate monitoring in critically ill patients: a systematic health technology assessment. *Critical Care Medicine*, **37**, 2827–39.
14. Leverve XM and Mustafa I. (2002). Lactate: a key metabolite in the intercellular metabolic interplay. *Critical Care*, **6**, 284–5.
15. Polonen P, Ruokonen E, Hippelainen M, Poyhonen M, and Takala J. (2000). A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. *Anesthesia and Analgesia*, **90**, 1052–9.
16. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, and Kline JA. (2010). Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *Journal of the American Medical Association*, **303**, 739–46.
17. Lewis RJ. (2010). Disassembling goal-directed therapy for sepsis: a first step. *Journal of the American Medical Association*, **303**, 777–9.
18. Jansen TC, van Bommel J, Schoonderbeek FJ, et al. (2010). Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *American Journal of Respiratory and Critical Care Medicine*, **182**, 752–61.

CHAPTER 140

Measurement of extravascular lung water in the ICU

Danny F. McAuley and Thelma Rose Craig

Key points

- Extravascular lung water (EVLW) is associated with increased morbidity and mortality in critically-ill patients.
- The single indicator transpulmonary thermodilution technique is an available bedside technique to measure EVLW.
- There are no clear guidelines as to what constitutes a normal 'EVLW' value.
- Indexing EVLW to predicted body weight, rather than actual body weight is a better predictor of ICU mortality.
- EVLW estimation may be inaccurate in children and, in certain situations, including lung resection and abdominal aortic aneurysm.

Methods of quantifying extravascular lung water

For several decades there has been a comprehensive quest to find a reliable and reproducible technique to measure extravascular lung water (EVLW) in critically-ill patients. The chest radiograph is routinely used to identify pulmonary oedema, but is ineffective in estimating changes in EVLW when compared with a thermodilution technique [1]. EVLW estimation can also be performed by quantitative computed tomography (CT). Measurements of pulmonary oedema by thermodilution techniques show good correlation with those of quantitative CT [2]. However, CT is disadvantaged by radiation exposure, risks of transfer outside the ICU, expense, and difficulties with making serial measurements.

The reference gold standard method of calculating lung water is the gravimetric method [3]. This is based on comparing wet and dry lung weights. The lungs are weighed and then dried until a constant dry weight is achieved. Blood volume is estimated using a spectrophotometer. The EVLW is the amount of water contained in the lungs outside the pulmonary vasculature. This model has an obvious limitation as it can only be performed post-mortem. Serial measurements are obviously not possible and it is uncertain how lung removal affects EVLW quantification.

The transpulmonary thermodilution technique

There has been greater interest in developing bedside techniques to measure EVLW. Transpulmonary thermodilution is a reliable method used in haemodynamic monitoring of critically-ill patients. Earlier work focused on a double indicator dilution technique, which involves simultaneous injection of a freely diffusible 'cold' indicator and a plasma-bound indicator, such as indocyanine green (ICG) [4]. The diffusible constituent enters both the intra- and extravascular compartments, while the ICG enters the intravascular component only. EVLW accounts for the difference between the compartments. However, this method is expensive, cumbersome, time-consuming, and is now no longer available.

The need for a more straightforward technique that could be easily performed at the bedside led to the development of the single indicator transpulmonary thermodilution technique. This involves injection of a bolus of cold saline into a central venous line with the thermodilution curve being measured via a thermistor device sited within an arterial catheter. This is currently only available using the PiCCO system (Pulsion Medical, Munich, Germany). EVLW estimation using this method requires arterial and central venous catheters. The injectate sensor is attached to the central venous catheter. Following calibration, a bolus of 0.9% normal saline at 4°C is injected into the central venous catheter. The thermodilution curve is measured in the descending aorta (Fig. 140.1). The volume of distribution of the cold saline is calculated from these curves and EVLW calculated. This system heavily relies on the derivation of certain variables.

The volume of distribution of an indicator is the product of cardiac output and mean transit time (intrathoracic thermal volume, ITTV).

$$ITTV = CO \times MTT$$

$$CO = HR \times SV \text{ (HR heart rate, SV stroke volume)} \qquad \text{[eqn 1]}$$

where mean transit time (MTT) is time it takes from injection to half the indicator has passed the detection point

The pulmonary thermal volume (PTV), the largest mixing chamber of the cold indicator, is defined as the product of cardiac output and the exponential downslope time of the thermodilution curve:

$$PTV = CO \times DSt \qquad \text{[eqn 2]}$$

where DSt is exponential downslope time (see Figure 140.2)).
DSt = Down Slope time = Linear decay function of the indicator. Means how fast does the concentration of the indicator pass the detection point

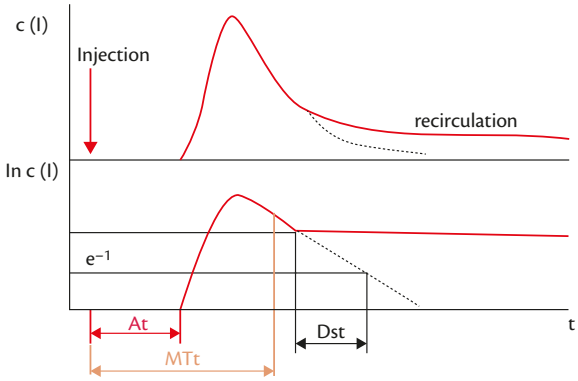


Fig. 140.1 Thermodilution curve.
At, appearance time; MTt, mean transit time; DSt, exponential downslope time.
Reproduced with permission from Pulsion Medical Systems.

The global end-diastolic volume (GEDV) is the difference between ITTV and PTV:

$$GEDV = ITTV - PTV \quad \text{[eqn 3]}$$

This technique assumes a linear relationship between GEDV and intrathoracic blood volume (ITBV). This relationship in humans has been determined by Sakka et al. [5] to equate to:

$$ITBV = 1.25 \times GEDV \quad \text{[eqn 4]}$$

The difference between ITBV and ITTV is EVLW:

$$EVLW = ITTV - ITBV \quad \text{[eqn 5]}$$

(see Figure 140.2)).

The single indicator transpulmonary thermodilution technique has been validated against the gold standard method of gravimetric analysis, and compared with the double indicator technique [6] demonstrating good reproducibility and close agreement.

Measurement of EVLW in a paediatric population can be problematic. Correlation between transpulmonary thermodilution estimation of EVLW and chest X-ray (CXR) quantification of pulmonary oedema is poor [7]. Measurement of EVLW in smaller children (age <10 years) may be inaccurate regardless of the technique used to estimate EVLW. In addition, the physiological principles regarding the relationship between GEDV and ITBV may not apply in a paediatric population. There may also be technical issues, for example, the need to use a femoral venous catheter or the arterial catheter size relative to the child's size may limit measurement of EVLW in young children [8].

Other techniques

Measurement of EVLW using the transpulmonary lithium indicator technique using the LiDCO system (LiDCO Ltd, Cambridge, UK) has also been investigated. Here, a small dose of lithium chloride is injected into a peripheral or central venous access. The resultant arterial lithium concentration time curve is recorded by withdrawing blood past a lithium sensor attached to the patient's in-dwelling arterial line. Only a small concentration of lithium is required, and this is considered non-toxic and pharmacologically inert. However, comparison of EVLW measurements between the double and single thermodilution techniques, and the lithium indicator technique

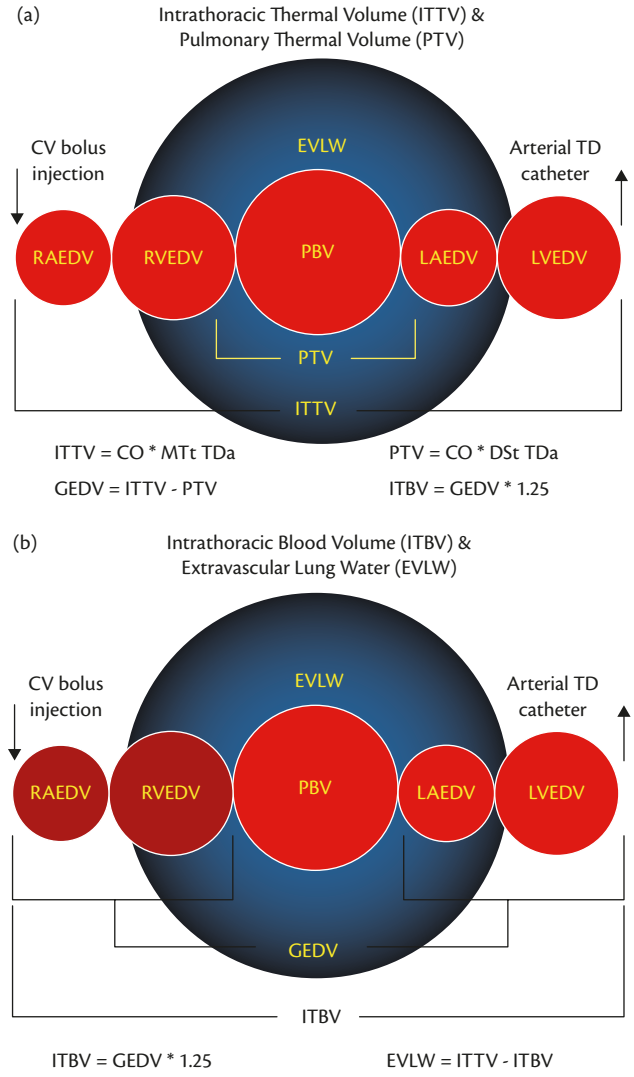


Fig. 140.2 (a) Calculation of ITTV and PTV by the single indicator dilution technique. (b) Calculation of EVLW from ITBV and GEDV.
RAEDV, right atrium end-diastolic volume; RVEDV, right ventricle end-diastolic volume; PBV; pulmonary blood volume; LAEDV, left atrium end-diastolic volume; LVEDV, left ventricle end-diastolic volume; TD, thermodilution.
Reproduced with permission form Pulsion Medical Systems.

in patients post-cardiac surgery suggest that the lithium indicator technique is not a reliable measure of EVLW [9]. In this study, the single and double indictor transpulmonary thermodilution techniques demonstrated an acceptable degree of bias, but poor limits of agreement.

Clinical uses

There remains no agreed definition as what constitutes a 'normal' EVLW. Some studies consider <7 mL/kg to be normal [10], whereas others consider values <10 mL/kg as within normal physiological limits [11].

EVLW is traditionally indexed to actual body weight, but since lung volumes are dependent on gender and height, not weight, indexing to predicted body weight has gained favour as it reduces falsely low EVLW measurements in obese patients. This may help to explain why EVLW has been misinterpreted as 'normal' in some

patients with ARDS. EVLW measured within 48 hours of fulfilling ARDS criteria, irrespective of aetiology, when indexed to predicted body weight is a predictor of ICU mortality after adjusting for severity of illness and other important covariates [12]. In this study, the odds ratio for ICU death was 4.3 per standard deviation increase in EVLW.

In a recent systematic review of 11 studies comprising 607 patients, EVLW was significantly higher in non-survivors compared with survivors in critically-ill patients, with a mean difference of 5 ml/kg [13]. The cut-off values differed across studies, which showed significant heterogeneity and ranged from 6.3 to 16 mL/kg. Two studies have suggested that a cut-off value of 16 mL/kg in patients with ARDS is associated with increased mortality [12,14]. A recent study of 200 consecutive subjects found EVLW was an independent risk factor for 28-day mortality in ARDS patients [15].

Measuring EVLW to guide fluid management in patients with pulmonary oedema may reduce the duration of mechanical ventilation and length of ICU stay [16]. EVLW can be pharmacologically manipulated in both animal models [17] and in patients with ARDS [18] suggesting EVLW is adequately sensitive to detect clinically important changes in pulmonary oedema. Measurement of EVLW using the transpulmonary thermodilution technique has been used as a primary endpoint in randomized controlled clinical trials [18,19], and appears to be able to detect clinically significant differences in pulmonary oedema.

Potential pitfalls in EVLW estimation

The accuracy of EVLW quantification relies on two assumptions. First, the downslope time of the thermodilution curve multiplied by the cardiac output gives the pulmonary thermal volume and thus an estimate of GEDV. Secondly, the ratio between GEDV and pulmonary blood volume equates to 4:1. There are other limitations to indicator dilution measurements of EVLW [20]. The most serious problem associated with any indicator dilution measurement of compartmental volumes is the potential failure of the injected indicator to reach all portions of the compartment in the given time period. There are also potential concerns regarding assumptions made on the recirculation of indicator. Comparisons between the single indicator method overestimated EVLW when compared with the gravimetric analysis in animal models [11]. This may be accounted for by the equilibration with the myocardium and surrounding vessels, and by recirculation of the indicator leading to an elevated EVLW.

Several clinical situations, including valve insufficiency, can lead to inaccuracy in CO calculation and, hence, EVLW assessment. An abdominal aortic aneurysm may raise GEDV and ITBV if the indicator passes through the aneurysm. The accuracy of transpulmonary thermodilution is affected by lung resection as pulmonary blood volume will be decreased and affect the GEDV/ITBV ratio.

Regardless, the measurement of EVLW is a potential technique to advance research into the underlying mechanisms of pulmonary oedema, as well as predict clinical outcomes and assess future potential therapies.

References

1. Halperin B, Feeley T, Mihm F, Chiles C, Guthaner D, and Blank N. (1985). Evaluation of the portable chest roentgenogram for quantitating extravascular lung water in critically ill adults. *Chest*, **88**, 649–52.
2. Patroniti N, Bellani G, Maggioni E, Manfio A, Marcora B, and Pesenti A. (2005). Measurement of pulmonary edema in patients with acute respiratory distress syndrome. *Critical Care Medicine*, **33**, 2547–54.
3. Pearce ML, Yamashita JOE, and Beazell J. (1965). Measurement of pulmonary edema. *Circulation Research*, **16**, 482–8.
4. Lewis FR, Elings VB, Hill SL, and Christensen JM. (1982). The measurement of extravascular lung water by thermal-green dye indicator dilution. *Annals of the New York Academy of Sciences*, **384**, 394–410.
5. Sakka S, Ruhl CC, Pfeiffer UJ, et al. (2000). Assessment of cardiac preload and extravascular lung water by single transpulmonary thermodilution. *Intensive Care Medicine*, **26**, 180–7.
6. Neumann P. (1999). Extravascular lung water and intrathoracic blood volume: double versus single indicator dilution technique. *Intensive Care Medicine*, **25**, 216–19.
7. Lemson J, van Die L, Hemelaar A, and van der Hoeven J. (2010). Extravascular lung water index measurement in critically ill children does not correlate with a chest x-ray score of pulmonary edema. *Critical Care*, **14**, R105.
8. McAuley DF, Brown LM, and Matthay MA. (2010). Assessing the quantity of pulmonary edema in critically ill children. *Critical Care*, **14**, 189.
9. Maddison B, Wolff C, Findlay G, Radermacher P, Hinds C, and Pearse R. (2009). Comparison of three methods of extravascular lung water volume measurement in patients after cardiac surgery. *Critical Care*, **13**, R107.
10. Kuzkov V, Kirov M, Sovershaev M, et al. (2006). Extravascular lung water determined with single transpulmonary thermodilution correlates with the severity of sepsis-induced acute lung injury. *Critical Care Medicine*, **34**, 1647–53.
11. Katzenelson R, Perel A, Berkenstadt H, et al. (2004). Accuracy of transpulmonary thermodilution versus gravimetric measurement of extravascular lung water. *Critical Care Medicine*, **32**, 1550–4.
12. Craig T, Duffy M, Shyamsundar M, et al. (2010). Extravascular lung water indexed to predicted body weight is a novel predictor of ICU mortality in patients with acute lung injury. *Critical Care Medicine*, **38**, 114–20.
13. Zhang Z, Lu B, and Ni H. (2012). Prognostic value of extravascular lung water index in critically ill patients: a systematic review of the literature. *Journal of Critical Care*, **27**, 420.e1–8.
14. Phillips C, Chesnutt M, and Smith SM. (2008). Extravascular lung water in sepsis-associated acute respiratory distress syndrome: Indexing with predicted body weight improves correlation with severity of illness and survival. *Critical Care Medicine*, **36**, 69–73.
15. Jozwiak M, Silva S, Persichini R, et al. (2013). Extravascular lung water is an independent prognostic factor in patients with acute respiratory distress syndrome. *Critical Care Medicine*, **41**, 472–80.
16. Mitchell J, Schuller D, Calandrino F, and Schuster D. (1992). Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catherisation. *American Reviews of Respiratory Diseases*, **145**, 990–8.
17. McAuley DF, Frank JA, Fang X, and Matthay MA. (2004). Clinically relevant concentrations of beta2-adrenergic agonists stimulate maximal cyclic adenosine monophosphate-dependent airspace fluid clearance and decrease pulmonary edema in experimental acid-induced lung injury. *Critical Care Medicine*, **32**, 1470–6.
18. Perkins G, McAuley D, Thickett D, and Gao F. (2006). The Beta-Agonist Lung Injury Trial (BALTI) a randomized placebo-controlled clinical trial. *American Journal of Respiratory and Critical Care Medicine*, **173**, 281–7.
19. Craig T, Duffy M, Shyamsundar M, O'Kane C, Elborn J, and McAuley D. (2010). Results of the HARP study; a randomized double blind phase II trial of 80mg simvastatin in acute lung injury. *American Journal of Respiratory and Critical Care Medicine*, **181**, A5100.
20. Effros RM, Pornsuriyasak P, Porszasz J, and Casaburi R. (2008). Indicator dilution measurements of extravascular lung water: basic assumptions and observations. *American Journal of Physiology—Lung Cellular and Molecular Physiology*, **294**, L1023–31.

CHAPTER 141

Doppler echocardiography in the ICU

Julien Maizel and Michel Slama

Key points

- Echocardiography provides the most complete and safest examination of haemodynamic status in the intensive care unit patient.
- Echocardiography can identify most cardiac causes of shock in ICU patients.
- Intensivists should acquire competencies in echocardiography.
- Echocardiography aids understanding of mechanisms leading to haemodynamic instability.
- Echocardiography can assess the effects of prescribed treatments.

Introduction

The use of echocardiography in the intensive care unit (ICU) has steadily grown in parallel with a decreasing use of right heart catheterization for which multiple studies showed no outcome benefit. Although echocardiography has never shown any positive impact on ICU patient outcomes, its capacity to non-invasively identify the major causes of circulatory failure has made it increasingly popular. Initially focused on stroke volume and cardiac output measurement, echocardiography is being progressively used for more complex and comprehensive haemodynamic assessments. As with ultrasound, ICU physicians should acquire their own echocardiography skills to complement those of the cardiologist. This requires educational programmes to generate sufficient trained operators in every ICU [1].

General principles

Ultrasound is defined as a frequency >20 kHz. In clinical echocardiography the probe usually emits ultrasound frequencies between 2–4 MHz for transthoracic echocardiography (TTE) and 5-8 MHz for transoesophageal echocardiography (TEE). Higher frequencies provide better picture resolution, but cannot reach deep tissue. Lower frequencies provide deeper structure visualization, but with weaker resolution. The propagation velocity of the ultrasound wave depends on the composition of the medium from 300 m/sec in air to 1540 m/sec in human soft tissue. Air interposed between the probe and the structure of interest will dramatically decrease echogenicity.

While TTE has the big advantage of being non-invasive, the impact of lung air and chest wall dressing or tubes in producing poor-quality images can be a real concern. Nonetheless, the reported percentage of anechoic ICU patients using TTE is <10%. As this approach allows delineation of haemodynamic status in most ICU patients, it is generally recommended before TEE. However, if the patient is anechoic, or when posterior structures of the heart (superior vena cava, valvular systems, auricles, thoracic aorta, pulmonary veins) need to be visualized, the use of TEE becomes more appropriate (Table 141.1). TEE is usually considered a semi-invasive procedure with an overall reported complication rate between 2 and 3%, mostly due to transient hypo- or hypertension [2]. Major complications include orogastric perforation, gastrointestinal bleeding, arrhythmias, and respiratory complications (e.g. hypoxaemia, accidental extubation, laryngospasm, bronchospasm) do not exceed 2% of all procedures [2,3]. No related mortality was reported in a series of 2508 ICU procedures [4]. Table 141.2 displays absolute and relative contraindications of TEE.

Haemodynamic evaluation

Cardiac performance in shocked patients is a key point in therapeutic support decision-making. TTE could prospectively identify most cardiac causes in a study of 100 ICU shocked patients, impacting on management in half [5].

Left ventricular systolic function and cardiac output

Determining systolic function is an integral part of the TTE examination. Both ventricles should always be examined.

Table 141.1 Particular advantages of transthoracic and transoesophageal echocardiographic approaches

Transthoracic echocardiography	Transoesophageal echocardiography
Visualization of the IVC	Visualization of SVC
Examination of the pericardium	Examination of atria and auricules (thrombus)
Examination of the LV apex (thrombus, myocardial infarction)	Evaluation of native and prosthetic valve function (endocarditis, regurgitation)
Evaluation of pulmonary artery pressure via the degree of tricuspid regurgitation	Visualization of thoracic aorta (dissection, trauma)
LV tract outflow obstruction	Visualization of pulmonary artery (trauma, thrombus, embolism)
	Examination of proximal coronary flow

LV, left ventricle; RV, right ventricle; IVC, inferior vena cava; SVC, superior vena cava.

Table 141.2 Absolute and relative contraindications for transoesophageal echocardiography

Absolute contraindications	Relative contraindications
Mediastinal irradiation	Oesophageal varices
Unstable cervical trauma	Symptomatic hiatal hernia
Oesophageal tumour	Non-intubated patient with respiratory distress or a full stomach
Oropharyngeal tumour	Agitation
Oesophagectomy	
Active or recent gastrointestinal bleeding	

Echocardiography is the only device that separately analyses right and left ventricular performance. This is particularly important as right ventricular dysfunction requires specific management of fluid, drugs, and ventilator settings.

Several methods quantify left ventricle (LV) contractility, e.g. LV maximal systolic elastance, tissue Doppler, fractional shortening. However, from a practical viewpoint, measurement of left ventricular ejection fraction (LVEF) combined with cardiac output is usually sufficient. LVEF can be assessed by visual estimation or Simpson's method. Visual estimation by an experienced echocardiographer could detect systolic dysfunction with high feasibility and reproducibility (compared with Simpson's method) [6], and with clinical utility in ICU patients [7]. Systolic function can also be evaluated by TEE using LVEF in a longitudinal four-chamber view or LV fractional area contraction in a transgastric short-axis view.

Cardiac output (CO) is considered a cornerstone in haemodynamic evaluation. For both TTE and TEE, the most reliable method consists of measuring (in the same position) both LV outflow tract diameter and the aortic flow velocity-time integral (VTI) recorded with Doppler ultrasound. Stroke volume is computed as aortic cross-sectional area multiplied by VTI, and CO as the product of stroke volume and heart rate. Excellent agreement has been demonstrated with the thermodilution technique in ICU patients.

Left ventricular diastolic function and filling pressure

Evaluation of diastolic function provides important information [8]. In patients with a steep LV pressure-volume relationship (impaired LV relaxation), infusion of small fluid volumes may increase LV diastolic pressure and precipitate acute pulmonary oedema. It is crucial to consider differences between diastolic dysfunction and increased LV filling pressure. Diastolic dysfunction is the alteration of LV properties marked by decreased LV relaxation and increased stiffness. Diastolic dysfunction is seen in diastolic heart failure, but also in heart failure patients with systolic dysfunction. LV filing pressure, or end-diastolic pressure (LVEDD), is not necessarily increased with diastolic (or systolic) dysfunction in the absence of congestive heart failure.

Several variables can be used to explore diastolic function—mitral inflow, early septal and lateral mitral annular systolic velocities, left atrial volume, pulmonary venous return flow, and the Valsalva manoeuvre. Some are difficult to obtain in an ICU patient (e.g. Valsalva manoeuvre) or require TEE (e.g. pulmonary venous flow). For ICU patients we can reasonably recommend focusing upon mitral inflow, the early mitral annular systolic velocity in tissue Doppler mode, and pulmonary venous return flow if TEE is used (Figs 141.1, 141.2, and 141.3). Three grades of diastolic dysfunction have been identified—mild (grade I), moderate (grade II), and severe (grade III). This classification strongly prognosticates all-cause mortality in a general population. Grade II dysfunction represents impaired relaxation and moderate elevations of LV filling pressure, whereas Grade III denotes a restrictive LV filling pattern with high LV filling pressures that could revert to impaired relaxation (grade II or I) after successful therapy. However, this grading presents some limitations. In patients over 60 years old it is not rare to find a grade I pattern (E/A ratio <1 and deceleration time >200 ms) without diastolic dysfunction. Here, a history of cardiovascular disease or the presence of left ventricular hypertrophy will confirm the existence of diastolic dysfunction. Athlete's heart can present with an increased left atrial size (≥34 mL/m^2) but the presence of normal septal and lateral E' velocities confirms the absence of diastolic dysfunction.

Despite these limitations this classification does provides useful information for ICU practice. For example, determining LV filling pressure helps to establish a cardiac origin of acute respiratory failure. Many Doppler indices derived from mitral flow E/A ratio (the ratio between early (E) and late (A) mitral inflows recorded with pulsed Doppler), pulmonary venous flow (D wave deceleration time and systolic fraction) and tissue Doppler E/E' ratio (the ratio between early (E) mitral inflow recorded with pulsed Doppler and the early diastolic velocity (E') recorded from Doppler tissue

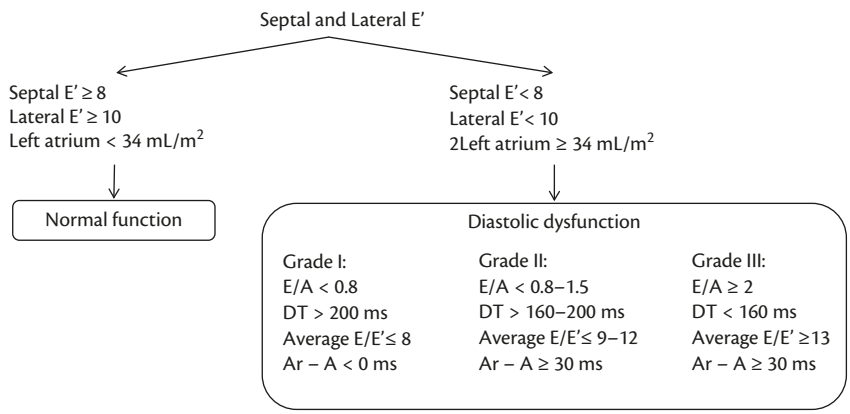


Fig. 141.1 Left ventricular diastolic function assessment.

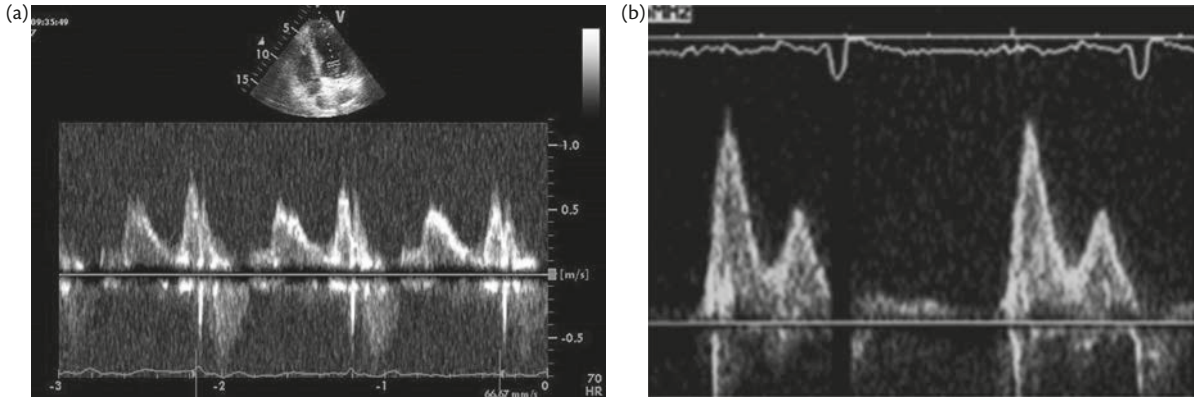


Fig. 141.2 Mitral flow recorded using pulsed wave Doppler. (a) Diastolic dysfunction grade 1. (b) Grade 3.

imaging with the sample cursor placed in the lateral or medial mitral annulus) can help to further explore LV filling pressures (Table 141.3). These parameters have been validated against pulmonary artery occlusion pressure in mechanically-ventilated ICU patients. Data are lacking for spontaneously breathing ICU patients and are therefore extrapolated from the catheter laboratory. However, each parameter has its limitations. The E/A ratio offers better diagnostic value in patients with depressed systolic function (Fig. 141.2), while the E/E' threshold differs (particularly in cases of myocardial ischemia) depending on whether E' is recorded in the lateral or medial junction of the mitral annulus. Both should thus be recorded (Fig. 141.3). Pulmonary artery flow generally necessitates the use of TEE. Estimation of LV filling pressures in ICU patients requires several parameters, rather than just one. For systolic dysfunction, E/A or E/E' should be measured [9].

Right ventricular function

Right ventricle (RV) assessment should be systematically performed when evaluating critically-ill patients. The RV's role is to aid venous return and eject it into the low-pressure pulmonary circulation. Most RV dysfunction in ICU patients is secondary to an increased RV afterload related to elevations in pulmonary vascular resistance (PVR). Bronchospasm, acute respiratory distress syndrome, pulmonary embolism, and mechanical ventilation are potential aetiologies. RV dysfunction may also result from volume overload or myocardial dysfunction including RV infarction, contusion, and sepsis.

In the ICU setting, RV examination includes assessment of size, thickness, contractility (including paradoxical septal movement), and an estimation of pulmonary pressures. RV dimensions are recorded in apical or subxiphoid four-chamber views. The ratio between RV and LV end-diastolic diameters (or areas) defines the presence of RV dilatation. The ratio is normally <0.6, whereas moderate dilatation is defined by ratios between 0.6–1, and severe dilatation by ratios ≥1. The presence of RV dilatation should be complemented by measuring RV wall thickness at the level of the mid-lateral free wall (excluding any papillary muscle or epicardial fat tissue). Thickness ≥7 mm (normal <4 mm) suggests chronic, rather than acute RV pressure overload [10]. RV systolic function may be assessed using the ejection fraction method

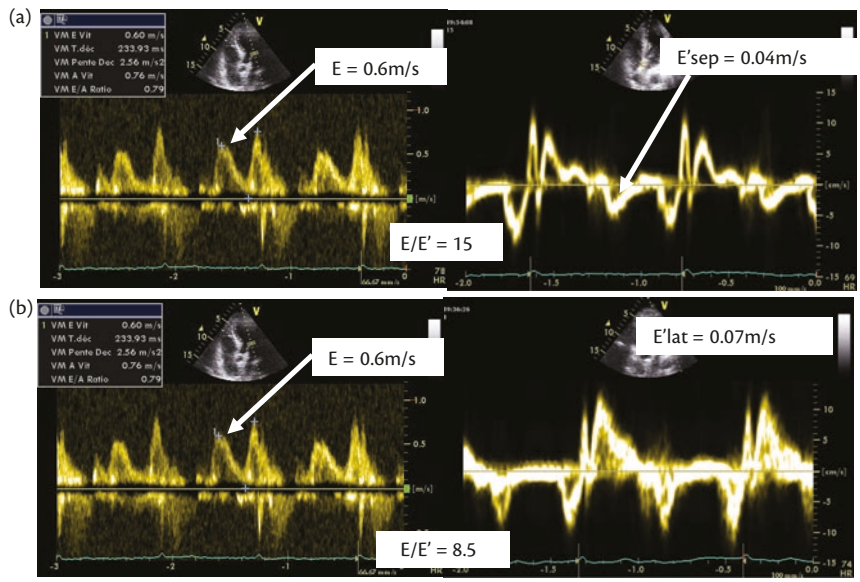


Fig. 141.3 E/E' ratio at the septal level (a) and the lateral wall (b).

Table 141.3 Echocardiographic parameters to predict LV filling pressure

Parameter	Threshold	Predicted parameter	Diagnostic value	Population	Reference
E/A	≥2	PAOP >20 mmHg	Se 43% Spe 99%	Cardiology, LVEF<45%	Giamnuzzi P, *J Am Coll Cardiol* 1994, **23**, 1630–7
	≤1.4	PAOP ≤18 mmHg	Se 75% Spe 100%	ICU, TTE, mechanical ventilation	Vignon P, *Crit Care* 2008, **12**, R18
E/E'	>10	PAOP >15 mmHg	Se 91% Spe 81%	Cardiology, spontaneous ventilation	Nagueh SF, *J Am Coll Cardiol* 1997, **30**, 1527–33
	>7.5 lateral (>9 medial)	PAOP >15 mmHg	Se 86% Spe 81%	ICU, mechanical ventilation	Combes A, *Intensive Care Med* 2004, **30**, 75–81
E/Vp	>2.5	PAOP >15 mmHg	Se 86% Spe 85%	Cardiology, spontaneous ventilation	Gonzalez-Vilchez F, *J Am Coll Cardiol* 1999, **34**, 515–23
DDT	<175 ms	PAOP >18 mmHg	Se 100% Spe 95%	Cardiology, mechanical ventilation	Kinnaird TD *J Am Coll Cardiol* 2001, **37**, 2025–30
Systolic fraction	≤40%	PAOP >18 mmHg	Se 100% Spe 100%	ICU, TTE, mechanical ventilation	Vargas F *J Crit Care* 2004, **19**, 187–97
	>44%	PAOP ≤18 mmHg	Se 92% Spe 88%	ICU, TTE, mechanical ventilation	Vignon P *Crit Care* 2008, **12**, R18

DDT, D wave deceleration time (pulmonary venous flow); TTE, transoesophageal echocardiography; systolic fraction (%) = VTI systolic wave/VTI systolic + diastolic waves of pulmonary venous flow.

in a four-chamber view. This can be problematic due to RV shape complexity and a lack of standardized methods for calculating RV volumes.

RV fractional area change (normal >35%) can also assess systolic function. End-systolic and diastolic RV areas are measured in the apical four-chamber view using TTE, or in the transgastric short-axis mid-papillary view with TEE. Displacement of the tricuspid annulus recorded in M-mode (TAPSE) analyses anterior movement during systole. Normally between 17–30 mm, TAPSE <16 mm suggests RV systolic dysfunction. A systolic velocity of the free wall tricuspid annulus recorded in tissue Doppler mode (S wave) <10 cm/sec likewise suggests RV systolic dysfunction [10]. The right and left ventricles are closely related, sharing the interventricular septum. During RV dysfunction, septal motion is shifted towards the LV during either systole (pressure overload) or diastole (volume overload). This can be observed in M mode parasternal longitudinal view (TTE) or in transventricular short-axis view (TTE or TEE). This phenomenon of paradoxical septal movement can be quantified by the eccentric index in a transventricular short-axis view. This is the ratio between two diameters, one of which bisects and the second being perpendicular to the septum (Fig. 141.4). This ratio is normally 1 (round shape of the LV), but becomes >1 (D-shaped) with a paradoxical septum.

Modifications in RV and interventricular septal morphology are associated with increases in pulmonary arterial and right atrial pressures. When evaluating right atrial pressure (RAP) one must recognize the impact of mechanical ventilation. In spontaneously breathing patients, an end-expiratory inferior vena cava (IVC) diameter (measured in subxiphoid transverse M-mode view perpendicular to the long axis and 1–3 cm proximal to the right atrial ostium) ≤2 cm predicts RAP <10 mmHg. Collapsibility <40% during inspiration (maximum diameter – minimum diameter/maximum diameter × 100) also predicts RAP <10 mmHg [11]. In mechanically-ventilated patients, an end-expiratory IVC diameter <12 mm also predicted RAP <10 mmHg, but respiratory variations in diameter were not predictive [12]. Pulmonary artery systolic pressures can be evaluated non-invasively from the maximal velocity of the tricuspid regurgitant jet (Fig. 141.5). This should be carefully interpreted as it also depends on stroke volume and can be easily underestimated due to a weak regurgitant Doppler signal in mechanically-ventilated patients.

Pericardium

The pericardial space is a virtual cavity, but blood, fluid, pus, or air can occasionally be responsible for an effusion and dramatically affect cardiac performance with tamponade. TTE combining parasternal, apical, and subxiphoid views is usually sufficient to exclude an effusion. With poor echogenicity or after recent cardiac surgery, TEE may be required to visualize behind the atria and exclude any confined compressive clot. Echocardiography can help to quantify the effusion (circumferential or partial, measuring also its thickness in end-diastole) and to assess any consequences

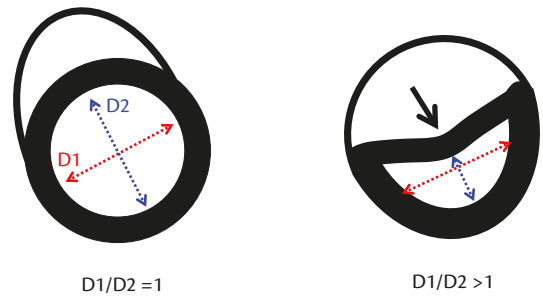


Fig. 141.4 Left ventricular short-axis view. Eccentric index assessment.

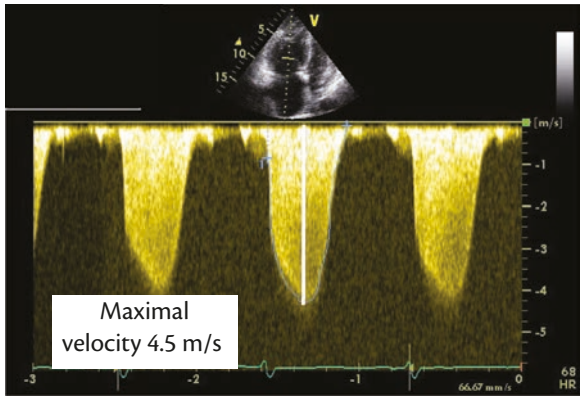


Fig. 141.5 Tricuspid regurgitation recorded using continuous wave Doppler. Pulmonary artery systolic pressure (SPAP) is calculated as 4× (Maximal velocity)^2 + right atrial pressure. In this patient RAP = 9 mmHg and SPAP = 80 mmHg.

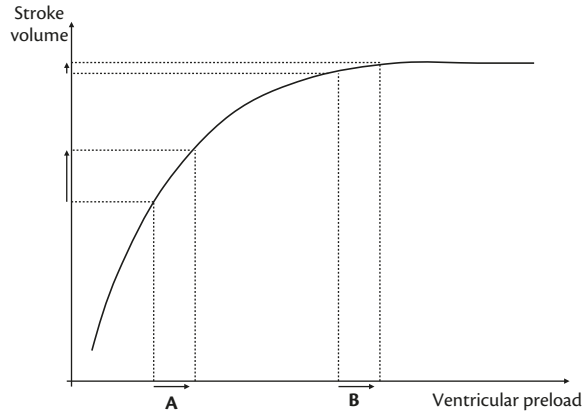


Fig. 141.7 Frank—Starling relationship.

on right-heart cavities. Tamponade represents circulatory failure due to RV and/or right atrium (RA) diastolic collapse related to compression. More than just size alone, the risk of tamponade relates to the rapidity of formation. Tamponade does not necessarily require a large-sized effusion. Movement of the RV free wall (apex and mid portions) and the RA wall during diastole should be carefully analysed to detect the presence of a compressive effusion (Fig. 141.6). Another indirect, but non-specific sign of compression is a congested IVC. Respiratory variations in tricuspid Doppler signals can aid in detecting compression in spontaneously breathing patients, but not during mechanical ventilation. During spontaneous inspiration physiological acceleration of the tricuspid velocity is considerably increased (+80%) and mitral velocity deceleration decreased (–40%). Echocardiography also guides the physician during pericardiocentesis.

Fluid responsiveness

Management of circulatory failure usually requires fluid administration to improve cardiac output and oxygen supply. An excessive fluid input can be deleterious, provoking congestive heart failure and pulmonary oedema. It is therefore important to predict the efficacy of a fluid challenge and avoid futile increases in left ventricular end-diastolic pressure. Fluid only increases stroke volume if both ventricles are working on the steep part of the Frank–Starling curve. Otherwise, fluid will simply increase preload without any significant increase in stroke volume (Fig. 141.7). In the ICU, except for obvious situations (active bleeding, burns, trauma), clinical findings do not predict fluid responsiveness [13] so complementary information should therefore be used. Static and dynamic measures can predict fluid responsiveness. Static parameters evaluate left ventricular filling pressure or RAP under one loading condition, assuming the lower the preload the higher the probability of a response to volume expansion. A virtual end-systolic LV area <4 cm^2 in the short-axis view also predicts likely fluid responsiveness [14]. However, except for this extreme situation, no cut-off value exists to predict fluid responsiveness because of the wide variety of LV dimensions. Other static parameters described include Doppler parameters listed previously and in Table 141.3.

Dynamic parameters are clearly superior to static. These are described as dynamic as they try to determine whether the patient is situated on the ascending portion of the Frank–Starling curve where any preload variation affects stroke volume (i.e. preload-dependent), or on the plateau portion where preload variations are not accompanied by variations in stroke volume, i.e. preload-independent (Fig. 141.4).

Many criteria have been described using loading modifications generated by mechanical ventilation, fluid challenge or passive leg-raising (Table 141.4). Tidal ventilation generates a positive intrathoracic pressure during inspiration, decreasing venous return, increasing resistance in the pulmonary capillaries, decreasing LV preload a few cardiac cycles later and, finally, decreasing stroke volume if both right and left ventricles are functioning on the ascending portion of the Frank–Starling curve. Variations in stroke volume >13%, in Ao VTI >20%, or in Ao maximal velocity >12% predict fluid responsiveness. This can be used only in sedated, mechanically-ventilated, non-spontaneously breathing patients in sinus rhythm. The positive pressure generated by the ventilator during inspiration will also generate cyclic modifications in superior and inferior vena caval diameters recorded by TTE (IVC) or TEE (SVC) (Table 141.4).

Muller et al. recently tested the accuracy of a 100 mL 'mini-fluid' challenge given over a minute to predict fluid responsiveness in mechanically ventilated critically-ill patients [15]. An increase >10% in Aortic velocity-time integral (Ao VTI) predicted fluid responsiveness with

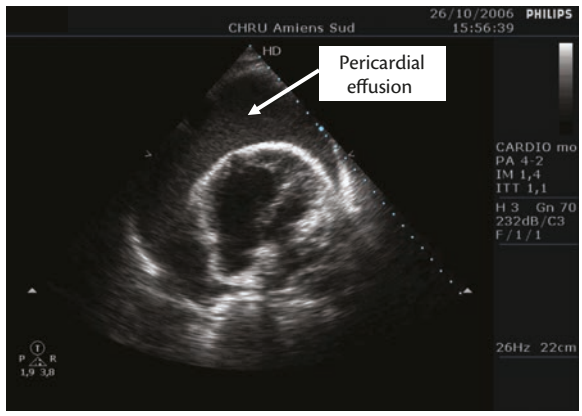


Fig. 141.6 Pericardial tamponade.

Table 141.4 Dynamic indices using respiratory variations or passive leg raising to predict fluid responsiveness

Parameter	Threshold	Diagnostic value	Population	Reference
Respiratory variations				
ΔVTI Ao*	>20%	Se 78%, Spe 92%	MV	Charron C. *Anesth Analg* 2006, **102**, 1511–17
ΔAoVel*	>12%	Se 100%, Spe 89%	MV	Feissel M. Chest 2001; 119:867–73
dIVC	>18%	Se 90%, Spe 90%	MV	Barbier C. *Intensive Care Med* 2004, **30**, 1740–6
ΔIVC	>12%	Se 87%, Spe 96%	MV	Feissel M. *Intensive Care Med* 2004, **30**, 1834–7
SVC collapsibility	>36%	Se 90%, Spe 100%	MV and TEE	Vieillard-Baron A. *Anesthesiology* 2001, **95**, 1083–8
ΔABF*	>18%	Se 90%, Spe 94%	MV, oesophageal Doppler	Monnet X. *Intensive Care Med* 2005, **31**, 1195–201
Fluid challenge				
VTI Ao**	>10%	Se 95% and Spe 78%	MV	Muller L. *Anesthesiology* 2011, **115**, 541–7
Passive leg raising				
ABF	>8%	Se 90% and Spe 83%	MV	Lafanechère A. *Crit Care* 2006, **10**, R132
ABF	>10%	Se 97% and Spe 94%	MV + spontaneous activity, arrhythmia	Monnet X. *Crit Care Med* 2006, **34**, 1402–7
dVTI Ao	>12%	Se 69% and Spe 89%	Spontaneously breathing	Maizel J. *Intensive Care Med* 2007, **33**, 1133–8

*Controlled ventilation, adapted to the ventilator and an absence of any arrhythmia.

**Fluid challenge consisting of 100 mL of hetastarch given over 1 minute.

MV, mechanical ventilation; ΔVTI Ao, Respiratory variations of the aortic flow time velocity integral; ΔAo Vel, respiratory variations of the maximal aortic blood velocity; IVC, inferior vena cava; SVC, superior vena cava; dIVC = $(IVC_{max} - IVC_{min})/IVC_{min}$; ΔIVC= $(IVC_{max} - IVC_{min}) \div (IVC_{max}+IVC_{min}/2)$; SVC collapsibility = $(SVC_{min} - SVC_{max})/SVC_{min}$; ABF: aortic blood flow recorded with oesophageal Doppler; dVTI Ao = (VTI Ao post-PLR – VTI Ao pre-PLR)/VTI Ao pre-PLR. (PLR = passive leg raising).

95% sensitivity and 78% specificity. Passive leg-raising is probably one of the safest and most accurate tools to predict fluid responsiveness in both mechanically- and spontaneously-breathing patients [16]. By mobilizing venous blood from the legs and lower abdomen, this provides a transient 300 mL blood infusion into the right heart. Its reversibility avoids any futile increase in LV filling pressure. In mechanically-ventilated patients (with or without spontaneous breathing activity) an increase in aortic blood flow measured by oesophageal Doppler after passive leg-raising also predicts preload responsiveness [17]. Nonetheless, an elevation in intra-abdominal pressure alters the diagnostic accuracy of passive leg-raising with a higher risk of false positives [18]. In non-intubated ICU patients, an increase in aortic VTI >12% is currently the only reliable echocardiographic parameter to predict fluid responsiveness [16].

Conclusion

The use of echocardiography in the ICU has considerably increased in recent years to become a central device to detect and understand the complexity of circulatory and respiratory failure. Clinicians should be aware of the benefits and limitations of the numerous parameters provided by echocardiography in order to correctly interpret the examination and appropriately adapt patient management.

References

1. Vieillard-Baron A, Slama M, Cholley B, Janvier G, and Vignon P. (2008). Echocardiography in the intensive care unit: From evolution to revolution? *Intensive Care Medicine*, **34**, 243–9.
2. Hilberath JN, Oakes DA, Shernan SK, Bulwer BE, D'Ambra MN, and Eltzschig HK. (2010). Safety of transesophageal echocardiography. *Journal of the American Society for Echocardiography*, **23**, 1115–27.
3. Slama MA, Novara A, Van de Putte P, et al. (1996). Diagnostic and therapeutic implications of transesophageal echocardiography in medical ICU patients with unexplained shock, hypoxemia, or suspected endocarditis. *Intensive Care Medicine*, **22**, 916–22.
4. Hüttemann E, Schelenz C, Kara F, Chatzinikolaou K, and Reinhart K. (2004). The use and safety of transoesophageal echocardiography in the general ICU—a minireview. *Acta Anaesthesiologica Scandinavica*, **48**, 827–36.
5. Joseph MX, Disney PJ, Da Costa R, and Hutchison SJ. (2004). Transthoracic echocardiography to identify or exclude cardiac cause of shock. *Chest*, **126**, 1592–7.
6. Gudmundsson P, Rydberg E, Winter R, and Willenheimer R. (2005). Visually estimated left ventricular ejection fraction by echocardiography is closely correlated with formal quantitative methods. *International Journal of Cardiology*, **101**, 209–12.
7. Vieillard-Baron A, Charron C, Chergui K, Peyrouset O, and Jardin F. (2006). Bedside echocardiographic evaluation of hemodynamics in sepsis: Is a qualitative evaluation sufficient? *Intensive Care Medicine*, **32**, 1547–52.

8. Nagueh SF, Appleton CP, Gillebert TC, et al. (2009). Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Journal of the American Society for Echocardiography*, **22**, 107–33.
9. Feissel M, Maizel J, Robles G, Badie J, Faller JP, and Slama M. (2009). Clinical relevance of echocardiography in acute severe dyspnea. *Journal of the American Society for Echocardiography*, **22**, 1159–64.
10. Rudski LG, Lai WW, Afilalo J, et al. (2010). Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *Journal of the American Society for Echocardiography*, **23**, 685–713.
11. Brennan JM, Blair JE, Goonewardena S, et al. (2007). Reappraisal of the use of inferior vena cava for estimating right atrial pressure. *Journal of the American Society for Echocardiography*, **20**, 857–61.
12. Jue J, Chung W, and Schiller NB. (1992). Does inferior vena cava size predict right atrial pressures in patients receiving mechanical ventilation? *Journal of the American Society for Echocardiography*, **5**, 613–19.
13. Michard F and Teboul JL. (2002). Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest*, **121**, 2000–8.
14. Leung JM and Levine EH. (1994). Left ventricular end-systolic cavity obliteration as an estimate of intraoperative hypovolemia. *Anesthesiology*, **81**, 1102–9.
15. Muller L, Toumi M, Bousquet PJ, et al. (2011). An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: The mini-fluid challenge study. *Anesthesiology*, **115**, 541–7.
16. Maizel J, Airapetian N, Lorne E, Tribouilloy C, Massy Z, and Slama M. (2007). Diagnosis of central hypovolemia by using passive leg raising. *Intensive Care Medicine*, **33**, 1133–8.
17. Lafanechère A, Pène F, Goulenok C, et al. (2006). Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients. *Critical Care*, **10**, R132.
18. Mahjoub Y, Touzeau J, Airapetian N, et al. (2010). The passive leg-raising maneuver cannot accurately predict fluid responsiveness in patients with intra-abdominal hypertension. *Critical Care Medicine*, **38**, 1824–9.

CHAPTER 142

Monitoring the microcirculation in the ICU

Can Ince and Alexandre Lima

Key points

- The microcirculation is the final destination of the cardiovascular system responsible for delivering oxygen to the respiring tissue cells so that they can perform their functional activities to sustain organ function.
- The microcirculation consists of microvessels <100 μm in diameter and are composed of arterioles, capillaries, and venules. The capillaries are the smallest (±5 μm) vessels and the predominant site where oxygen leaves the circulation by passive diffusion to tissue cells. They are also the most vulnerable component of the microcirculation.
- The ability of the microcirculation to deliver oxygen to cells depends on its convective capacity (red blood cell flow delivery) and diffusive capacity (the distance oxygen has to travel from capillaries to cells. This is quantified by the functional capillary density that can only be measured by observing the microcirculation.
- Shock is defined as a condition in which cells need more oxygen to sustain their functional activity than is being supplied by the microcirculation. In critical illness, distributive shock defines the condition where shunting denies oxygen transport to these vulnerable areas causing tissue hypoxia in the presence of normalized systemic variables. Such a condition requires therapy to recruit such shunted microcirculatory units.
- Orthogonal polarization spectral (OPS), sidestream darkfield (SDF) and other imaging techniques have allowed microcirculatory imaging to be accomplished, but are cumbersome to use as clinical tools. Recent imaging techniques based on computer-controlled sensors and Cytocam-incident darkfield (IDF) imaging suggest the possibility of integrating this crucial physiological compartment into conventional haemodynamic monitoring.

Introduction

The microcirculation is the key physiological compartment of the cardiovascular system, where oxygen is delivered by convection and diffusion to respiring parenchymal cells to support cellular, and thereby organ, function. The microcirculation consists of microvessels less than 100 μm in diameter consisting of arterioles, capillaries, and venules. The smallest vessels (<6 μm) are the capillaries where most oxygen leaves the circulation by passive diffusion to cells. The critical role of the microcirculation has long been recognized, but only recently has it been possible to image its function at the bedside, thus making it a clinically important compartment to monitor. Prior to this type of monitoring, peripheral perfusion was used as a surrogate before more advanced optical techniques were developed to image microcirculatory function, both non-invasively and at the bedside. Here, we provide a brief overview of microcirculatory assessment.

Clinical assessment of peripheral perfusion

The rationale of monitoring peripheral perfusion is based on the phenomenon that the sympathetic neurohumoral response decreases skin perfusion (and thereby temperature) during hypotension to maintain central blood pressure. Thus, toe temperature has been used since the 1960s as an indicator of the severity of circulatory shock [1]. Although reduced peripheral temperature is associated with different shock states, such abnormalities are not always related to microcirculatory alterations, especially in septic shock. Subjective assessment of peripheral perfusion can be accomplished by assessment of skin temperature or by measuring capillary refill time. This physical examination can identify patients at high risk of circulatory complications, as well as otherwise haemodynamically stable patients who have organ dysfunction [2]. More quantitative assessment of peripheral perfusion can be accomplished by use of the pulse oximetry signal where the ratio between pulsatile and non-pulsatile components of the signal can be used to calculate a peripheral perfusion index. This index can be used to assess the effects of therapeutic interventions on peripheral perfusion in critically-ill patients [3].

Imaging of microcirculatory morphology and haemodynamics

In the late 1990s hand-held video microscopes were introduced by Ince and co-workers to image the microcirculation at the bedside using orthogonal polarization spectral (OPS) imaging [4,5]. They were also the first to image the human brain microcirculation during surgery [4,6]. Direct video observation of flowing red blood cells (RBC) in the microcirculation is accomplished by illumination of the microcirculation. This technique utilizes green light that is absorbed by haemoglobin within the RBC, making them visible as flowing dark globules under microscopic magnification. This illumination is combined with optical modalities that filter

out surface reflections of light so that microcirculatory structures below the tissue surface can be visualized. Such optical modalities (orthogonal polarization spectral (OPS) imaging and its successor, sidestream dark field (SDF) imaging) had previously been developed for intravital microscopy, but were incorporated into hand-held microscopes [5]. Over the last decade, clinical investigations using these techniques in intensive care patients have shown that microcirculatory dysfunction plays a key role in the development of complications and can be used for prognostication [7–10].

Microcirculatory alterations in critically-ill patients have been predominantly measured sublingually. This readily accessible location is also a clinically relevant compartment due to its vascularization originating from the external carotid artery. Sublingual microcirculatory monitoring is the most sensitive haemodynamic marker of adverse outcomes in both adult and paediatric critically-ill patients [e.g. 8,9]. Early goal-directed therapy that could successfully resuscitate the microcirculation was associated with improved organ function assessed 24 hours later [10]. Intestinal and rectal microcirculatory measurements have also been undertaken in critically ill patients [e.g. 11].

The microcirculatory effects of numerous therapies have been studied in critically-ill patients, including blood transfusions, vasoactive drugs, and steroids [e.g. 12–14]. Its monitoring is considered especially relevant to the diagnosis of hypovolaemia and its treatment with fluid [15,16]. Microcirculatory imaging techniques have also been used to measure other cellular structures important to microcirculatory function, such as leukocyte adherence and endothelial cell glycocalyx alterations. The glycocalyx is a gel-like layer lining endothelial cells and is central in the control of vascular homeostasis. Its compromise is associated with leukocyte activation and a collapse of (micro)vascular integrity. Monitoring of glycocalyx function could potentially provide important clinical data regarding the function of the cardiovascular system.

Studies using bedside microcirculatory imaging have shown that different pathophysiological insults can have different effects on microcirculation perfusion patterns. For example, haemodilution during on-pump surgery reduces the density of RBC-filled capillaries. This results in a fall in oxygen extraction capacity through increasing the diffusion distances over which oxygen has to travel. Heart failure with reduced pump function on the other hand results in a decrease in capillary convective blood flow. Thus, convective failure can be caused by hypotension, arterial obstruction, or cardiogenic failure.

In critical illness, especially during sepsis with concurrent shock, microcirculatory dysfunction is further characterized by heterogeneous flow abnormalities with some obstructed capillaries sitting alongside others that exhibit normal- or even hyper-flow [8,10,14]. These heterogenous abnormalities define the nature of distributive shock seen in sepsis, within the classification scheme of circulatory shock types defined by Weil and Shubin [17]. Such heterogeneity can occur in the presence of a normal or even elevated cardiac output. It results in patchy areas of tissue hypoxia caused by shunting of vulnerable microcirculatory areas within the organs that can occur despite normal or even elevated venous saturation levels [18]. This explains, at least in part, the clinical finding of an oxygen extraction deficit in sepsis. Thus, microcirculatory observations offer valuable insights into the nature of the circulatory defect seen in different shock states and warrant incorporation into routine haemodynamic monitoring.

To describe the functional status of the microcirculation, the following parameters need to be quantified—microcirculatory flow (convective capacity, quantified for the different size of microvessels) and functional capillary density (diffusive capacity of the microcirculation) [5]. The latter is an important parameter for oxygen transport that can only be determined by imaging techniques. A measure of heterogeneous microcirculatory convective flow is also needed to identify microcirculatory alterations associated specifically with sepsis. To date, these parameters can only be determined by time-consuming off-line analyses of recorded microcirculatory movies.

Although OPS and SDF imaging have provided important insights into the microcirculation, several technical limitations hamper the integration of microcirculatory microscopy into the routine clinical monitoring environment [19]. Current OPS and SDF imaging devices can be regarded as first- and second-generation devices, respectively, employing relatively low-resolution analogue camera technology, and requiring recording and off-line analysis for image quantification. Recently, a third generation hand-held microcirculatory imaging device based on incident dark field (IDF)) imaging has been introduced called Cytocam-IDF device with a computer-controlled, high-resolution sensor, and illumination unit [20]. This new device provides the hardware requirements necessary to allow instant online analysis of microcirculatory images for bedside clinical decision-making in order to guide (microcirculatory-targeted) therapies.

Conclusion

Assessment of the microcirculation is a valuable adjunct in haemodynamic monitoring during critical illness, providing direct insights into the nature of the underlying disease and the response to therapy at the level of an essential physiological compartment. It enables a functional haemodynamic evaluation of the circulation, assessing its ability to transport oxygen to the tissues at the level of its cellular components. Its integration into conventional haemodynamic monitoring offers a more integrated evaluation of the cardiovascular system in different critical illness conditions. Recent technological advancements allow this technology to potentially advance from a research tool to a routine clinical device.

References

1. Joly HR and Weil MH. (1969). Temperature of the great toe as an indication of the severity of shock. *Circulation*, **39**, 131–8.
2. Lima A, Jansen TC, van Bommel J, Ince C, and Bakker J. (2009). The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients. *Critical Care Medicine*, **37**, 934–8.
3. Lima AP, Beelen P, and Bakker J. (2002). Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. *Critical Care Medicine*, **30**, 1210–13.
4. Groner W, Winkelman JW, Harris AG, et al. (1999). Orthogonal polarization spectral imaging: a new method for study of the microcirculation. *Nature Medicine*, **5**, 1209–12.
5. Bezemer R, Bartels SA, Bakker J, and Ince C. (2012). Clinical imaging of the sublingual microcirculation in the critically ill—where do we stand? *Critical Care*, **19**, 16, R224.
6. Mathura KR, Bouma GJ, and Ince C. (2001). Abnormal microcirculation in brain tumours during surgery. *Lancet*, **358**, 1698–9.
7. Ince C. (2005). The microcirculation is the motor of sepsis. *Critical Care*, **4**, S13–19.
8. De Backer D, Donadello K, Sakr Y, et al. (2013). Microcirculatory alterations in patients with severe sepsis: impact of time of

assessment and relationship with outcome. *Critical Care Medicine*, **41**, 791–9.
9. Top AP, Ince C, de Meij N, van Dijk M, and Tibboel D. (2011). Persistent low microcirculatory vessel density in nonsurvivors of sepsis in the pediatric intensive care. *Critical Care Medicine*, **39**, 8–13.
10. Trzeciak S, McCoy JV, Phillip Dellinger R, et al. (2008). Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. *Intensive Care Medicine*, **34**, 2210–17.
11. Boerma EC, van der Voort, PHJ, Spronk PE, and Ince C. (2007). Relationship between sublingual and intestinal microcirculatory perfusion in patients with abdominal sepsis. *Critical Care Medicine*, **35**, 1055–60.
12. Sakr Y, Chierego M, Piagnerelli M, et al. (2007). Microvascular response to red blood cell transfusion in patients with severe sepsis. *Critical Care Medicine*, **35**, 1639–44.
13. Boerma CE, and Ince C. (2010). The role of vasoactive agents in the resuscitation of microvascular perfusion and tissue oxygenation in critically ill patients. *Intensive Care Medicine*, **36**, 2004–18.
14. Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, and Zandstra DF. (2002). Nitroglycerin in septic shock after intravascular volume resuscitation. *Lancet*, **360**, 1395–6.
15. Dubin A, Pozo MO, Casabella CA, et al. (2010). Comparison of 6% hydroxyethyl starch 130/0.4 and saline solution for resuscitation of the microcirculation during the early goal-directed therapy of septic patients. *Journal of Critical Care*, **25**, 659.e1–8.
16. Pottecher J, Deruddre S, Teboul JL, et al. (2010). Both passive leg raising and intravascular volume expansion improve sublingual microcirculatory perfusion in severe sepsis and septic shock patients. *Intensive Care Medicine*, **6**, 1867–74.
17. Weil MH and Shubin H. (1971). Proposed reclassification of shock states with special reference to distributive defects. *Advances in Experimental Medicine and Biology*, **23**, 13–23.
18. Ince C and Sinaasappel M. (1999). Microcirculatory oxygenation and shunting in sepsis and shock. *Critical Care Medicine*, **27**, 1369–77.
19. Mik EG, Johannes T, and Fries M. (2009). Clinical microvascular monitoring: a bright future without a future? *Critical Care Medicine*, **37**, 2980–1.
20. Aykut G, Veenstra G, Scorcella C, Ince C, and Boerma C. (2015). Cytocam-IDF (incident dark field illumination) imaging for bedside monitoring of the microcirculation. *Intensive Care Medicine Experimental*, **3**,4.

CHAPTER 143

Imaging the cardiovascular system in the ICU

Richard Paul and Susanna Price

Key points

- Imaging must be interpreted in the clinical context of the patient.
- Interpretation is highly practitioner-dependent—'the eye only sees what it is trained to look for'.
- The risk–benefit ratio of each investigation should be evaluated on an individual patient basis.
- The specific diagnostic question should be discussed directly with the imager/interpreter.
- Despite improved CT performance, the gold standard investigation for suspected endocarditis remains transoesophageal echocardiography.

Introduction

Cardiac imaging in the critically-ill patient can be challenging. Many modalities remain poorly validated, while most imaging specialists are unfamiliar with critical care. Applying first principles and interpreting findings in the clinical context are mandatory, demanding knowledge of cardiovascular pathophysiology in critical care, the range of investigations available, their sensitivity and specificity, and the potentially complementary roles of imaging techniques.

Chest X-ray

The utility of daily portable anterior-posterior (AP) chest X-ray (CXR) in the ICU is debated. New, relevant findings are reported in up to 20% of plain films [1], but use remains widespread in cardiothoracic intensive care units (ICUs). Routine CXR should be performed following placement/removal of lines/drains to minimize exposure to ionizing radiation, and compared with previous images.

An AP-CXR helps to exclude or diagnose complications of in-dwelling catheters and may indicate some causes of haemodynamic instability. Cardiomegaly and valve-related calcification should be investigated further using echocardiography. Pericardial collections may be suggested by 'cardiomegaly' and/or apparent migration of venous lines/pacing wires in serial films. Pericardial calcification may indicate tuberculosis and/or constrictive pericarditis. The central venous catheter (CVC) tip should lie in the superior vena cava—up to 30% are incorrectly positioned and an atypical CVC path may suggest abnormal venous connections (i.e. persistent left superior vena cava), knowledge of which will influence the insertion site for a pulmonary artery catheter or pacing wire. Pulmonary vascular markings provide information regarding pulmonary blood flow distribution, but may be misleading in supine films. CXR is unhelpful in excluding pulmonary embolus, but tension haemothorax or pneumothorax is usually obvious. Lung collapse or severe atelectasis can cause haemodynamic instability in patients with poor right ventricular function or univentricular circulation, see Table 143.1.

CT pulmonary angiography

Pulmonary embolism should be suspected in patients with disproportionate hypoxaemia and pulmonary hypertension. Isotope scans are frequently non-diagnostic in the critically ill [2], therefore multislice CT pulmonary angiography is recommended, enabling visualization of emboli in subsegmental branches of the pulmonary arteries (>85% sensitivity, 90% specificity).

CT coronary angiography

Increasingly used in the outpatient population, multislice, electrocardiogram-gated systems provide an accuracy of up to 95%, and a negative predictive value approaching 100% in detection of coronary stenosis [3]. It represents a useful non-invasive tool in the low-to-intermediate risk population before progressing to invasive angiography. CT coronary angiography can evaluate coronary stent and graft patency, arterial wall morphology, coronary artery dissection [4], and can identify extra-mural/non-stenotic plaques that pass undiagnosed by conventional angiography. While modern equipment has an equal diagnostic yield for coronary artery disease in patients with either slow atrial fibrillation or sinus rhythm [5], there is less evidence for its use in faster, less stable tachyarrhythmias where motion artefact renders the images suboptimal. Little evidence supports its use in the critically ill where coronary angiography (with potential for immediate intervention) remains the investigation of choice.

CT thorax

This yields more information (Table 143.2) than CXR, but requires patient transportation, a not insignificant dose of radiation and potentially harmful contrast administration for studies of the aortic and pulmonary vasculature. It is useful in chest trauma, aortic

Table 143.1 Potential radiographic findings on CXR

Clinical context	Radiography	Notes
Elevated LAP	Increased vascular pedicle width Upper lobe blood vessel dilation Increased cardiothoracic ratio. Thickened interlobular septae Alveolar oedema	Reasonable correlation [20] Care with supine films. Specific chamber dilatation should be identified Not specific—may be due to increased permeability
Chest trauma	Widened mediastinum Pleural effusion Oesophageal/LMB displacement	Suggests aortic trauma
Pneumothorax	Hypolucency Lung edge Absence of vascular markings Deep diaphragmatic sulcus	May not be apparent in anterior pneumothoraces Challenging in presence of bullous emphysema—USS and CT more sensitive

LMB; left main bronchus, USS; ultrasound, CT; computed tomography.

dissection, suspected pulmonary embolism, and for diagnosing and guiding drainage of anterior or loculated pneumothoraces.

CT can be useful in evaluating endocarditis, demonstrating complications (coronary artery occlusion, fistulae) and peripheral embolization [6]. Electrocardiogram-gated multidetector cardiac CT is potentially superior to transoesophageal echocardiography (TEE) in demonstrating prosthetic valve malfunction due to pannus/thrombus (particularly with multiple valve replacements), and in demonstrating paraprosthetic complications and vegetations [7]. A main advantage of CT over TEE is in the diagnosis of extracardiac endocarditis, with demonstration of systemic, pulmonary, and cerebral embolization [8] and mycotic aneurysm/abscess formation (Table 143.3). However, due to its better resolution, MRI may be required for diagnosis of micro-abscesses or infarcts [9]. As CT has limitations (e.g. failure to demonstrate leaflet perforations, lack of haemodynamic information, high radiation dosage for repeated studies), routine use for diagnosing endocarditis is not recommended, and TEE remains the investigation of choice.

Invasive catheterization

The ready availability of senior and experienced operators is essential for investigating and managing critically ill cardiac patients, providing the potential for immediate diagnosis and therapy.

Table 143.2 CT thorax in the critically ill

Clinical problem	Findings and notes	
Chest trauma	Aorta	Aortic tear, intimal flap, haematoma, haemomediastinum
	Lung	Consolidation. Pneumothorax, haematoma, pneumatocoele
	Chest wall	Vertebral, rib and sternal fracture 1st rib fracture—associated with vascular injury 9th, 10th, 11th rib fractures—associated hepatic/splenic injury
	Pleura	Haemothorax, pneumothorax, chylothorax Pleural effusion/pleural fluid
	Trachea/bronchi	Pneumothorax, pneumomediastinum
	Oesophagus	Pneumothorax, pneumomediastinum Pleural effusion/pleural fluid
Pneumothorax	Particularly useful in the diagnosis of anterior and loculated pneumothoraces—CT-guided drainage may reduce complication risk	
Pulmonary embolus	Spiral contrast CT pulmonary angiography has high sensitivity and specificity, and provides information regarding other potential diagnoses	
Occult infection	Diagnosis of sternal wound and mediastinal infection, empyema, and lung abscess	
ARDS/ALI	Assessment and diagnosis of coexisting problems, e.g. pleural effusions, anterior pneumothorax, lung abscess Differentiation from underlying interstitial lung disease/other pulmonary disease	
Pleural effusions	Useful in differentiating effusion, empyema and lung abscess, and guiding percutaneous drainage	
Pre-cardiac or aortic surgery	Assessment of aortic aneurysm/dissection Planning of re-sternotomy	
Diagnosis of pulmonary disease	Pneumonia, interstitial lung disease, neoplasm	

CT, computed tomography; ARDS, acute respiratory distress syndrome; ALI, acute lung injury.

Table 143.3 Strengths and weaknesses of echocardiography and CT for evaluation of endocarditis

	TEE	CT
Vegetations and perforations	◆ Excellent spatial and temporal resolution ◆ Challenging imaging in PVE ◆ Demonstration of leaflet perforation in aortic valve endocarditis challenging	◆ May miss vegetations <4 mm ◆ Possible superior performance in demonstration of prosthetic vegetations ◆ Probable inferior performance in demonstration of leaflet perforations
Haemodynamic effects	Well-validated technique for evaluation of haemodynamics, but may be difficult to assess when very severe acute lesions present	Limited predominantly to planimetry
Abscess cavities	◆ Highly operator dependent ◆ Challenging in early endocarditis ◆ Emerging data suggests possibly CT superior	◆ Excellent visualization of abscesses, aneurysms and pseudo-aneurysms ◆ Able to image whole of thorax ◆ Combination with PET may assist in diagnosis of root abscesses
Fistulae/abnormal connections	◆ Highly operator-dependent, but well demonstrated	◆ Excellent visualization
Coronary artery involvement	◆ Delineation of proximal coronary artery segments generally possible ◆ RCA may be difficult to image in the presence of AVR ◆ Anomalous coronary arteries in the presence of an enlarged aortic root may be difficult to image ◆ Inadequate for demonstration of anything other than ostial coronary artery stenosis ◆ Myocardial infarction and/or ischaemia may be suggested by new RWMA	◆ Excellent demonstration of coronary arteries with respect to cardiac anatomy ◆ Potential avoidance of pre-operative cardiac catheterization in high-risk cases
Extracardiac 'endocarditis' and peripheral embolization	◆ Intra-cardiac and ascending aorta (including previous cannulation sites) well visualized ◆ Peripheral embolization not visualized ◆ Extracardiac shunts challenging	◆ Well documented with respect to embolization (neurological, pulmonary and systemic) and abscess formation ◆ Extra-cardiac endocarditis (including extracardiac shunts) well visualized, but need additional imaging techniques to demonstrate infection

AVR, aortic valve replacement; PET, positron emission tomography; PVE, prosthetic valve endocarditis; RCA, right coronary artery; RWMA, regional wall motion abnormality; TEE, transoesophageal echocardiography; CT, computed tomography.

Left heart catheterization

Indications for coronary angiography in the critically ill are shown in Table 143.4. In patients where cardiac surgery has involved re-implantation/manipulation of the coronary arteries, instability should trigger a high index of suspicion of disruption to coronary flow. Prompt liaison with, and early re-exploration by, the surgical team is mandated, particularly if catheterization might lead to delayed intervention.

Right heart catheterization (RHC)

Formal RHC remains the gold standard for haemodynamic assessment of pulmonary hypertension, being required for diagnosis, classification, prognostication and vasoreactivity testing [10]. Further uses include differentiation of pericardial tamponade from constrictive pericarditis, diagnosis of intracardiac shunt [11], and evaluation of bronchial and pulmonary haemorrhage, and chronic thromboembolic disease [12].

Ultrasound

Ultrasound is widely used in the diagnosis, monitoring, and management of critically-ill patients. Its real-time diagnostic capabilities, together with the progressive miniaturization of devices, and increasing ease of use, has led to a rapid expansion of its applications outside cardiology [13]. Ultrasound is used for insertion of central, peripheral venous, and arterial cannulae, particularly where anatomy is abnormal or with multiple previous interventions, marked obesity, or oedema.

Echocardiography

Echocardiography has many roles in the ICU, ranging from use during cardiac arrest to more complex diagnostic applications. The first mode of choice is generally TTE, although this may be limited by patient issues (e.g. immobility, body habitus, pulmonary pathology), pathology (e.g. prosthetic valve endocarditis), or interventions (e.g. IPPV, dressings/drains), where TEE may be required. Intracardiac echocardiography provides high-resolution images, although its cost is prohibitive for routine ICU use.

Peri-arrest echocardiography

Ultrasound/echocardiography by appropriately-trained practitioners is recommended in current resuscitation guidelines as a supplement to advanced life support to determine the underlying diagnosis leading to the (peri-)arrest state, e.g. pericardial

Table 143.4 Indications for coronary angiography in the critically ill

Clinical features	Potential diagnosis	Potential causes	Other investigations
◆ Haemodynamic instability	◆ Myocardial ischaemia ◆ Myocardial infarction (types I–IV)	◆ Coronary obstruction ◆ Graft malfunction ◆ Coronary spasm	ECG Echocardiography Elevated biomarkers
◆ Ventricular arrhythmias	◆ Myocardial ischaemia ◆ Myocardial infarction (types I–IV)	◆ Coronary obstruction ◆ Coronary stenosis ◆ Graft malfunction ◆ Coronary spasm	ECG Echocardiography Elevated biomarkers
◆ Failure to wean from ventilator	Myocardial ischaemia	◆ Coronary obstruction ◆ Coronary stenosis ◆ Graft malfunction	Stress echo CXR
◆ Failure to wean from ventilator ◆ Haemodynamic instability	Dynamic MR	◆ Ischaemic heart disease ◆ Ventricular dilatation	Stress echo CXR RHC
◆ Clinical history ◆ Unequal pulses ◆ Haemodynamic instability	Aortic disruption	◆ Dissection ◆ Trauma	Echo CXR CT/CMR Aortography Coronary angiography

ECG, electrocardiogram; CXR, chest radiograph; MR, mitral regurgitation; RHC, right heart catheterization; CT, computed tomography; CMR, cardiac magnetic resonance.

tamponade, acute pulmonary embolism, hypovolaemia, right and/or left ventricular failure, and severe valvular pathology [14].

Echocardiography as a monitoring device

Echocardiography is widely used in the ICU for a non-invasive assessment of right and left heart filling status, to measure cardiac output and pulmonary arterial pressures [15], and to assess the response to therapeutic interventions, including the adjustment of ventilator settings to minimize the impact of IPPV on right ventricular performance. Although not ideal as a monitor (requiring multiple, repeated studies), useful haemodynamic information may be obtained rapidly and reliably, in addition to suggesting the underlying cause of the haemodynamic insufficiency [16].

Echocardiography as a diagnostic tool

Echocardiography may assist in the diagnosis and management of pathology commonly seen in the cardiothoracic ICU (see Table 143.5).

Lung ultrasound

Lung ultrasound in the ICU is frequently limited to detecting and drainage of pleural collections. Other potential applications include diagnosis and delineation of pneumothorax (particularly anteriorly in the supine position), lung abscess, interstitial fluid, and alveolar consolidation [13]. In some ICUs, the use of ultrasound has largely replaced routine CXR.

Other imaging modalities

Cardiac magnetic resonance scanning

The image quality of cardiac magnetic resonance scanning (CMR) makes it an attractive imaging modality, but there are particular considerations for ICU patients. All equipment must be MR-compatible, the transfer intensivist appropriately trained, piped oxygen should be used and intravenous infusion devices remain in the 'safe zone' beyond the 50 Gauss line, connected to the patient with long lines passed through a waveguide.

Positron emission (computed) tomography

Myocardial perfusion scintigraphy, using either single photon emission computed tomography (SPECT) or positron emission computed tomography (PET), is well established as a functional cardiac imaging technique in ischaemic heart disease [17]. SPECT is widely available, using multiplanar perfusion imaging of photon-emitting radionucleotides. Images are software-reconstructed and give an accurate assessment of myocardial perfusion and ventricular function. PET detects γ-rays from an injected radioactive tracer, the most useful cardiac tracers being ^{82}rubidium and the newer fluorine-18 fluorodeoxyglucose (^{18}F-FDG)—a glucose analogue and therefore highly suitable for the assessment of myocardial viability. PET has superior resolution and lower radiation usage, and carries high sensitivity and specificity for detecting coronary artery disease [18]; both methods can be used in the critically ill to determine ventricular wall motion and function, and the extent of ischaemia and infarction. Use is generally confined to circumstances where the diagnosis cannot be made using bedside imaging (e.g. echocardiography), or imaging that allows for potential intervention (e.g. angiography), or where it can be used as an adjunct to echocardiography in the diagnosis of endocarditis. Here, scintigraphy may be useful where cases are complicated by extracardiac infection (aortic cannulation sites, previous shunts in congenital heart disease), and where uncertainty persists over whether a lesion seen on echocardiography remains actively infected.

Table 143.5 Echocardiographic findings in the ICU

Clinical finding	Cardiac cause	Echocardiographic finding	Notes
1. Low cardiac output (unresponsive to inotropes)	Valvular disease	Any severe stenotic or regurgitant lesion	Difficult to assess in ICU. Sequential stenotic lesions may mask severity of individual lesions
	Intrinsic cardiac disease	HOCM/LVH with LVOTO Large VSD/ASD Severe LV/RV dysfunction	See text
	Extrinsic cardiac disease	Tamponade Pericardial effusion Pericardial disease	NB: Post-operative cardiac surgical patients (see text)
2. Oliguria	Underfilling	Low transmitral/tricuspid velocities Small ventricular volumes Apposition of LV papillary muscles in systole	If severe LVH papillary apposition may be unreliable sign
	Intrinsic cardiac disease	Poor LV function Severe AS	High LA pressure demonstrated
	Pericardial disease	Pericardial effusion Pericardial tamponade Pericardial constriction	NB. Post-operative cardiac surgical patients (see text)
3. Increased filling pressures (left-sided)	Impaired LV	Increased E > A ratio (corrected for age) Short IVRT	
	Mitral valve disease	Significant MS or MR	**MR: dynamic ventricle, increased forward velocities (>1 m/sec) Short duration and low velocity (<3 m/sec) regurgitant jet
4. Increased filling pressures (right-sided)	Secondary to left-sided disease	Significant AS, AR, MS, MR or LV disease	
	Impaired RV	Reduced RV LAX function	Any reduction in association with PHT is significant Mild impairment after CABG is normal
	Tricuspid regurgitation	Annular dilatation or endocarditis	If severe, RV dynamic with increased forward velocities (>1 m/sec) Short duration and low velocity regurgitant jet
5. Sepsis/SIRS	LV/RV dysfunction	Ventricular dilatation Systolic/diastolic dysfunction	Changes controversial and may be masked by inotropes
	Source of sepsis	Endocarditis	
6. Endocarditis	Native/prosthetic valve Pacemaker wires Extracardiac 'endocarditis'	Vegetations Paraprosthetic leaks Aortic root abscess	Vegetations rare in prosthetic valve endocarditis
7. Pulmonary hypertension	Acute PE	Dilated RV, severe TR	May rarely demonstrate intracardiac thrombus
	Post-pneumonectomy	Displaced heart Increased pulmonary acceleration time	Views often difficult even with TEE
	Mitral valve disease	Significant MS or MR (2D, PW, CW, and colour Doppler)	Severe MR in ICU may be difficult to diagnose (see text and **)
8. Failure to wean from ventilator	Intrinsic cardiac disease	Ischaemia Severe MR HOCM LV/RV dysfunction	Stress echo may be necessary to make diagnosis

9. CVA/embolic event	Intracardiac thrombus	LA appendage RA Apical LV thrombus Endocarditis	Exclude intracardiac shunt with contrast study
10. Cyanosis	Intracardiac shunting	Positive contrast study	Use agitated blood/saline. Perform Valsalva manoeuvre

HOCM, hypertrophic obstructive cardiomyopathy; LVH, left ventricular hypertrophy; VSD, ventricular septal defect; ASD, atrial septal defect; LV, left ventricle; RV, right ventricle; IVRT, isovolaemic relaxation time; MS, mitral stenosis; MR, mitral regurgitation; AS, aortic stenosis; AR, aortic regurgitation; LAX, long axis; PHT, pulmonary hypertension; CABG, coronary artery bypass grafting; SIRS, systemic inflammatory response syndrome; PE, pulmonary embolism; TR, tricuspid regurgitation TEE, transoesophageal echocardiography; PW, pulsed wave; CW, continuous wave; CVA, cerebrovascular accident; LA, left atrium.

Integration of PET with CT enables highly accurate coronary angiography and myocardial perfusion imaging in a single investigation. Dual-energy CT (DECT) also shows promising similar results when compared to SPECT [19], allowing faster acquisition of superior images, more suited to imaging of critically-ill patients in remote locations.

Conclusion

Undertaking cardiac imaging in the critically ill demands balancing the potential diagnostic benefit versus the risk of harm from invasive/remotely conducted investigations. Basic investigations remain valuable in intensive care, even if many are not validated in this population. Despite the risk of harm from the investigations themselves, the greatest risk to the patient remains misinterpretation; expert opinion should always be sought.

References

1. Graat ME, Stoker J, Vroom MB, and Schultz MJ. (2005). Can we abandon daily routine chest radiography in intensive care patients? *Journal of Intensive Care Medicine*, **20**, 238–46.
2. British Thoracic Society, Standards of Care Committee. (1997). Suspected acute pulmonary embolism: a practical approach. British Thoracic Society, Standards of Care Committee. *Thorax*, **52**(Suppl. 4), S1–24.
3. de Graaf FR, Schuijf JD, van Velzen JE, et al. (2010). Diagnostic accuracy of 320-row multidetector computed tomography coronary angiography in the non-invasive evaluation of significant coronary artery disease. *European Heart Journal*, **31**, 1908–15.
4. Kantarcı M, Doganay S, Karçaaltıncaba M, et al. (2012). Clinical situations in which coronary CT angiography confers superior diagnostic information compared with coronary angiography. *Diagnostic and Interventional Radiology*, **18**, 261–9.
5. Pasricha SS, Nandurkar D, Seneviratne SK, et al. (2009). Image quality of coronary 320-MDCT in patients with atrial fibrillation: initial experience. *American Journal of Roentgenology*, **193**, 1514–21.
6. Konen E, Goitein O, Feinberg MS, et al. (2008). The role of ECG-gated MDCT in the evaluation of aortic and mitral mechanical valves: initial experience. *American Journal of Roentgenology*, **191**, 26–31.
7. Feuchtner GM, Stolzmann P, Dichtl W, et al. (2009). Multislice computed tomography in infective endocarditis: comparison with transesophageal echocardiography and intraoperative findings. *Journal of the American College of Cardiology*, **53**, 436–44.
8. Jones HR and Siekert RG. (1989). Neurological manifestations of infective endocarditis. Review of clinical and therapeutic challenges. *Brain*, **112**, 1295–315.
9. Bertorini TE, Laster RE, Thompson BF, and Gelfand M. (1989). Magnetic resonance imaging of the brain in bacterial endocarditis. *Archives of Internal Medicine*, **149**, 815–17.
10. Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC), European Respiratory Society (ERS), International Society of Heart and Lung Transplantation (ISHLT), et al. (2009). Guidelines for the diagnosis and treatment of pulmonary hypertension. *European Respiratory Journal*, **34**, 1219–63.
11. Bangalore S and Bhatt DL. (2011). Images in cardiovascular medicine. Right heart catheterization, coronary angiography, and percutaneous coronary intervention. *Circulation*, **124**, e428–33.
12. Hoeper MM, Lee SH, Voswinckel R, et al. (2006). Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. *Journal of the American College of Cardiology*, **48**, 2546–52.
13. Lichtenstein D. (2007). *General Ultrasound in the Critically Ill*, 2nd edn. Berlin: Springer.
14. Breitkreutz R, Price S, Steiger HV, et al. (2010). Focused echocardiographic evaluation in life support and peri-resuscitation of emergency patients: a prospective trial. *Resuscitation*, **81**, 1527–33.
15. Charron C, Caille V, Jardin F, and Vieillard-Baron A. (2006). Echocardiographic measurement of fluid responsiveness. *Current Opinions in Critical Care*, **12**, 249–54.
16. Cholley BP and Payen D. (2005). Noninvasive techniques for measurements of cardiac output. *Current Opinions in Critical Care*, **11**, 424–9.
17. Notghi A and Low CS. (2011). Myocardial perfusion scintigraphy: past, present and future. *British Journal of Radiology*, **84**, S229–36.
18. Nandalur KR, Dwamena BA, Choudhri AF, Nandalur SR, Reddy P, and Carlos RC. (2008). Diagnostic performance of positron emission tomography in the detection of coronary artery disease: a meta-analysis. *Academic Radiology*, **15**, 444–51.
19. Ruzsics B, Schwarz F, Schoepf UJ, et al. (2009). Comparison of dual-energy computed tomography of the heart with single photon emission computed tomography for assessment of coronary artery stenosis and of the myocardial blood supply. *American Journal of Cardiology*, **104**, 318–26.
20. Miller RR and Ely EW. (2006). Radiographic measures of intravascular volume status: the role of vascular pedicle width. *Current Opinions in Critical Care*, **12**, 255–62.

PART 5.3

Acute chest pain and coronary syndromes

CHAPTER 144

Causes and diagnosis of chest pain

Caroline Patterson and Derek Bell

Key points

- Differentiating life-threatening from benign causes of chest pain is a challenge, especially in the critical care setting, when symptoms and signs overlap, and patients may be unable to communicate fully.
- Achieving a prompt diagnosis is important in critically unwell patients, who typically have reduced cardiorespiratory reserve. A high index of suspicion is required for occult disease.
- After ensuring haemodynamic stability, it is imperative to rule out myocardial infarction in the first instance. Other life-threatening causes of chest pain to consider include aortic dissection, critical aortic stenosis, pulmonary embolism, tension pneumothorax, and oesophageal rupture. More benign causes include pleurisy, pericarditis, myocarditis, and rib fractures.
- ECG, chest X-ray, and routine observations are often non-diagnostic. Targeted investigations such as computed tomography, transthoracic or transoesophageal echocardiography may be indicated.
- Timely intervention optimizes survival benefit. Treatment may be commenced prior to confirmation of diagnosis, based on high clinical suspicion and risk scoring (e.g. GRACE score for myocardial ischaemia, Wells score for PE).

Introduction

Over 50% of patients questioned after admission to intensive care recall having significant pain [1–3], which is commonly localized to the thorax [1]. Chest pain in the critical care setting, more so than in the emergency department or acute assessment unit, is often an indicator of complex or life-threatening pathology, necessitating immediate assessment and management (see Table 144.1). Diagnosis is limited by difficulties patients have in communicating the severity or location of their pain [2]. The advantage of the critical care setting is that patients are intensively monitored within a resource-rich environment to aid timely investigation with prompt targeted interventions.

Initial assessment

The approach to the patient with chest pain or suspected chest pain should follow the standard airway, breathing, circulation algorithm. Immediate standard clinical observations plus a resting 12-lead electrocardiogram (ECG) and chest X-ray (CXR) are essential, supported by rapid examination, and a targeted or collateral history. Conditions such as ventricular arrhythmia and tension pneumothorax, which require immediate intervention, should be excluded.

The clinician should identify whether the chest pain is of new onset or a chronic problem and, if so, when the last episode occurred. History-taking should define the nature of the pain, the presence of any cardiovascular risk factors, prior investigations for chest pain, and prior coronary artery intervention. Pain can be defined by the 'PQRST' mnemonic (position, quality, radiation, severity, and timing, where timing includes the rate of onset, duration, and frequency of chest pain episodes). Exacerbating/relieving factors and additional symptoms should also be identified.

In mechanically-ventilated patients, head nodding and movements of the upper limbs are the most frequent means of patient communication and the clinician should be vigilant for these non-verbal cues [1]. Patients may be able to blink or point in response to a pain scale.

Physical examination should include inspection of the chest, looking for asymmetric expansion or chest wall deformity. Chest wall palpation should identify tenderness and crepitus. The clinician should assess pulse character, radio-radial delay and blood pressure in both arms. Auscultation should include the symmetry and quality of breath sounds, and listening for muffled heart sounds, murmurs, rubs, or gallops. A full clinical examination should be performed as soon as practically possible, but should not delay immediate treatment. Abdominal examination may reveal bruits or palpable aortic aneurysm. Lower limbs should be examined for asymmetry and tenderness suggestive of deep vein thrombosis (DVT).

Investigations

As always, investigation should be guided by history and examination. A CXR is mandatory, unless the patient is scheduled for imminent computed tomography (CT). CXR is useful to exclude complications of acute coronary syndrome (e.g. pulmonary oedema) and to identify alternative diagnoses (e.g. pneumothorax, pneumonia). CT imaging of the thorax, including CT angiography, supports the exclusion of non-cardiac diagnoses (e.g. aortic dissection, pulmonary embolism) and allows visualisation of the coronary anatomy. Transthoracic echocardiography is useful to identify significant valvular and myocardial pathology, pulmonary hypertension and to diagnose/exclude pericardial effusion.

Table 144.1 Causes of acute chest pain

Immediately life threatening	Other serious pathology
Acute coronary syndrome	Pneumonia/pleurisy
Aortic dissection	Pericarditis
Critical aortic stenosis	Oesophageal pathology
Pulmonary embolism	Sickle cell crisis
Pneumothorax	Neuralgia (herpes zoster)
Oesophageal rupture	Musculoskeletal pathology (fractured ribs)
Perforated viscus	

Transoesophageal echocardiography offers superior imaging of the aorta. Targeted biomarkers, such as cardiac troponin, D-dimer, and N-terminal pro-B type natriuretic peptide (NT-BNP) are useful adjuncts for diagnosis and risk stratification.

Life-threatening conditions

Acute coronary syndrome

Routine critical care unit surveillance has a sensitivity of only 12% for the detection of myocardial ischaemia [4]. In critical care patients with chest pain it is mandatory to rule out myocardial infarction in the first instance. Risk assessment should consider family history, hypertension, hyperlipidaemia, diabetes mellitus, and prior smoking history. GRACE and TIMI scores provide prognostic information.

Typical symptoms of myocardial ischaemia are retrosternal chest pain (and/or arm, back, or jaw pain) lasting several minutes, nausea, vomiting, sweating, or breathlessness. There may also be haemodynamic instability. Rarely, myocardial ischaemia mimics gastrointestinal disease with epigastric discomfort and belching. Atypical presentations are more common in women, ethnic minorities, and those of advancing age.

A 12-lead ECG is essential for diagnosis. Acute chest pain associated with ST-elevation lasting ≥20 minutes is associated with total coronary artery occlusion. Hence, persistent ST-elevation requires immediate treatment with the therapeutic objective of achieving rapid, complete, and sustained myocardial reperfusion by primary angioplasty or fibrinolytic therapy [5].

Patients without ST-elevation may have persistent or transient ST-segment depression or T-wave inversion, flattened T waves, or no ECG changes at all. The aim in these patients is to alleviate ischaemia and symptoms, while monitoring the patient with serial ECGs and markers of myocardial necrosis [5]. In patients where the changes appear dynamic, an urgent cardiology opinion should be sought.

Cardiac troponins are useful in differentiating between unstable angina and non-ST-elevation myocardial infarction, and in stratifying risk. An initial troponin rise occurs within 4 hours of myocardial ischaemia and the diagnostic cut-off for myocardial infarction is a troponin value exceeding the 99th percentile of a normal reference population. This can vary between laboratories and assays, therefore it is essential for the clinician to know their local normal range.

Aspirin should be given to all patients unless contraindicated. If the GRACE score suggests a 6-month mortality >1.5%, clopidogrel should also be given. Fondaparinux is recommended unless there is a high bleeding risk or angiography is planned within 24 hours. If angiography is likely or there is significant renal impairment, unfractionated heparin is preferred [6]. Critically unwell patients are at increased risk of bleeding. Nitrates, β-blockers, angiotensin-converting enzyme inhibitors and statins may be initiated in discussion with local cardiologists.

Thoracic aortic dissection

Aortic dissection should be considered in all patients with a history suggestive of myocardial infarction. The ECG may be normal, but, in some cases, dissection of the aortic root can cause right coronary occlusion with associated ECG changes. A higher degree of suspicion is necessary if there are risk factors for dissection, such as hypertension, prior cardiac surgery (e.g. aortic valve replacement) or aortic manipulation (e.g. angiography, stenting).

The pain of aortic dissection typically has an abrupt onset and with maximal severity at onset. The location of the pain can suggest the location of the dissection. In the Stanford classification, type A dissections involve the ascending aorta, whereas type B dissections do not. Anterior chest pain is often the result of aortic root or anterior arch involvement. Inter-scapular pain suggests involvement of the descending aorta and pain in this region is often described as tearing in nature. Around 10% of patients with dissection experience no pain. Presentation may be with dyspnoea and/or orthopnoea if there is cardiac failure secondary to aortic regurgitation or cardiac tamponade.

Clinical signs include the diastolic murmur of aortic regurgitation, and a pulse deficit/blood pressure differential between both arms. Horner's syndrome, syncope, and neurological compromise, mimicking cerebrovascular accident, are also recognized.

As described, ECG changes are usually non-specific, but may mimic inferior myocardial infarction. A negative D-dimer makes aortic dissection unlikely [7], while elevated D-dimer levels support dissection as a possible diagnosis. Around 80% of patients with acute dissection demonstrate widening of the aortic silhouette on CXR, but a normal film does not exclude the diagnosis [8]. CT aortography, transoesophageal echocardiography, and magnetic resonance imaging are all highly accurate in the diagnosis of aortic dissection.

Immediate management should focus on blood pressure reduction. Intravenous β-blockers are considered first-line therapy. Multiple blood pressure agents are commonly required. Emergency surgery is recommended for acute type A dissection, but all patients should undergo multidisciplinary evaluation involving cardiothoracic/vascular surgical specialists [9].

Pulmonary embolism

Critical care patients frequently have ≥1 predisposing factors for thromboembolism (e.g. surgical intervention, immobility, sedation, and paralysis). Despite the high frequency of deep vein thrombosis in these patients, concerns remain that pulmonary embolism (PE) is underdiagnosed [10].

In non-ventilated patients, around 90% of patients with PE report dyspnoea, chest pain, and syncope, either singly or in combination [11]. Chest pain is typically pleuritic in nature and occurs as a result of pleural irritation due to distal pulmonary infarction, mild pleural

effusion, and alveolar haemorrhage, which may be associated with haemoptysis. In massive PE, the pain may be central in nature, and associated with syncope or recurrent syncope.

The most common signs are tachypnoea, tachycardia, suspected deep vein thrombosis (more difficult to detect in critical care patients due to peripheral oedema), fever, and cyanosis [11]. In ventilated patients, PE may present as a sudden episode of hypotension, tachycardia, or desaturation, or contribute to difficulties in ventilator weaning [12].

The CXR is insensitive for the detection of pulmonary embolism. ECG demonstrates variable ST-segment changes, T wave inversion or right heart strain. Widening of the alveolar–arterial gradient is non-specific in critical care patients and there may be metabolic acidosis secondary to circulatory compromise. A normal D-dimer level has a strong negative predictive value, but a positive result is not diagnostic. The diagnosis should be confirmed, preferably by CT pulmonary angiography, as this is the most reliable test. However, echocardiography may be suggestive or show clot in the pulmonary artery, and ventilation–perfusion scanning may be useful in selected cases.

Patients with an intermediate to high probability of PE on Wells Score should be treated with heparin, even before the diagnosis is confirmed. Low molecular weight heparin is preferred to unfractionated heparin unless there is haemodynamic compromise or rapid reversal may be required. Thrombolysis is indicated if the patient is shocked or has a large clot burden with limited cardio-respiratory reserve. Placement of caval filters should be considered in critical care patients with significant lower limb venous thrombosis, especially if anticoagulation is contraindicated.

Pneumothorax

Barotrauma and invasive procedures (e.g. central venous catheter insertion, thoracocentesis) contribute to pneumothorax in around 3% of patients admitted to the intensive care setting[13]. Iatrogenic pneumothorax is more common in patients with adult immunodeficiency syndrome, acute respiratory distress syndrome, and cardiogenic pulmonary oedema. Prompt diagnosis helps reduce the risk of a simple pneumothorax becoming a tension pneumothorax. Risk assessment should include history of previous pneumothorax, underlying lung disease, and history of smoking.

Symptoms are typically of acute onset chest pain and dyspnoea. Pain is pleuritic in nature and often radiates to the ipsilateral shoulder tip. Secondary pneumothorax (i.e. in the presence of known risk factors) is generally less well tolerated due to reduced respiratory reserve.

Signs are reduced breath sounds on the affected side, hyper-resonant percussion note and pulsus paradoxus. In the ventilated patient there may be a sudden increase in airway pressures. In the event of tension pneumothorax there may be contralateral tracheal deviation, jugular venous distension, and sudden haemodynamic instability with tachycardia and hypotension.

CXR is the most common screening test for pneumothorax; however, bedside thoracic ultrasound is more sensitive than supine CXR (often used in critical care) [14]. A CT scan is the gold standard investigation and also differentiates pneumothorax from complex bullous lung disease.

If there is a suspicion of tension pneumothorax, diagnostic investigation should not delay treatment. Immediate needle decompression is indicated, followed by insertion of an intercostal drain. A simple pneumothorax causing symptoms or decreased gas exchange in a patient on positive pressure ventilation (invasive or non–invasive) requires intercostal drainage. In a non-ventilated patient, needle aspiration may suffice but should be followed by close patient monitoring and consideration of drainage [15].

Aortic stenosis

Angina, syncope, and dyspnoea occur with progressive aortic stenosis. Symptoms typically occur once the aortic valve area is <1.0 cm^2. Exertional chest pain is present in around two-thirds of patients with severe aortic stenosis, of whom half also have significant coronary artery disease. Pain occurs very rarely at rest. Risk factors for degenerative calcific aortic stenosis are similar to those for vascular atherosclerosis. Urgent echocardiography is the investigation of choice in the unwell patient with suspected aortic stenosis.

Clinical signs include a slow rising, low-volume pulse and a narrow pulse pressure. A low-volume carotid pulse and a soft S2 sound are considered the best clinical indicators. The typical crescendo–decrescendo systolic murmur of aortic stenosis is best heard in the aortic area, and may radiate to the carotids. As the left ventricle fails, flow through the stenotic valve is reduced and the murmur quietens. Pulsus alternans occurs most commonly in patients with severe left ventricular systolic dysfunction.

ECG evidence of left ventricular hypertrophy is present in 85% of individuals with severe aortic stenosis [16]. T-wave inversion and ST-segment depression become more common as hypertrophy progresses and there is a risk of pulseless electrical activity with cardiac arrest. CXR is usually unremarkable until left ventricular failure develops and then cardiac silhouette is increased in diameter. Echocardiography assesses the degree and impact of aortic stenosis by characterizing the anatomy of the aortic valve, grading the severity of stenosis severity and assessing left ventricular function.

In critically-ill patients, the definitive management is aortic valve surgery, providing the patient is fit for surgery. Peri-operative work-up should include coronary angiography. β-blockers, digoxin, diuretics, and angiotensin-converting enzyme inhibitors can help relieve chest pain and dyspnoea related to pulmonary congestion but these medications should be prescribed with caution.

Oesophageal rupture (Boerhaave's syndrome)

Although the classic features of oesophageal rupture are chest pain and cervical subcutaneous emphysema following an episode of vomiting (the Mackler triad), spontaneous rupture accounts for less than a third of cases. Most oesophageal rupture is iatrogenic, occurring after medical instrumentation (e.g. upper GI endoscopy, particularly dilation of the oesophagus). Oesophageal perforation from external blunt trauma is exceedingly rare, but well recognized in patients involved in high speed road traffic accidents.

Most patients present with pain (71%), fever (51%), dyspnoea (24%), and palpable crepitus (22%) [17]. Pain is localized to the neck, chest, epigastrium, or back, and may be referred to the shoulder tips. Gastrointestinal symptoms occur less commonly and include dysphagia, vomiting, haematemesis, melaena, and abdominal rigidity, particularly with distal perforation. Facial swelling, hoarseness, and dysphonia are recognized with perforation of the cervical oesophagus. Hamman's sign is a crunching sound, audible synchronous with the heartbeat, associated with pneumomediastinum.

CXR suggests the diagnosis in up to 90% of cases [18] with indirect markers of rupture including effusion (typically left-sided), hydropneumothorax, pneumothorax, pneumomediastinum and subcutaneous emphysema. Diagnosis is confirmed by water-soluble contrast studies (e.g. gastrografin swallow). Diagnostic pleural fluid findings are food debris, pH <6.0, or an elevated amylase level.

Prompt intervention is required to avoid mediastinitis, which is associated with a high mortality. Initial management is volume resuscitation, broad spectrum antibiotics, and analgesia. Patients should be kept nil by mouth and have a nasogastric tube inserted. Surgery is the treatment of choice and should be considered by the multidisciplinary team [19].

A perforated peptic ulcer, or other abdominal viscus, may also present with acute chest pain. The diagnosis may be identified by finding sub-diaphragmatic air on an erect CXR, but a CT scan of the abdomen may be necessary, particularly in ventilated patients.

Potentially serious pathologies causing chest pain

Although the origin of chest pain is not always immediately life-threatening, chest pain may reflect underlying serious illness, or illness that may lead to significant complications. Anxiety and somatisation disorders may also present as chest pain mimicking more serious conditions.

Pulmonary causes of chest pain

Pleuritic chest pain typically has a stabbing quality and worsens with inspiration. The most common cause in critical care patients is pneumonia, with chest pain occurring in around a third of cases. Pleuritic pain may also occur with tuberculosis, autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis), malignancy (e.g. mesothelioma), pulmonary embolism and chest trauma (e.g. post-operative). Airway diseases such as asthma and COPD may present with chest pain related to airway inflammation and bronchospasm.

Cardiovascular causes of chest pain

The pain of acute pericarditis occurs over the anterior chest, has a sudden onset, and is exacerbated by lying flat. Diagnosis is supported by signs of pericardial friction rub, pericardial effusion and widespread ST-elevation on ECG. In critically-unwell patients, the presence of pericarditis should prompt consideration of systemic inflammatory disease or uraemic complications in the presence of severe kidney injury. Myocarditis may coincide with pericarditis and presents across a spectrum of disease, from mild viral illness to acute cardiac failure. An elevated troponin suggests the presence of myocarditis.

Gastrointestinal causes of chest pain

Owing to the shared innervation of the heart and oesophagus, visceral pain from these organs can be similar in character. Oesophageal conditions causing chest pain include oesophagitis, gastro-oesophageal reflux, and dysmotility disorders (e.g. achalasia).

Sickle cell disease

Chest pain is common in sickle cell disease and may result from pneumonia, pulmonary infarction, myocardial ischemia, bone infarction, or a diffuse pain crisis. Acute chest syndrome is a vaso-occlusive crisis of the pulmonary vasculature, often precipitated by respiratory infection. Clinicians should be alert to the risk of hypoxaemia and the occasional need for endotracheal intubation and mechanical ventilation.

Neuralgia

In immunosuppressed or older patients the pain of herpes zoster may precede the rash. Post-herpetic and post-radiation neuralgia may also cause chest pain.

Musculoskeletal chest pain

Onset is often insidious and pain may last for hours to weeks. It is frequently sharp and well localized. Pain may be reproducible on palpation, positional, or movement-related. In critically unwell patients, particularly those with a history of trauma or falls, it is important to exclude rib fractures, which may lead to pneumothorax in some cases.

Conclusion

Chest pain should be treated seriously in all critically-unwell patients, especially when a history is not readily available. Causes of chest pain should be considered in the differential diagnosis, and investigated as indicated by clinical findings and available test results.

References

1. Gelinas C. (2007). Management of pain in cardiac surgery ICU patients: have we improved over time? *Intensive Critical Care Nursing*, **23**, 298–303.
2. Puntillo KA. (1990). Pain experiences of intensive care unit patients. *Heart Lung*, **19**, 526–33.
3. van de Leur JP, van der Schans CP, Loef BG, Deelman BG, Geertzen JH, and Zwaveling JH. (2004). Discomfort and factual recollection in intensive care unit patients. *Critical Care*, **8**, R467–73.
4. Martinez EA, Kim LJ, Faraday N, et al. (2003). Sensitivity of routine intensive care unit surveillance for detecting myocardial ischemia. *Critical Care Medicine*, **31**, 2302–8.
5. Hamm CW, Bassand JP, Agewall S, et al. (2011). ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*, **32**, 2999–3054.
6. NICE. (2010) Unstable angina and NSTEMI: The early management of unstable angina and non-ST-segment-elevation myocardial infarction, Clinical guideline 94. London: NICE. Available at: https://www.nice.org.uk/guidance/cg94 (accessed 14 April 2015).
7. Shimony A, Filion KB, Mottillo S, Dourian T, and Eisenberg MJ. (2011). Meta-analysis of usefulness of D-dimer to diagnose acute aortic dissection. *American Journal of Cardiology*, **107**, 1227–34.
8. Hagan PG, Nienaber CA, Isselbacher EM, et al. (2000). The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *Journal of the American Medical Association*, **283**, 897–903.
9. Braverman AC. (2010). Acute aortic dissection: clinician update. *Circulation*, **122**, 184–8.
10. Moser KM, Fedullo PF, LitteJohn JK, and Crawford R. (1994). Frequent asymptomatic pulmonary embolism in patients with deep venous thrombosis. *Journal of the American Medical Association*, **271**, 223–5.
11. Konstantinides SV, Torbicki A, Agnelli G, et al. (2014). ESC guidelines on the diagnosis and management of acute pulmonary embolism. *European Heart Journal*, **35**(43), 3033–69

12. Cook D, Meade M, Guyatt G, et al. (2004). Clinically important deep vein thrombosis in the intensive care unit: a survey of intensivists. *Critical Care*, **8**, R145–52.
13. de Lassence A, Timsit JF, Tafflet M, et al. (2006). Pneumothorax in the intensive care unit: incidence, risk factors, and outcome. *Anesthesiology*, **104**, 5–13.
14. Wilkerson RG and Stone MB. (2010). Sensitivity of bedside ultrasound and supine anteroposterior chest radiographs for the identification of pneumothorax after blunt trauma. *Academic Emergency Medicine*, **17**, 11–17.
15. MacDuff A, Arnold A, and Harvey J. (2010). Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. *Thorax*, **65**(Suppl. 2), **ii**, 18–31.
16. Maganti K, Rigolin VH, Sarano ME, and Bonow RO. (2010). Valvular heart disease: diagnosis and management. *Mayo Clinical Proceedings*, **85**, 483–500.
17. Nesbitt JC and Sawyers JL. (1987). Surgical management of esophageal perforation. *American Surgery*, **53**, 183–91.
18. Han SY, McElvein RB, Aldrete JS, and Tishler JM. (1985). Perforation of the esophagus: correlation of site and cause with plain film findings. *American Journal of Research*, **145**, 537–40.
19. Wu JT, Mattox KL, and Wall MJ, Jr. (2007). Esophageal perforations: new perspectives and treatment paradigms. *Journal of Trauma*, **63**, 1173–84.

CHAPTER 145

Pathophysiology of coronary syndromes

Robert M. Bell

Key points

- A disease characterized by endothelial dysfunction and inflammation.
- It is a chronic disease process, with atheroma commencing at an early age, but with acute coronary syndrome (ACS) presenting in later life.
- Disease in vessels is dictated by haemodynamic flow characteristics within the coronary vessel.
- Non-thrombotic ACS is characterized by increased demand and thrombotic ACS by acute limitation of blood flow.
- Common risk factors, including hypercholesterolemia, hypertension, diabetes, and smoking, all impact upon endothelial function and nitric oxide bioavailability.

Introduction

Acute coronary syndromes (ACS), unstable angina, non-ST elevation myocardial infarction and ST-elevation myocardial infarction (MI) are characterized by an acute insufficiency of the coronary circulation. Downstream myocardium is rendered ischaemic and will undergo necrotic injury unless blood flow is speedily restored. The primary aetiology is coronary artery disease (CAD) in the form of coronary atherosclerosis. While there are other, much rarer causes of ACS (Box 145.1), for the purposes of this chapter, the pathogenesis of ACS and coronary atherosclerosis will be considered as synonymous.

The natural history of atherosclerosis in CAD

The natural history, derived from cadaveric examination at various ages, has been described for over 60 years [1]. From fatty streaks through intermediate lesions and the development of complex atheromatous plaques to potential culprit lesions with thin fibromuscular plaques prone to rupture, the process appears to commence from a young age. While aortic fatty streaks may be found in children in the first decade of life and are widely prevalent by the age of 3, they are found at the same frequency in all populations irrespective of cardiovascular risk and cannot be considered a reliable harbinger of future pathogenic coronary atherosclerotic disease [2]. More pathologically-relevant fatty streaks of the coronary vasculature become more evident in the second decade of life. By the third decade of life, advanced, raised coronary atherosclerotic lesions can be found, as witnessed in autopsy studies of soldiers (mean age 22 years) killed during the Korean war [3]. However, presentation of ACS typically occurs much later in life–for non-ST elevation ACS, the mean age of presentation is midway through the seventh decade [4]. Thus, prolonged exposure over many decades to pro-atherosclerotic factors is important to the clinical manifestation of the disease. It can be regarded as a disease of ageing, characterized by a slow, but progressive expansion of the intima, the normally thin layer of the coronary wall between endothelium and underlying smooth muscle, through invasion of lipid, inflammatory cells, and deposition of extracellular matrix (see Fig. 145.1) [5].

Shear stress and localization of coronary plaques

The location of atherosclerotic plaques within the coronary tree can largely be predicted by haemodynamic flow characteristics within the three main epicardial arteries. The crucial property of coronary flow that predisposes to atheromatous changes is areas of low or oscillatory shear stress, typically found on the inner curvature of the vessel wall or adjacent to vascular bifurcations [6]. Altered shear stress contributes to endothelial dysfunction, predisposing these areas of vessel wall to further injury and inflammation. Not only does low shear stress appear to predicate the location of

Box 145.1 Non-atheromatous causes of acute coronary syndrome presentation

Rare causes of spontaneous (type 1) myocardial infarction.

Causes

- Toxin-induced coronary vasospasm (e.g. cocaine).
- Allergic-induced vasospasm—Kounis syndrome.
- Spontaneous acute coronary dissection.
- Coronary embolization.
- Anomalous coronary vascular anatomy, myocardial bridging.
- Takotsubo syndrome.
- Coronary arteritis.

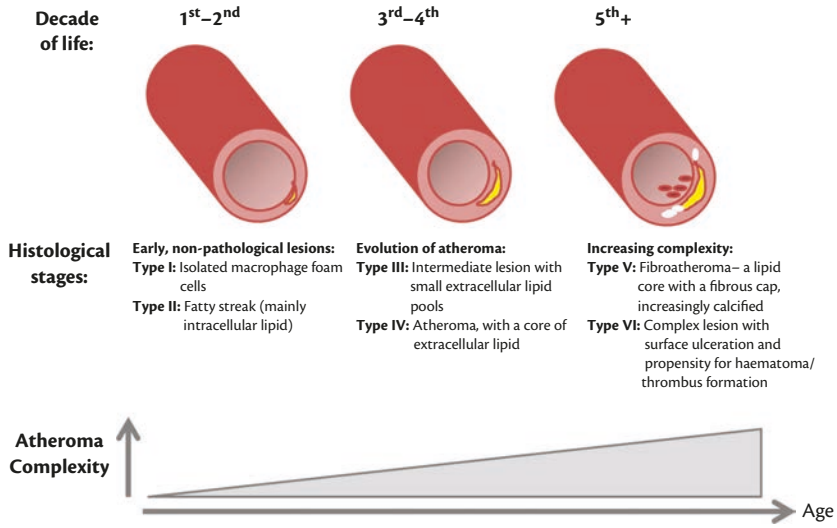


Fig. 145.1 Progression of the atherosclerotic plaque. Atherosclerosis starts with deposition of the inflammatory fatty streak. Over a period of a decade, this evolves into more complex atheromatous plaques. This may ultimately culminate in the development of a vulnerable plaque, susceptible to erosion or rupture, and intraluminal thrombosis, and the development of an acute coronary syndrome.

atherosclerotic plaques, but it may also play an important role in raised lesion progression [7].

Evolution of the coronary plaque

A key initiating event in the development of the fatty streak is oxidative modification and non-enzymatic glycation of both apolipoprotein B (Apo B) and lipid components of low density lipoprotein (LDL) in the extracellular matrix of the vascular intima. Accumulation of oxidized, modified LDL generates a pro-inflammatory/pro-atherosclerotic milieu [8]. Lipid deposition preferentially occurs in areas where the endothelium has already been primed in areas of low shear stress or injury, leading to altered endothelial function. The coronary vascular endothelium possesses important regulatory roles—modulating vascular tone and permeability, maintaining the blood–heart barrier, and preventing platelet–leukocyte adhesion, aggregation, and thrombosis. Disruption of endothelial function through the initiation of chronic inflammation thus leads to an adverse chain of events culminating with development of atheromatous lesions. Through endothelial expression of various chemokines (e.g. monocyte chemotactic protein-1 (MCP-1) and interleukin (IL)-8), and adhesion molecules (e.g. intercellular vascular adhesion molecules (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and P- and E-selectin), plus recruitment of the innate immune system with activation of monocytes, T- and B-lymphocytes and polymorphonuclear granulocytes [9], monocyte-derived macrophages are attracted and become adherent to the endothelium before migrating through the vascular wall into the tunica intima. Here, the macrophages take up modified LDL via scavenger receptors, leading to the characteristic intimal accumulation of cholesterol-laden macrophages that become the foam cell pathognomonic of the fatty streak and subsequently, the atherosclerotic plaque [8]. While phagocytic uptake of modified cholesterol is initially beneficial, the uptake of modified LDL into macrophages engages further inflammation and expression of endothelial adhesion molecules and chemoattractants to maintain a progressive inflammatory state, becoming an almost self-perpetuating cycle of pro-atheromatous inflammation and deposition. This deposition does not result in immediate narrowing of the vessel's lumen, but rather a slow, progressive thickening of the vascular wall in a process known as 'remodelling.' There is relative luminal diameter preservation until the plaque occupies >40% of the internal elastic luminal area [10]. Thereafter, the plaque starts to protrude into the vessel's lumen, altering flow characteristics and impacting upon shear-stress characteristics in the affected vessel wall.

Non-thrombotic CAD: coronary stenosis

ACS may occur where there is a stable, raised plaque, albeit one capable of resulting in significant blood flow limitation under high or extreme cardiovascular demand. Usually, these may be either effectively asymptomatic or result in stable exertional angina. However, under extreme conditions, these normally comparatively 'benign' lesions can induce ACS by preventing a sufficient increase of coronary blood supply to meet the large increase in myocardial metabolic demand, leading to myocardial injury and necrosis (type 2 myocardial infarction by the Universal Classification system [11]). Such severe physiologic conditions can occur following marked reductions in circulating volume following dehydration or blood loss, attenuated oxygen carriage due to severe anaemia or hypoxaemia, hypotension as may occur in severe sepsis, or increased metabolic load as occurs in thyrotoxicosis. Many of these factors are frequently encountered in critical care situations and result in acute myocardial ischaemia through a demand/perfusion mismatch of the myocardium downstream to the occlusive lesion.

Acute ACS without an elevation in demand however necessitates impairment in supply; typically, this is due to destabilization of a vulnerable plaque.

Thrombotic CAD: the vulnerable plaque

As the natural history of atherosclerosis progresses, there is continued accumulation of inflammatory cellular components that, with release of hydrolytic enzymes and chemoattractants, induce further intimal damage and focal necrosis. This can lead to the

development of a necrotic lipid core of the atherosclerotic plaque [12]. Proliferation of smooth muscle cells and synthesis of fibrous tissue occur as part of the plaque's reorganisation, with the formation of a fibrous cap characteristic of the complicated atherosclerotic lesion [12]. Most cases of ACS occur as a result of disruption of an atherosclerotic lesion that was previously haemodynamically insignificant. This high-risk 'vulnerable plaque' [13] is the ultimate pathophysiologic culmination of decades of progressive atherosclerotic inflammation [14]. These lesions are characterized by a thin fibrous cap susceptible to rupture or erosion, leading to intravascular thrombus formation and potential occlusion [13]. The fibrous cap is not a quiescent structure: it undergoes constant dynamic remodelling, but excessive activation of macrophage-derived collagenase/gelatinase matrix metalloproteinases may lead to dangerous thinning and destabilization in the shoulder region of the fibrous cap, resulting in the culprit lesions of ACS [15].

Once the plaque has ruptured or has undergone significant erosion, a cascade of platelet aggregation, activation of coagulation/fibrin deposition, and vasoconstriction is triggered, leading to intraluminal thrombosis and variable degrees of vascular occlusion. The classification of the resultant ACS—ST-elevation MI, non-ST-elevation MI, or unstable angina—depends upon the severity and duration of obstruction, and the metabolic demand placed upon the jeopardised myocardium. Thereafter, the volume of myocardium affected and the ability of the rest of the heart to compensate following the acute injury dictates the ultimate clinical course of the injury—the larger the volume of necrotic myocardium, the poorer the outcome.

Risk factors for CAD

While shear stress is an important component in the development of the early atherosclerotic plaque, it is neither the sole perturbation nor is it necessarily sufficient in isolation to lead to the development of pathological ACS-inducing atherosclerotic lesions. For the lesion to be initiated and to progress requires a further insult to the vascular lining of the coronary vessel to trigger the prerequisite endothelial dysfunction. This represents the Ross 'response-to-injury' hypothesis of atheroma formation [12]. Endothelial dysfunction [16] is a common denominator of a wide range of cardiovascular risk factors identified in epidemiological studies; the majority have an important genetic aetiological contribution.

Hypercholesterolemia

Almost uniquely among cardiovascular risk factors, hypercholesterolemia is capable of resulting in significant CAD in the absence of other risk factors. Supply of LDL and its oxidative modification in the intima leads to the inflammatory impairment of endothelial function as already described, with significant reduction in nitric oxide bioavailability and impaired vasodilation [17]. The endothelial impairment appears multifactorial—not only does oxidised LDL induce an inflammatory state, but hypercholesterolemia results in increased AT1-receptor density, increasing vasoconstriction and reactive oxygen species (ROS) generation [18]. ROS impairs bioavailability of nitric oxide through reaction into peroxynitrite. Furthermore, hypercholesterolemia increases generation of asymmetric dimethylarginine (ADMA), an endogenous competitive inhibitor of NO synthase [18]. Therefore, hypercholesterolemia leads to an increased availability of LDL cholesterol that is pivotal to the formation of the lipid-rich atheroma, and also attenuates endothelial defences against further lipid and inflammatory cell deposition.

Diabetes

Development of hyperglycaemia and insulin resistance is a well-recognized risk factor in the development of atherosclerosis and endothelial dysfunction. Increasing oxidative stress and reducing nitric oxide bioavailability, hyperglycaemia may also lead to the generation of advanced glycosylation end-products (AGEs)—stable proteins that are, in themselves, capable of generating ROS and altering endothelial function as a direct consequence [19]. Moreover, diabetes and hyperglycaemia also impact adversely upon the renin-angiotensin system and is procoagulant through platelet dysfunction, increased fibrinogen, increased von Willebrand factor and Factor VII, and reduced tissue plasminogen activator levels [20].

Hypertension

As with other cardiovascular risk factors, hypertension is associated with impaired nitric oxide bioavailability and characteristic morphological changes in endothelial cells [17]. The changes associated with impaired vascular relaxation and diminished L-arginine to nitric oxide generation [16] may in part reflect altered renin-angiotensin aldosterone signalling.

Smoking

Smoking is associated with endothelial dysfunction and with decreased vasodilation found in a variety of experimental models. Tobacco smoke contains a various toxins including nicotine—the consequent generation of ROS results in oxidative modifications of lipoproteins resulting in attenuated nitric oxide bioavailability. This provides the most likely mechanism of the endothelial dysfunction [16].

Conclusion

The pathophysiology of acute coronary syndromes is a complex interplay between multiple causes of endothelial dysfunction, the triggering of inflammatory processes that, over many decades of life, leads to the deposition of modified lipids, ingress of inflammatory cells, cellular and collagen organization, and the development of a fibrous cap. These lesions may ultimately evolve into the high risk vulnerable plaque that is susceptible to erosion or rupture. In the event of exposure of the sub-endothelial layers or the atheroma itself, activation of pro-coagulant pathways are capable of causing intraluminal thrombosis and even complete occlusion of an epicardial coronary vessel. This can culminate in significant myocardial necrosis with its attendant mortality and morbidity.

Recognition of the pathophysiology of ACS and atheromatous disease will continue to inform ongoing development of protective strategies in the management of this disease in primary, secondary, and critical care.

References

1. Duff GL and McMillan MG.(1951). Pathology of atherosclerosis. *American Journal of Medicine*, **11**, 92–108.
2. McGill HC, Jr, McMahan CA, Herderick EE, Malcom GT, Tracy RE, and Strong JP. (2000). Origin of atherosclerosis in childhood and adolescence. *American Journal of Clinical Nutrition*, **72**(5 Suppl.), 1307S–15S.
3. Enos WF, Holmes RH, and Beyer J. (1953). Coronary disease among United States soldiers killed in action in Korea; preliminary report. *Journal of the American Medical Association*, **152**, 1090–3.
4. Collinson J, Flather MD, Fox KA, et al. (2000). Clinical outcomes, risk stratification and practice patterns of unstable angina and myocardial infarction without ST elevation: Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK). *European Heart Journal*, **21**, 1450–7.
5. Moore KJ and Tabas I. (2011). Macrophages in the pathogenesis of atherosclerosis. *Cell*, **145**, 341–55.
6. Cecchi E, Giglioli C, Valente S, et al. (2011). Role of hemodynamic shear stress in cardiovascular disease. *Atherosclerosis*, **214**, 249–56.
7. Gijsen F, van der Giessen A, van der Steen A, and Wentzel J. (2013). Shear stress and advanced atherosclerosis in human coronary arteries. *Journal of Biomechanics*, **46**, 240–7.
8. Glass CK and Witztum JL. (2001). Atherosclerosis. the road ahead. *Cell*, **104**(4), 503–16.
9. Weber C and Noels H. (2011). Atherosclerosis: current pathogenesis and therapeutic options. *Nature Medicine*, **17**, 1410–22.
10. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, and Kolettis GJ. (1987). Compensatory enlargement of human atherosclerotic coronary arteries. *New England Journal of Medicine*, **316**, 1371–5.
11. Thygesen K, Alpert JS, Jaffe AS, et al. (2012). Third universal definition of myocardial infarction. *Journal of the American College of Cardiology*, **60**, 1581–98.
12. Ross R. (1999). Atherosclerosis—an inflammatory disease. *New England Journal of Medicine*, **340**, 115–26.
13. Virmani R, Kolodgie FD, Burke AP, Farb A, and Schwartz SM. (2000). Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arteriosclerosis Thrombosis and Vascular Biology*, **20**, 1262–75.
14. Schaar JA, Muller JE, Falk E, et al. (2004). Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. *European Heart Journal*, **25**, 1077–82.
15. Newby AC. (2007). Metalloproteinases and vulnerable atherosclerotic plaques. *Trends in Cardiovascular Medicine*, **17**, 253–8.
16. Grover-Paez F and Zavalza-Gomez AB. (2009). Endothelial dysfunction and cardiovascular risk factors. *Diabetes Research and Clinical Practice*, **84**, 1–10.
17. Luscher TF, Tanner FC, Tschudi MR, and Noll G. (1993). Endothelial dysfunction in coronary artery disease. *Annual Review of Medicine*, **44**, 395–418.
18. Sitia S, Tomasoni L, Atzeni F, et al. (2010). From endothelial dysfunction to atherosclerosis. *Autoimmunity Reviews*, **9**, 830–4.
19. Esper RJ, Vilarino JO, Machado RA, and Paragano A. (2008). Endothelial dysfunction in normal and abnormal glucose metabolism. *Advances in Cardiology*, **45**, 17–43.
20. Deedwania P and Srikanth S. Diabetes and vascular disease. *Expert Reviews in Cardiovascular Therapy*, **6**, 127–38.

CHAPTER 146

Diagnosis and management of non-STEMI coronary syndromes

David Erlinge and Göran Olivecrona

Key points

- The strongest objective signs of non-ST segment elevation myocardial infarction (NSTEMI) are a positive troponin and ST segment depression.
- NSTEMI should be acutely treated with aspirin, an adenosine diphosphate (ADP)-receptor antagonist, and an anticoagulant (fondaparinux or low molecular weight heparins).
- NSTEMI should be investigated with coronary angiography within 72 hours.
- Curative treatment is percutaneous coronary intervention or coronary artery bypass grafting.
- Secondary prevention includes aspirin, statins, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, ADP receptor antagonists, and lifestyle changes.

Definition of non-STEMI coronary syndromes

Acute coronary syndromes were previously classified as ST segment elevation myocardial infarction (STEMI), non- ST segment elevation myocardial infarction (NSTEMI) or unstable angina. Diagnosis of unstable angina was based on a history describing novel occurrence or worsening of angina, or angina at rest. NSTEMI diagnosis was based on elevation of cardiac markers and typical symptoms. Today, patients with either novel ST-depression or elevated cardiac markers (together with chest pain or chest pain equivalent) are grouped together as non-STE-acute coronary syndromes (NSTE-ACS) [1]. However, the increased sensitivity of the high sensitivity troponin assays reveals that most ACS patients release cardiac markers and are therefore classified as NSTEMI.

Myocardial infarction criteria

In 2007, new criteria were defined to classify myocardial ischaemic injury according to aetiology and, importantly, to exclude non-ischaemic myocardial injury from the entity of myocardial infarction (Table 146.1) [2]. This classification is important for the choice of treatment. Type 1 is the classical myocardial infarction caused by plaque rupture and thrombus formation that threatens to occlude the coronary artery. This should be treated with antithrombotic drugs and revascularization. Type 2 is not caused by thrombus formation and requires other measures, such as vasodilators, blood transfusion, volume expansion or control of tachycardias, such as atrial fibrillation. These definitions are also important for clinical trials. Many previously positive drug studies have reduced the risk of procedure-related infarction related to percutaneous coronary intervention (PCI; type 4a); whether these are as clinically important as type 1 infarcts is questionable [3].

Diagnostics

Most patients with NSTE-ACS present with a history of chest pain that has subsided spontaneously before or soon after arrival at the emergency room, but with positive cardiac makers (usually troponin T or I) indicative of myocardial infarction. While chest pain is a common symptom of patients presenting to emergency departments, in about 70% of cases it is not due to an acute coronary syndrome. Symptoms of myocardial infarction are highly variable. The most typical is central chest pain radiating down the left arm (referred pain). However, pain may also be experienced in the throat or the back. Patients with a longstanding diabetic polyneuropathy often feel no pain at all, and may present with other symptoms, such as reduced fitness, shortness of breath, or non-specific discomfort.

A good history is the cornerstone of all diagnostics and provides important information; however, it has poor sensitivity and specificity for diagnosing acute coronary syndromes. History and physical examination can often identify obvious non-cardiac conditions, such as muscle pain, inflammation of the costal cartilages (Tietze´s syndrome), pleuritis, pericarditis herpes zoster, joint pain, gastrointestinal, or biliary pain. Aortic dissection is a serious differential diagnosis with a high mortality if not diagnosed and treated quickly. This often presents with very sudden onset and intense pain, often radiating to the back. It can present with hypotension, but also initially with hypertension. Lack of ST-segment elevation or ST-segment depression in a patient with severe chest pain mimicking symptoms of acute myocardial infarction should raise the suspicion of aortic dissection. A blood pressure difference between the arms and a newly-identified murmur may indicate aortic dissection, but diagnosis is made formally with acute transoesophageal echocardiography or computed tomography, followed by immediate referral to (cardio)thoracic surgeons.

Pulmonary embolism may produce chest pain often combined with dyspnoea. There may be ST-depression in right ventricular leads (V1–V2) and hypoxaemia. Echocardiography may show elevated pulmonary pressures though computed tomography confirms the diagnosis.

Table 146.1 Clinical classification of different types of myocardial infarction

Type	Features
Type 1	Spontaneous myocardial infarction related to ischaemia due to a primary coronary event, such as plaque erosion and/or rupture, fissuring, or dissection
Type 2	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST-elevation, or new left bundle branch block, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a	Myocardial infarction associated with PCI
Type 4b	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5	Myocardial infarction associated with CABG

Electrocardiogram

The strongest objective signs of NSTE-ACS are new ST depression, and elevated cardiac markers, particularly troponin. Chronic ST depression may occur in patients with old infarcts, a hypertrophic ventricle or heart failure, but these are usually known from previous electrocardiogram (ECGs). Digoxin also commonly causes slight ST depression. Novel ST-segment depression is a very serious prognostic sign requiring immediate treatment. Negative T waves are more non-specific, especially among women, but can indicate NSTE-ACS.

Troponin and other biomarkers of myocardial injury

An increased plasma troponin level above the 99th percentile limit is indicative of NSTE-ACS, and requires prompt investigation and treatment. Troponin is heart-specific, but can be elevated in other conditions, such as renal failure, severe sepsis, myocarditis, and pulmonary embolism (Box 146.1). Troponin is usually released when thrombus in the damaged plaque releases micro-emboli, causing micro-infarctions downstream in the coronary artery. Troponin rises after 3–6 hours. If larger amounts are released, it may take several days before levels are normalized, but smaller elevations may normalize rapidly. Creatinine kinase MB isozyme (CKMB), and myoglobin are less specific and sensitive compared with troponin, but can be useful to detect re-infarction when troponin is already elevated, since they return to normal levels more rapidly.

If initial ECG and laboratory tests do not provide the diagnosis in a patient suspected of having ACS, the patient needs continuous ECG and ST-segment monitoring and repeated troponin measurements. Pro-BNP may provide guidance on the patient's mortality risk status and may indicate the presence of heart failure. An exercise test can be performed in some patients, but has low sensitivity and specificity. Nuclear myocardial perfusion with stress-rest imaging gives important information regarding inducible ischaemia. Echocardiography may be useful for diagnosing pericarditis, aortic dissection and larger pulmonary embolism, and for finding areas of regional hypokinesia indicating ischaemic heart disease. Stress echocardiography is diagnostic for ischaemia.

Modern CT angiography with lower radiation and higher image quality is rapidly becoming a diagnostic alternative [4]. However, accuracy is still limited in patients with calcifications and previous stenting, and is currently only recommended for low-to-intermediate risk patients.

Box 146.1 Elevations of troponin not caused by an acute coronary syndrome

- Cardiac contusion, or other trauma including surgery, ablation, pacing, etc.
- Congestive heart failure—acute and chronic.
- Aortic dissection.
- Aortic valve disease.
- Hypertrophic cardiomyopathy.
- Tachy- or bradyarrhythmias, or heart block.
- Apical ballooning syndrome (Takotsubo).
- Rhabdomyolysis with cardiac injury.
- Pulmonary embolism, severe pulmonary hypertension.
- Renal failure.
- Age (>70 years).
- Acute neurological disease, including stroke or subarachnoid haemorrhage.
- Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, and scleroderma.
- Inflammatory diseases, e.g. myocarditis or myocardial extension of endo- and pericarditis.
- Drug toxicity or toxins.
- Critically-ill patients, especially with respiratory failure or sepsis.
- Burns, especially if affecting >30% of body surface area.
- Extreme exertion.

Risk scores

Structured risk scores enable a more objective quantitative assessment of risk [1]. Commonly used scores to assess ischaemic risk are GRACE [5] and TIMI [6], both of which are useful in guiding clinical decision-making. Several of the treatments administered to reduce ischaemic risk (antiplatelet drugs, anticoagulants, invasive procedures) increase the risk of bleeding complications that, in turn, increases mortality. It is therefore advisable to also use a bleeding risk score (e.g. the CRUSADE risk score [7]) to balance treatment correctly.

Treatment of NSTE-ACS

Patients exhibiting objective signs of NSTE-ACS (especially ST-depression or positive troponin) should immediately receive intensive treatment with continuous ECG monitoring, and be scheduled for coronary angiography as soon as possible. Guidelines recommend a maximum time limit of 72h before angiography [1,8–10], but should be done immediately (<2 hours) if the patient becomes more unstable, with recurrent chest pain or recurrent ST-depression not resolving with nitroglycerin and beta-blockade.

Initial drug treatment should consist of short-acting nitroglycerin, morphine, and beta-blockers to relieve chest pain. Oxygen is often routinely administered, but there is no strong evidence to support its use in patients with arterial saturations >90% [1]. Antithrombotic therapy should be given quickly, aiming at both platelet and coagulation inhibition to prevent thrombus progression that may lead to occlusion of the affected coronary artery, potentially resulting in loss of heart muscle and life-threatening arrhythmias.

Platelets are inhibited by rapidly administered bolus doses of aspirin and an ADP receptor antagonist. Prasugrel and ticagrelor are new, more efficient ADP receptor blockers that are recommended as first choice agents. Clopidogrel should only be used for patients who cannot take ticagrelor or prasugrel [1,10], e.g. those on warfarin or with a very high bleeding risk. Prasugrel is not recommended for patients >75 years, with low body weight (<60 kg) or previous stroke.

The subcutaneous Xa inhibitor fondaparinux is recommended to inhibit the coagulation system as it has the most favourable efficacy-safety profile [1]. Compared with low molecular weight heparins (LMWH), fondaparinux has reduced bleeding complications yet maintains a similar efficacy for cardiac events, with a greater overall reduction in mortality [11]. For patients in urgent need of surgery, LMWH may be preferred because of its shorter half-life. Coronary artery bypass grafting (CABG) within 36 hours from the last fondaparinux dose is associated with an increased bleeding risk [12]. Fondaparinux and LMWH dosages need to be adjusted according to renal function to decrease the risk of bleeding complications.

Reversible GPIIb/IIIa inhibitors (e.g. eptifibatide, tirofiban) provide additional platelet inhibition and may protect against new coronary events. They do cause bleeding complications, and there is no strong evidence to support their clinical value when ADP receptor antagonists are used as baseline treatment [13]. They should not be used routinely pre-angiography, but reserved for high-risk groups, such as patients with recurrent chest pain or ST segment depression despite aspirin, ADP-inhibitors, and anticoagulation.

Angiography and PCI

Patients with NSTE-ACS should normally be investigated by coronary angiography [1], with most of the lesions found being treated immediately by percutaneous coronary intervention (PCI). Drug-eluting stents reduce rates of repeat revascularization, but should be avoided in patients unable to tolerate dual antiplatelet therapy (DAPT) due to an increased risk of bleeding complications, or in those requiring surgery. Warfarin treatment is a relative contraindication for DAPT. If warfarin is deemed necessary, DAPT combined with warfarin should be given for as short a time as possible, usually only 1 month, followed by warfarin and aspirin. After PCI, therapy with ADP receptor antagonists should continue for 12 months and aspirin lifelong. The more potent agents prasugrel and ticagrelor are currently preferred due to better long-term outcomes (reductions in coronary events, stent thrombosis, and mortality) compared with clopidogrel [14,15].

CABG could be favoured over PCI in patients with significant left main stem lesions or in those with advanced multivessel coronary disease, particularly if they are diabetic [1]. Clopidogrel and ticagrelor are discontinued 5 days and prasugrel 7 days pre-CABG to reduce the risk of bleeding complications. After CABG, patients should be treated with aspirin for life, ADP blockers for 12 months, and with statins, ACE inhibitors and beta-blockers for secondary prevention.

Non-invasive medical treatment of NSTEMI is an option, usually in very elderly patients with multiple comorbidities and high bleeding risks. However, such patients have the most to gain from invasive procedures. It is important to ensure that adequate medical therapy is given to patients not undergoing PCI or CABG. ADP blockers are clearly under-utilized for conservatively managed NSTE-ACS. Fondaparinux is also an excellent option for patients with a high risk of bleeding who are treated medically. On discharge, patients should ideally receive ADP-receptor blockers for up to 1 year, aspirin for life, plus statins, beta-blockers, and ACE inhibitors.

Prognosis and follow-up

NSTE-ACS has a risk of recurrent myocardial infarction of 15–20% and a 15% 1-year mortality. Patients with NSTE-ACS are at similar risk as a STEMI patient at 1 year. It is therefore very important to offer optimal secondary prophylaxis with aspirin, statins, beta-blockers, ACE inhibitors, and ADP receptor antagonists, as well as lifestyle changes. Statin treatment should aim for an LDL <1.8 mmol/L (<70 mg/dL), while lifestyle changes should include cessation of smoking, physical exercise five times a week, and diet recommendations.

References

1. Hamm CW, Bassand JP, Agewall S, et al. (2011). ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*, **32**, 2999–3054.
2. Thygesen K, Alpert JS, and White HD. (2007). Universal definition of myocardial infarction. *Journal of the American College of Cardiology*, **50**, 2173–95.
3. Prasad A, Gersh BJ, Bertrand ME, et al. (2009). Prognostic significance of periprocedural versus spontaneously occurring myocardial infarction after percutaneous coronary intervention in patients with

acute coronary syndromes: an analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *Journal of the American College of Cardiology*, **54**, 477–86.
4. Hoffmann U, Truong QA, Schoenfeld DA, et al. (2012). Coronary CT angiography versus standard evaluation in acute chest pain. *New England Journal of Medicine*, **367**, 299–308.
5. Fox KA, Dabbous OH, Goldberg RJ, et al. (2006). Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *British Medical Journal*, **333**, 1091.
6. Antman EM, Cohen M, Bernink PJ, et al. (2000). The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *Journal of the American Medical Association*, **284**, 835–42.
7. Subherwal S, Bach RG, Chen AY, et al. (2009). Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation*, **119**, 1873–82.
8. Katritsis DG, Siontis GC, Kastrati A, et al. (2011). Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. *European Heart Journal*, **32**, 32–40.
9. Mehta SR, Granger CB, Boden WE, et al. (2009). Early versus delayed invasive intervention in acute coronary syndromes. *New England Journal of Medicine*, **360**, 2165–75.
10. Wright RS, Anderson JL, Adams CD, et al. (2011). 2011 ACCF/AHA focused update of the guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*, **123**, 2022–60.
11. Jolly SS, Faxon DP, Fox KA, et al. (2009). Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes treated with glycoprotein IIb/IIIa inhibitors or thienopyridines: results from the OASIS 5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) trial. *Journal of the American College of Cardiology*, **54**, 468–76.
12. Landenhed M, Johansson M, Erlinge D, Olsson ML, and Bjursten H. (2010). Fondaparinux or enoxaparin: a comparative study of postoperative bleeding in coronary artery bypass grafting surgery. *Scandinavian Cardiovascular Journal*, **44**, 100–6.
13. Giugliano RP, White JA, Bode C, et al. (2009). Early versus delayed, provisional eptifibatide in acute coronary syndromes. *New England Journal of Medicine*, **360**, 2176–90.
14. Wiviott SD, Braunwald E, McCabe CH, et al. (2007). Prasugrel versus clopidogrel in patients with acute coronary syndromes. *New England Journal of Medicine*, **357**, 2001–15.
15. Wallentin L, Becker RC, Budaj A, et al. (2009). Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *New England Journal of Medicine*, **361**, 1045–57.

CHAPTER 147

Diagnosis and management of ST-elevation of myocardial infarction

David Erlinge and Göran Olivecrona

Key points

- STEMI should be diagnosed rapidly, based on the combination of ST-segment elevation and symptoms of acute myocardial infarction.
- The main treatment objective is myocardial tissue reperfusion as quickly as possible.
- The preferred method of reperfusion is primary percutaneous coronary intervention if transport time is below 2 hours, and thrombolysis if longer.
- STEMI patients with acute onset cardiogenic shock should be evaluated by echocardiography to exclude mechanical complications, such as flail mitral insufficiency, ventricular septal defect, or tamponade.
- Secondary prevention includes aspirin, adenosine diphosphate receptor antagonists, statins, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and lifestyle changes.

Symptoms and diagnosis, and the importance of rapid reperfusion

ST-elevation myocardial infarction (STEMI) is generally caused by a ruptured plaque that triggers local thrombus formation, which occludes the coronary artery [1]. This mechanism is similar to non-ST elevation myocardial infarction and unstable angina, but differs only in the degree of obliteration of the lumen by the thrombus. When the artery is completely occluded, oxygen and nutrient supply to the myocardium is completely interrupted. Most patients suffering from STEMI have a clear onset of central chest pain; diagnosis is confirmed by regional ST-segment elevations (Fig. 147.1). By definition, 0.1 mV ST elevation must be present in two adjacent distal leads, V1, or V4–V6. The V2–V3 leads require 0.2 mV ST-elevation for men and 0.15 mV for women. There is often reciprocal ST segment depression in opposite ECG areas (Fig. 147.1) [2,3]. However, an isolated ST elevation in aVL may represent a large anterior wall infarction. New elevated T waves often occur before the ST elevation and may be an early sign of an occluded coronary artery. Novel left bundle branch block (LBBB) may represent an anterior STEMI, where septal ischaemia results in the LBBB. This represents a widespread and usually long-standing infarction.

Completely 'silent' heart attacks with no chest pain may occur, especially in diabetics. 'Referred pain' is when patients experience pain in areas other than the heart, most typically radiating down the left arm, but also to the jaw and teeth. Inferior infarctions are often experienced in the back or the epigastrium. They often cause vagal symptoms, bradycardia, and nausea.

Acute malignant ventricular arrhythmias, such as ventricular fibrillation may lead to sudden death if not treated with cardiopulmonary resuscitation (CPR) and defibrillation. Up to 30% of patients with STEMI suffer cardiac arrest and die, many within the first hour. The second danger is loss of heart muscle. The longer the coronary artery is occluded, the larger the infarct size—time is muscle. Large myocardial infarctions frequently lead to severe heart failure and increased mortality.

Diagnosis of STEMI is often relatively straightforward. The challenge lies in reducing time to treatment to re-establish myocardial tissue perfusion promptly. A well-functioning logistical chain of events needs to be established. Patients should recognize the symptoms and call an ambulance immediately. Bystanders should be able to give CPR in case of cardiac arrest and paramedics must be in place quickly to defibrillate, give medication, and transport the patient to a hospital with the capability to perform percutaneous coronary interventions (PCI), ideally within 2 hours from arrival of the ambulance at the scene. If transport time is longer, fibrinolytic therapy should be administered in the ambulance or at the closest hospital as an alternative to PCI for myocardial tissue reperfusion. Prehospital ECGs performed by ambulance crews can be sent by telecommunication for confirmation of a STEMI diagnosis. Patients should then be administered aspirin, ADP receptor blockers, heparin, oxygen, and morphine en route to hospital. On arrival the patient should be fast-tracked directly to the catheterization laboratory for PCI, without stopping at the emergency room. Coronary angiography confirms the diagnosis and usually identifies an occluded, thrombotic artery (Figs 147.2 and 147.3).

Differential diagnosis

As mentioned previously, diagnosis of STEMI is usually based on symptoms and ECG. There is no time to wait for laboratory tests.

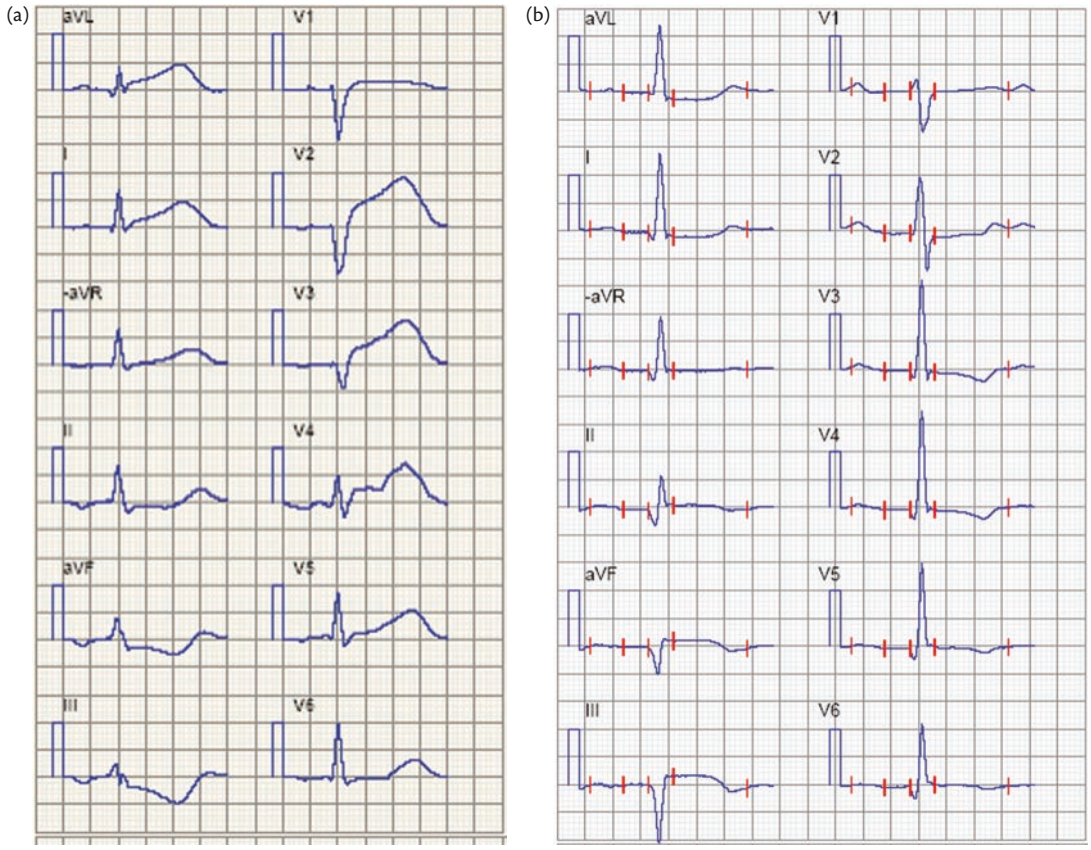


Fig. 147.1 Schematic representation of ST-T changes in acute coronary syndromes. ST segment elevations in anterior and inferior infarction. (a) Anterior STEMI. (b) Inferior STEMI.

However, the diagnosis may be unclear and more tests may have to be performed. It is important to not risk delaying reperfusion of a STEMI so some normal acute angiograms should be accepted.

Myocarditis

Pericarditis or myocarditis may cause a clinical picture similar to STEMI, but chest pain usually presents more gradually and is worsened by deep inspiration [4]. Patients are often young, the pain has a slower onset, and an increase in CRP is often detected. ST-segment elevations are not restricted to any of the coronary artery regions, but are often more general (Fig. 147.4). As a rule, ST-elevations are not as pronounced, usually upward concave, and usually without reciprocal ST depression. If in doubt, cardiac magnetic resonance imaging (MRI) is a valuable tool to diagnose perimyocarditis. Echocardiography may demonstrate pericardial fluid, which strengthens the diagnosis.

Takotsubo cardiomyopathy

This relatively newly-discovered condition mainly affects post-menopausal women [5]. The etiology is probably a stress-induced hyperactivity of sympathetic nerves resulting in catecholaminergic toxicity of the apical portions of the heart. The condition often presents as an anterior STEMI triggered by severe emotional stress. Angiography shows normal epicardial vessels, but left ventricular angiography or echocardiography shows typical ballooning of a severely hypokinetic or akinetic apex. Conventional heart failure treatment usually provides resolution within a few months (Fig. 147.4).

Electrolyte imbalances and Brugada's syndrome

ST elevations are not uncommon during marked electrolyte imbalances, or in Brugada's syndrome [6], a rare hereditary sodium channel defect (Fig. 147.4).

Aortic dissection

Aortic dissection is a serious differential diagnosis with a high mortality if not diagnosed and treated quickly. The history is often of very sudden onset and severe chest pain, often radiating to the back, mimicking a heart attack in symptoms, but without ST elevation. A blood pressure difference between the arms and a newly-identified murmur may indicate aortic dissection. Diagnosis is formally made with acute transoesophageal echocardiography or computed tomography, followed by (cardio)thoracic surgical referral.

Treatment

STEMI patients should be treated acutely with aspirin, ADP receptor antagonists (primarily ticagrelor [7] or prasugrel [8], but clopidogrel in those with a high bleeding risk), nitroglycerin, morphine, and oxygen. Immediate transfer to hospital for diagnostic coronary angiography followed by PCI is called primary PCI. This reduces infarct size, and the risk of intracranial bleeding, re-infarction, stroke, and death compared with thrombolysis.

Primary PCI is the preferred treatment if transport time is within 2 hours [2,9]. Angiography usually shows a coronary artery

occluded or semi-occluded (TIMI1-flow) by a thrombus (Fig. 147.3). Heparin and GpIIb/IIIa inhibitors, or the direct thrombin inhibitor bivalirudin, are administered as adjunctive treatment during PCI. Bivalirudin reduces major bleeding complications, resulting in lower mortality rates up to 3 years later compared to GpIIb/IIIa inhibitors [10]. To re-establish coronary blood flow, the thrombotic occlusion is treated either with thrombectomy, where the thrombus is removed by aspiration, or via balloon angioplasty. In most cases, the artery is then stented (Fig. 147.3). In a few cases when PCI is not technically possible, emergency coronary artery bypass grafting operation (CABG) is a reasonable option. This is undertaken in approximately 1% of STEMI patients.

Primary PCI is clearly indicated up to 12 hours after onset of pain. This time limit is based on thrombolysis trial data [2], however the longer the time delay, the less myocardium can be salvaged. For thrombolysis, the passage of time also makes it more difficult

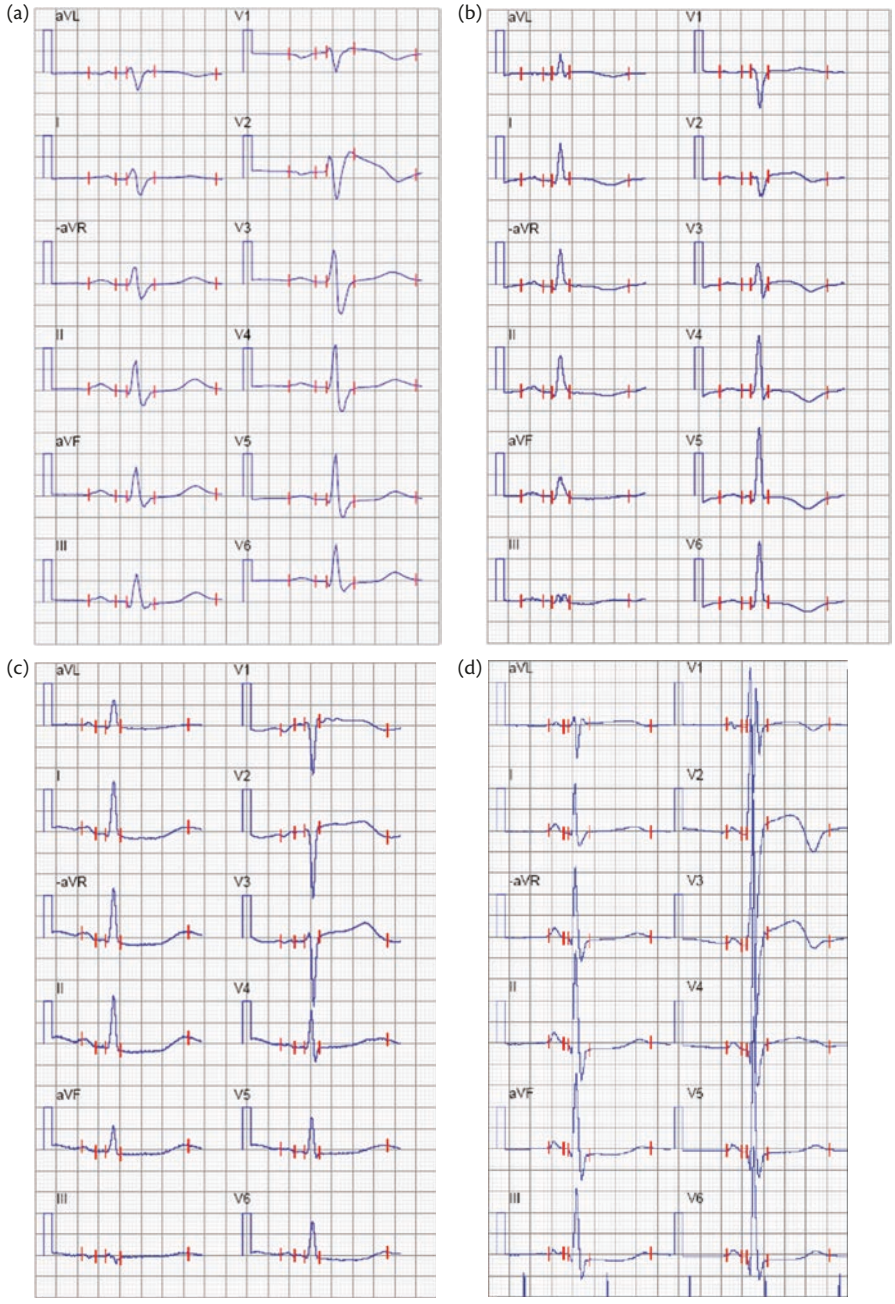


Fig. 147.2 Differential diagnosis of STEMI. (a) Brugada's syndrome involves a sodium channel mutation that confers loss of action potentials selectively in the right ventricular epicardium. (b) Takotsubo-cardiomyopathy in a 78-year-old woman whose husband died the previous day. Upward convex ST-elevation and negative T-waves anteriorly, compared to an older ECG. Maximum troponin T level was 920 ng/l. Echocardiography showed severe apical hypokinesia with hyperkinesia in other areas. (c) Subarachnoid haemorrhage in a 57-year-old woman. Anteroseptal ST elevation and ST-depression laterally, compared with prior ECG. Maximum troponin T level of 440 ng/l. (d) Hypertrophic cardiomyopathy with high R-wave amplitudes and secondary ST-T changes. (e) Perimyocarditis with general concave ST-elevation. (f) Hyperkalaemia with high T-waves.

(e)

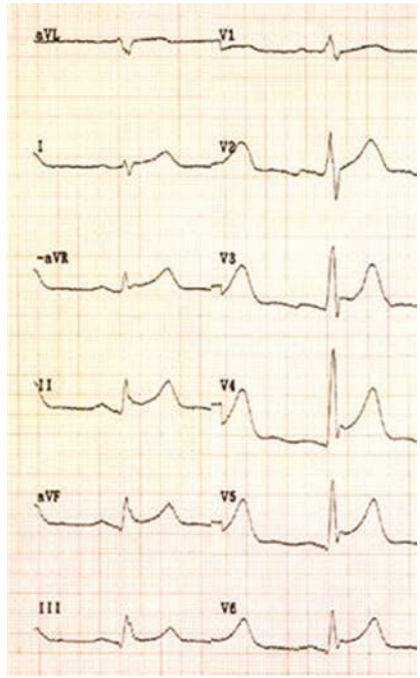


Fig. 147.2 Continued

to dissolve the clot as it becomes increasingly organized. With PCI, clot organization is not an issue; 95% of occlusions can be successfully treated with PCI, even after many hours [11]. After 12 hours, PCI is indicated for patients with persistent or newly recurrent chest pain, or for cardiogenic shock. Late angiography in patients without ongoing chest pain does not necessarily have to be performed out-of-hours. However, estimation of the duration of occlusion of a coronary artery can be difficult in patients that present late. This must be primarily based on symptoms and patient history, which may be uncertain.

Pulmonary oedema is treated with loop diuretics, nitroglycerin, and continuous positive airway pressure (CPAP). Inferior STEMI with right ventricle involvement can present with severe hypotension and bradycardia. This requires plenty of fluid (2–3 L or sometimes more), and is associated with an increased risk of atrioventricular block or bradycardia, which may require atropine or temporary pacing.

Coronary angiography and PCI requires awareness of the risks of contrast-induced nephropathy. To reduce the risk of kidney damage, the amount of contrast should be minimized, and plenty of fluids given before and after the procedure.

When coronary artery reperfusion is established with PCI, the patient may suffer reperfusion injury and arrhythmias such as ventricular fibrillation or tachycardia. More commonly, bradycardia, or asystole occur, the latter especially for inferior STEMI patients. Following reperfusion, the coronary blood flow is assessed, with optimal normal flow termed TIMI-3 flow. A few patients with slightly reduced flow have TIMI-2 flow, while a very small number have little or no flow, despite a fully patent coronary vessel. Reduced coronary flow (<TIMI-3) can be caused by micro-embolization or reperfusion injury leading to microcirculatory swelling and inflammation, resulting in microvascular obstruction. This is a poor prognostic sign. Such patients may develop systemic hypotension, larger infarct sizes, and cardiogenic shock. There is currently no treatment for reperfusion injury, but promising clinical trials with cyclosporin, adenosine, post-conditioning, and hypothermia are ongoing [12].

Thrombolysis

Thrombolysis (most commonly modified variants of tissue plasminogen activator, t-PA) is an alternative treatment for STEMI if initiated within 12 hours from onset of symptoms, and where transfer time to a PCI laboratory exceeds 2 hours. Thrombolysis carries a risk of bleeding, especially intracranial, and only succeeds in reperfusing the occluded artery in 50–60% of cases. Following successful thrombolysis the patient should be transferred within 3–24 hours to the nearest PCI centre for angiography and possible PCI. If thrombolysis does not achieve reperfusion within 90 minutes, the patient may be transferred for rescue PCI.

Post-infarction treatment

Beta-blockers should be used with great caution in the early phase of STEMI in patients with signs of heart failure [13]. They should only be used in patients with clearly elevated blood pressure and

(a) (b)

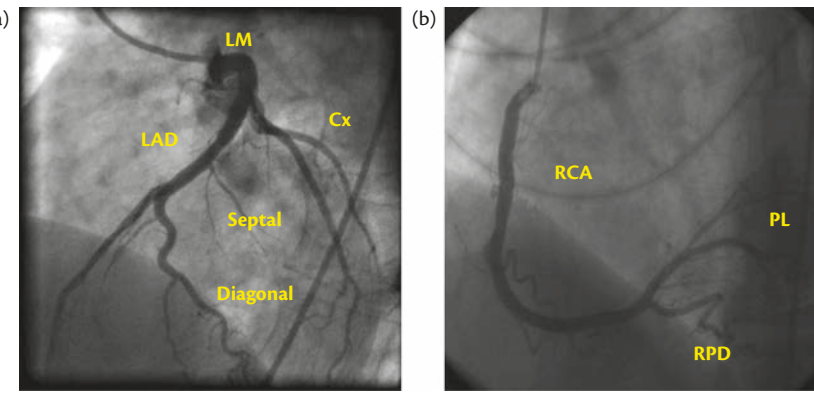


Fig. 147.3 Coronary angiography. The left coronary artery begins with the left main artery (LM) which branches into the left anterior descending (LAD) and circumflex artery (Cx). The LAD branches into diagonal and septal branches and supplies the anterior and apical septal parts of the heart. The Cx supplies the lateral part of the heart. The right coronary artery (RCA) branches into the right posterior descending artery (RPD) and posterolateral (PL) arteries that supply the inferior part of the heart and the basal area of the septum.

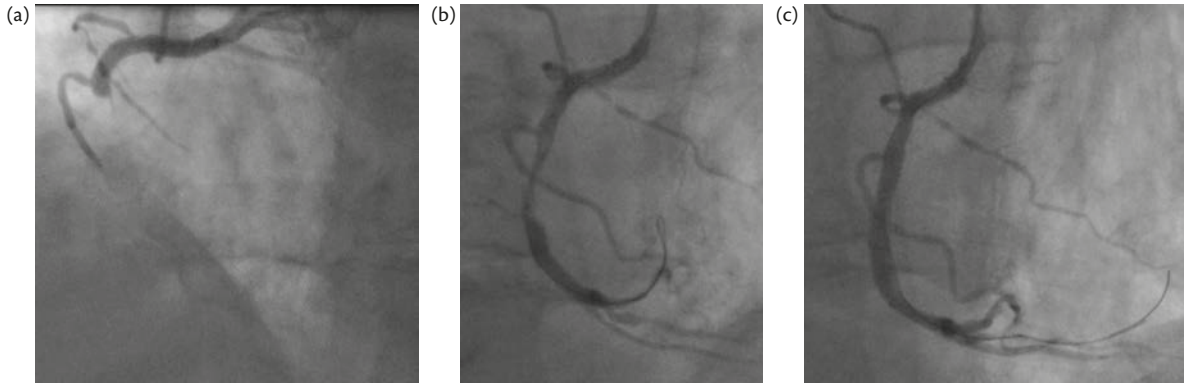


Fig. 147.4 Primary PCI. 61-year-old man with acute inferior STEMI. He was a smoker with three previous PCIs, and a previous anterior STEMI (a). An occlusion in the mid-right coronary artery was recanalized with balloon angioplasty (b), then stented with a bare metal stent (4.0x28 mm) (c).

tachycardia in the early phase. However, following haemodynamic recovery, it is important to start oral beta-blocker therapy, and to continue this post-infarction to reduce the risk of new infarction and death.

Lifelong treatment with aspirin and treatment with ADP receptor antagonists for up to 1 year is recommended. Statin therapy should be initiated quickly and reach the target levels of lowering LDL below 1.8mmol/L (70 mg/dL). Hypertension should be treated to target levels. Approximately 25% of patients with acute coronary syndromes have a history of diabetes, but an additional third have early stage diabetes that can be diagnosed by an oral glucose tolerance test. Precise treatment is essential for prognosis so glucose levels should be carefully monitored and treated with insulin, as indicated. ACE inhibitors should be given to most patients. The routine STEMI patient should thus be discharged with aspirin, ADP receptor antagonists (preferably ticagrelor or prasugrel), statins, beta-blockers, and ACE inhibitors. Diabetic patients should be followed up separately with regard to their diabetes. Equally important is to encourage lifestyle changes, such as smoking cessation, avoiding weight gain and increasing physical activity. A good goal is physical activity for 30 minutes in which patients experience increased heart rate, at least five times a week.

Complications of STEMI

Cardiogenic shock (persistent systolic BP <90 mmHg) is a life-threatening condition. Mortality rates used to be 90%, but primary PCI has reduced this to about 50%. Patients with cardiogenic shock should be primarily treated with PCI, if possible. Echocardiography should be done immediately to rule out possible mechanical complications, e.g. ventricular septal defect (VSD), cardiac tamponade, or flail mitral insufficiency. Other treatments include inotropic drugs (noradrenaline, dobutamine, or levosimendan), intra-aortic balloon pump, and percutaneous left ventricular assist devices.

Papillary muscle rupture leading to acute flail mitral insufficiency manifests a few days following STEMI, usually as cardiogenic shock and pulmonary oedema of sudden onset. Concurrent tachycardia may accentuate the ST elevations incurred from the previously untreated infarction. The flail mitral insufficiency causes an extreme low output syndrome. It is important to recognize this small subgroup of patients as they need continuous pulmonary airway pressure (CPAP) or mechanical ventilation, and immediate referral to cardiac surgery.

Acute VSD is a rupture caused by necrosis of the infarcted zone in the septum resulting in blood from the left ventricle pumping into the right ventricle. It often occurs after a few days to a week and results in rapidly developing hypotension and shock. A systolic murmur can be heard, but the larger the defect, the weaker the murmur. Diagnosis is made with echocardiography and immediate surgery is necessary.

Tamponade in a patient post-STEMI carries a very poor prognosis. Rupture of the free left ventricular wall leads to rapid filling of the pericardium with blood. This compresses the right ventricle and then the left ventricle, leading to hypotension. As a rule, the patient dies quickly, but sometimes the rupture is covered partially by adhesions that allow slower progression. Clinical signs are hypotension and tachycardia. The heart rate can vary with respiration (pulsus paradoxus) and the ECG may show electrical alternans (R-wave amplitude changes). Rapid infusion of fluid is a first treatment, followed by pericardial drainage and immediate transfer to surgery.

Post-myocardial infarction syndrome (Dressler's syndrome) is an inflammatory reaction that may occur usually 1–3 weeks post-STEMI. Fever, raised CRP, and pericardial effusion are seen. Treatment is with corticosteroids or NSAIDs for prolonged periods.

Coronary artery stent thrombosis is a dangerous condition with high mortality. The most common reasons are premature cessation of antiplatelet therapy or an undersized stent. Patients should be treated with PCI and the stent checked with intravascular ultrasound to verify that the struts are well opposed to the vessel wall. Platelet reactivity may be tested in patients with stent thrombosis.

Arrhythmias

Bradycardia and heart block is treated with atropine, isoprenaline (isoproterenol), or temporary transvenous pacing. It is a common complication following inferior infarction. Atrial fibrillation rate control is regulated primarily by beta-blockade and electrical cardioversion within 48 hours. Amiodarone can also be used. Ventricular arrhythmias leading to cardiac arrest are treated with cardiopulmonary resuscitation and defibrillation. Ventricular arrhythmias within 48 hours are considered part of the normal

course of an infarction and reperfusion, but if they occur later, an intracardiac defibrillator should be considered.

Prognosis and follow-up

Patients experiencing STEMI have a worse short-term prognosis than those with NSTE-ACS, but after 1 year, patients with NSTE-ACS fare almost as badly. Both conditions have a 1-year mortality of almost 15%. When comparing STEMI patients with NSTEMI patients with ST-depression, survival rates are similar, in part due to NSTEMI patients being generally older. The co-occurrence of diabetes or renal failure significantly impairs prognosis. It is important to provide the best secondary prevention as possible. This includes aspirin, ADP receptor antagonists, statins, beta-blockers, ACE inhibitors, and lifestyle changes, such as cessation of smoking, physical exercise five times a week, and diet recommendations.

References

1. Cheruvu PK, Finn AV, Gardner C, et al. (2007). Frequency and distribution of thin-cap fibroatheroma and ruptured plaques in human coronary arteries: a pathologic study. *Journal of the American College of Cardiology*, **50**, 940–9.
2. Van de Werf F, Bax J, Betriu A, et al. (2008). Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *European Heart Journal*, **29**, 2909–45.
3. Kushner FG, Hand M, Smith SC, Jr, et al. (2009). 2009 Focused updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*, **120**, 2271–306.
4. Kindermann I, Barth C, Mahfoud F, et al. (2012). Update on myocarditis. *Journal of the American College of Cardiology*, **59**, 779–92.
5. Hurst RT, Prasad A, Askew JW, 3rd, Sengupta PP, and Tajik AJ. (2010). Takotsubo cardiomyopathy: a unique cardiomyopathy with variable ventricular morphology. *JACC Cardiovascular Imaging*, **3**, 641–9.
6. Berne P and Brugada J. (2012). Brugada syndrome 2012. *Circulation Journal*, **76**, 1563–71.
7. Wallentin L, Becker RC, Budaj A, et al. (2009). Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *New England Journal of Medicine*, **361**, 1045–57.
8. Wiviott SD, Braunwald E, McCabe CH, et al. (2007). Prasugrel versus clopidogrel in patients with acute coronary syndromes. *New England Journal of Medicine*, **357**, 2001–15.
9. Boersma E. (2006). Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *European Heart Journal*, **27**, 779–88.
10. Mehran R, Lansky AJ, Witzenbichler B, et al. (2009). Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *Lancet*, **374**, 1149–59.
11. Grines CL. (1996). Should thrombolysis or primary angioplasty be the treatment of choice for acute myocardial infarction? Primary angioplasty—the strategy of choice. *New England Journal of Medicine*, **335**, 1313–16.
12. Gotberg M, Olivecrona GK, Koul S, et al. (2010).A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. *Circulation Cardiovascular Interventions*, **3**, 400–7.
13. Chen ZM, Pan HC, Chen YP, et al. (2005). Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*, **366**, 1622–32.

PART 5.4

Aortic dissection

CHAPTER 148

Pathophysiology, diagnosis, and management of aortic dissection

Samuel J. Youssef and John A. Elefteriades

Key points

- Have a high index of suspicion for aortic dissection in patients presenting with chest pain and remember it is 'the great masquerader' that can mimic disease of any organ.
- Aortic dissection kills via: rupture, cardiac tamponade, acute aortic insufficiency, and organ ischaemia.
- Use liberal imaging (usually by CT and echocardiography). Remember the utility of the 'triple rule-out CT' (to rule out dissection, myocardial infarction, pulmonary embolism).
- Upon diagnosis, start 'anti-impulse' treatment (Rx). Do not use unopposed afterload reduction (glyceryl trinitrate, nitroprusside) without concomitant ß-blockade to decrease dp/dt.
- Ascending aortic dissection requires urgent surgery; Descending aortic dissection is treated medically.

Introduction

A patient who presents to the emergency department with acute onset chest pain will more often be correctly diagnosed with an acute myocardial infarction, rather than an acute aortic dissection. However, if present and not accurately diagnosed, an acute aortic dissection will undoubtedly become a lethal event. This combination of characteristics—difficulty in diagnosis and lethality—poses a real challenge to caregivers on the front lines.

Acute aortic dissection has a well-known reputation as 'the great masquerader'. Presenting symptoms and signs may mimic the pathology of any organ system in the body (myocardial infarction, stroke, abdominal catastrophe, spinal cord injury, and limb ischaemia) [1]. By the time the aortic specialist is called, the hard work of sifting out and identifying the patient who is dissecting has already been done. Those of us who care for the thoracic aorta have a great deal of respect for the talented physicians charged with sorting out the aetiology and triaging the care for this critical illness.

Definition

Aortic dissection is a splitting of the aortic wall into inner and outer layers. The split occurs in mid media, at varying depths of penetration into the medial lamellae (Fig. 148.1). The split then propagates for varying distances longitudinally along the aorta. The most important distinction is between **ascending** (Type A) and **descending** (Type B) aortic dissection (Fig. 148.2).

Ascending aortic dissection begins with a tear 1–2 cm above the coronary ostia and propagates longitudinally along the aorta (usually to the aortic bifurcation or beyond). Ascending aortic dissection requires urgent surgery. Descending aortic dissection begins with an intimal tear 1–2 cm beyond the origin of the left subclavian artery and propagates for various distances down the aorta, usually to the aortic bifurcation or beyond. Descending aortic dissection is usually treated medically.

Aside from the distinction of ascending versus descending, it is important to recognize that aortic dissection can take three morphologies: **typical dissection** (with the splitting of two layers as just described), **penetrating ulcer** (in which an ulcer in the aortic wall permits entry of blood into the thickness of the aorta), and **intramural haematoma** (in which a crescentic layer of blood forms in the aortic wall, but without a frank separation of layers with an inner intimal flap) (Figs 148.3 and 148.4) [2]. All three can present with acute symptoms (pain), recently termed as the '**acute aortic syndrome**'.

Pathophysiology

Aortic disease was long thought to be a manifestation of arteriosclerosis. However, it is becoming increasingly clear that, for the ascending aorta especially, the development of aneurysm and dissection are not at all related to arteriosclerosis, or to arteriosclerotic risk factors, but rather are manifestations of inborn, genetically-mediated, connective tissue weakness [3–7].

The pathological sequence that leads to acute aortic dissection is now clarified [3], with its origins in the recognition that aortic aneurysm and dissection run strongly in families [3–7], and that acute physical and emotional stress can trigger aortic dissection [8–10]. We first identified this factor in five healthy young weight lifters treated at our institution within a short time for acute ascending aortic dissection.

Acute aortic dissection can kill a patient quickly in four ways (Fig. 148.5):

- Cardiac tamponade (from intrapericardial rupture of ascending aortic dissection).
- Acute aortic insufficiency (from distortion of the aortic valve).
- Free rupture (usually into the left pleural space).
- Organ ischaemia (any organ can be affected).

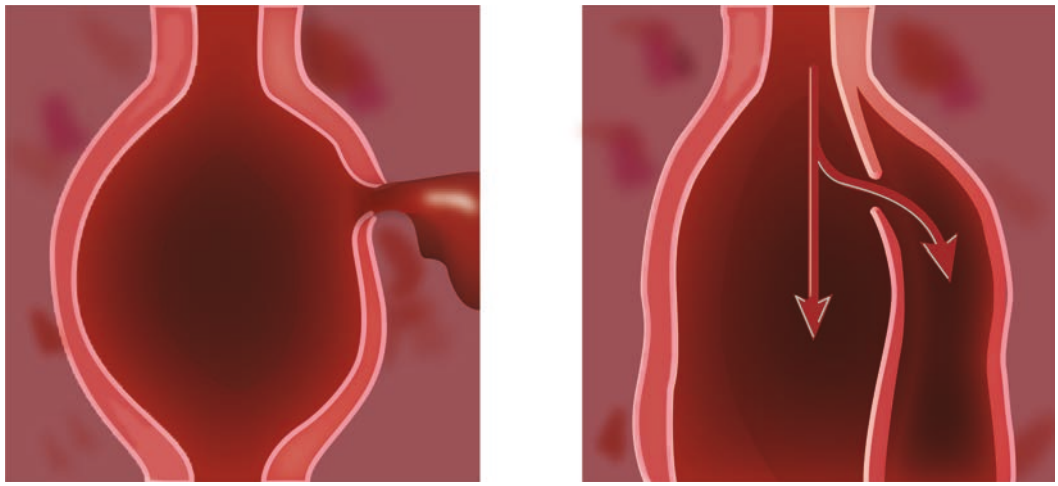


Fig. 148.1 Artist's depiction of aortic dissection. Note the difference between **free rupture**, shown schematically (left), and **aortic dissection** (right). In bottom right, note dissection in mid-media in this pathological specimen. Bottom left shows typical CT scan appearance of aortic dissection. Note flap in ascending and descending aorta.

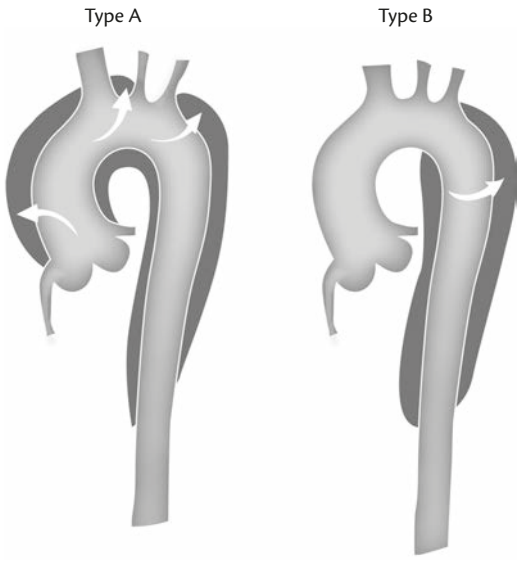


Fig. 148.2 Classification system for aortic dissection: Type A (ascending) and Type B (descending). Treatment is predicated on type (ascending usually requires urgent surgical replacement of the aorta, whereas descending is usually treated medically).

Diagnosis

Diagnosis of aortic dissection is both difficult and of paramount importance for the reasons mentioned in the introductory paragraph. The quintessential symptom is pain with characteristics that vividly reflect the nature of the disorder. The pain is described as the most severe possible (more than a kidney stone and more than childbirth), with a tearing or knife-like quality. With ascending dissection, the pain originates and is maximal under the breastbone. With descending dissection, the pain typically originates between the shoulder blades in the upper thoracic back. The pain may migrate distally as the dissection splits the layers further, travelling toward the abdomen and legs. The pain usually has an abrupt onset and is often preceded by acute physical exertion or an acute emotional event.

History

A family history of aortic aneurysm, aortic valve disease (bicuspid valve is strongly associated with aortic dissection), or premature sudden cardiac death should be sought.

Physical examination

This may be negative, but occasionally, the murmur of aortic insufficiency is heard, reflecting unseating of the aortic valve by an ascending aortic dissection. A pulse may be absent, usually a femoral, or perhaps a brachial or carotid. A difference in blood pressure between the two arms may be a clue that the branch arteries are being compromised. Patients may present in shock, usually reflecting internal bleeding from rupture of the dissection or cardiac tamponade from intrapericardial rupture. In the latter case, jugular venous distention and greyish discoloration of the face may be found.

The patient who presents with sharp, extremely severe, substernal chest pain of sudden onset following strenuous exertion may be easy to recognize as an acute ascending aortic dissection. However, aortic dissection may masquerade as a disease of virtually any organ of the body as any feeding branch of the aorta may be compromised or occluded by the dissection process (Fig. 148.5). Thus, aortic dissection may present as stroke, arm ischaemia, myocardial infarction, or pericarditis, paraplegia from involvement of critical intercostal arteries, an acute abdomen, or as leg ischaemia. Abdominal presentation is especially difficult to recognize. Aortic dissection is often misdiagnosed as anxiety attack, transient ischaemic attack, lumbar disc disease, cholecystitis, or gastroenteritis, among other possible diagnoses [1].

Certain physical stigmata may be part of the overall appearance in patients with connective tissue disease. A tall, thin body

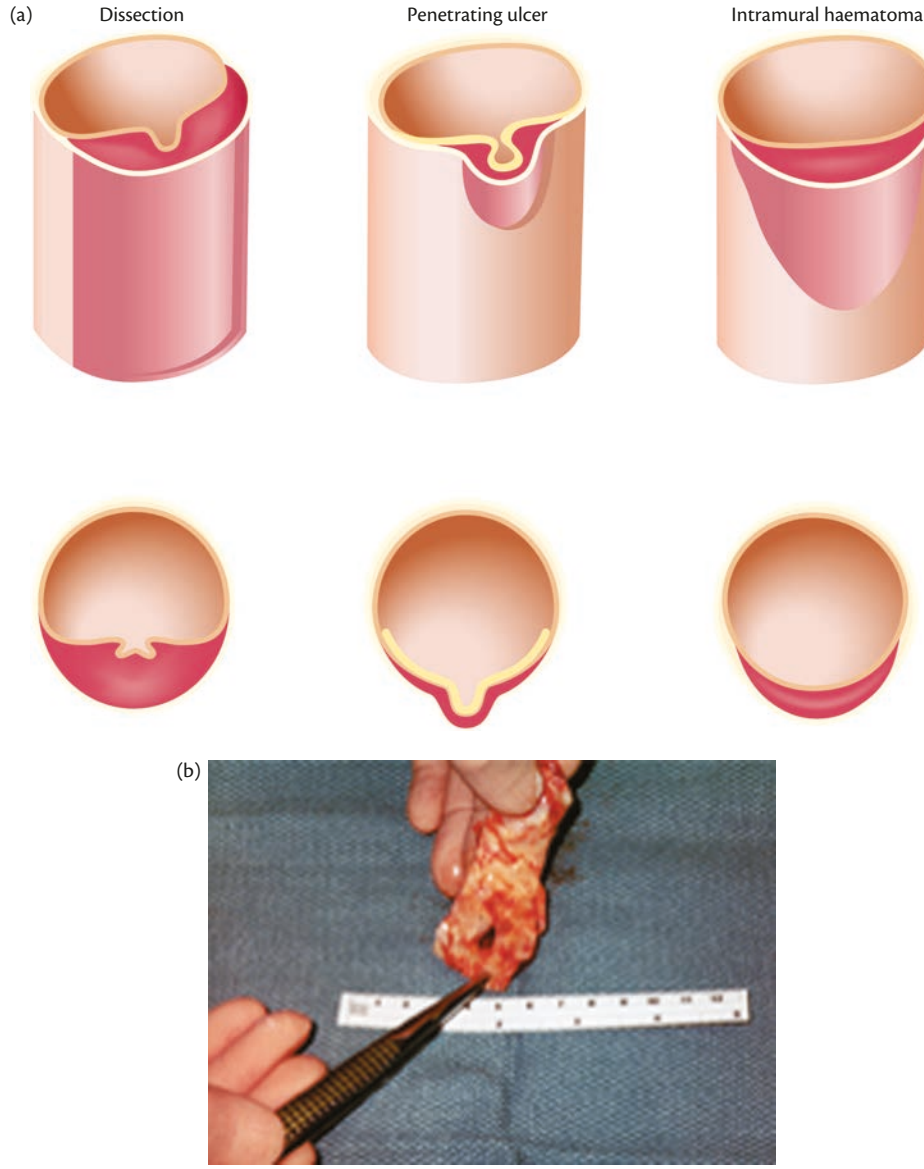


Fig. 148.3 Types of aortic dissection. (a) Typical aortic dissection with a flap traversing the lumen. Penetrating ulcer permits entry of blood into the aortic wall at the base of the ulcer. Intramural haematoma involves a circumferential collection of blood in the aortic wall, but without a frank flap. (b) Penetrating ulcer of the aorta (surgical specimen shown) closely resembles duodenal ulcer in its overall appearance.

build should be a clue, not only for Marfan's disease, but also for non-Marfanoid connective tissue disease. Pectus excavatum or carinatum is another sign of connective tissue disease, as is the 'thumb-palm sign' in which the thumb can stretch all the way beyond the flat palm. A history of 'double-jointedness' is another clue that the connective tissues are lax.

Laboratory tests

A full battery of blood tests is typically done for these patients. The D-dimer test is especially useful [11,12] as this is released very quickly from the breakdown of thrombus that invariably forms in the space between the dissected layers. The test is >99% sensitive at detecting aortic dissection so a negative test essentially excludes acute aortic dissection. It is poorly specific as it is also released in acute myocardial infarction, pulmonary embolism and other conditions. However, its sensitivity makes it of paramount value. Despite concerted efforts, no other predictive (before the fact) or diagnostic (after the fact) blood markers for aortic dissection have come into clinical practice, although promising progress is being made [12].

Imaging studies

The main advice is to **image liberally**. Whenever aortic dissection is in the differential diagnosis—and it should frequently be so—an imaging study should be obtained. Echocardiography, CT, and MRI are all sensitive and specific for aortic dissection. MRI is usually more difficult to obtain and the imaging facilities are often located remote from acute care areas. Transthoracic echocardiography

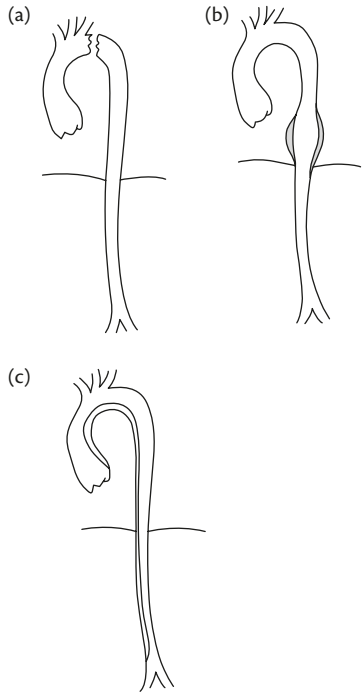


Fig. 148.4 Differentiation of three commonly confused conditions, whose terminology is often inappropriately applied—aortic transection (a), 'degenerative' aortic ulcer (b), and acute aortic dissection (c). See text.
Used with permission from Cardiotext Publishing. Elefteriades JA, et al., *House Officer's Guide to ICU Care*, Third Edition. 2012. Cardiotext. New York.

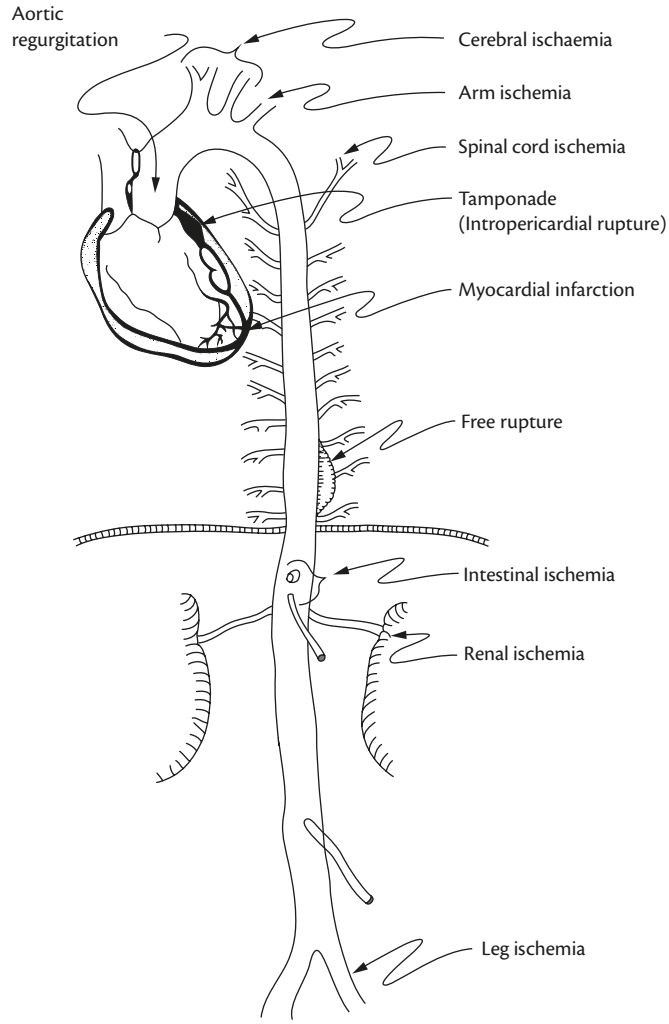


Fig. 148.5 The four ways that aortic dissection can kill in the early first hours—intrapericardial rupture with cardiac tamponade, acute aortic insufficiency (AI), free rupture into left pleural space, and ischaemia related to any branch of aorta (from coronary arteries to iliac vessels). See text.
Used with permission from Cardiotext Publishing. Elefteriades JA, et al., *House Officer's Guide to ICU Care*, Third Edition. 2012. Cardiotext. New York.

(TTE) is available in essentially every emergency department and is completely benign. It is important to recognize, however, that TTE cannot 'see' more than a few centimetres up the aorta from the aortic valve. CT imaging is also recommended for a complete visualization of the aorta, especially the TTE-inaccessible descending aorta. Transoesophageal echo (TEE) gives even more precise images and can certainly be employed. It is important to avoid the patient's bucking and straining against the TEE probe; we have seen many cases where the stimulus of a TEE probe or an endotracheal tube is just enough to produce rupture of an ascending aortic dissection.

Between TTE and CT scan, aortic dissection will essentially be ruled in or out conclusively. The CT scan will also be of other benefit. The 'triple rule-out CT' [1] recognizes the three chest conditions that may commonly take the life of an acutely-ill patient and all may be ruled in or out by CT scanning. These are aortic dissection, acute pulmonary embolism, which will be seen clearly on contrast CT, and acute myocardial infarction. While the CT will not visualize the myocardial infarct itself, it will show the coronary calcification that leads to the infarction.

A plain chest X-ray can also give important clues about the aorta. The aortic contours can usually be well discerned. The ascending aorta, if enlarged or dissected, will 'peek out' beyond the right mediastinal shadow. The aortic knob, representing the aortic arch will be enlarged if the arch is large or dissected. The paravertebral straight line representing the descending aorta will be enlarged and/or deviated if the descending aorta is enlarged or dissected. Not infrequently, alterations in the aortic silhouette may be the 'smoking gun' left behind by an acute aortic dissection.

Management

The main goal upon presentation is to entertain and confirm the diagnosis of aortic dissection.

The second goal is to begin medical management of the dissection [13,14]. Initial management, regardless of the type of dissection and irrespective of whether or not surgery is pending, entails the so-called 'anti-impulse' therapy. Blood pressure must be lowered to decrease aortic wall tension. This is done by straightforward means, usually with intravenous (iv) glyceryl trinitrate or nitroprusside. However, it is vital to recognize that, without concomitant beta-blocking therapy to decrease the strength of the cardiac impulse, or dp/dt, lowering the blood pressure will actually increase stress on the aortic wall. Thus, along with the afterload-reducing drugs, we administer a β-blocker, usually esmolol intravenously. Labetalol, which has both α- and β-blocking properties and thus offers afterload reduction, is an acceptable alternative to the

two-drug combination. In patients with bronchospasm in whom β-blockers are to be avoided, we often use a calcium channel blocker to decrease dp/dt. Table 148.1 gives a complete roster of therapeutic alternatives for anti-impulse therapy.

In a patient with an acute aortic dissection, we usually aim to drop the systolic blood pressure to about 90 mmHg, at least initially. Mentation and urine output are closely monitored, and if such a low pressure produces mental changes or oliguria, we mildly liberalize our blood pressure (BP) target. Some patients with chronic hypertension and severe vascular disease may not be able to function at low pressures, and there may be no alternative but to permit systolic BPs of 120–130 mmHg.

Pearls and pitfalls

The heavy burden of misdiagnosis comes not necessarily from the mere fact of having a wrong diagnosis, but rather from the sequelae of initiating a treatment plan that can exacerbate another condition. Such is the case in an acute aortic dissection mistaken for an acute coronary event. The mainstay of emergency room treatment in ruling out a coronary syndrome is to anticoagulate, and then rush the patient to the catheterization laboratory. While a heparin bolus or TPA administration will benefit the coronary syndrome, such treatment will let loose the aortic dissection, leading to aortic rupture and sudden death. Hence, no patient with sudden onset chest pain should go to the catheterization laboratory or receive anticoagulation without first having at least a chest X-ray or echo, and a full physical exam including all peripheral pulses. Once a dissection is ruled out, then the emergency room physician can proceed to expedite the 'door-to-balloon' time.

The pearls of diagnosing a dissection reside in careful evaluation of the presenting history and physical exam. A genetic predisposition coupled with an inciting event (emotional or physical stress) may bring a young weight lifter or a post-partum mother into the emergency department with severe tearing chest pain—and an aortic dissection. Also, it is essential to remember the possible masquerade behind any patient presenting with a stroke, unilateral arm weakness, sudden onset abdominal pain, or severe back pain; these deceptive symptoms may have their origin in aortic dissection.

Definitive treatment

Definitive treatment depends on the location of the aortic dissection. Ascending aortic dissections, with a tear just above the coronary arteries, require urgent surgery because of the danger of death from rupture, tamponade, coronary ischaemia, or aortic insufficiency. It has been estimated that these patients die at about 1% per hour, in the absence of surgical treatment. However, if the diagnosis of aortic dissection is made in a delayed fashion, as is often the case, the 'eye of the storm' may have passed, and surgery may be done semi-electively. Specifically, if more than 48–72 hours has passed between the onset of symptoms and correct diagnosis, we usually do not operate in the middle of the night. It is not uncommon for a late diagnosis of this type to be made, usually by accident through an imaging study done for another purpose.

Descending aortic dissections are managed by a 'complication-specific' approach. If there are no complications, they are managed exclusively medically with anti-impulse therapy, transitioned after several days to oral therapy. A repeat CT scan is

Table 148.1 Intravenous agents for treatment of ascending dissection

Name	Category	Loading dose	Maintenance dose	Adverse effects	Caution
Sodium nitroprusside	Vasodilator	0.3–3 mcg/kg/min; max. limit for an adult is 10 mcg/kg/min for 10 min	1–3 mcg/kg/min	Nausea, vomiting, agitation, muscle twitching, sweating, cutis anserina and cyanide toxicity, tachycardia	In patients with hepatic or renal dysfunction
Propranolol	β-blocker	1–3 mg (given at 1 mg intervals over 1 minutes). Can be repeated not less than every 4 hours	1–3 mg every 4 hours	Hypotension, nausea, dizziness, cold extremities, reversible hair loss, bradycardia	In patients with bradycardia or history of CHF and bronchospasm. Max. initial dose should not exceed 0.15 mg/hour
Esmolol	β-blocker	500 mcg/kg bolus	Continuous iv infusion from 50 to 200 mcg/kg/min	Hypotension, nausea, dizziness, bronchospasm, dyspepsia, constipation, increases digoxin level	In patients with CHF or asthma or on concomitant CCB therapy
Labetalol	α- & β-blockers	20 mg over 2 minutes, then 40–80 mg every 10–15 minutes (max. 300)	Continuous iv infusion starting at 2 mg/min and titrate up to 5–10 mg/min	Vomiting, nausea, scalp tingling, burning in throat, dizziness, heart disease, block, orthostatic hypotension	In patients with concomitant CCB therapy
Diltiazem	CCB	0.25 mg/kg iv bolus (up to 25 mg)	5–10 mg/hour by continuous infusion	Heart block, constipation, liver dysfunction	In patients with heart failure, concomitant β–blocker therapy
Enalapril	Vasodilator ACE inhibitor	0.625–1.25 mg bolus	0.625–5 mg every 6 hours	Precipitates fall in BP in high renin states, variable response, renal failure	In patients with high possibility of MI, renal dysfunction
Fenoldopam	Dopamine D1 receptor agonist	0.03–0.1 mcg/kg/min initially	0.1–0.3 mcg/kg/min, max. 1.6 mcg/kg/min	Tachycardia, hypotension, headache, nausea, flushing, hypokalaemia, elevation of IOP	In patients with glaucoma

CCB, calcium channel blocker; ACE, angiotensin-converting enzyme; iv, intravenous; BP, blood pressure; IOP, intraocular pressure; CHF, congestive heart failure; MI, myocardial ischaemia.

performed at 72 hours and then again before hospital discharge, to ensure there is no rapid early progression on medical therapy.

If there are complications of descending aortic dissection, then surgery is required. For rupture, aortic replacement is performed. For organ ischaemia, surgical fenestration is performed, taking the pressure off the true lumen, and permitting resumption of organ flow. For persistent pain or rapid enlargement, surgical replacement is performed.

Interventional therapy, with endovascular stent therapy, is developing a role in the treatment of aortic dissection. Some ruptures and rapid enlargements may be treated by stent. Organ ischaemia may be treated by stenting open the compromised vessel. Fenestration can be done by deliberate endovascular rupture or incision of the offending false membrane. These therapies have produced satisfactory early results. Although often performed with the goal of 'obliterating the false lumen', endovascular therapy of uncomplicated descending aortic dissection is unproven and potentially harmful. Retrograde dissection into the ascending aorta, a very serious complication, is seen in a percentage of patients subjected to routine stent placement for uncomplicated descending aortic dissection.

Conclusion

Aortic dissection is a virulent foe for those on the front lines in the Emergency Department and those doing later battle in the operating room. By following key principles, based on recent data, this shrewd opponent can be combatted. Although still a humbling disease, as for Osler 100 years ago, aortic dissection is slowly yielding to thoughtful, evidence-based diagnosis, and therapy.

References

1. Elefteriades JA, Barrett PW, and Kopf GS. (2008). Litigation in non-traumatic aortic diseases—a tempest in the malpractice maelstrom. *Cardiology*, **1–9**, 263–72.
2. Tittle SL, Lynch RJ, Cole PE, et al. (2002). Midterm follow-up of penetrating ulcer and intramural hematoma of the aorta. *Journal of Thoracic and Cardiovascular Surgery*, **123**, 1051–9.
3. Elefteriades JA and Farkas EA. (2010). Thoracic aortic aneurysm: clinically pertinent controversies and uncertainties. *Journal of the American College of Cardiology*, **55**, 841–57.
4. Coady MA, Davies RR, Roberts M, et al. (1999). Familial patterns of thoracic aortic aneurysms. *Archives of Surgery*, **134**, 361–7.
5. Albornoz G, Coady MA, Roberts M, Davies RR, Rizzo J, and Elefteriades JA. (2006). Familial thoracic aortic aneurysms and dissections—incidence, modes of inheritance, and phenotypic patterns. *Annals of Thoracic Surgery*, **82**, 1400–5.
6. Milewicz DM, Michael K, Fisher N, Coselli JS, Markello T, and Biddinger A. (1996). Fibrillin-1 (FBN1) mutations in patients with thoracic aortic aneurysms. *Circulation*, **94**, 2708–11.
7. Putnam EA, Zhang H, Ramirez F, and Milewicz DM. (1995). Fibrillin-2 (FBN2) mutations result in the Marfan-like disorder, congenital contractual arachnodactyly. *Nature Genetics*, **11**, 456–8.
8. Elefteriades JA, Hatzaras I, Tranquilli MA, et al. (2003). Weight lifting and rupture of silent aortic aneurysms. *Journal of the American Medical Association*, **290**, 2803.
9. Hatzaras I, Tranquilli M, Coady MA, Barrett PW, Bible J, and Elefteriades JA. (2006). Weight lifting and aortic dissection: more evidence for a connection. *Cardiology*, **107**, 103–6.
10. Hatzaras IS, Bible JE, Koullias GJ, Tranquilli M, Singh M, and Elefteriades JA. (2007). Role of exertion or emotion as inciting events for acute aortic dissection. *American Journal of Cardiology*, **100**, 1470–2.
11. Ohlmann P, Faure A, Morel O, et al. (2006). Diagnostic and prognostic value of circulating D-dimers in patients with acute aortic dissection. *Critical Care Medicine*, **34**, 1358–64.
12. Trimarchi S, Sangiorgi G, Sang X, et al. (2010). In search of blood tests for thoracic aortic diseases. *Annals of Thoracic Surgery*, **90**, 1735–42.
13. Sanz J, Einstein J, and Fuster V. (2007) Acute aortic dissection: anti-impulse therapy. In: Elefteriades JA (ed.) *Acute Aortic Disease*. New York, NY: Informa Healthcare.
14. Feldman M, Shah M, and Elefteriades JA. (2009). Medical management of acute type A aortic dissection. *Annals of Thoracic and Cardiovascular Surgery*, **15**, 286–93.

PART 5.5

The hypotensive patient

CHAPTER 149

Pathophysiology of shock

Antoine Kimmoun and Bruno Levy

Key points

- Commonly described shock states can be categorized into 'distributive shock' usually characterized by high cardiac output and low peripheral vascular resistance, and 'resistive shock' characterized by low cardiac output and high peripheral vascular resistance.
- Cardiogenic and hypovolaemic shock induce an ischaemia reperfusion syndrome.
- Septic shock and ischaemia reperfusion syndrome share a common pathophysiology.
- Nitric oxide overproduction is the cornerstone of vascular hyporeactivity in shock states.
- Decreased myofilament calcium sensitivity probably plays a major role in cardiac dysfunction in shock states.

Introduction

Shock has been defined as 'a life-threatening, generalized maldistribution of blood flow resulting in failure to deliver and/or utilize adequate amounts of oxygen, leading to tissue dysoxia' [1]. Shock is traditionally categorized into:

- **Cardiogenic shock**: impairment of cardiac reserve.
- **Obstructive shock**: obstruction of normal circulatory flow.
- **Hypovolaemic shock**: fluid losses decreasing ventricular preload.
- **Distributive shock**: vascular hyporesponsiveness resulting in abnormal blood flow distribution.

These initial haemodynamic disorders all lead to tissue hypoperfusion and are often inter-related. Clinically, they share a common presentation—hypotension with a particular pattern for each shock type, tachycardia, oliguria, mottling, pallor, coldness, peripheral cyanosis, altered mental status, and dyspnoea. Lactic acidosis is most often observed during shock states.

Over the last two decades, a new pathophysiological approach has emerged following recognition of the immune-inflammatory response as both cause and consequence of various shock states, and related complications, such as vascular hyporesponsiveness. Thus, pro-inflammatory cytokines play a major role in the initiation of sepsis leading to hypotension, tissue hypoperfusion, and vascular hyporeactivity. Similarly, ischaemia reperfusion injury during cardiogenic or hypovolaemic shock is also associated with massive cytokine release and multi-organ failure.

We will briefly review the different shock states and the common characteristics of vascular and cardiac hyporesponsiveness to catecholamines. Anaphylactic shock is discussed elsewhere.

Shock categories

The commonly described shock states can be categorized into 'distributive shock' (septic, anaphylactic) usually characterized by high cardiac output and low peripheral vascular resistance, and 'resistive shock' (cardiogenic, hypovolaemic, obstructive) characterized by low cardiac output and high peripheral vascular resistance.

Septic shock

This is currently defined by pre-existing sepsis with systolic arterial pressure (SAP) <90 mmHg or mean arterial pressure (MAP) <70 mmHg in the absence of other causes of hypotension and despite adequate fluid resuscitation [2]. The initial reduction in vascular tone with a hyperdynamic cardiac state accounts for the relatively sustained SAP, low diastolic arterial pressure (DAP) and wide pulse pressure (PP) (= SAP – DAP). The decreased vascular resistance to left ventricular ejection allows a maintained/elevated cardiac output despite a frequent myocardial depression. At the tissue level, there is an initial increase in oxygen demand associated with a limited oxygen extraction capacity and microcirculatory flow redistribution. At the cellular level, mitochondria cannot utilize oxygen for oxidative phosphorylation and ATP production [3]. Consequently, SvO_2, a global marker of tissue oxygen balance, is usually normal or elevated in the euvolaemic septic patient.

During any phase of septic shock, although more frequently seen later on, cardiac performance can decrease with depressed systolic function and a low cardiac output. This septic cardiomyopathy is, however, completely reversible with the resolution of shock.

Hypovolaemic shock

This is the commonest shock state and often relates to blood loss from blunt and/or penetrating traumatic injuries, gastrointestinal bleeding, aortic rupture, and post-operative haemorrhage. Severe dehydration (extensive burns, massive emesis, profuse diarrhoea, etc.) is also a frequent cause of hypovolaemic shock.

The reduction in venous return leads to a decreased cardiac output with, early on, preserved vascular tone and reactivity. Thus, a typical haemodynamic pattern is of a low SAP (<90 mmHg) and MAP (<65 mmHg) with a relatively sustained DAP and narrow PP. Sympathetic adrenergic stimulation is preserved, increasing central vascular contraction. However, in some organ beds, blood flow is preserved, while in others there is vasoconstriction and reduced flow.

Two adaptive mechanisms permit an increase in tissue oxygen extraction:

- Redistribution of organ blood flow towards organs with high oxygen extraction (brain, heart), while sacrificing flow to organs with low extraction (e.g. skin, splanchnic area).

- Microcirculatory recruitment within heart and brain.

Hence, mixed venous oxygen saturation is decreased due to increased oxygen extraction, but in the most severe cases, massive release of pro-inflammatory cytokines occurs through prolonged ischaemia and subsequent reperfusion, promoting a sepsis-like syndrome with multiple organ failure.

Cardiogenic and obstructive shock

Here, cardiac failure results from either myocardial pump injury or obstruction of ventricular ejection. Extensive myocardial infarction, myocardial stunning (post-cardiac surgery, post-cardiac arrest, Takotsubo syndrome), myocarditis, severe arrhythmias, and valvular cardiomyopathies are the most common causes of non-obstructive cardiogenic shock.

Massive pulmonary embolism and cardiac tamponade are the two principal aetiologies underlying obstructive shock. In the former, the obstacle is in the right outflow tract leading to specific right ventricular dysfunction with the paradoxical septal motion of acute cor pulmonale. In contrast, cardiac tamponade directly affects filling of the left and right ventricles. It typically presents as a low cardiac index (<2.2 L/min/m^2) with increased left ventricular diastolic pressure and high systemic vascular resistance. As in hypovolaemic shock, sympathetic adrenergic stimulation is preserved, and tissue oxygen extraction increases via the same mechanisms. Thus, the haemodynamic pattern is similar to hypovolaemic shock, and only the clinical context (e.g. history of chest pain, pulmonary oedema symptoms), preload-dependency (or otherwise) for cardiac output, and echocardiography can reliably distinguish between them.

While this haemodynamic classification serves an educational purpose, in reality it often becomes increasingly complex when the consequences of resuscitation including ischaemia reperfusion and bacterial translocation are considered. These may contribute towards vascular hyporesponsiveness that may exacerbate symptoms and worsen prognosis.

Septic shock-induced vasoplegia and ischaemia reperfusion: a common pathophysiology for cardiovascular hyporeactivity

Shock states are associated with a dysregulated inflammatory response due to either the primary insult (sepsis) or secondary to an ischaemia reperfusion syndrome (haemorrhagic or cardiogenic shock). In advanced stages, all shock states evolve to a common haemodynamic pattern usually characterized by both vascular and cardiac dysfunction.

During septic shock, pathogen-associated molecular patterns (PAMPs) such as endotoxins, lipoproteins, and outer membrane proteins are recognized by pattern recognition receptors (e.g. Toll-like receptors [TLRs]) located on immune cell types. This induces signal transduction resulting in increased transcription of nuclear factor-κb (NF-κb) and other factors that, in turn, initiate and amplify the pro-inflammatory response leading to cardiovascular dysfunction.

Ischaemia-reperfusion injury plays a major role in both prolonged, and resuscitated haemorrhagic and cardiogenic shock. TLRs are also involved, responding to endogenous damage-associated molecular patterns (DAMPs) released from reperfusion (e.g. heat shock protein-70, haem, mitochondria).

Irrespective of the initial aetiology, the NF-κb system activates >150 pro-inflammatory genes and receptors (iNOS, COX-2, IL-1, IL-6, TNFα …), thereby explaining the shared pathophysiology of different shock states. The role of counter-inflammatory signalling, including the cholinergic anti-inflammatory pathway, is also being investigated. The balance between pro- and counter-inflammatory mechanisms is increasingly recognized as an important area for focus.

Vascular hyporesponsiveness

While there is currently no clear published definition, we propose that vascular hyporesponsiveness represents an inability to increase blood pressure despite vasopressors in shocked patients. Accordingly, vascular hyporeactivity is the failure of vascular smooth muscle constriction to sustain a sufficient blood pressure. Various mechanisms are involved:

Nitric oxide

Nitric oxide (NO) has many roles, including participation in the regulation of blood flow, coagulation, neural activity, and immune functions. It is produced in picomolar concentrations from L-arginine in endothelial and other cells by cNOS, a constitutive isoform of NO synthase. NO diffuses through the endothelium to the vascular smooth muscle cell (VSMC) cytoplasm, inducing vasorelaxation. However, inflammation during shock leads to expression of the inducible isoform, iNOS, in vessel walls and within the smooth muscle with a 1000-fold increase in NO production.

Vasodilator effects of NO have been widely studied, particularly in septic shock. The pressor response to noradrenaline is significantly affected, but restored by NOS inhibition. As this reversal is endothelium-independent, this strongly implies VSMC NO production by iNOS. This probably explains the profound vasoplegia and limited response to stimuli that normally regulate blood flow and tissue perfusion.

NO overproduction during ischaemia reperfusion injury from cardiogenic or haemorrhagic shock is also largely involved in vascular hyporesponsiveness. In the SHOCK trial of patients with cardiogenic shock, one-fifth exhibited clinical evidence of systemic inflammation [4]. High levels of iNOS and NO have been observed in models of reperfusion following myocardial infarction [5]. Haemorrhagic shock also induces NOS activation with vascular hyporesponsiveness to adrenergic agonists that can be reversed by NOS inhibition [6]. However, blocking NO production can lead to serious negative effects.

Free radicals: peroxynitrite and superoxide

Free radicals, such as superoxide, are highly unstable molecules generated via incomplete reduction of molecular oxygen that have one or more unpaired electrons in their outer orbital. Increased formation of NO and superoxide generates large quantities of peroxynitrite. This reactive nitrogen species may be responsible for much of the biological effect of NO [7]. Overproduction during a state of 'oxidative stress' can induce organ injury and, more specifically, endothelial dysfunction and hypovasoreactivity.

During septic shock, vascular hyporeactivity can be reversed by peroxynitrite inhibition or by genetic suppression of NADPH, which reduces peroxynitrite [7]. Catecholamines can also be auto-oxidized by superoxide. Likewise, peroxynitrite worsened

vascular hyporesponsiveness to catecholamines in cardiogenic shock, while ischaemia reperfusion injury generated excess peroxynitrite in experimental haemorrhagic shock [8].

Prostacyclin and COX-2 pathways

Prostacyclin (PGI2), a lipid mediator belonging to the prostaglandin family, is a main product of arachidonic acid metabolism produced in the endothelium by cyclo-oxygenase (COX) and prostacyclin synthase. PGI2 has potent antithrombotic and vasodilator effects. Vasorelaxant effects on VSMCs are mediated through cAMP after stimulation of inositol phosphate [9]. In sepsis, PGI2 is up-regulated, mainly by COX-2, an inducible isoform of COX. Use of a COX-2 blocker restored blood pressure experimentally [10].

PGI2 is also elevated in experimental resuscitated haemorrhagic shock. Splanchnic blood flow decreased with a compensatory release of PGI2 and an increase in COX expression. High prostacyclin levels have been measured in lung and hepatic injury following ischaemia reperfusion [11].

ATP-sensitive potassium channels

Under normal conditions, channel opening induces K^+ loss from the cell resulting in membrane repolarization. Excessive activation on VSMC membranes leads to hyperpolarization and inhibition of voltage-sensitive calcium channels, inducing cell relaxation, vasodilation, hypotension, and vascular hyporeactivity. Hypoxia, acidosis, hyperlactataemia, NO, and peroxynitrite all activate ATP-sensitive (K_{ATP}) K^+ channels, leading to vasorelaxation.

K_{ATP} channels are implicated in vascular hyporeactivity during septic shock, where they are over-expressed and partially regulated by NO via NF-κB activation [12]. K_{ATP} channel inhibition by glibenclamide (glyburide) can effectively restore systemic haemodynamics and regional perfusion in prolonged haemorrhagic shock. However, this activation may actually protect the myocardium against ischaemia or during reperfusion acidosis [13].

Large conductance calcium-activated potassium channels

Large conductance calcium-activated potassium (BKCa) channels are the most widespread vascular K^+ channel. During depolarization, high levels of intracellular calcium activate BKCa channels, inducing hyperpolarization and contributing to VSMC relaxation. NO, peroxynitrite, and superoxide are involved in BKCa modulation during shock states. Specific inhibition of the BKCa channel however produced variable results [12].

Vascular hyporesponsiveness following resuscitated haemorrhagic shock is also, in part, mediated by BKCa activation. As with K_{ATP} channels, BKCa may have a protective effect on ischaemic myocardium [14].

Critical illness-related corticosteroid insufficiency

Critical illness-related corticosteroid insufficiency (CIRCI) is characterized by adrenal insufficiency, tissue resistance to glucocorticoids and an excessive pro-inflammatory response. Glucocorticoids and mineralocorticoids improve the vasoconstrictor response to catecholamines [15]. However, underlying mechanisms remain complex and probably involve various pathways, e.g. iNOS, COX-2 inhibition, phosphoinositide stimulation, and inhibition of NF-κb. By decreasing NF-κb, corticosteroids decrease NO production via iNOS. Corticosteroids involve both genomic and non-genomic effects after activation of its nuclear receptor [16].

Adrenal insufficiency has not been formally assessed during cardiogenic shock. However, during severe trauma and haemorrhagic shock, limited retrospective studies reported a significantly higher mortality, longer hospital, and intensive care lengths of stay, and fewer ventilator-free days in untreated adrenal-insufficient patients [17].

Modifications of catecholamine signalling

During the early hyperkinetic phase of septic shock, myocardial α_1-adrenoreceptors are externalized to the sarcolemma, but are internalized during the late hypokinetic phase. Peroxynitrite decreases the number of α_{1a}- and α_{1d}-adrenoreceptors without altering their affinities and also inhibits the increase in intracellular calcium normally stimulated by norepinephrine.

Catecholamine signalling has been less studied during haemorrhagic or cardiogenic shock. Prolonged ischaemia can result in a 'no reflow' phenomenon with intense vasoconstriction at the early stage of reperfusion completely impeding blood flow, resulting in vascular damage and catecholamine hyporesponsiveness.

Myocardial dysfunction during shock

Septic shock

Myocardial dysfunction, a frequent (30–70%) complication of septic shock, is characterized by reversible biventricular systolic and diastolic dysfunction. Many factors contribute to cardiac depression at both supracellular and cellular levels, although reduced coronary blood flow is not contributory. The sepsis-related increase in plasma troponin is not related to necrosis, but possibly to transient pro-inflammatory cytokine-related increases in cardiomyocyte membrane permeability [18]. Circulating myocardial depressant factors (e.g. IL-1, IL-6, TNFα) probably explains the myocardial depression observed during initial sepsis. However, cardiac performance remains altered over 7 days, whereas cytokine levels normalize within 48 hours. Therefore, intrinsic impairments of cardiac muscle probably participate in prolonged cardiac impairment:

- Beta-adrenergic receptors and beta-agonist efficacy are decreased during late septic shock in humans [19].
- Decreased cardiomyofilament calcium sensitivity likely plays a major role [20].
- Excess peroxynitrite decreases ventricular contractility by depressing mitochondrial function and by inducing calcium flux abnormalities [7].

Ischaemia reperfusion

Ischaemia reperfusion during cardiogenic or haemorrhagic shock may contribute to transient cardiac dysfunction. During the no-flow phase, prolonged ischaemia leads to a decrease in ATP synthesis, plasma membrane depolarization and activation of voltage-dependent calcium channels. The sarcolemma releases calcium into the cytoplasm, and this is responsible for myocardial cellular damage and contractile dysfunction.

Reperfusion, subsequent to resuscitation, induces major cytotoxicity with the formation of reactive oxygen species, which, in

turn, inactivates cytochromes and damages cellular membranes. Reperfusion is also associated with endothelial damage and an acute pro-oxidant state leading to production of pro-inflammatory cytokines, adhesion molecules and complement activation. These processes extend the myocardial dysfunction.

Conclusion

The classification of shock states is traditionally driven by typical haemodynamic assessment. However, this pragmatic approach remains part of the pathophysiological process. Clinicians must be aware that, in the latter stages, cardiovascular hyporesponsiveness is not only a consequence of shock aetiology, but is also secondary to the shock-induced pro-inflammatory process.

References

1. Antonelli M, Levy M, Andrews PJ, et al. (2007). Hemodynamic monitoring in shock and implications for management. International Consensus Conference, Paris, France, 27–28 April 2006. *Intensive Care Medicine*, **33**, 575–90.
2. Dellinger RP, Levy MM, Carlet JM, et al. (2008). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Critical Care Medicine*, **36**, 296–327.
3. Brealey D, Brand M, Hargreaves I, et al. (2002). Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet*, **360**, 219–23.
4. Kohsaka S, Menon V, Lowe AM, et al. (2005). Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. *Archives of Internal Medicine*, **165**, 1643–50.
5. Wildhirt SM, Dudek RR, Suzuki H, and Bing RJ. (1995). Involvement of inducible nitric oxide synthase in the inflammatory process of myocardial infarction. *International Journal of Cardiology*, **5**, 253–61.
6. Thiemermann C, Szabo C, Mitchell JA, and Vane JR. (1993). Vascular hyporeactivity to vasoconstrictor agents and hemodynamic decompensation in hemorrhagic shock is mediated by nitric oxide. *Proceedings of the National Academy of Sciences, USA*, **90**, 267–71.
7. Pacher P, Beckman JS, and Liaudet L. (2007). Nitric oxide and peroxynitrite in health and disease. *Physiology Reviews*, **87**, 315–424.
8. Szabo C, Salzman AL, and Ischiropoulos H. (1995). Peroxynitrite-mediated oxidation of dihydrorhodamine 123 occurs in early stages of endotoxic and hemorrhagic shock and ischemia-reperfusion injury. *FEBS Letters*, **372**, 229–32.
9. Vane J and Corin RE. (2003). Prostacyclin: a vascular mediator. *European Journal of Vascular and Endovascular Surgery*, **26**, 571–8.
10. Hocherl K, Dreher F, Kurtz A, and Bucher M. (2002). Cyclooxygenase-2 inhibition attenuates lipopolysaccharide-induced cardiovascular failure. *Hypertension*, **40**, 947–53.
11. Ljungman AG, Grum CM, Deeb GM, Bolling SF, and Morganroth ML. (1991). Inhibition of cyclooxygenase metabolite production attenuates ischemia-reperfusion lung injury. *American Reviews of Respiratory Diseases*, **143**, 610–17.
12. Collin S, Sennoun N, Dron AG, et al. (2011). Vascular ATP-sensitive potassium channels are over-expressed and partially regulated by nitric oxide in experimental septic shock. *Intensive Care Medicine*, **37**, 861–9.
13. Hsu CY, Fang SY, Chen YZ, et al. (2012). Cardiovascular protection of activating KATP channel during ischemia-reperfusion acidosis. *Shock*, **37**, 653–8.
14. Cao CM, Xia Q, Gao Q, Chen M, and Wong TM. (2005). Calcium-activated potassium channel triggers cardioprotection of ischemic preconditioning. *Journal of Pharmacology and Experimental Therapy*, **312**, 644–50.
15. Yard AC and Kadowitz PJ. (1972). Studies on the mechanism of hydrocortisone potentiation of vasoconstrictor responses to epinephrine in the anesthetized animal. *European Journal of Pharmacology*, **20**, 1–9.
16. Leach M, Hamilton LC, Olbrich A, Wray GM, and Thiemermann C. (1998). Effects of inhibitors of the activity of cyclo-oxygenase-2 on the hypotension and multiple organ dysfunction caused by endotoxin: a comparison with dexamethasone. *British Journal of Pharmacology*, **124**, 586–92.
17. Rushing GD, Britt RC, Collins JN, Cole FJ, Weireter LJ, and Britt LD. (2006). Adrenal insufficiency in hemorrhagic shock. *American Surgery*, **72**, 552–4.
18. Wu AH. (2001). Increased troponin in patients with sepsis and septic shock: myocardial necrosis or reversible myocardial depression? *Intensive Care Medicine*, **27**, 959–61.
19. Silverman HJ, Penaranda R, Orens JB, and Lee NH. (1993). Impaired beta-adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: association with myocardial hyporesponsiveness to catecholamines. *Critical Care Medicine*, **21**, 31–9.
20. Tavernier B, Garrigue D, Boulle C, Vallet B, and Adnet P. (1998). Myofilament calcium sensitivity is decreased in skinned cardiac fibres of endotoxin-treated rabbits. *Cardiovascular Research*, **38**, 472–9.

CHAPTER 150

Diagnosis and management of shock in the ICU

Antoinette Spevetz and Joseph E. Parrillo

Key points

- If the underlying process leading to shock is corrected quickly and circulating volume is restored in a timely fashion, the progression of shock can be reversed.
- Despite different causes of shock there is a common pathway that involves similar biochemical and metabolic pathways, such that the cardiovascular system is unable to cope with the insult.
- The body has the capability to autoregulate over a wide range of blood pressures (mean arterial pressure 50–150 mmHg).
- Shock affects multiple organs in the body. These effects may or may not be reversible depending upon the duration of the shock state.
- Shock may not be recognized initially based upon vital signs and common physiological parameters. Lactate production seems to be a better marker for the recognition of shock.

Introduction

The word 'shock' used in everyday conversation usually refers to an emotional reaction to a stressful situation. In medicine 'shock' refers to a disease state that describes the body's response to a stressful situation. It is more specifically defined as inadequate tissue perfusion resulting in cellular injury. For varying reasons, the tissues do not receive enough oxygen and nutrients to function normally. This can ultimately lead to cell death that can progress to organ failure and, finally, death of the individual if left untreated for an extended period of time.

Inadequate organ perfusion and tissue oxygenation must be recognized early on in the patient's course. Delay in diagnosis and management can eventually lead to a point of no return. Vital signs and traditional measures of illness are often not sensitive enough to make an early diagnosis. The presence of acidosis and an elevated serum lactate as a measure of cellular perfusion may be a better marker of serious pathology [1].

The intensivist must be well versed in the management of shock as this is a frequent cause of death. Cardiogenic, hypovolaemic, and septic shock are commonly seen in the ICU, and are associated with other comorbidities, such as infection and multiple organ dysfunction.

The purpose of this chapter is to give an overview of the types of shock, the underlying mechanisms, and a brief discussion regarding management of each type of shock, details of each will be discussed elsewhere in the book. Shock is often the final common pathway through which a patient experiences cardiovascular collapse and subsequent death. The manner in which the patient arrives at this point varies with the disease process. However, the final common pathway focuses on microvascular dysfunction, cellular injury, oxygen supply dependency, and compensatory responses.

Mechanisms of shock: pathogenesis and organ response

While there are different aetiologies of shock, most involve similar biochemical and metabolic pathways. In essence, the cardiovascular system cannot adapt to an insult regardless of the aetiology, such that cardiac output (CO) and blood pressure (BP) are compromised.

BP depends upon CO and systemic vascular resistance (SVR). The brain and heart are able to autoregulate blood flow over a wide range of BPs (mean arterial pressure (MAP) 50–150 mmHg) [2]. Hence, a MAP that falls below this range indicates a severe reduction in CO. Blood flow to organs may be affected by microvascular regulation to maintain blood flow to those organs requiring the highest metabolic activity.

Organ blood flow depends upon the maintenance of BP within defined ranges that vary from organ to organ. Good autoregulation exists between mean pressures of 60–100 mm Hg in the context of normal physiology [3].

Autoregulation of blood flow occurs through two mechanisms. Changes in neurovascular tone are mediated through endothelial stretch receptors, such that as perfusion falls there is an opposing increase in vascular resistance so that overall perfusion is maintained. Additionally, the increased metabolic activity in the tissue causes an increase in CO_2 and H^+, resulting in vasodilatation and increased perfusion.

During periods of shock the autoregulatory response of most vascular beds are overwhelmed. Blood flow to the vital organs of the heart and brain are preserved due to dominant autoregulation of flow. The brain and heart have high metabolic rates, and a low storage of substrate. Neither will tolerate ischaemia for long. Flow to other organs falls secondary to the decrease in CO as organ SVR increases to maintain BP [4]. This adaptation of the body preserves blood flow to vital organs with just a mild drop in CO. If the insult continues, organ failure, and death can ensue. Even with resuscitation the abnormalities of the microvasculature can persist for days.

Shock is also associated with disruption of the endothelial cell barrier integrity, which maintains oncotic pressure within the circulatory space. With this loss, oncotic pressure falls, interstitial oedema develops and circulating volume decreases. Microthrombi may also occur, leading to further endothelial cell injury.

Cellular response

As the interstitial transport of nutrients is impaired, there is a fall in intracellular high energy phosphate (adenosine triphosphate, ATP) stores. This leads to the accumulation of hydrogen ions, lactate, and other by-products of aerobic metabolism. As shock progresses these metabolites reduce vasomotor tone and further hypotension ensues [5].

Cellular ischaemia occurs as a result of supply dependence on oxygen and the imbalance between supply of oxygen and the demands of the tissues. The critical value seems to be 8–10 mL oxygen/min/kg body weight. In the shocked patient there is a pathological oxygen supply dependency.

Inflammatory mediators (including cytokines, platelet-activating factor, leukotrines, prostaglandins, and thromboxanes) lead to inadequate perfusion or can cause direct cell injury to the cells in a number of organs, through causing transmembrane ion gradient dysfunction. Typically, release of inflammatory mediators is beneficial to the host by increasing blood flow to damaged tissues and activating host defences. In sepsis, the response becomes excessive and unregulated. Free radicals develop after ischaemia and reperfusion, which can then inactivate proteins, damage DNA, induce lipid peroxidation, and lead to tissue injury and cell death. Apoptosis can occur as heat shock proteins, interfere with synthetic pathways, and initiate programmed cell death.

Compensatory mechanisms in shock attempt to maintain effective tissue perfusion. This is achieved via stimulation of the sympathetic nervous system, release of hormones such as angiotensin II, norepinephrine, epinephrine, and vasopressin, and by enhancing the unloading of oxygen. This compensation is effective for a period of time, but then becomes overwhelmed by the ongoing shock process with subsequent tissue damage.

Manifestations of shock

Multiple organs can be affected in shock states. This diffuse damage may lead to multiple organ dysfunction.

Central nervous system

Cerebral perfusion is impaired in shock, but flow remains relatively well preserved until the MAP is <50–60 mmHg [6]. The cerebral cortex is the area most sensitive to ischaemia. Prior to this the patient may have an altered level of consciousness ranging from confusion to coma.

Heart

Sympatho-adrenal stimulation causes an increase in heart rate that may lead to supraventricular tachycardia or ventricular ectopy in the setting of ischaemia. Just like the brain, the blood supply to the heart is autoregulated making it resistant to sympathetically-driven vasoconstriction and hypoperfusion injury from shock.

Contractility is increased in most forms of shock. Hypotension is associated with decreased coronary artery perfusion pressure, which may lead to ischaemia in patients with coronary artery disease. Circulating myocardial depressant factors are seen in sepsis, haemorrhagic and cardiogenic shock [7,8].

Respiratory system

Patients may have an increased minute volume, hypocapnia, and a respiratory alkalosis. An increase in the work of breathing, plus respiratory and diaphragmatic muscle impairment from hypoperfusion may lead to respiratory failure. They may also develop an acute respiratory distress syndrome with fibrin-neutrophil aggregates in the pulmonary microvasculature, inflammatory damage to the interstitium and alveoli, and exudation of proteinaceous fluid into the alveolar space. As the work of breathing increases, respiratory muscles may fatigue and result in respiratory failure.

Kidneys

Acute renal failure increases mortality by 35–80% in the setting of shock [9]. Urine output initially decreases, followed by a rise in blood urea nitrogen and creatinine that occurs over the next few days. The kidney is moderately autoregulated maintaining glomerular perfusion by increasing efferent arteriolar tone. Cortical followed by medullary ischaemic injury occurs late in shock.

Gastrointestinal system

The splanchnic circulation is highly sensitive to sympathetic vasoconstriction. Ileus, gastritis, pancreatitis, acalculous cholecystitis, and colonic submucosal haemorrhage can be seen. Ischaemia of the gut can lead to translocation of bacteria from the gut to the circulation [10].

Similarly, the liver may exhibit elevated transaminases and LDH. These usually peak in 1–3 days and then resolve. Synthetic function of prealbumin, albumin, and hepatic coagulation factors are affected and evidence of biliary stasis can be seen.

Haematological

Septic shock causes disseminated intravascular coagulation (DIC) by activation of coagulation and fibrinolysis cascades. Differentiation of DIC from sepsis can be done by measuring the plasma Factor VIII level, which is normal or increased in hepatic dysfunction. Thrombocytopenia, which is often dilutional, is commonly seen following resuscitation [11].

Metabolic

Hyperglycaemia is most commonly seen in shock states resulting from decreased insulin release. Additionally, epinephrine release results in skeletal muscle insulin resistance in order to preserve glucose for the heart and brain. Another common metabolic derangement is increased protein catabolism resulting in a negative nitrogen balance.

Immune system

Immune dysfunctions probably contributes to late mortality of the patient with shock. The mucosal barrier of the colon and gut may be disrupted, leading to translocation of bacteria. There is also inflammation, ischaemia, and free radical injury, as well as dysfunction of the cellular and humoral immune system.

Drugs used in resuscitation may also play a role. For example, dopamine suppresses pituitary production of prolactin, which

then suppresses T cell proliferative responses [12]. This immunological dysfunction may contribute towards the ultimate mortality of patients late in their course from ongoing or new sources of infection.

General approach to treatment

Shock is a life-threatening emergency that must be recognized immediately and aggressive therapy initiated. While early diagnosis of the aetiology of the shock is important, studies often cannot be done immediately due to the patient's severity of illness and the inability to be safely transported.

Shock patients typically present with hypotension, tachycardia, tachypnoea, and oliguria. Extremities are cool and may become mottled. The patient may have an altered mental status. There may be clues to differentiate among the aetiologies of shock. Cardiogenic shock patients have jugular venous distension, S3 and S4 heart sounds, and regurgitation murmurs. With pulmonary embolus, patients have hypoxaemia, dyspnoea and elevated right heart pressures. Cardiac tamponade has pulses paradoxus and distant heart sounds. Septic shock patients have fever, chills, and usually a nidus of infection.

The immediate goals in shock are to restore BP and circulating volume. Goals are to achieve MAP >60 mmHg, CVP >8 mmHg and a cardiac index >2.2L/min/m^2 to maintain oxygen delivery and, hopefully, reverse organ dysfunction.

Types of shock and an approach to management

Hypovolaemic shock

Hypovolaemic shock is characterized by a fall in preload, resulting in decreased filling pressures and a drop in BP. It can be caused by dehydration, haemorrhage, gastrointestinal fluid or urinary losses, or as a result of a decrease in vascular permeability from sepsis. Patients have cool, clammy, mottled skin, tachycardia, hypotension, decreased filling pressures, low urine output, and altered mental status. The severity of hypovolaemic shock depends upon both the amount and severity of the fluid loss. Acute loss of 10% circulating blood volume results in tachycardia and an increase in SVR, but BP is maintained. A loss of 20–25% results in mild hypotension. CO starts to fall and lactate levels start to rise. With a loss of 40% the patient becomes hypotensive with signs of shock indicating tissue hypoperfusion, plus activation of the inflammatory cascade and the risk of widespread cellular damage. Rapid reversal of this process with blood, colloid, or crystalloid is required. The underlying source of the blood or fluid loss must be determined using endoscopy, angiography, CT/MRI, or other means.

Cardiogenic shock

Cardiogenic shock is caused by failure of the heart as a pump and is the most common cause of in-hospital mortality in patients with Q wave myocardial infarction. It can be caused by myocardial, valvular, or other structural abnormalities. There is an increased ventricular preload with increases in ventricular filling pressures and, often, ventricular volume. This results in a fall in BP and cardiac output as a result of the failing pump. Patients have signs of congestive heart failure, an S3 heart sound, elevated neck veins, and peripheral hypoperfusion. Mortality is lower in patients with cardiogenic shock caused by surgically correctable lesions.

In the setting of left ventricular infarction, apart from optimizing fluid loading and administering inotropes, cardiac assist devices, cardiac angiography, and revascularization are options for management. With right-sided infarcts, fluids and inotropes are the mainstay of therapy, and more aggressive haemodynamic monitoring may be necessary to guide therapy. Right ventricular infarction should also be treated with coronary angiography, revacularization, and in certain circumstances, a cardiac assist device. For valvular or mechanical abnormalities, echocardiography, cardiac catheterization, and surgery may be warranted.

Extracardiac obstructive shock

Extracardiac obstructive shock results from obstruction to blood flow in the cardiovascular circuit. Causes include pericardial tamponade, constrictive pericarditis, and pulmonary embolus.

Tamponade and constrictive pericarditis impair diastolic filling of the right ventricle. An increased and equalized right and left ventricular diastolic pressure usually develops. Acute pulmonary embolus results in right heart failure with elevated pulmonary artery and right heart pressures, but with low or normal left heart filling pressures. Other causes of obstructive shock include tension pneumothorax and mediastinal tumours. As with other types of shock, the acuity of the shock impacts on the body's ability to compensate. An acute accumulation of as little as 150 mL of blood in the myocardium can result in immediate tamponade and shock. Conversely, the slow accumulation of 1–2 L of fluid can occur before showing signs of shock.

Management involves rapid diagnosis that can often be made with echocardiography. If pericardial tamponade is diagnosed, percutaneous needle/catheter pericardiocentesis or surgical drainage is needed. In the case of a pulmonary embolus, diagnosis is usually made by CT scanning. Heparinization is initiated and, in the case of profound shock and hypoxaemia, thrombolytic therapy, or catheter or surgical embolectomy should be considered.

Distributive shock

Distributive shock is defined by a loss of peripheral resistance with an overall decrease in SVR. Septic shock is the leading example, but other examples include anaphylaxis, drug overdose, neurogenic insults, and Addisonian crisis. Fluid leaks from the microvasculature leading to inadequate intravascular volume and decreased preload. Volume resuscitation improves the preload. Characteristically, a normal or elevated CO, normal stroke volume, and tachycardia are seen, as well as hypotension. However, myocardial depression is also seen which is characterized by decreased stroke work in response to volume loading, plus a biventricular reduction in ejection fraction, and ventricular dilatation. This ventricular dilatation is probably an attempt to compensate for the depressed ejection fraction and maintain stroke volume.

Treatment involves identification of the source of infection, if possible, with drainage or surgery. Prompt initiation of appropriate antibiotic therapy, fluid resuscitation, and vasopressors (norepinephrine is favoured) or inotropes as needed, should be performed to optimize blood pressure and cardiac index using a sepsis protocol. Most patients with severe sepsis will also require ventilator support for respiratory failure.

Anaphylactic shock

Anaphylactic shock is a type of distributive shock caused by release of mediators from mast cells and basophils. It is an immediate hypersensitivity reaction mediated by interaction between the antibodies on the surface of mast cells and basophils with the appropriate antigen. It can be triggered by insect envenomations, drugs, particularly antibiotics and, less frequently, heterologous serum, blood transfusions, immunoglobulin, and egg-based vaccines. Anaphylactoid reactions result from direct non-immunological release of mediators from mast cells and basophils, and can also lead to shock. They can be caused by ionic contrast media, opiates, protamine, dextran and hydroxyethyl starch, muscle relaxants and anaesthetic agents.

Haemodynamic features of anaphylactic shock are similar to septic shock with hypovolaemia and myocardial depression. In addition to the typical findings of shock, they may have urticaria, angioedema, laryngeal oedema and severe bronchospasm.

Treatment consists of stopping or removing the offending agent, and administration of epinephrine either subcutaneously or via infusion for haemodynamic instability, plus appropriate management of other complications, such as bronchospasm and laryngospasm. Other useful agents are steroids, benadryl, and H_1 and H_2 blockers.

Neurogenic shock

Neurogenic shock involves loss of peripheral vasomotor control secondary to injury or dysfunction of the nervous system. Examples include shock associated with spinal injury, as well as vasovagal syncope and spinal anaesthesia. These are usually self-limited and transient. Therapy includes volume repletion and vasoactive support.

Adrenal crisis

Adrenal crisis is uncommon and difficult to differentiate from other types of shock. It is life-threatening, and requires prompt diagnosis and management. It is caused by a deficiency of mineralocorticoids and glucocorticoids. In the critical care setting, it may arise from bilateral adrenal haemorrhage in conjunction with overwhelming infections, such as meningococcal infections or HIV. It may also be seen with anticoagulation, fungal infections, and malignancy. In the ICU it is not uncommon to see an inadequate adrenal response leading to hypotension.

Symptoms of adrenal insufficiency are non-specific and may include anorexia, nausea, vomiting, diarrhoea, abdominal pain, myalgia, joint pains, headaches, weakness, confusion, and delirium. Fever and hypotension are usually present.

Adrenal crisis is treated by glucocorticoid replacement, and fluid resuscitation as needed. Dexamethasone should be used to avoid interference with the ACTH stimulation test.

Conclusion

Although there are various aetiologies for shock there is a final common pathway. Early and aggressive intervention in the underlying disease state can result in an improved outcome for the patient.

References

1. Kjelland CB and Djogovic D. (2010). The role of serum lactate in the acute care setting. *Journal of Intensive Care Medicine*, **25**, 286–300.
2. Guyton AC. (1991). *Textbook of Medical Physiology*, 8th edn. Philadelphia, PA: W.B. Saunders Co.
3. Bond RF. (1993). Peripheral macro- and microcirculation. In: Schlag G and Redl H (eds) *Pathophysiology of Shock, Sepsis and Organ Failure*, pp. 893–907. Berlin: Springer-Verlag.
4. Gutteriez G and Brown SD. (1993). Response of the macrocirculation. In: Schlag G and Redl H (eds) *Pathophysiology of Shock, Sepsis and Organ Failure*, pp. 215–29. Berlin: Springer-Verlag.
5. Kumar A, Unligil U and Parrillo J. (2014). Circulatory shock. In: Parrillo JE and Dellinger RP (eds) *Critical Care Medicine: Principles of Diagnosis and Management in the Adult*, pp. 299–324, Philadelphia, PA: Elsevier Saunders.
6. Harper AM. (1966). Autoregulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow though the cerebral cortex. *Journal of Neurology, Neurosurgery & Psychiatry*, **29**, 398–403.
7. Parrillo JE, Burch C, Shelhamer JH et al. (1985). A circulating myocardial depressant substance in humans with septic shock. Septic shock patients with a reduced ejection fraction have a circulating factor that depresses in vitro myocardial cell performance. *Journal of Clinical Investigations*, **76**, 1539–53.
8. Hallstrom S, Vogl C, Redl H, and Schlag G. (1990). Net inotropic plasma activity in canine hypovolemic traumatic shock: low molecular weight plasma fraction after prolonged hypotension depresses cardiac muscle performance in-vitro. *Circulatory Shock*, **30**, 129–44.
9. Hou SH, Bushinsky DA, Wish JB, et al. (1983). Hospital acquired renal insufficiency: a prospective study. *American Journal of Medicine*, **74**, 243–8.
10. Mainous MR and Deitch EA. (1993). Bacterial translocation. In: Schlag G, Redl H (eds) *Pathophysiology of Shock, Sepsis and Organ Failure*, pp. 265–78. Berlin: Springer-Verlag.
11. Counts HB, Haisch C, Simon TL, et al. (1979). Hemostasis in massively transfused trauma patients. *Annals of Surgery*, **190**, 91–9.
12. Devins SS, Miller A, Herndon BL, et al. (1992). The effects of dopamine on T-cell proliferative response and serum prolactin in critically ill patients. *Critical Care Medicine*, **20**, 1644–9.

PART 5.6

Cardiac failure

CHAPTER 151

Pathophysiology and causes of cardiac failure

Alexandre Mebazaa and Mervyn Singer

Key points

- Organ congestion upstream of the dysfunctional left and/or right ventricle, with preserved stroke volume, is the most frequent feature of myocardial failure.
- Clinical manifestations do not necessarily correlate with the degree of left ventricular systolic dysfunction (i.e. left ventricular ejection fraction).
- Systolic and/or diastolic dysfunction may be present; systolic dysfunction usually predominates.
- Pulmonary oedema is related to left ventricular diastolic dysfunction.
- Compensatory mechanisms (within the heart and/or periphery) may prove paradoxically disadvantageous on ventricular stroke work and stroke volume.

Pathophysiology

The most frequent scenario of heart failure is organ congestion upstream of the heart with an adequate stroke volume. In acute coronary syndrome, heart failure may be primarily due to an inadequate stroke volume.

Aetiology

Although high-output failure states exist (e.g. sepsis, hyperthyroidism), the usual situation is pump failure leading to congestion upstream the ventricles with or without a low cardiac output [1]. Ischaemic heart disease and long-standing hypertension are the most common causes of myocardial failure, although other aetiologies affecting muscle function (e.g. cardiomyopathy), valvular function (e.g. stenosis, endocarditis), electrical activity (e.g. bradycardia, tachyarrhythmia), or ventricular filling (e.g. pericardial tamponade) should also be considered (see Box 151.1). Atheromatous coronary artery disease leads to either progressive myocardial ischaemia and damage, or alternatively, an abrupt deterioration, such as that seen following plaque and thrombus formation in acute myocardial infarction. A further scenario is acute decompensation where a chronically dysfunctional heart is subjected to an undue degree of stress, for example, following infection or haemorrhage.

The critically-ill patient may be admitted to the ICU with de novo heart failure, or it may develop from a combination of factors including hypoperfusion, sepsis (where myocardial function is often depressed despite a normal or even high cardiac output), arrhythmias, drugs with undesired negative inotropic properties (e.g. most anti-arrhythmics), and metabolic abnormalities such as hypocalcaemia, pericardial effusion, and endocarditis.

Although an intracellular acidosis is negatively inotropic, myocardial dysfunction is often wrongly ascribed to extracellular (arterial) acidosis. Bicarbonate and equimolar saline have been compared in cardiac failure patients and no benefit was found from arterial pH correction. Patients with severe diabetic ketoacidosis rarely show any evidence of co-existing failure.

Another important distinction, albeit clinically difficult to assess, is to distinguish between a 'hibernating' and a 'stunned' myocardium [2]. In the former, myocardial ischaemia is ongoing, whereas in the stunned myocardium, which often follows an ischaemia–reperfusion injury, blood flow is (almost) fully restored. Both retain a myocardial reserve and have reversible contractile dysfunction. However, with hibernation, an increase in contractile function is at the expense of metabolic recovery and treatment should aim to restore flow to the hypoperfused tissue. Myocardial stunning often requires no treatment and usually recovers spontaneously, although if the patient is compromised, inotropic stimulation can be used without inducing further myocardial damage.

Clinical features

The most frequent clinical features of heart failure in the ICU are acute pulmonary oedema and cardiogenic shock.

Pulmonary oedema

Breathlessness and fatigue are very common symptoms in patients with acute heart failure. Acute pulmonary oedema is frequently seen in patients with a history of chronic heart failure (altered left ventricular ejection fraction and dilated left ventricle) or in patients with a sudden elevation of systolic blood pressure (preserved left ventricular ejection fraction and altered left ventricular diastolic dysfunction). In those with a more chronic history of heart failure, dyspnoea is often present for several days prior to presentation and is associated with body weight gain. In cases related to sudden increases in blood pressure, pulmonary oedema is often associated with no increase in body weight.

Cardiogenic pulmonary oedema formation occurs as a consequence of raised pulmonary venous pressures leading to an increase in hydrostatic pressure. Increased pulmonary capillary permeability has been reported after myocardial infarction. Removal of

Box 151.1 Causes of heart failure

Overload

- **Pressure**: e.g. hypertension, aortic stenosis, aortic coarctation.
- **Volume**: e.g. excess intravascular fluid, oligoanuric renal failure, valvular regurgitation (such as endocarditis), congenital left-to-right shunts, high output states (e.g. beriberi, hyperthyroidism).

Abnormal filling

Mitral stenosis, atrial myxoma, restrictive cardiomyopathy, pericardial tamponade, constrictive pericarditis, pulmonary embolus, arrhythmias.

Loss of myocardial contractility

- **Partial**: e.g. coronary artery disease (focal infarction/ischaemia).
- **Generalized**: e.g. widespread atheroma, dilated cardiomyopathy, myocarditis, malnutrition, drugs/poisons, (e.g. β-blockers, alcohol), sepsis, metabolic (e.g. hypocalcaemia).

interstitial oedema is predominantly via the lymphatics. In chronic failure states, lymphatic clearance levels are raised considerably. However, in the acute situation, the lymphatics may take several days to reduce extravascular lung water and improve the radiographic appearance. The presence of pulmonary oedema bears no relationship to intravascular volume and such patients should not be automatically assumed to be fluid overloaded.

Interstitial oedema is erroneously considered to be the predominant reason for dyspnoea in heart failure. Other factors include attempted respiratory compensation for the concurrent metabolic acidosis, respiratory muscle fatigue secondary to hypoperfusion, arterial hypoxaemia arising from a low SvO_2, anxiety, and/or pain, and pulmonary venous engorgement leading to activation of afferent stretch receptors.

Right ventricular failure, which also frequently occurs in chronic heart failure, is another cause of dyspnoea in acute heart failure due to a diminished cardiac output. Right ventricular congestion induces leg oedema, turgescent jugular veins, and hepatomegaly; it also induces alterations in kidney function with or without oliguria.

Cardiogenic shock

In acute myocardial infarction, pump failure may produce symptoms at rest, with evidence of impaired organ perfusion (oliguria, confusion, drowsiness) and/or lung congestion. Cardiogenic shock refers to the situation where oxygen supply by the heart is inadequate to prevent significant tissue hypoxia. This term is usually applied in error to describe a co-existing hypotensive state that need not be present.

Mechanisms of ventricular failure

With decompensated chronic heart failure, systolic and diastolic dysfunction often co-exist, although the systolic component usually predominates (see Fig. 151.1). This relates to impaired ventricular contractility and a defective ability of the myofibrils to shorten

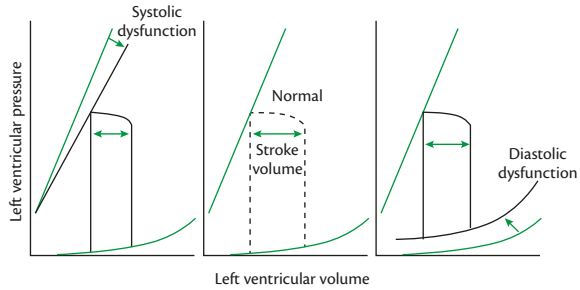


Fig. 151.1 Effects of systolic and diastolic dysfunction on the ventricular pressure–volume curve.

against a load with a consequent decrease in ejection fraction. The ventricle lies on a flatter left ventricular function curve (see Fig. 151.2) and, consequently, the ability to increase stroke volume by an increase in preload is impaired. The ventricle is particularly sensitive to increases in afterload.

In cases of pulmonary oedema associated with sudden elevations in blood pressure, left ventricular diastolic dysfunction predominates despite a relatively normal ejection fraction and ventricular size. The fundamental process underlying this syndrome is a progressive decrease in ventricular compliance, resulting in marked increases in filling pressures at relatively normal end-diastolic volumes (see Fig. 151.1). This abnormal pressure–volume relationship is related to changes in active relaxation during the initial phases of diastole and/or passive compliance during the slow-filling phase. Depending on the ventricle affected, rises in pressure will produce systemic and/or pulmonary venous congestion and interstitial oedema. Compared with systolic dysfunction, there appears to be a lower sensitivity to increases in afterload and compensatory neuroendocrine activation is probably less marked. With decreases in compliance there is a progressively limited ability to respond positively to a fluid challenge (see Fig. 151.3).

Diastolic dysfunction is more common in the elderly (up to 40% of patients). Aetiologies include recurrent ischaemia, hypertrophic cardiomyopathy, hypertension, and aortic stenosis. The response to standard failure therapy is generally worse in patients with predominant diastolic dysfunction.

One or both ventricles may be primarily affected by the underlying disease process. While symptoms and signs of systolic dysfunction are similar for both left and right ventricles, diastolic dysfunction affecting the left heart produces pulmonary oedema

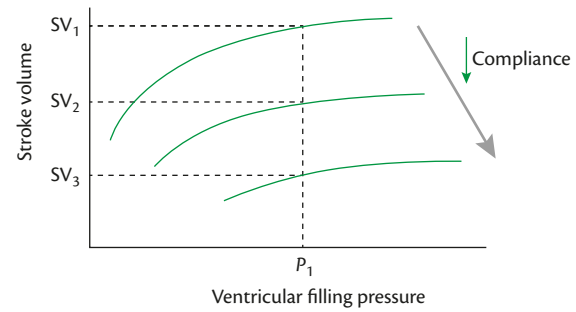


Fig. 151.2 Effect of progressive reductions in ventricular compliance on ventricular function curves. If blood pressure remains constant, a similar end-diastolic pressure will generate progressively lower stroke volumes as compliance decreases.

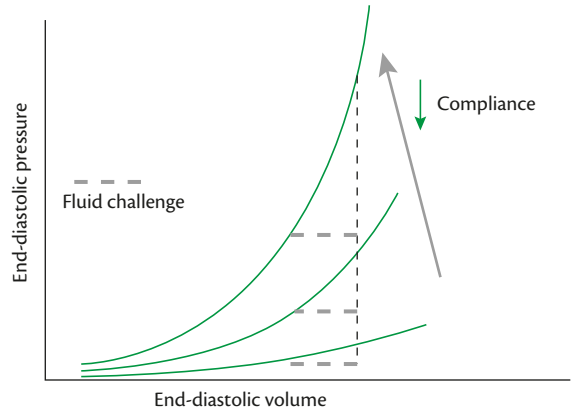


Fig. 151.3 Ventricular end-diastolic pressure–volume relationship. As compliance decreases, an increase in end-diastolic volume by a fluid challenge will generate a much higher increase in end-diastolic pressure. This can lead to venous congestion and oedema.

and, for the right heart, liver and kidney congestion, and dependent peripheral oedema. A diseased ventricle will often impact upon the functioning ventricle (e.g. septal shift, increased pulmonary vascular resistance).

At the cellular level there appear to be abnormalities in cytosolic calcium handling, myofilament sensitivity to calcium, myocyte energetics, and phosphodiesterase and adenyl cyclase production/activity. Other changes include down-regulation of both $ß_1$- and $ß_2$-adrenergic receptors and possible uncoupling of these ß-adrenoreceptors from adenylate cyclase. Alterations in the activity and/or number of myocyte enzymes and transport channels involved in the excitation–contraction coupling mechanism are also implicated in many of the processes described.

Compensatory mechanisms in low cardiac output states

Heart ventriculo-arterial coupling

In low-output failure the cardiac output is often maintained by increases in heart rate, chamber size and muscle mass. Stroke volume usually falls unless severe bradycardia is present. Acute compensation occurs via sympathetic activation of heart rate. However, over days to weeks, progressive ventricular dilatation increases end-diastolic volume, thereby helping to maintain stroke volume in the face of a falling ejection fraction. By the Laplace law, dilatation will increase systolic wall stress; this is partially offset by a remodelling process in which functioning myofibres hypertrophy. The resultant increase in muscular mass permits an increase in cardiac work, although not at the expense of wall stress. Hypertrophy is a slow compensatory process that will nevertheless adversely affect diastolic function, ventricular compliance, and the end-diastolic pressure–volume relationship.

The left ventricle can be considered an elastic chamber that periodically increases its volume elastance V_e to a value equal to the slope of the relationship between end-systolic pressure and end-systolic volume. The arterial load property is measured as arterial elastance E_a, i.e. the slope of the relationship between arterial end-systolic pressure P_{es} and stroke volume. The end-systolic elastance E_{es} varies in response to ventricular contractility, while P_{es} varies inversely with stroke volume SV for a given end-diastolic volume V_{ed}:

$$P_{es} = E_{es}\left(V_{ed} - SV - V_0\right) = E_{es}\left(V_{es} - V_0\right) \qquad \text{[eqn 1]}$$

where V_0 is a constant reference volume.

The ventricle produces maximal external work to the arterial load when the ventricular and arterial elastances are equalized [3]. In normal subjects, the ventricular elastance is nearly twice as large as arterial elastance, thereby affording maximal efficiency. However, in moderate heart failure, the two elastance values are almost identical, thereby maximizing stroke work from a given end-diastolic volume, but at the expense of work efficiency. Finally, in severe failure, ventricular elastance is less than half arterial elastance values, resulting in increased potential energy, and an inability to maintain either stroke work or work efficiency properly.

Peripheral

In response to inadequate stroke volume, neuroendocrine activation leads to vasoconstriction and, in the longer term, salt and water retention. Vasoconstriction is mediated via sympathetic and renin–angiotensin pathways, redistributing blood flow away from cutaneous, splanchnic, and muscular beds to more 'vital' organs, such as brain and heart. Venous tone also increases, enhancing venous return. While vasoconstriction is an appropriate response to haemorrhage and hypovolaemia, it is often deleterious in heart failure as myocardial work and function are adversely affected. The body initially attempts to compensate by raising circulating levels of atrial natriuretic peptide and adrenomedullin that enhance natriuresis and vasodilatation. However, over time, salt and water retention will predominate. This is primarily mediated by increased secretion of aldosterone and, to a lesser extent, antidiuretic hormone.

The negative consequences of these compensatory mechanisms include:

- A progressive decrease in renal blood flow and the potential development of renal dysfunction [4].
- Pulmonary and systemic interstitial oedema which may worsen oxygenation and symptoms.
- A further fall in ventricular compliance and an increase in cardiac work, placing greater strain upon an already damaged heart.

Thus, increased ventricular stiffness will result from pathophysiological processes, occurring either as a direct consequence of heart failure or secondary to the body's compensatory mechanisms. Ischaemia, ventricular hypertrophy, excessive afterload or preload, or an inadequate preload with compensatory vasoconstriction will all contribute, as will misguided treatment regimens, such as excessive diuresis. For the same end-diastolic pressure, a less compliant ventricle on a flatter ventricular function curve will generate a much lower stroke volume (see Fig. 151.2). This underlines the potentially catastrophic consequences of afterload increases, the therapeutic importance of optimizing compliance, and the problems inherent in an over-reliance on pressure measurements (central venous pressure, pulmonary artery wedge pressure) to the exclusion of volume or flow. It further illustrates how a vicious downward spiral is actually facilitated by the body's attempts at correction.

Biomarkers

In patients admitted in the emergency department or in the intensive care unit (ICU) with acute dyspnoea, therapy should be started promptly. Together with the clinical signs, the level of plasma natriuretic peptides discriminate acute heart failure from acute dyspnoea related to other causes. In addition, natriuretic peptides measured at admission allow the prediction of outcome.

Other biomarkers or organ dysfunction should also be measured in case of myocardial failure—troponin (myocardial ischaemia), renal biomarkers, or liver function tests.

References

1. Gheorghiade M, Follath F, Ponikowski P, et al. (2010). Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine *European Journal of Heart Failure*, **12**, 423–33.
2. Schulz R and Heusch G. (1994). Characterization of hibernating and stunned myocardium. *Herz*, **19**, 189–203.
3. Sasayama S and Asanoi H. (1991). Coupling between the heart and arterial system in heart failure. *American Journal of Medicine*, **90**(Suppl. 5B), 14S–18S.
4. Jois P and Mebazaa A. (2012). Cardio-renal syndrome type 2: epidemiology, pathophysiology, and treatment. *Seminars in Nephrology*, **32**, 26–30.

CHAPTER 152

Therapeutic strategy in cardiac failure

Alexandre Mebazaa and Mervyn Singer

Key points

- In hospital mortality from acute cardiogenic shock remains in the order of 40–60%.
- Management of pulmonary oedema comprises non-invasive ventilation, large doses of vasodilators and small dose of diuretics.
- The oxygen supply–demand balance should be optimized within both the myocardium and the body as a whole. Therapy should be aimed at both decreasing demand and increasing supply.
- This can be achieved through judicious use of drug, fluid, and mechanical support therapies.
- A considerable improvement in the outcome of cardiogenic shock can be obtained with an aggressive regimen of myocardial revascularization, drug therapy with appropriately targeted monitoring and, if needed, a cardiac assist device or other organ support.

Introduction

The 1-year mortality for patients admitted with dyspnoea related to acute heart failure is approximately 20%. However, acute cardiogenic shock generally carries a hospital mortality in the order of 40–60%, although recent data suggest a considerable improvement with an aggressive regimen of myocardial revascularization and, if needed, early use of a cardiac assist device.

The fundamental therapeutic principles of heart failure management are for acute heart failure mainly with signs of pulmonary congestion, normal or high blood pressure, and no signs of low cardiac output to reduce pulmonary congestion without affecting blood pressure.

Management principles of cardiogenic shock management comprise improvement of forward flow with restoration/maintenance of adequate organ perfusion.

Appropriate management requires sound appreciation of the underlying pathophysiology, awareness of the actions and potential side-effects of each therapeutic intervention, and a level of monitoring and investigation sophisticated enough to assess disease severity and the effectiveness (or otherwise) of any treatment being given [1]. Where possible, consideration of previous comorbid factors and chronic symptomatology should guide how aggressive intervention should be. However, these must be based on documented fact, rather than hearsay or supposition. The patient should always be given the benefit of the doubt.

Principles of management

Acute pulmonary oedema

The aim is to improve left ventricular diastolic dysfunction and should focus on reducing left ventricular afterload. Reducing blood pressure will reduce myocardial oxygen consumption and favour (in the case of coronary disease) a mismatch between oxygen delivery and consumption in the endocardial portion of the myocardium. Heart rate should be maintained as low as possible.

Low cardiac output

The aim is to maintain an adequate oxygen supply–demand balance within both the myocardium and the body as a whole. A decrease in cardiac output relative to the body's oxygen requirements is manifest as symptoms of poor forward flow, for example weakness, fatigue, oligoanuria, confusion, drowsiness, and tachypnoea secondary to metabolic acidosis. Thus, therapy should be aimed at both increasing supply and decreasing demand (see Box 152.1).

Reducing demand

Reducing both myocardial and total body oxygen requirements is beneficial to the failing heart by lowering the cardiac work demanded of an already compromised and dysfunctional myocardium. This can be achieved pharmacologically by optimizing pre- and afterload, and thus ventricular compliance. Such measures include appropriately monitored fluid challenges, vasodilators, and, in the relatively unusual situation of intravascular volume overload, diuretics. Mechanical support devices are also effective; these include early mechanical ventilation, which rests the heart by reducing pre- and afterload, maintaining normoxaemia, and removing the work of breathing; 30–40% of cardiac output may be required purely to support the work of breathing in a dyspnoeic subject. Respiratory muscle fatigue leading to hypercapnia is a prelude to cardiorespiratory collapse.

Total body oxygen consumption can be reduced further by alleviation of pain or anxiety. This is achieved by psychological support in addition to adequate analgesia (usually opiates that also have intrinsic vasodilating and anxiolytic properties).

Increasing supply

Apart from reducing cardiac work, optimizing pre- and afterload also enhances forward flow. Additional augmentation can be achieved by inotropic agents, although usually at the expense of

Box 152.1 Achieving an adequate oxygen supply–demand balance

Decreasing the demand

- Sedation, pain relief.
  - **Mechanical ventilation**: permits heavier sedation and removes the work of breathing.
- Reduction in pyrexia (e.g. by antipyretics, tepid sponging).

Increasing the supply

- **Oxygen**: FiO_2 0.6–1.0 to maintain (near) complete arterial oxygen saturation.
- **Blood transfusion**: the optimal figure is still contentious. A haemoglobin level of 10–12 g/dL is a reasonable compromise between oxygen carriage and microcirculatory flow.
- **Optimization of pre- and afterload**:
  - *If fluid overloaded (rare)*—venodilatation + diuretics to optimal stroke volume.
  - *If hypovolaemic*—fluid challenge to optimal stroke volume.
  - *If vasoconstriction persists* (SVR > 1400 dyn s/cm^5)—arterial dilatation through a combination of dilator + fluid may be necessary.
- **Inotrope administration**: inotropes increase cardiac work and place additional stress on an already diseased heart, so should ideally be used after pre-/afterload optimization when an inadequate organ perfusion and/or blood pressure remains.
- **Mechanical ventilation + PEEP**: positive-pressure ventilation + additional PEEP will often augment cardiac output in heart failure states by preload and left ventricular afterload reduction.
- **Intra-aortic balloon counterpulsation**:
  - Improves forward flow, augments coronary perfusion, and reduces afterload.
  - Its outcome benefits are still debatable.
- **Correction of any anatomical abnormalities**: e.g. valve replacement, pericardiocentesis.
- **Other cardiac assist devices**: no large randomized trials have been performed. There are suggestions of benefit in case series of patients with reversible causes of myocardial dysfunction, e.g. viral myocarditis, or as a bridge to surgery (including transplantation).

increased cardiac work. Mechanical supports such as intra-aortic balloon counterpulsation and ventricular assist devices can also increase output [2].

Achieving adequate perfusion pressure

Despite improving flow, organ function may still remain compromised by an inadequate perfusion pressure. Inotropes, intra-aortic balloon counterpulsation, and for high-output states, vasopressors may be used alone or in combination to elevate perfusion pressure. The ideal perfusion pressure varies between individuals. In general, patients who were not previously hypertensive can often cope with mean systemic blood pressures in the range 60–70 mmHg (or lower), while long-term hypertensives often require higher mean pressures (e.g. 70–80 mmHg). The drawbacks of an excessive blood pressure are an increase in cardiac work and a decreased output.

Relief of symptoms

Tachypnoea results from pain, anxiety, metabolic acidosis, hypoxaemia, and engorgement of the pulmonary vasculature. Management should aim at providing analgesia and anxiolysis, improving organ perfusion, and reducing pulmonary venous pressures, with supplemental high-flow oxygen administration. This strategy will often improve symptoms dramatically. Non-invasive ventilatory support, for example, continuous positive airways pressure (CPAP), may also be useful. Pain relief is provided by adequate analgesia and improved coronary perfusion. Symptoms of poor forward flow (e.g. confusion, oliguria, fatigue, respiratory failure) are relieved by improving organ perfusion.

Investigation and monitoring

While 'first-aid' therapeutic measures are being implemented, continuous ECG and pulse oximetry monitoring, and frequent sphygmomanometric blood pressure measurements should be commenced.

Early and prompt invasive monitoring of cardiovascular function should be instituted, not only in the severely-ill patient, but also in those patients who are either deteriorating or responding poorly to initial therapy. This usually consists of arterial cannulation for continuous measurement of systemic blood pressure and intermittent blood gas analysis, bladder catheterization for hourly measurement of urine output (mostly for cases of low cardiac output), and in the more severe cases, more sophisticated haemodynamic monitoring including, e.g. stroke volume, intracardiac pressures, and mixed venous oxygen saturation, with calculation of systemic and pulmonary vascular resistances.

Urgent investigations include the following: 12-lead (and sometimes right-sided) electrocardiography to diagnose any rhythm disturbances, evidence of infarction (new or old), or ongoing ischaemia (ST-segment depression, T-wave inversion). Cardiac enzymes to indicate recent infarction and, perhaps, prompt urgent thrombolysis with or without angioplasty or surgical revascularization.

Echocardiography should be performed for any patients admitted with myocardial dysfunction and haemodynamic instability. It will detect structural defects including heart chamber and wall dimension abnormalities (including the presence of right heart failure that may be very difficult to detect based on clinical signs alone), valvular disorders, septal defects, pericardial effusion, and segmental wall motion irregularities.

Chest radiography ± computed tomography (CT) scans should seek abnormalities suggestive of specific disorders, such as pneumothorax, aortic aneurysm, and pulmonary embolus.

Markers of severity

A greater degree of heart failure is suggested by progressive dyspnoea, obtundation, hypotension, oliguria, and cyanosis. Biochemical markers of severity include a metabolic acidosis with

associated hyperlactataemia. A low stroke volume and mixed venous oxygen saturation below 60% are additional indicators of poor cardiac performance and inability to meet tissue oxygen demands. Pulmonary artery wedge pressures and central venous pressures are not necessarily elevated.

Treatment

Heart failure should be treated swiftly. The presence of any marker of severity as outlined previously should prompt a more aggressive and interventionist approach to both monitoring and therapy. Aetiology can usually be ascertained rapidly from history, examination, and investigations including electrocardiography, chest radiography, echocardiography, CT scanning, and biochemistry (cardiac enzymes, troponin, B-type natriuretic peptide). Specific diagnoses warrant specific treatments, for example, angioplasty or thrombolysis for myocardial infarction (unless contraindicated), anti-arrhythmics or cardioversion for any compromising arrhythmia, pericardiocentesis for tamponade, and valve replacement for significant valvular stenosis.

Pulmonary oedema

In the prehospital, emergency department or intensive care unit (ICU) setting, oxygen therapy and non-invasive ventilation should be rapidly commenced. Vasodilators (nitrates IV) ± diuretics (<1 mg/kg intravenous furosemide) should also be started promptly [3].

Vasodilatation is desirable and can be rapidly achieved by four sublingual puffs of glyceryl trinitrate (nitroglycerin) spray, resulting in prompt symptomatic relief. This can be then followed by an intravenous nitrate infusion titrated to optimal effect. A patient presenting with low-output failure and hypotension may be unable to tolerate nitrates unless hypovolaemia has been corrected and obstruction to flow (e.g. pericardial tamponade) excluded. Myocardial function will remain compromised until an adequate perfusion pressure and flow are achieved. This may necessitate the 'blind' use of an inotrope, such as adrenaline (epinephrine), until more sophisticated monitoring can be introduced.

The patient's condition (dyspnoea, respiratory rate, blood pressure, heart rate, urine output) should be monitored closely (at least every 30 minutes) until stabilized.

Directed therapy

This requires instrumentation for monitoring as described previously. Suggested targets, many of which indicate adequate organ perfusion, are given in Box 152.2. No target figures are given for cardiac output, oxygen delivery, or oxygen consumption, as individual variations in the oxygen supply–demand balance are such that, while some patients may remain undertreated, many others will have their myocardium needlessly driven.

Box 152.2 Therapeutic endpoints

- Adequate blood pressure to support adequate organ perfusion.
- Optimization of pre- and afterload to maximize stroke volume.
- Mixed venous oxygen saturation >60%.
- Urine output >0.5 mL/kg/hour.
- Removal of any metabolic acidosis secondary to lactic acid production.
- Removal of any evidence of persisting ischaemia (seen on ECG).

Pharmacological support

The choice of therapeutic agent is dictated by therapeutic benefit, familiarity, and desired pharmacological action. If a drug proves unpredictably detrimental, it should either be substituted by another agent that achieves the required effect, or any hitherto unrecognized problem should be dealt with appropriately. Dobutamine or levosimendan may be used as an illustrative agent for both circumstances—in some patients it may induce excessive vasodilatation and hypotension, and require substitution with epinephrine, whereas generation of tachycardia or tachyarrhythmias implies possible concurrent hypovolaemia requiring volume administration. Familiarity with the drugs being used, and awareness of both their actions and potential side-effects are crucial.

- Oxygen should be administered to ensure an arterial oxygen saturation of 95–98%.
- Pain secondary to ongoing myocardial ischaemia is best treated by nitrates, although opiates are useful for their additional anxiolytic and vasodilating properties.
- Vasodilator agents, such as glyceryl trinitrate, hydralazine, and sodium nitroprusside all have effects on both pre-d and afterload. Significant falls in blood pressure with small doses of the aforementioned imply either hypovolaemia or flow obstruction. Nitrate tolerance develops after 24 hours, with increasing doses required to maintain effect. Cyanide accumulation may develop after 24 hours with sodium nitroprusside usage. It is our preference to commence angiotensin-converting enzyme inhibitors such as captopril at this time, provided that blood pressure and lack of contraindications permit, in rapidly escalating dosage, while slowly weaning the original vasodilator.
- Judicious fluid challenges are often appropriate as the heart failure patient may arrive at the ICU in a hypovolaemic state. The end point is no rise in stroke volume to a 100–200-mL fluid challenge. In the absence of flow monitoring, a rise in central venous or wedge pressure ≥3 mmHg following a fluid challenge is suggestive of an adequately filled intravascular compartment.
- Loop diuretics are often inappropriate and detrimental in the first instance for the reasons described earlier (i.e. causation or exacerbation of prior hypovolaemia). However, they may be indicated in fluid-overload situations, when the patient is on chronic diuretic therapy, and when symptoms or oliguria persist after adequate loading with fluid and angiotensin-converting enzyme inhibitors.
- Inotropes are indicated where low pressure and/or low output result in inadequate organ function. Inotropes with associated vasodilator activity, including dobutamine or levosimendan, may all usefully improve output, although they can occasionally produce excessive falls in blood pressure.
- Pressors are rarely indicated, although noradrenaline (norepinephrine) is occasionally needed to generate a blood pressure sufficient to perfuse the organ; it should only be used in case of low blood pressure.

Mechanical support

For the reasons described in the previous list, positive-pressure ventilation with or without positive end-expiratory pressure (PEEP), CPAP, and venticular assist devices may be useful adjuncts to treatment. In particular, mechanical ventilation is a much underestimated support mode. A large study in cardiogenic shock complicating acute myocardial infarction however failed to show any outcome benefit.

References

1. McMurray JJ, Adamopoulos S, Anker SD, et al. (2012). ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *European Heart Journal*, **33**, 1787–847.
2. Thiele H, Zeymer U, Neumann F-J, et al. (2012). Intraaortic balloon support for myocardial infarction with cardiogenic shock. *New England Journal of Medicine*, **367**, 1287–96.
3. Mebazaa A, Parissis J, Porcher R, et al. (2011). Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. *Intensive Care Medicine*, **37**, 290–301.

CHAPTER 153

Intra-aortic balloon counterpulsation in the ICU

Alain Combes and Nicolas Bréchot

Key points

- A recent large randomized study showed that intra-aortic balloon pump (IABP) did not impact upon the outcome for patients with cardiogenic shock complicating acute myocardial infarction.
- The IABP has been downgraded from a Class I to a Class III recommendation in this setting and IIb in case of mechanical complication following myocardial infarction.
- Current data do not support the use of prophylactic IABP during percutaneous intervention (PCI) in ST-elevation myocardial infarction (STEMI) without shock, or for high-risk coronary procedures (class III recommendation).
- Latest data do not suggest a benefit for pre-operative IABP insertion in patients with poor LV function undergoing CABG.
- IABP should not be used in other forms of shock.

Introduction

The intra-aortic balloon pump (IABP) is a mechanical device consisting of a cylindrical polyethylene balloon that sits approximately 2 cm from the left subclavian artery [1]. A computer-controlled console linked to either an electrocardiogram or a pressure transducer inflates the balloon with helium during diastole (counterpulsation). The balloon actively deflates in systole. The resulting effects are an increase in coronary artery blood flow and cardiac output, and reduced left ventricular afterload. These actions combine to decrease myocardial oxygen demand and increase myocardial oxygen supply [2]. Contraindications include severe aortic valve insufficiency, aortic dissection, and severe aorto-iliac artery disease. Major complications include bleeding at the insertion site and retroperitoneal haemorrhage, critical ischaemia of the catheterized leg, catheter infection, and stroke [3–6]. The IABP usually remains in situ from 48 to 72 hours. Weaning from IABP is not well defined. The most common approach is to reduce cycling of inflation to 1:2 or 1:4 for 15 minutes to several hours before device removal [3,7,8].

Results in humans

Cardiogenic shock in the setting of acute myocardial ischaemia

Based on cohort studies and registries [5,9–11], both European and American cardiology society guidelines strongly recommended (level I recommendation) IABP insertion for cardiogenic shock in the setting of acute myocardial ischaemia [12]. However, evidence supporting these recommendations has recently been challenged. In a meta-analysis of cohort studies of STEMI patients with cardiogenic shock, IABP benefit was restricted to patients who had received thrombolysis, while PCI-treated patients had a significantly higher mortality [13]. A meta-analysis of three small randomized studies [5] also produced disappointing results. Despite some improvements in haemodynamic parameters, IABP had no impact on mortality after cardiogenic shock, and was even associated with higher rates of ischaemic and bleeding complications. Lastly, the large (600-patients), randomized IABP-SHOCK II trial [14] recently showed that use of IABP did not significantly reduce 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction for whom an early revascularization strategy was planned (relative risk with IABP, 0.96; 95% CI, 0.79–1.17; $p = 0.69$). There were no significant differences in time to haemodynamic stabilization, length of stay in intensive care, serum lactate levels, dose and duration of catecholamine therapy, renal function, and rates of major bleeding, peripheral ischaemic complications, sepsis, and stroke. Therefore, given the concordance of data from meta-analyses and the IABP-SHOCK II trial, the routine use of IABP in patients with acute myocardial infarction complicated by cardiogenic shock received only a class III recommendation in the latest international guidelines for the care of cardiogenic shock and IIb in case of mechanical complication [15].

Myocardial infarction without shock and high-risk percutaneous coronary intervention

IABP has been proposed to prevent haemodynamic compromise in high-risk PCI and STEMI without cardiogenic shock. However, several small randomized studies found no benefit in this patient population [13]. These results were confirmed in the large CRISP-AMI multicentre trial that randomized 337 anterior STEMI patients without cardiogenic shock to undergo IABP prior to PCI versus PCI alone [3]. Mortality and infarct size estimated by MRI were identical in both groups. Similarly, prophylactic IABP before high-risk PCI in patients with severe left ventricular dysfunction (LVEF <30%) and extensive coronary artery disease, did not decrease the rate of the composite primary endpoint of death, myocardial infarction, stroke and revascularization rate, or 6-month mortality [4]. Furthermore, IABP was associated with more bleeding events and complications at the vascular access site [4]. Thus,

current data do not support the use of prophylactic IABP during PCI in STEMI without shock, or during high-risk coronary procedures (class III recommendation) [12].

Pre-operative IABP in patients undergoing coronary artery bypass grafting

Pre-operative IABP is considered to be the gold standard therapy for CABG surgery in high-risk patients (LVEF<40%, three-vessel artery disease or left main artery stenosis, redo-CABG, or unstable angina) [16]. In a meta-analysis of five single-centre randomized studies, mortality was reduced from 23 to 4% in the pre-operative IABP group (OR 0.18, 95% CI 0.08–0.49, $p < 0.0001$), and the incidence of a low post-operative cardiac output from 59 to 21% (OR 0.14, 95% CI 0.08–0.25, $p < 0.0001$) [17]. However, generalizability of the results of this meta-analysis is limited, as it included studies with limited number of patients, conducted by the same investigator, and in which observed mortality was unexpectedly high in control groups. In another randomized study of 221 high-risk patients undergoing off-pump CABG, pre-operative IABP was also associated with a reduction in mortality rate from 3.8 to 2.6% ($p < 0.05$) low cardiac output syndrome (10.4 versus 18.9%, $p < 0.05$), malignant arrhythmias and acute renal failure [18]. Conversely, in a randomized trial suppressed in 110 high-risk patients undergoing CABG, pre-incision implantation of IABP provided no advantage in term of mortality or severe morbidity [19]. Thus, the body of evidence available to date in favour of pre-operative IABP in patients undergoing CABG appears limited, and implanting an IABP in this setting remains highly controversial.

IABP as an adjunct to non-pulsatile cardiopulmonary bypass and cardiac assistance

Pulsatile flow has been suggested to confer haemodynamic advantages in experimental studies of cardiopulmonary bypass by reducing systemic vasoconstriction and improving systemic perfusion. Two small, randomized single-centre studies suggested that IABP could improve post-operative haemodynamics and organ perfusion in high-risk cardiac surgery patients [18,20]. Using IABP in conjunction with peripheral veno-arterial extracorporeal membrane oxygenation moreover decreases pulmonary capillary wedge pressure, and may help to prevent pulmonary oedema in patients with laminar blood flow (personal data not shown).

IABP during other forms of shock

Several animal studies suggested a potential role for IABP in cardiogenic shock due to right ventricular failure or myocardial dysfunction associated with septic shock. However, evidence to date is too limited to recommend its insertion in these situations.

Conclusion

IABP insertion is now only a class III recommendation in patients with cardiogenic shock complicating acute myocardial ischaemia [15]. Indeed, very recently, the large randomized IABP-SHOCK II trial [14] showed that IABP did not significantly reduce 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction for whom an early revascularization strategy was planned. The utility of IABP in high-risk patients undergoing CABG surgery is also questioned. Therapeutic strategies for cardiogenic shock patients are evolving rapidly. IABP may no longer be recommended in the near future and research on other mechanical devices should be encouraged to reduce the unacceptably high (40%) mortality rate still observed in patients who develop cardiogenic shock.

References

1. Kantrowitz A, Tjonneland S, Freed PS, Phillips SJ, Butner AN, and Sherman JL, Jr. (1968). Initial clinical experience with intraaortic balloon pumping in cardiogenic shock. *Journal of the American Medical Association*, **203**, 113–18.
2. Weber KT and Janicki JS. (1974). Intraaortic balloon counterpulsation. A review of physiological principles, clinical results, and device safety. *Annals of Thoracic Surgery*, **17**, 602–36.
3. Patel MR, Smalling RW, Thiele H, et al. (2011). Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: the CRISP AMI randomized trial. *Journal of the American Medical Association*, **306**, 1329–37.
4. Perera D, Stables R, Thomas M, et al. (2010). Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. *Journal of the American Medical Association*, **304**, 867–74.
5. Unverzagt S, Machemer MT, Solms A, et al. (2011). Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock. *Cochrane Database of Systematic Reviews*, CD007398.
6. Jiang CY, Zhao LL, Wang JA, and Mohammod B. (2003). Anticoagulation therapy in intra-aortic balloon counterpulsation: does IABP really need anti-coagulation? *Journal of Zheijang University Science*, **4**, 607–11.
7. Thiele H, Sick P, Boudriot E, et al. (2005). Randomized comparison of intra-aortic balloon support with a percutaneous left ventricular assist device in patients with revascularized acute myocardial infarction complicated by cardiogenic shock. *European Heart Journal*, **26**, 1276–83.
8. Ohman EM, Nanas J, Stomel RJ, et al. (2005). Thrombolysis and counterpulsation to improve survival in myocardial infarction complicated by hypotension and suspected cardiogenic shock or heart failure: results of the TACTICS Trial. *Journal of Thrombosis and Thrombolysis*, **19**, 33–9.
9. Sanborn TA, Sleeper LA, Bates ER, et al. (2006). Impact of thrombolysis, intra-aortic balloon pump counterpulsation, and their combination in cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? *Journal of the American College of Cardiology*, **36**(3 Suppl. A), 1123–9.
10. Anderson RD, Ohman EM, Holmes DR, Jr, et al. (1997). Use of intraaortic balloon counterpulsation in patients presenting with cardiogenic shock: observations from the GUSTO-I Study. Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries. *Journal of the American College of Cardiology*, **30**, 708–15.
11. Barron HV, Every NR, Parsons LS, et al. (2001). The use of intra-aortic balloon counterpulsation in patients with cardiogenic shock complicating acute myocardial infarction: data from the National Registry of Myocardial Infarction 2. *American Heart Journal*, **141**, 933–9.
12. Wijns W, Kolh P, Danchin N, et al. (2010). Guidelines on myocardial revascularization. *European Heart Journal*, **31**, 2501–55.
13. Sjauw KD, Engstrom AE, Vis MM, et al. (2009). A systematic review and meta-analysis of intra-aortic balloon pump therapy in ST-elevation myocardial infarction: should we change the guidelines? *European Heart Journal*, **30**, 459–68.
14. Thiele H, Zeymer U, Neumann FJ, et al. (2012). Intraaortic balloon support for myocardial infarction with cardiogenic shock. *New England Journal of Medicine*, **367**, 1287–96.
15. (2014). 2014 ESC/EACTS Guidelines on myocardial revascularization. *European Heart Journal*, **35**, 2541–619.
16. Theologou T, Bashir M, Rengarajan A, et al. (2011). Preoperative intra aortic balloon pumps in patients undergoing coronary

artery bypass grafting. *Cochrane Database of Systematic Reviews*, CD004472.
17. Qiu Z, Chen X, Xu M, et al. (2009). Evaluation of preoperative intra-aortic balloon pump in coronary patients with severe left ventricular dysfunction undergoing OPCAB surgery: early and mid-term outcomes. *Journal of Cardiothoracic Surgery*, **4**, 39.
18. Onorati F, Presta P, Fuiano G, et al. (2007). A randomized trial of pulsatile perfusion using an intra-aortic balloon pump versus non-pulsatile perfusion on short-term changes in kidney function during cardiopulmonary bypass during myocardial reperfusion. *American Journal of Kidney Diseases*, **50**, 229–38.
19. Ranucci M, Castelvecchio S, Biondi, A, et al. (2013). A randomized controlled trial of preoperative intra-aortic balloon pump in coronary patients with poor left ventricular function undergoing coronary artery bypass surgery. *Critical Care Medicine*, **41**, 2476–83.
20. Onorati F, Santarpino G, Presta P, et al. (2009). Pulsatile perfusion with intra-aortic balloon pumping ameliorates whole body response to cardiopulmonary bypass in the elderly. *Critical Care Medicine*, **37**, 902–11.

CHAPTER 154

Ventricular assist devices in the ICU

Alain Combes

Key points

- Extracorporeal membrane oxygenation (ECMO) is the first-line therapy in the setting of acute cardiogenic shock refractory to conventional treatments.
- The INTERMACS severity classification is used to assess the degree of clinical severity of patients with NYHA class IV symptoms, and helps to define the appropriate timing for ventricular assist device (VAD) insertion.
- VAD indications are as a bridge to recovery, or as a bridge to transplantation and destination therapy.
- Miniaturized axial and centrifugal fully implantable left ventricular assist devices have gradually replaced first-generation intracorporeal pulsatile ventricles.
- The SynCardia® CardioWest® Total Artificial is a biventricular, pneumatic, pulsatile pump that totally replaces the native ventricles, solving the problems of persistent ventricular arrhythmias, right ventricular failure or severe valvular heart disease.

Introduction

Despite major advances in pharmacological therapies for heart failure with left ventricular pump dysfunction, the number of hospitalizations for decompensated heart failure is increasing, with most patients ultimately dying of disease complications. Heart transplantation remains the only treatment providing substantial individual benefit for patients with advanced disease. However, fewer than 3000 organ donors are available worldwide per year, limiting its overall impact. Therefore, alternative approaches such as mechanical circulatory support have been the subject of intense research over recent decades [1–6].

The development of mechanical circulatory devices parallels that of cardiac surgery and cardiac transplantation. The first clinical implantation of a pneumatically-driven ventricular assist device (VAD) was performed by De Bakey in 1966. Since then, collaborative efforts between scientists, engineers and clinicians have resulted in major improvements in the design, biocompatibility, and performance of these machines. Better patient selection and management have also improved outcomes. Traditional indications or strategies for mechanical circulatory support included bridge to bridge, in which a first device is used as a bridge to another long-term machine, bridge to recovery of heart function, bridge to transplantation, and destination therapy. However, current practice and the development of economically affordable short-term devices have resulted in updated indications for mechanical circulatory assistance for both short- and long-term support.

Short-term indications for mechanical support

Rescuing the 'crash and burn' patient, and bridging others to recovery

Short-term mechanical circulatory support devices are indicated in patients with medical conditions (acute myocardial infarction, myocarditis, intoxication with cardiotoxic drugs, end-stage dilated cardiomyopathy), post-cardiotomy or post-transplantation acute cardiogenic shock. Most of these 'crash and burn' patients receive a device as salvage therapy after having already developed signs of multiple organ failure. In these situations, mechanical assistance is used as a bridge to decision-making or to 'whatever seems reasonable' if the patient survives the first days to reach the 'decision-making' point. In patients with potentially reversible cardiac failure (e.g. myocarditis, myocardial stunning post-myocardial infarction), a short-term device may also be used as a bridge to recovery [1].

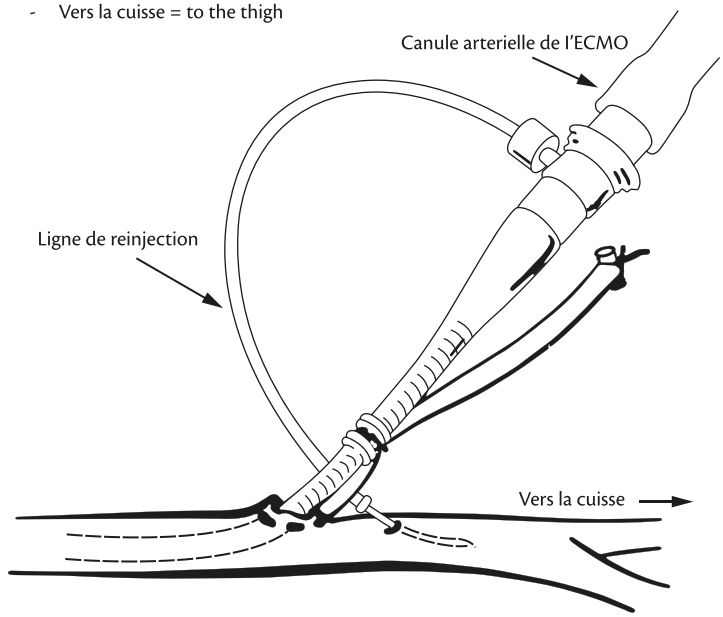
Devices inserted in such situations are catheter- or cannula-based pumps. The Impella CardioSystem® AG is a catheter-based axial flow pump with a propeller at the catheter tip, which is positioned retrogradely across the aortic valve into the LV. The TandemHeart® is a percutaneous ventricular assist device consisting of an extracorporeal centrifugal continuous flow pump that sucks blood from the left atrium via a cannula introduced trans-septally through the femoral vein. Blood is then pumped back to the femoral artery at flow rates of up to 3.5 L/min. The Levitronix CentriMag® is a continuous-flow, centrifugal-type rotary blood pump placed outside the body (extracorporeally). The pump can rotate at speeds of 1500–5500 rpm and can provide flow rates of up to 9.9 L/min. However, in recent years extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS) has become the first-line therapy in the setting of acute cardiogenic shock. This is due to its easy insertion, even at the bedside, the higher flow rates provided, and its association with less organ failure after implantation compared with biventricular assist devices.

ECMO as first-line support for refractory cardiogenic shock

The ECMO extracorporeal system (Fig. 154.1) consists of venous and arterial cannulae, polyvinyl chloride tubing, a membrane

(a) Translations of labels:

- Canule arterielle de l'ECMO = ECMO arterial cannula
- Ligne de reinjection = Reinjection line
- Vers la cuisse = to the thigh



(b)

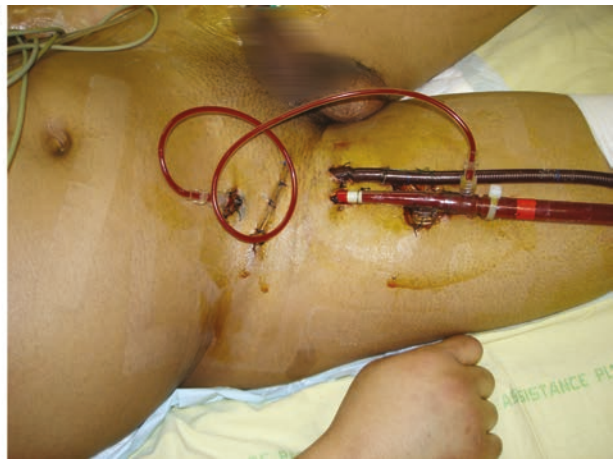


Fig. 154.1 (a) and (b) Femoral cannulation for veno-arterial ECMO. An additional perfusion catheter is sometimes inserted distally into the femoral artery to reduce the risk of limb ischaemia. Part of image 154.1(b) has been deliberately blurred.

oxygenator and a centrifugal pump. It provides both respiratory and cardiac support [1]. Using the peripheral veno-arterial configuration, where femoral vein and artery are cannulated percutaneously, the circuit is perfectly suited for emergency situations. It can be inserted in less than 30 minutes, under local anaesthesia, can supply blood flow up to 8 L/min, and is either more efficient and durable or less costly than other first-line devices.

Several considerations must be taken into account before instituting ECMO. First, the device should be inserted before the patient has developed multiple organ failure or myocardial failure has led to refractory cardiac arrest, since these conditions are associated with significantly worse outcomes. Secondly, highly unstable patients may benefit from urgent on-site ECMO initiation by a rapid resuscitation team able to operate a portable and quick-to-prime ECMO circuit before transportation to the ECMO referral centre. Thirdly, cardiac failure and other organ injuries should be deemed reversible and the patient's underlying condition should not contraindicate a bridge to a more permanent device or to transplantation. Fourthly, management of patients on ECMO for refractory cardiogenic shock is complex and should be conducted in experienced centres.

ECMO can also be configured using central cannulation where the right atrium, ascending aorta and, sometimes, the left atrium or LV are directly cannulated. This is the first-line configuration used for post-cardiotomy or post-transplantation cardiogenic shock, or if peripheral ECMO has failed to deliver adequate flows or is complicated by severe pulmonary oedema.

In most patients the duration of ECMO support is approximately 1 week. However, ECMO can be maintained for weeks, especially if the central configuration is used. ECMO weaning is considered when there has been a partial or full cardiac recovery, or maintained as a bridge to transplantation or VAD implantation because

of insufficient LV functional recovery. ECMO can also be simply withdrawn in cases of therapeutic futility (severe brain lesions, end-stage multiple organ failure, or absence of myocardial recovery in the context of a definitive contraindication to transplantation or VAD implantation).

Long-term indications for mechanical support

Patient selection and indications

In the large Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry, indications for VAD implantation at the time of surgery were bridge to transplantation (80%), bridge to recovery (5%), and destination therapy (15%) [3]. Before surgery, patients should undergo a thorough clinical and psychosocial evaluation, specifically assessing the severity of cardiac failure, co-existing life-limiting, or psychiatric illnesses, and the risks associated with surgery. The INTERMACS severity classification (Table 154.1) is commonly used to classify the different degrees of clinical severity of patients with New York Heart Association class IV symptoms, and helps to define the appropriate timing for device insertion [3]. The two most common indications for LVAD placement are cardiogenic shock (INTERMACS level 1, or 'crash and burn') and worsening of symptoms in inotrope-dependent patients (INTERMACS level 2 or 'sliding on inotropes'), which accounts for 80% of all implantations. However, as previously stressed, the most severe patients (INTERMACS level 1, 'crash and burn' or those at INTERMACS 'level 0' 'cardiac arrest, dying, or severe multi-organ failure (MOF)) may benefit from insertion of a first-line device such as ECMO, and later be bridged to a long-term cardiac assist machine after clinical and haemodynamic stabilization. For INTERMACS class 2 patients, an increase in inotrope dose, use of vasopressors, or signs of end-stage organ failure should indicate urgent device placement. Stable, but truly inotrope-dependent patients (INTERMACS level 3) are those who might derive the greatest benefit from heart transplantation or VAD insertion. At this stage of the disease, VAD insertion may be elective, especially for patients expected to have a long waiting time on the transplantation list (large body size, anti-HLA antibodies, or O blood group). VAD implantation in INTERMACS class 4–6 patients is still controversial and depends on the evolution of the disease, and its impact on the patient's functional status and quality of life. Newest generation devices, which are better tolerated and have fewer complications, may significantly increase the number of patients implanted at that stage. Furthermore, since LV function recovery has been demonstrated after prolonged VAD support in a limited series of patients, earlier implantation may become more frequent. Finally, LVAD implantation as destination therapy in non-transplant candidates should be discussed only in selected groups of haemodynamically stable patients, taking into account complication rates and the high costs still associated with these procedures.

Device selection

Selecting the appropriate device depends on many considerations, including body size, the anticipated duration of support, the need for associated right-sided ventricular support, the experience of the medical-surgical team, and total cost. Devices can be categorized as extracorporeal or intracorporeal. The Abiomed® BVS 5000 and the Thoratec® VAD are pneumatic pulsatile extracorporeal pumps that can achieve flow rates up to 6 L/min and can be used for uni- or bi-ventricular support. The main advantages of these systems are their versatility for mono- or bi-ventricular assistance, and their ability to be used in small patients. They have been extensively used worldwide as a bridge to recovery after cardiotomy, for medical cardiogenic shock, or as a bridge to transplantation. However, they limit autonomy and the four large percutaneous blood lines constitute an infection risk. In the first decade of the twenty-first century,

Table 154.1 Interagency Registry for Mechanically Assisted Circulatory Support level of limitation at time of implant

Profile	Description	Time frame for intervention
1	'*Crash and burn*': patient with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion with increasing lactate levels, and/or systemic acidosis.	Needed within hours
2	'*Sliding on inotropes*': patient with declining function despite intravenous inotropic support may be manifest by worsening renal function, nutritional depletion, and inability to restore volume balance.	Needed within few days
3	'*Stable but inotropes dependent*': patient with stable BP, organ function, nutrition, and symptoms on intravenous inotropic support, but demonstrating repeated failure to wean due to recurrent symptomatic hypotension or renal dysfunction.	Elective over a few weeks
4	'*Frequent flyer*': patient can be stabilized with near-normal volume status, but experiences frequent relapses into fluid retention, generally with high diuretic doses. Symptoms are recurrent, rather than refractory. More intensive management strategies should be considered, which in some cases, reveal poor compliance.	Elective over weeks to months as long as treatment of episodes restores stable baseline, including nutrition
5	'*Housebound*': patient is living predominantly within the house, performing activities of daily living and walking from room to room with some difficulty. Patient is comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction.	Variable, depends upon nutrition, organ function, and activity
6	'*Walking wounded*': patient without evidence of fluid overload is comfortable at rest, and with activities of daily living and minor activities outside the home, but fatigues after the first few minutes of any meaningful activity.	Variable, depends upon nutrition, organ function, and activity
7	'*Limited activity*': advanced NYHA III patients without recent unstable fluid balance, living comfortably with meaningful activity limited to mild exertion.	Transplantation or circulatory support not currently indicated

Reprinted from Journal of the American College of Surgeons, 208, 5, Holman WL, 'INTERMACS: Interval Analysis of Registry Data', pp. 755–761, Copyright 2009, with permission from American College of Surgeons.

miniaturized axial (Jarvik 2000®, Thoratec HeartMate® II) and centrifugal (DuraHeart®, Ventrassist®, and HeartWare®) pumps have gradually replaced first-generation intracorporeal pulsatile devices (e.g. HeartMate® XVE and Novacor®). These non-pulsatile devices deliver up to 10 L/min and their small size facilitates placement and explantation. They also have extended durability because of simpler mechanics, fewer moving parts and points of friction, and they operate more quietly than larger pulsatile pumps (Fig. 154.2). Successful implantation of either first or newest generation left ventricular assist devices depends on preserved right ventricular function, which should be carefully evaluated beforehand.

Two orthotopic artificial hearts have also been developed. These have unique advantages over other machines as they solve problems of persistent ventricular arrhythmias, RV failure, or severe heart valve disease. The AbioCor® Artificial Heart is still under clinical evaluation and only a few patients have received this device as a bridge to transplantation. The SynCardia® Temporary CardioWest® Total Artificial (formerly Jarvik® 7) was recently approved by the FDA as a bridge to transplantation. This biventricular, pneumatic, pulsatile pump totally replaces the native ventricles. Over 1000 implantations have been performed worldwide over the last three decades and the recent development of a smaller driving console may allow greater patient mobility and, eventually, discharge from hospital. Recent data from the large INTERMACS registry indicate that 75% of devices implanted are LVAD, 20% biventricular assist device (BiVAD), and <10% total artificial hearts [3].

Fig. 154.2 Thoratec HeartMate II™ implantable axial continuous flow pump [5]. Reprinted with permission of the Thoratec Corporation.

Outcomes

In the INTERMACS registry, 6-month and 1-year survival after VAD implantation were 73 and 62%, respectively. One year post-implantation 35% had been transplanted, 35% were alive with the device in place, and <5% had been explanted because of LV functional recovery [3]. Overall survival was worse for older patients, those in INTERMACS class 1 status, patients with ascites and higher bilirubin, and those who received a BiVAD or a total artificial heart because of more advanced disease or complicated conditions, such as RV failure. However, 1-year survival was >70% for patients who received a machine in INTERMACS stages 2–7. Device-related complications were frequent, with <50% of patients being free of infection after 1 year.

A few landmark trials of patients implanted with a VAD have been published in the last decade. The REMATCH trial randomized 129 patients with end-stage heart failure who were ineligible for cardiac transplantation to receive a LVAD (HeartMate® XVE) or optimal medical management [4]. Survival analysis showed a 48% reduction in the risk of death from any cause in the LVAD group with 1-year survival being 52 and 25% in the device and medical therapy groups, respectively ($p = 0.002$). This demonstrates for the first time that 'destination therapy' strategy with an LVAD is an acceptable alternative strategy in selected patients who are not candidates for cardiac transplantation. A non-randomized prospective study showed that the Syncardia CardioWest® total artificial heart could rescue transplant-eligible patients at risk of imminent death from irreversible biventricular cardiac failure [2]. The rate of survival to transplantation was 79% for CardioWest patients versus 35% in historical control patients who met the same entry criteria, but did not receive an artificial heart. Overall, the 1-year survival rate among patients who received the artificial heart was 70%, compared with 31% in controls ($p < 0.001$). One- and five-year survival rates after transplantation among patients who had received a total artificial heart as a bridge to transplantation were 86 and 64%, respectively. These are close to those observed after elective heart transplantation. Finally, a randomized trial compared outcomes of patients with advanced heart failure who were ineligible for transplantation and who received a continuous-flow device (HeartMate® II) or the first-generation electric pulsatile-flow device (HeartMate® XVE) as destination therapy [5]. At 2 years, survival free from disabling stroke or re-operation to repair/replace the device was 46% of patients with continuous-flow devices, but only 11% with pulsatile-flow devices ($p < 0.001$). Patients with continuous-flow devices had superior actuarial 2-year survival rates (58 versus 24%, $p = 0.008$). Adverse events and device replacement were also less frequent in patients with the continuous-flow device. Finally, the small, intrapericardially positioned, continuous-flow, HeartWare® centrifugal pump was recently shown to be non-inferior to other latest generation implanted LVADs, improving functional capacity and quality of life, and having a favourable adverse event profile [6].

Conclusion

Mechanical circulatory assistance is now a frequent therapeutic option for patients with advanced heart failure. Indications for device implantation have changed significantly in the last decade. For patients with acute cardiogenic shock and impaired organ function, short-term assistance using ECMO is now the leading therapeutic option and enables a 'bridge to decision-making', i.e. withdrawal of the device after myocardial recovery or after recognition of therapeutic futility, or as a bridge to transplantation or long-term mechanical support. For INTERMACS classes 2–6 patients, implantation of a long-term VAD should be considered before progression to multiple organ failure. Most patients receive a VAD as a bridge to transplantation in this setting. However, implantations as bridge-to-recovery and, more recently, as a permanent heart function support or 'destination therapy' are increasing, mostly because of major technological and engineering advances making newer devices more reliable, less invasive, and associated with fewer complications than first-generation machines.

References

1. Combes A, Leprince P, Luyt CE, et al. (2008). Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. *Critical Care Medicine*, **36**, 1404–11.
2. Copeland JG, Smith RG, Arabia FA, et al. (2004). Cardiac replacement with a total artificial heart as a bridge to transplantation. *New England Journal of Medicine*, **351**, 859–67.
3. Holman WL, Pae WE, Teutenberg JJ, et al. (2009). INTERMACS: interval analysis of registry data. *Journal of the American College of Surgery*, **208**, 755–61; discussion 61–2.
4. Slaughter MS, Rogers JG, Milano CA, et al. (2009). Advanced heart failure treated with continuous-flow left ventricular assist device. *New England Journal of Medicine*, **361**, 2241–51.
5. Rose EA, Gelijns AC, Moskowitz AJ, et al. (2001). Long-term mechanical left ventricular assistance for end-stage heart failure. *New England Journal of Medicine*, **345**, 1435–43.
6. Aaronson KD, Slaughter MS, Miller LW, et al. (2012). Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. *Circulation*, **125**, 3191–200.

PART 5.7

Tachyarrhythmias

CHAPTER 155

Causes and diagnosis of tachyarrhythmias

Allan J. Walkey and David D. McManus

Key points

- Tachyarrhythmias occur in approximately 12% of critically-ill patients.
- Adenosine administration or vagal manoeuvres during continuous ECG monitoring can assist in ascertaining the specific diagnosis for undetermined supraventricular tachycardia.
- After acute stabilization of the patient, the underlying arrhythmia trigger should be identified and addressed.
- Atrial fibrillation during severe sepsis is associated with increased risk for in-hospital mortality and stroke.
- *Torsades de pointes* is often the result of QT-interval-prolonging medications administered during critical illness.

Introduction

Sustained tachyarrhythmias are common in patients with critical illness, occurring in approximately 12% of patients admitted to general medical/surgical ICUs [1]. The occurrence of new tachyarrhythmia (i.e. heart rate greater than 100 beats/min) during critical illness is associated with increased mortality, morbidity, length of stay, and cost [1–6]. This chapter reviews the causes and diagnostic approach to supraventricular and ventricular tach*y*arrhythmias in the critically-ill patient. We exclude sinus tachycardia, which is generally an adaptive response that increases cardiac output to match increased metabolic (e.g. fever), haemodynamic (e.g. hypovolaemia), or catecholamine (e.g. pain/anxiety) stressors of critical illness. Instead, tachyarrhythmias are maladaptive responses to a wide range of insults. Tachyarrhythmias may result in acute decompensation of the critically-ill patient, usually due to decreased cardiac output from supraphysiological heart rates. After acute stabilization of patients, health care providers should evaluate and address potentially reversible triggers of new tachyarrhythmia in the critically ill (Table 155.1).

Supraventricular tachyarrhythmias

Supraventricular tachyarrhythmias (SVTs) include atrial fibrillation (AF), atrial flutter, atrial tachycardia, atrioventricular nodal tachycardia (AVNRT) or atrioventricular re-entry tachycardia (AVRT), and multifocal atrial tachycardia (MAT). SVTs most commonly present as a narrow QRS complex (QRS <120 ms) tachycardia, although they may have wide QRS rhythms in the setting of aberrant conduction. Mechanisms of SVT involve enhanced automaticity, triggered activity, or re-entry. Management of SVT involves correct diagnosis of the arrhythmia, elucidation of the electrophysiological mechanisms underlying the arrhythmia, and targeted treatment.

Diagnosis of supraventricular tachycardia

Proper diagnosis requires electrocardiographic (ECG) analysis. Use of adenosine (6 mg intravenous (iv) bolus, followed by 12 mg iv bolus if the first dose is ineffective in producing AV block) or vagal manoeuvres (e.g. carotid massage in patients without atherosclerosis, Valsalva) can temporarily block or slow atrioventricular nodal conduction to assess the underlying atrial activity. In atrioventricular node-dependent arrhythmias, adenosine or vagal manoeuvers may also terminate the arrhythmia. Since atrioventricular block can promote antegrade conduction of AF down an accessory pathway, adenosine is contraindicated in patients with a Wolff-Parkinson White pattern on the ECG; adenosine is also contraindicated in patients with bronchospasm.

Atrial fibrillation

AF (Fig. 155.1) is the most common arrhythmia in critical illness. Classically, AF presents paroxysmally as an 'irregularly irregular'

Table 155.1 Potentially reversible causes of new-onset tachyarrhythmias in the critically ill

Cause	Example
Electrolyte disturbances	Hyper or hypo: -kalaemia, -magnesaemia, -calcaemia, -natremia; hypoxaemia
Beta$_1$-agonist medications	Dobutamine > epinephrine > dopamine > norepinephrine
Acute atrial or ventricular stretch	Acute pulmonary embolism, volume overload, or cardiomyopathy
Systemic inflammatory response syndrome	Sepsis
Cardiac injury	Myocardial ischaemia/infarction, central venous catheter irritation
Intrathoracic pressure swings	Ventilator dyssynchrony, airway obstruction [12]
Overdose/ingestion	Digoxin

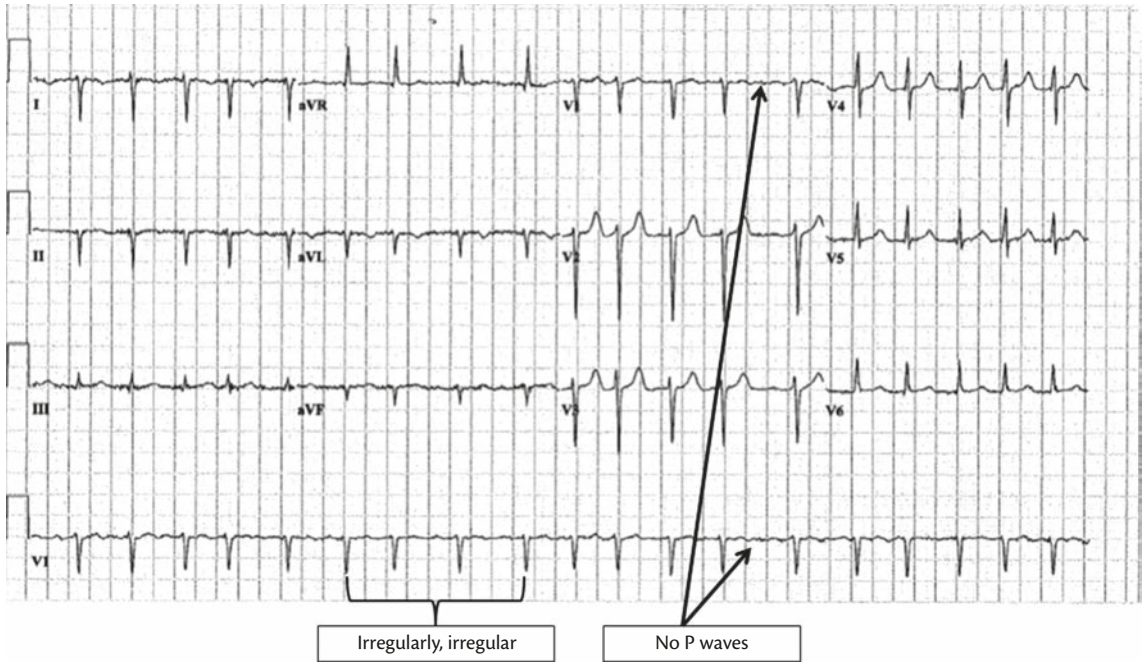


Fig. 155.1 Electrocardiogram demonstrating atrial fibrillation. Note narrow QRS complex, irregularly irregular rhythm, and absence of P waves.

narrow QRS complex tachycardia without discernible P waves. New-onset AF occurs in approximately 4% of the critically ill and 6–40% of patients with severe sepsis or septic shock [1–6]. In patients with sepsis, demographic factors (increasing age, male sex, and white race), comorbid conditions (a history of heart failure or obesity), and acute factors (number of acute organ failures, use of mechanical ventilation, vasopressors, pulmonary artery catheter) are associated with its development [1,2]. Multiple characteristics of critical illness are known triggers (Table 155.1) and represent potential therapeutic targets.

As is true of AF occurring in the community setting, AF complicating severe sepsis is also associated with an increased risk for death and ischemic stroke [2]. More than 50% of patients with new-onset AF during severe sepsis do not survive their hospitalization and 3% experience new, in-hospital stroke. The risk of ischaemic stroke in patients with new-onset AF during severe sepsis is approximately 0.2% per day, which is greater than stroke risks reported with AF in the community. Additionally, the increased risk of stroke with new-onset AF during severe sepsis may extend beyond hospital discharge. Traditional stroke risk scores (e.g. $CHADS_2$) excluded patients with critical illness and are of unknown predictive value in the critically ill. Thus, little evidence currently exists to guide the risk/benefit analysis of whether to initiate anticoagulants in patients with new-onset AF during critical illness.

Atrial flutter

Typical counter-clockwise atrial flutter is a macro-re-entrant tachyarrhythmia characterized by rapid atrial activity ('sawtooth' flutter waves, approximately 300 beats/min) that conducts to the ventricle to produce heart rates most commonly of ~150 beats/min. Atrial flutter is less common than atrial fibrillation, occurring in 1–2% of critically-ill patients. It is currently unknown whether risk factors or outcomes for atrial flutter during critical illness differ from those of atrial fibrillation.

Multifocal atrial tachycardia

This results from multiple ectopic sites of triggered atrial activity. MAT is diagnosed through identification of at least three different P wave morphologies. It is precipitated by acute illness, often in patients with chronic pulmonary disease. However, with the declining use of theophylline, MAT has become rare (<1% of hospitalized patients) [7,8]. Like AF, development of MAT in hospitalized patients is associated with poor outcomes [9].

Atrioventricular re-entry tachycardia and atrioventricular nodal re-entry tachycardia

Although common in the community setting, AVRT and AVNRT are rare in the general medical/surgical ICU, occurring in <1% of patients. Orthodromic AVRT and AVNRT are atrioventricular nodal-dependent arrhythmias that involve antegrade conduction down the AV node and retrograde conduction up an accessory or AV nodal pathway, respectively. Examination of the ECG R wave to P-wave interval (RP) can help differentiate between typical short-RP arrhythmias (RP interval < P-wave to R-wave interval, e.g. typical slow/fast AVNRT, Fig. 155.2) and AVRT (long RP) with a slowly conducting accessory pathway. Like most arrhythmias, AVRT and AVNRT may be exacerbated by electrolyte disturbances and high catecholamine states.

Atrial tachycardia

Atrial tachycardia (AT) is the result of a focus of atrial electrical activity ectopic to the sinoatrial node. It may be generated though micro-re-entry, enhanced automaticity, or triggered foci. AT is

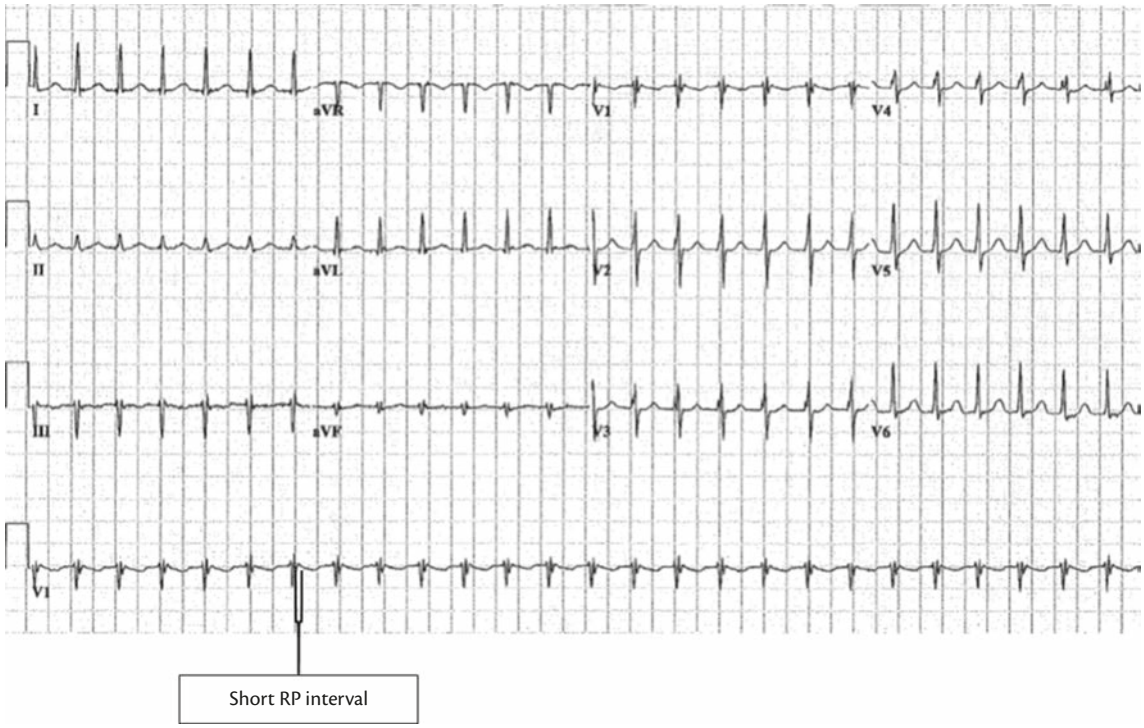


Fig. 155.2 Electrocardiogram demonstrating short RP interval supraventricular tachycardia. This patient reverted to normal sinus rhythm after intravenous administration of adenosine 6 mg.

generally paroxysmal, and diagnosed through identification of P wave morphology that differs from the patient's baseline sinus node conduction. Similar to other supraventricular tachyarrhythmias, initial evaluation consists of identification and reversal of the underlying trigger (Table 155.1).

Ventricular arrhythmias

Ventricular arrhythmias that develop secondary to pre-existing critical illness are associated with poor prognosis; in one study, only 27% of general intensive care unit (ICU) patients who developed ventricular arrhythmia survived the hospitalization [1]. Whereas SVT is associated with a small increase in hospital mortality that may or may not be directly attributed to the arrhythmia, ventricular arrhythmias are often the proximate cause of death [1]. Thus, rapid assessment of haemodynamic status, rhythm ascertainment, and institution of acute cardiac life support treatment are imperative.

Ventricular tachycardia (VT) is a wide complex tachyarrhythmia that can complicate critical illness, occurring in approximately 2% of general ICU patients. Monomorphic VT is generally a result of re-entry around fibrotic ventricular myocardium. Due to important prognostic and treatment considerations, monomorphic VT should be discriminated from SVT with aberrant conduction or antidromic AVRT. Discrimination of VT from aberrant SVT includes assessment of the pre-test probability of VT (known cardiomyopathy or prior myocardial infarction) versus SVT (known history of SVT, known bundle branch block of similar morphology to observed QRS, pre-existing accessory pathway). Identification of supraventricular–ventricular fusion beats and atrioventricular dissociation are specific, but insensitive for the identification of VT. Classic right bundle branch block (Lead I: broad S wave; Lead V1: rSR') or left bundle branch block patterns (Lead I: QS; Lead V1: un-notched RS) are unlikely to be seen in VT. Although not validated in critically-ill patients, Brugada's algorithm (Table 155.2) can be used to discriminate aberrant SVT from VT with high sensitivity (99%) and specificity (97%) [10]. However, if questions remain regarding a wide complex tachycardia, assume VT.

Polymorphic VT in the critically-ill patient is often associated with active myocardial ischaemia or acute myocardial injury, is rarely tolerated, and generally requires DC cardioversion. Torsades de pointes ('turning around a point', Tdp) is a type of polymorphic VT occurring in the setting of a prolonged QT interval and characterized by a varying QRS amplitude along an isoelectric line. In the ICU, Tdp is frequently associated with QT-prolonging medications, many of which are frequently administered to critically-ill patients.

Table 155.2 Brugada algorithm for diagnosis of monomorphic ventricular tachycardia (VT) [10]. Presence of any criterion indicates diagnosis of ventricular tachycardia

Brugada criterion	Sensitivity for VT	Specificity for VT
1. No RS in precordial leads	21%	100%
2. R to S interval >100 ms in any precordial lead	21%	100%
3. A–V dissociation	82%	98%
4. No classic RBBB or LBBB pattern	98%	97%

RBBB, right bundle branch block; LBBB, left bundle branch block; A–V, atrio-ventricular.

Reproduced from Brugada P et al., 'A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex', *Circulation*, **83**, pp. 1649–59, copyright 1991, with permission from American Heart Association and Wolters Kluwer Health.

Table 155.3 Medications with high-risk of QT prolongation commonly used in the critically ill

Class	Examples
Anti-psychotics/anti-emetics	Haloperidol, chlorpromazine, droperidol, domperidone
Anti-arrhythmic	Amiodarone, disopyramide, dofetilide, flecainide, ibutilide, procainamide, quinidine, sotalol
Antibiotics	Macrolides (e.g. erythromycin, azithromycin), fluoroquinolones (e.g. moxifloxacin), pentamidine
Anti-malarials	Chloroquine
Methadone derivatives	Methadone
Anti-depressants	Citalopram

Screening for prolonged QT interval prior to administration of QT-prolonging medications listed in Table 155.3 and avoidance of high-risk medications in patients with prolonged QTc intervals (> 500ms) is recommended; risk of Tdp is increased 2–3-fold for patients with QTc >500 ms [11].

References

1. Annane D, Sebille V, Duboc D, et al. (2008). Incidence and prognosis of sustained arrhythmias in critically ill patients. *American Journal of Respiratory and Critical Care Medicine*, **178**(1), 20–5.
2. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, and Benjamin EJ. (2011). Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. Journal of the American Medical Association, **306**, 2248–54.
3. Meierhenrich R, Steinhilber E, Eggermann C, et al. (2010). Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. *Critical Care*, **14**, R108.
4. Salman S, Bajwa A, Gajic O, and Afessa B. (2008). Paroxysmal atrial fibrillation in critically ill patients with sepsis. *Journal of Intensive Care Medicine*, **23**, 178–83.
5. Artucio H and Pereira M. (1990). Cardiac arrhythmias in critically ill patients: epidemiologic study. *Critical Care Medicine*, **18**, 1383–8.
6. Christian SA, Schorr C, Ferchau L, Jarbrink ME, Parrillo JE, and Gerber DR. (2008). Clinical characteristics and outcomes of septic patients with new-onset atrial fibrillation. *Journal of Critical Care*, **23**(4), 532–6.
7. Bittar G and Friedman HS. (1991). The arrhythmogenicity of theophylline. A multivariate analysis of clinical determinants. *Chest*, **99**, 1415–20.
8. McCord J and Borzak S. (1998). Multifocal atrial tachycardia. *Chest*, **113**, 203–9.
9. Scher DL, Arsura EL. Multifocal atrial tachycardia: mechanisms, clinical correlates, and treatment. *American Heart Journal*, **118**, 574–80.
10. Brugada P, Brugada J, Mont L, Smeets J, and Andries EW. (1991). A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation*, **83**, 1649–59.
11. Drew BJ, Ackerman MJ, Funk M, et al. (2010). Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*, **121**, 1047–60.
12. Linz D, Schotten U, Neuberger HR, Bohm M, and Wirth K. (2011). Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation. *Heart Rhythm*, **8**, 1436–43.

CHAPTER 156

Therapeutic strategy in tachyarrhythmias

Allan J. Walkey and Jared Magnani

Key points

- Critically-ill patients with acute tachyarrhythmia require immediate assessment of clinical stability, cardiac substrate, and precipitating factors.
- Tachyarrhythmias that cause severe haemodynamic instability require emergent direct current cardioversion.
- Effects of direct current cardioversion during critical illness are often transient, unless the underlying arrhythmia precipitant is eliminated and longer-acting rate- or rhythm-controlling medications are instituted.
- Atrial fibrillation often responds favourably to a rate-control strategy and treatment of the underlying precipitants.
- Assessment of the QT interval in patients with polymorphic ventricular tachycardia is important in determining the underlying etiology and treatment strategy.

General approach

The therapeutic strategy for tachyarrhythmias in critical illness depends upon the following patient assessments:

- **Haemodynamic status**: evidence of clinical instability associated with the arrhythmia requires urgent treatment.
- **The specific tachyarrhythmia and its precipitating factors**: successful arrhythmia treatment depends on elimination of precipitants, as well as institution of appropriate medications.

Clinical instability

Narrow complex or monomorphic wide complex tachycardias that cause acute clinical instability warrant emergent synchronized direct current cardioversion (DCCV), under conscious sedation whenever possible. Advanced cardiac life support principles and algorithms are required for patients who develop cardiac arrest or who become acutely unstable due to the arrhythmia. The acute decline in cardiac output induced by tachyarrhythmia may manifest as mental status change, shock, heart failure, or cardiac ischaemia. More subtle signs of low cardiac output—renal dysfunction, slow capillary refill, or lactic acidosis—also indicate urgency for arrhythmia treatment.

Narrow complex tachycardia

Critically-ill patients frequently experience narrow complex, supraventricular tachyarrhythmias (SVT). In critically-ill—but haemodynamically stable—patients, assessment of a continuous 12-lead ECG rhythm strip with simultaneous vagal stimulation or adenosine administration helps to discriminate between the narrow complex tachyarrhythmias. In all new-onset arrhythmias, care should be taken to address the underlying trigger in addition to instituting medications to treat the clinically significant arrhythmia.

Atrial fibrillation and atrial flutter

Clinically significant atrial fibrillation (AF) or atrial flutter (AFL) may be treated with either a heart rate-lowering (rate-control) or a rhythm conversion strategy (rhythm-control). Rate-control improves ventricular filling time, thereby increasing cardiac output. Rhythm-control may restore atrial systole, further enhancing cardiac output. AF is the most commonly encountered clinical arrhythmia and may be secondary to underlying cardiac disease, sympathetic stress, or an inflammatory state. Addressing the underlying critical illness and clinical stabilization are foremost goals for management.

With the exception of unstable patients requiring emergent DCCV, guidelines do not favour rate- or rhythm-control in the critically ill [1]. One trial comparing a rate-control approach (diltiazem, 25 mg bolus followed by 20 mg/hour infusion) to a rhythm-control approach (amiodarone, 300 mg bolus followed by 45 mg/hour infusion) in 60 critically-ill patients with SVT did not find a difference in conversion to sinus rhythm between the two groups [2]. However, heart rate was better controlled with diltiazem.

Atrial fibrillation and atrial flutter: rate control

Atrioventricular (AV) nodal-slowing agents are often used as initial therapy for AF or AFL with a rapid ventricular response (generally heart rates >150 beat/min) without immediately life-threatening clinical instability. However, little evidence guides the selection between various AV node-slowing agents. Intravenous non-dihydropyridine calcium channel (CCB) antagonists (e.g. verapamil, diltiazem) and intravenous β_1-selective (BB) antagonists (e.g. metoprolol, esmolol) are commonly used for AF/AFL heart

rate control in the critically ill. A randomized trial showed similar heart rate improvement between esmolol and diltiazem in patients with acute AF [3], although conversion to sinus rhythm occurred more frequently in patients given esmolol.

The major side effect of BB and CCB in the critically ill is hypotension. The cardiac glycoside digoxin is frequently chosen for rate control during critical illness because of its lower risk for precipitating hypotension or decreasing inotropy. However, digoxin alone does not achieve comparable heart rate control to BB or CCB therapy during acute AF [4]. The high sympathetic state of critical illness renders the vagomimetic actions of digoxin less effective. Digoxin may improve heart rate control when added to sub-optimal or hypotension-inducing BB or CCB therapy [5], or in patients who may not tolerate reduced inotropy (level I) [1], however toxicity is of concern in patients with acute renal failure.

Magnesium sulphate competes with calcium to prolong the action potential duration and may be an effective rate-control adjunct to CCB, BB, or digoxin therapy [6], but may be ineffective as a single agent [7].

In patients who develop hypotension after administration of BB or CCB therapy for AF/AFL, the addition of the selective α_1-adrenoreceptor agonist phenylephrine may improve blood pressure and suppress AF [8]. However, reflex vagal stimulation from phenylephrine also has potential to act as an AF trigger; the net effect of phenylephrine on outcomes in critically-ill patients with AF is unknown.

AF and AFL: rhythm control

Non-emergent rhythm-control therapy in AF/AFL is often instituted when attempts at rate-control have failed or produced complications. The most basic rhythm-control strategy is synchronized DCCV. However, in critically-ill patients with ongoing AF precipitants, AF is likely to recur after DCCV. A single ICU observational study found that 70% of patients with AF required at least three DCCV attempts to achieve successful cardioversion; only 16% of patients remained in sinus rhythm 24 hours after DCCV [9].

Due to high rates of reversion to AF/AFL after DCCV, longer-acting anti-arrhythmic therapy may be preferable to DCCV in critically-ill patients treated with a rhythm-control strategy. Amiodarone is commonly used for rhythm-control in the critically ill. Amiodarone's mild potency β_1- blocking activity may also effectively reduce heart rate in the absence of successful cardioversion. The efficacy of amiodarone in AF/AFL of critical illness was studied in approximately 100 patients, with 50–80% success rates for cardioversion within 12 hours after the first dose [10]. No studies have been placebo-controlled and, notably, amiodarone was not superior to magnesium sulphate (which achieved 72% successful 12-hour cardioversion rates) [11]. Side effects of amiodarone include hypotension (though less common than CCB or BB) and QT-prolongation; in addition, amiodarone may rarely induce fatal pulmonary toxicity in the critically ill.

Other anti-arrhythmics, such as procainamide, ibutilide, and flecainide may be efficacious for AF, but are limited by significant side effects and understudied in critical illness. For example, procainamide frequently causes hypotension (10% incidence), ibutilide is associated with significant ventricular arrhythmias from QT prolongation (~8% incidence) [12], while flecainide is associated with increased mortality in patients with acute cardiac ischaemia [13]. These therapies require electrophysiological consultation. Pulmonary vein isolation (i.e. ablation) is contraindicated during critical illness.

AF and AFL: anticoagulation

In addition to haemodynamic collapse, cardio-embolic stroke is a feared complication of AF/AFL. The risk of stroke is increased in patients with new-onset AF during severe sepsis [14]. New strokes occur in approximately 3% of patients with new-onset AF during severe sepsis, as compared with only 0.5% of patients without new-onset AF during severe sepsis. Stroke risk prediction scores developed in populations that excluded the critically ill (e.g. $CHADS_2$) are likely to be inapplicable to the ICU setting. An increased risk for post-cardioversion cardio-embolic stroke due to atrial stunning can occur after electrical, pharmacologic, or spontaneous [15] cardioversion. The American College of Chest Physicians Guidelines recommend institution of anticoagulation in all patients with AF undergoing cardioversion (electrical or pharmacological) for 4 weeks after cardioversion [AF lasting >48 hours, level IB; AF <48 hours, level IIC] [16]. Estimates of severe bleeding risk from anticoagulation during critical illness are currently unavailable and risk/benefit ratio for anticoagulation of AF during critical illness is not clear.

Atrial tachycardia and multifocal atrial tachycardia

The principles of treating atrial tachycardia (AT) and multifocal atrial tachycardia (MAT) are similar to that of AF—address underlying arrhythmia triggers, assess the clinical significance of the arrhythmia, and achieve adequate rate control in cases of clinically significant tachycardia. Common triggers include acute exacerbations of chronic obstructive pulmonary disease (COPD), heart failure, hypoxia, theophylline, hypokalaemia, and hypomagnesaemia. Correction of underlying factors is generally associated with resolution. If additional treatment is warranted, CCB and BB are treatments of choice to reduce atrial ectopy and slow AV nodal conduction. BB may be more effective than CCB, one small trial of 13 patients demonstrated that 89% of patients had improved heart rate or rhythm conversion after metoprolol as compared with 44% of patients given verapamil [17]. Cardioselective BB do not appear to induce bronchospasm in patients with COPD during MAT. DCCV is ineffective for MAT.

Other SVTs

Atrioventricular nodal re-entrant tachycardia (AVNRT) is rare in the critically ill. Its treatment is focused on interfering with the AV node micro-re-entry circuit. Vagal manoeuvres, adenosine, or AV nodal slowing agents all can be used to slow AV node conduction and treat AVNRT [18].

In contrast to AVNRT, AV nodal slowing agents are contraindicated in macro-re-entry atrioventricular tachycardia (AVRT) in which an accessory bypass tract may bypass the AV node to rapidly conduct atrial fibrillation or flutter waves. A pre-excitation (delta) wave preceding the QRS complex on a baseline EKG provides evidence of an accessory pathway. DCCV is the treatment of choice in unstable AVRT. Class IA (e.g. flecainide), IC (e.g. procainamide), and Class III (e.g. amiodarone) anti-arrhythmic agents

may be used to slow the accessory pathway and resolve AVRT [18]. Electrophysiology consultation is recommended for consideration of radiofrequency ablation of the accessory pathway following clinical stabilization.

Ventricular tachycardia

DCCV is used to treat unstable patients with wide complex tachycardia (level IC) [19]. Stable patients with wide complex tachycardia determined to be ventricular tachycardia should be assessed for arrhythmia morphology (monomorphic, polymorphic, torsades de pointes) and the presence of any underlying cardiomyopathy or myocardial ischaemia. Wide complex tachycardia is presumed ventricular tachycardia (VT) if the diagnosis is unclear. Electrophysiology consultation is indicated in patients with recurrent VT.

Monomorphic VT

Guidelines recommend intravenous procainamide as the most effective first line agent for stable monomorphic VT (level IIa) [19]. In patients who do not tolerate hypotension associated with procainamide, intravenous amiodarone is recommended as a second line agent (level IIa). Lidocaine may be effective when other agents are unavailable (level IIb). BB therapy may reduce the frequency of recurrent monomorphic VT.

Polymorphic VT

Polymorphic VT without evidence of a long QT interval is often precipitated by cardiac ischaemia, is rarely haemodynamically tolerated, and generally requires unsynchronized cardioversion. Intravenous BB therapy (level IB) is associated with decreased mortality in myocardial ischaemia-induced recurrent polymorphic VT. Amiodarone (level IC) may also be effective in terminating recurrent ischaemia-associated polymorphic VT. Patients with ischaemia-associated VT should be considered for a coronary revascularization procedure [19].

Polymorphic VT associated with long QT can be managed acutely by unsynchronized cardioversion and/or intravenous magnesium sulphate (level IIa). QT-interval prolongation is common in critical illness. After acute stabilization, polymorphic VT requires withdrawal of QT-prolonging medications (level IA), correction of potassium to 4.5–5 mmol/L (level IIb), and consideration of overdrive pacing (level IA) or isoproterenol therapy (IIa) [19].

References

1. Fuster V, Ryden LE, Cannom DS, et al. (2011). 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*, **123**, e269–367.
2. Delle Karth G, Geppert A, Neunteufl T, et al. (2001). Amiodarone versus diltiazem for rate control in critically ill patients with atrial tachyarrhythmias. *Critical Care Medicine*, **29**, 1149–53.
3. Platia EV, Michelson EL, Porterfield JK, and Das G. (1989). Esmolol versus verapamil in the acute treatment of atrial fibrillation or atrial flutter. *American Journal of Cardiology*, **63**, 925–9.
4. Olshansky B, Rosenfeld LE, Warner AL, et al. (2004). The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. Journal of American College of Cardiology, **43**, 1201–8.
5. Schreck DM, Rivera AR, and Tricarico VJ. (1997). Emergency management of atrial fibrillation and flutter: intravenous diltiazem versus intravenous digoxin. *Annals of Emergency Medicine*, **29**, 135–40.
6. Onalan O, Crystal E, Daoulah A, Lau C, Crystal A, and Lashevsky I. (2007). Meta-analysis of magnesium therapy for the acute management of rapid atrial fibrillation. *American Journal of Cardiology*, **99**, 1726–32.
7. Chu K, Evans R, Emerson G, Greenslade J, and Brown A. (2009). Magnesium sulfate versus placebo for paroxysmal atrial fibrillation: a randomized clinical trial. *Academic Emergency Medicine*, **16**, 295–300.
8. Tai CT, Chiou CW, Wen ZC, et al. (2000). Effect of phenylephrine on focal atrial fibrillation originating in the pulmonary veins and superior vena cava. *Journal of the American College of Cardiology*, **36**, 788–93.
9. Mayr A, Ritsch N, Knotzer H, et al. (2003). Effectiveness of direct-current cardioversion for treatment of supraventricular tachyarrhythmias, in particular atrial fibrillation, in surgical intensive care patients. *Critical Care Medicine*, **31**, 401–5.
10. Clemo HF, Wood MA, Gilligan DM, and Ellenbogen KA. (1998). Intravenous amiodarone for acute heart rate control in the critically ill patient with atrial tachyarrhythmias. *American Journal of Cardiology*, **81**, 594–8.
11. Moran JL, Gallagher J, Peake SL, Cunningham DN, Salagaras M, and Leppard P. (1995). Parenteral magnesium sulfate versus amiodarone in the therapy of atrial tachyarrhythmias: a prospective, randomized study. *Critical Care Medicine*, **23**, 1816–24.
12. Barranco F, Sanchez M, Rodriguez J, and Guerrero M. (1994). Efficacy of flecainide in patients with supraventricular arrhythmias and respiratory insufficiency. *Intensive Care Medicine*, **20**, 42–4.
13. Akiyama T, Pawitan Y, Greenberg H, Kuo CS, and Reynolds-Haertle RA. (1991). Increased risk of death and cardiac arrest from encainide and flecainide in patients after non-Q-wave acute myocardial infarction in the Cardiac Arrhythmia Suppression Trial. CAST Investigators. *American Journal of Cardiology*, **68**, 1551–5.
14. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, and Benjamin EJ. (2011). Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *Journal of the American Medical Association*, **306**, 2248–54.
15. Grimm RA, Leung DY, Black IW, Stewart WJ, Thomas JD, and Klein AL. (1995). Left atrial appendage 'stunning' after spontaneous conversion of atrial fibrillation demonstrated by transesophageal Doppler echocardiography. American Heart Journal, **130**, 174–6.
16. Lansberg MG, O'Donnell MJ, Khatri P, et al. (2012). Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th edn: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, **141**(2 Suppl.), e601S–36S.
17. Arsura E, Lefkin AS, Scher DL, Solar M, and Tessler S. (1988). A randomized, double-blind, placebo-controlled study of verapamil and metoprolol in treatment of multifocal atrial tachycardia. *American Journal of Medicine*, **85**, 519–24.
18. Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, et al. (2003). ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary. A report of the American college of cardiology/American heart association task force on practice guidelines and the European society of cardiology committee for practice guidelines (writing committee to develop guidelines for the management of patients with supraventricular arrhythmias. developed in collaboration with NASPE-Heart Rhythm Society. *Journal of the American College of Cardiology*, **42**, 1493–531.
19. European Heart Rhythm Association, Heart Rhythm Society, Zipes DP, et al. (2006). ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *Journal of the American College of Cardiology*, **48**, e247–346.

PART 5.8

Bradyarrhythmias

CHAPTER 157

Causes, diagnosis, and therapeutic strategy in bradyarrhythmias

Harminder S. Gill and Jaswinder S. Gill

Key points

- Bradycardias are common in the critical care setting.
- Early identification and intervention is important.
- Diagnosis of the arrhythmia is generally made from the electrocardiogram.
- Treat the arrhythmia with drugs, including atropine and sympathomimetics.
- Have a low threshold for using temporary (with or without permanent) pacing.

Introduction

Bradycardia is defined as a heart rate <60 beats/min, and can be either physiological or pathological. Bradycardias are common in critically-ill patients and occur in about 10% of patients admitted to an intensive care unit (ICU). Here, a number of different factors may underlie the abnormal rhythm. As with any dysrhythmia, it is crucial to identify the abnormal rhythm correctly, to then allow prompt institution of appropriate management [1].

Types

Bradyarrhythmias occur at three levels within the conduction system:

- Sino-atrial node.
- Atrioventricular node.
- Bundle branches.

Causes

Patients in the critical care setting are often seriously ill with multisystem disorders and receive multiple therapies that can influence the conduction system. Causes can be classified as shown in Box 157.1 [2,3].

Diagnosis

History

Bradycardias are sometimes identified in asymptomatic patients who present for other reasons, but the arrhythmia may require management. Other patients present with dizziness, syncope, or seizures. In the critical care setting, a patient may present with a sudden drop in blood pressure, impairment of conscious level or haemodynamic collapse which, in some cases, may require immediate resuscitation. Many patients will be continually monitored and this will draw immediate attention to rate abnormalities.

Clinical examination

Palpating the pulse reveals bradycardia. Features of a low cardiac output state (peripheral shutdown, sluggish capillary refill) should always have bradycardia considered as an underlying cause.

Box 157.1 Types of bradycardia

Physiological

Highly trained-athletes have low resting heart rates (often in the range classified as bradycardia).

Pathological

- **General systemic:**
  - Hypothermia.
  - Hypothyroidism.
  - Pain.
  - Vagal responses.
  - *Raised intracranial pressure*: stroke, haemorrhage, encephalopathy.
  - Cholestatic jaundice.
  - Operations.
  - Sepsis.
  - Diabetes.
  - Intubation.
- **Cardiovascular:**
  - Degenerative conduction disease.
  - Ischaemic heart disease.

- Valvular heart disease.
- Cardiomyopathy.
- Congenital heart disease.
- Infiltrative disease.
- Myocardial disease.

◆ **Medications:**

- β-blockers.
- Anti-arrhythmic drugs.
- Digoxin.
- Amiodarone.
- Calcium antagonists.
- Tricyclics.
- Neuroleptics.
- Dementia medications.
- Toxins.

Investigations

The most critical diagnostic investigation is the electrocardiogram (ECG). The presence of the P wave and its relationship to the QRS complex are critically important features. ICU patients frequently have one- or three-lead monitoring as routine, although a formal 12-lead is preferable and may help elucidate the cause. In most cases, Holter and loop recorders are not required, since patients are already undergoing intensive monitoring.

Types of bradycardia

Sinus node disease

This is common and can affect any age group, but is particularly prevalent in the elderly. The sinus node receives rich innervations from the cardiac sympathetic and parasympathetic nerves, and is therefore very sensitive to vagal influences and drugs.

Sinus bradycardia

Accounts for around 30% of all bradyarrhythmias and is manifest by a heart rate <60 beats/min which is inappropriate to the clinical state of the patient [4]. The heart rate frequently fails to respond appropriately to exercise or activity (see Fig. 157.1).

Diagnosis

P-wave slowing but each P wave is followed by a QRS complex.

Sinus arrest

This occurs when the SA node transiently fails to exhibit normal automaticity. The ECG demonstrates a pause without P waves and the length of the pause is not a multiple of the preceding P–P interval. Pauses of 2–3 seconds' duration are seen in 11% of healthy asymptomatic individuals, whereas pauses >3 seconds during waking hours are usually due to sinus node dysfunction. These may lead to life-threatening asystole and therefore require treatment with either drugs and/or pacing (see Figs 157.2 and 157.3).

Sinus exit block

The SA node fires, but the impulse is delayed or fails to propagate beyond the sinus node, resulting in failure of atrial depolarization. The ECG shows a pause without P waves. Type I second degree SA exit block demonstrates progressive P–P interval shortening before the pause (duration is less than two P–P cycles). In Type II second-degree sino-atrial exit block, the pause duration is theoretically an exact multiple of the previous P–P interval as the SA node continues to fire at its own intrinsic rate. Pauses with this condition are generally short and do not require treatment.

Diagnosis

P-wave absence occurs with no QRS, unless the patient has a junctional escape rhythm

AV-nodal conduction disease

It is important to distinguish between block within the AV node and block within or below the His bundle (infranodal AV block), as both prognosis and appropriate treatment depend on this distinction. A surface ECG can assist in making this differentiation. Prolongation of the P–R interval before block (Wenckebach pattern) is strongly suggestive of AV nodal block, whereas sudden block without prolongation of the P–R interval is very suggestive of infranodal block. The escape rate in the setting of complete AV block is higher (40–60 beats/min) in AV nodal block, as the escape pacemaker is usually in the His/proximal Purkinje system. Infranodal block results in a less reliable, more distal (often ventricular) escape rhythm (heart rate <40 beats/min). The width of the QRS complex is also helpful: the QRS duration in AV nodal block is generally relatively narrow (<120 milliseconds), whereas the QRS duration in infranodal block is relatively wide.

1st-degree AV block

Commonly seen where each atrial impulse is successfully conducted to the ventricle but with a delay (see Fig. 157.4).This is of little importance as it does not affect cardiac physiology and generally does not require treatment. However, this is liable to progress to higher degrees of heart block and should alert the physician.

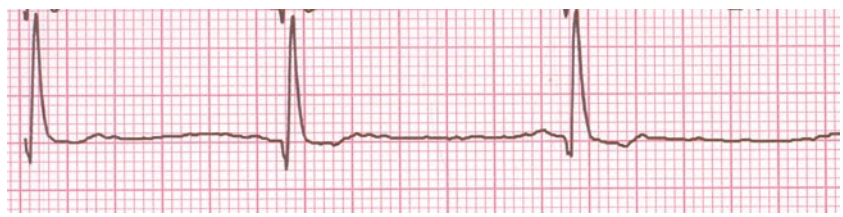


Fig. 157.1 Sinus bradycardia. Rate is below 60 beats/min, but each P wave is followed by a QRS complex.

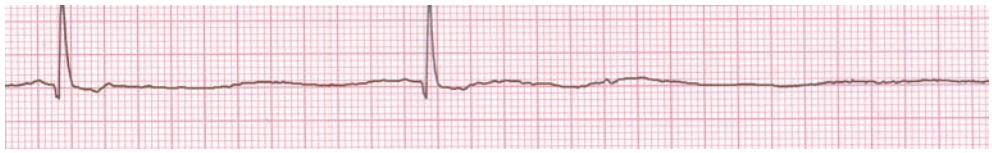


Fig. 157.2 Sinus arrest. Sudden bradycardia is followed by absence of P wave activity.

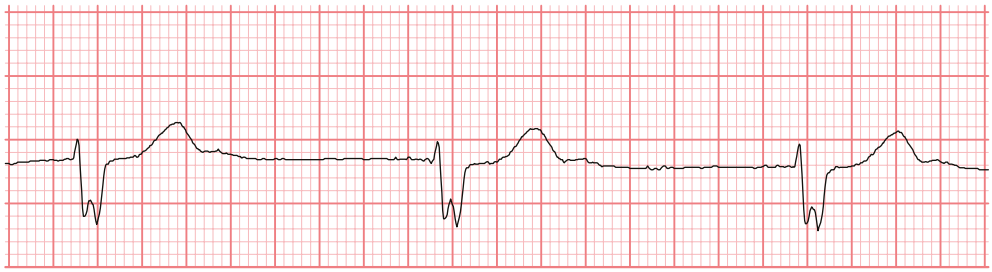


Fig. 157.3 Sinus arrest—with infra-Hissian escape rhythm.

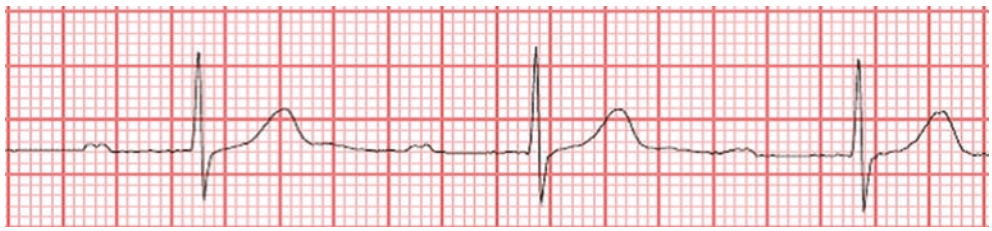


Fig. 157.4 First degree heart block. The PR interval is prolonged, but each P wave is followed by a QRS.

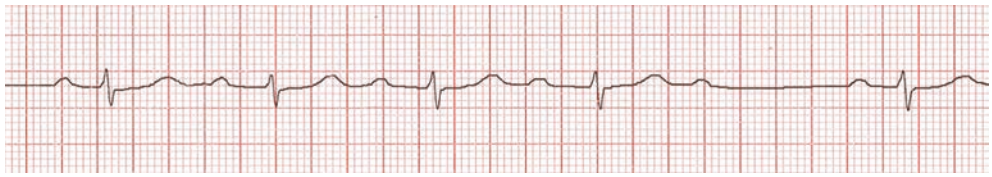


Fig. 157.5 Mobitz type 1 block. The PR interval demonstrates progressive prolongation until one fails to conduct.

Diagnosis

Each P wave is followed by a QRS, but with prolongation in the P–R interval >200 milliseconds

When the QRS complex is narrow, the level of conduction delay is within the AV node in >90% of cases. First-degree AV block with a bundle branch block/wide QRS may represent infranodal conduction delay in up to 45% of patients.

Second-degree AV block–Mobitz type

In this condition, some atrial impulses fail to reach the ventricle. The surface ECG demonstrates some P waves that are not followed by a QRS complex.

Mobitz type 1 (Wenkebach block)

Most commonly associated with AV nodal conduction system disease (see Fig. 157.5). The P–R interval shows progressive prolongation with shortening of the R–R interval until a P wave fails to conduct to the ventricle, and then the cycle starts again. This type of block is usually not of importance and is unlikely to be harmful unless the degree of block progresses. Wenckebach block is almost always a result of block in the AV node, particularly when associated with a narrow QRS complex. The pause during this cycle is short. This block does not generally require pacing, but may herald of higher degrees of block.

Diagnosis

PR-interval shows progressive prolongation until a P wave fails to conduct to the ventricle.

Mobitz type 2 block

The P wave fails to conduct to the ventricle and the previous QRS does not show any evidence of PR prolongation (see Fig. 157.6). The underlying QRS may be narrow or broad. This type of block can commonly occur nocturnally or in patients with high vagal tone, e.g. very fit individuals. Block during the day indicates more extensive conduction disease and usually merits pacing due to the unpredictable nature and duration of pauses.

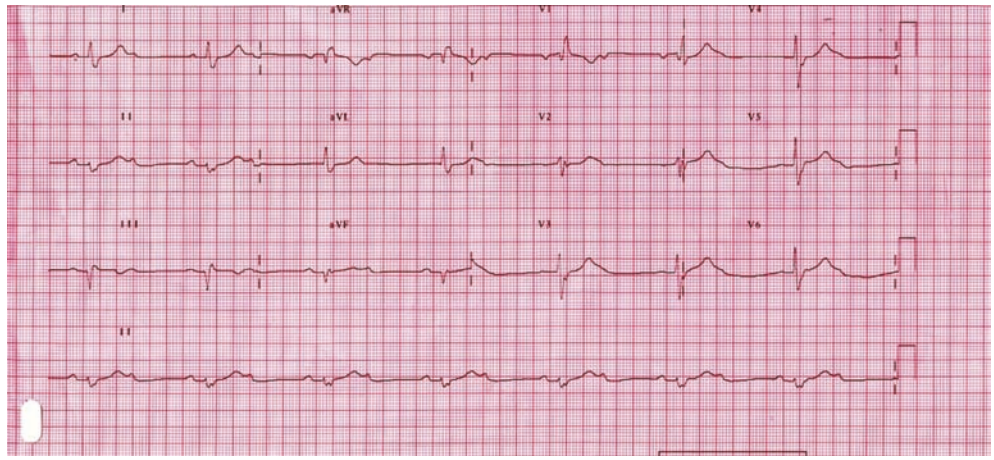


Fig. 157.6 Mobitz type 2 block with 2-to-1 conduction from the atrium to the ventricle. The P wave is dropped without any PR prolongation on the previous complex. The QRS is broad, suggesting infra-Hissian conduction system disease.

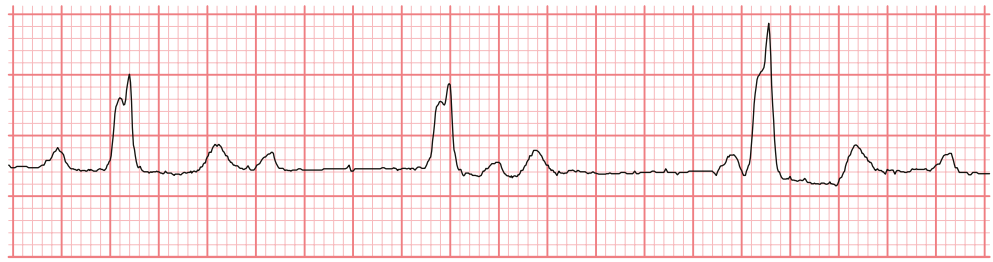


Fig. 157.7 Complete heart block with an infra-Hissian escape rhythm. The P waves have no relationship to the QRS complexes.

Diagnosis

P wave fails to conduct to the ventricle and the previous conducted P-QRS does not show any evidence of PR prolongation.

3rd-degree (complete) heart block

Here, the atria and ventricles function independently (see Fig. 157.7). The P wave has no relation to the QRS, which can be narrow or broad, and the level of block can be either in the AV node or infranodal. Acquired causes (which predominate in the ICU care setting) are often infranodal and potentially life-threatening. A common exception is after acute inferior myocardial infarction where the block is generally nodal and frequently reversible. Digitalis toxicity is a common cause of reversible AV block.

Prognostically, patients with a narrow QRS fare better than those with more extensive disease who demonstrate broad QRS complexes. Although some patients with complete heart block and narrow QRS can be left unpaced (e.g. congenital complete heart block), those with a broad QRS nearly always need pacing.

Diagnosis

The P wave has no relationship with the QRS.

Infra-Hisian conduction block

Right-bundle branch block

This can commonly be found in individuals where the heart is structurally normal. This usually does not need intervention.

Left bundle branch blocks

Left anterior fascicular block, left posterior fasicular block, and complete left bundle branch block are much more likely to be associated with underlying cardiac disease, are frequently progressive and may require pacemaker insertion.

These blocks are important when associated with sinus and AV nodal abnormalities, since they suggest more extensive disease of the conduction system that may fail suddenly.

Management

Identification of the type of bradycardia is of critical importance to the management. Particular interventions are likely to precipitate bradycardia in the critical care setting [5]. These include intubation, endotracheal suction, and sometimes bladder catheterization. In patients who demonstrate this tendency, the prior administration of glycopyrroniumbromide (0.1 mg IV) or 600 μg atropine before the intervention may avoid the bradycardia. Rarely patients may have several seconds of asystole in association with the intervention and this is not responsive to anti-cholinergics. In these cases insertion of a temporary pacing electrode prior to the intervention may be required.

In the acute setting where the patient suddenly becomes bradycardic or asystolic acute resuscitation may be required. A precordial thump may occasionally reverse asystole and start the heart beating again. If this does not occur, cardiorespiratory resuscitation may be required and should be maintained until pacing can be initiated.

Pacing should also be initiated in patients who do not respond to atropine (or second-line drugs). Pacing is also recommended for severely symptomatic patients, especially when the block is at or below the His-Purkinje level (i.e. type II second-degree or third-degree AV block).

Drugs

Atropine

The first-line drug for acute symptomatic bradycardia with an initial dose of 0.5 mg intravenous (iv) every 3–5 minutes to a maximum total dose of 3 mg. Atropine reverses cholinergic-mediated decreases in heart rate, symptomatic sinus bradycardia, symptomatic high-degree AV block and any type of AV block at the nodal level. The increased heart rate caused by atropine in acute coronary ischaemia or myocardial infarction may worsen the ischemia or increase the zone of infarction so this drug must be used cautiously. Avoid relying on atropine in type II second-degree or third-degree AV block or in patients with third-degree AV block with a new wide-QRS complex. These patients require immediate pacing.

Alternative drugs

May be considered with bradycardias that are unresponsive to atropine, while awaiting the availability of a pacemaker:

- **Adrenaline**: infusion at 2–10 μg/min and titrate to patient response. Provide intravascular volume and support as needed.
- **Dopamine**: infusion (at rates of 2–10 μg/kg/min) can be added to epinephrine, or administered alone.
- **Isoprenaline**: infuse at 2–10 μg/min and titrate against heart rate response. This drug is more likely to raise the blood pressure, but patients can often be maintained for several hours before pacing is initiated.
- **Glucagon**: one case series documented improvement in heart rates with iv glucagon (3 mg initially, followed by infusion at 3 mg/hour if necessary) when given to patients with drug-induced bradycardia not responding to atropine.

Pacing

Several modalities of pacing are available including external, oesophageal, and transvenous [6–8].

External pacing

Transcutaneous external pacemakers have a special pulse duration, surface electrodes, and a current generator:

- **Pulse duration**: long electrical pulse duration are used (40 milliseconds pulses for Zoll or 20 milliseconds pulses for all others).
- **Electrodes**: large surface electrodes (80–100 cm^2) are used since pain is directly related to the amount of current delivered and inversely related to the skin surface area over which it is delivered. Thus, pain is minimized by using electrodes with large surface areas.
- **Current**: the average current necessary for external pacing ranges from 50 to 100 milliamperes (mA). This delivers approximately 0.1 Joules (J), below the 1–2 J required to cause an uncomfortable tingling sensation in the skin. Transcutaneous external pacemaker discomfort at these low levels of current delivery is due to the force of skeletal muscle contraction, rather than the electric current. More than 90% of patients tolerate pacing for ≥15 minutes with modern devices capable of delivering up to 140–200 mA.
- Before beginning transcutaneous external pacing, the patient should be informed of the reason for pacing, the discomfort that may be experienced, and the option of providing analgesia or sedation, if possible.
- **Pad application**: pacemaker pads are applied over the cardiac apex and just medial to the left scapula. Excessive body hair should be shaved to ensure good contact.
- **Pacemaker operation**: heart rate should be set to 80 beats/min and the current initially set to 0 milliamperes (mA). The pacemaker unit is turned on, and the current increased in 10 mA increments until capture is achieved. Capture should be confirmed by palpable carotid pulses, and ECG evidence on monitoring.
- **Synchronous/asynchronous modes**: in the asynchronous (fixed-rate) mode, the electrical stimulus is delivered at preset intervals, independent of intrinsic cardiac activity. Synchronous pacing is a demand mode in which the pacer fires only when no complex is sensed for a predetermined amount of time. Generally, pacing should be started in synchronous mode.
- **Minimizing discomfort**: sedation with a short-acting agent, such as midazolam or an opiate, should be considered.
- **Complications**: pain, coughing, and hiccoughs may result from stimulation of the diaphragm and thoracic muscles. Skin burns have been reported with prolonged use.

Oesophageal pacing

A specialized pacing electrode can be placed via the oesophagus and manipulated to 30–40 cm from the teeth. At this level, the left atrium is in close proximity and pacing can give atrial capture reliably using a special stimulator, which has long amplitude pulses with high amplitude. Ventricular stimulation is less reliable because of the greater distance of the oesophagus from the ventricle; this technique should not be used for atrioventricular block. Leads inserted via the nostril (similar to nasogastric tubes) can be maintained for several days. Complications include oesophageal discomfort (rarely, burns with high outputs) and phrenic nerve stimulation.

Temporary intracardiac pacing

A pacing electrode is inserted through an introducer sheath sited in the subclavian or internal jugular vein (rarely, femoral) and then fluroscopically-guided to the right ventricular apex.

In the emergency situation a flotation electrode can be used. This is a Swan–Ganz type of balloon catheter with pacing electrodes. It is floated from the entry site into the heart with the electrocardiogram being recorded. When a ventricular trace is obtained, pacing is commenced, the balloon deflated and the lead secured. Pacing thresholds of <1 mV with a pulse duration of 0.5 milliseconds are satisfactory. Leads can also be placed in the atrium; specialized leads with screw-in tips are available designed for atrial pacing. Placement of leads in the atrium and ventricle allow co-ordinated atrioventricular pacing. These leads do not cause discomfort and pacing can be maintained for several days.

Complications are generally related to access (pneumothorax, haematoma, air embolism), myocardial perforation leading to tamponade, ventricular arrhythmias, and infection.

Permanent pacemaker insertion

A permanent pacing system can be acutely implanted for the treatment of sudden onset bradycardia without a reversible cause and at the discretion of the managing physician. The techniques of implantation are beyond the scope of this chapter

A summary algorithm for bradycardia management can be accessed for free on the American Heart Association website (www.heart.org/).

References

1. Mangrum JM and DiMarco JP. (2000). The evaluation and management of bradycardia. *New England Journal of Medicine*, **342**, 703–9.
2. Barnes BJ and Hollands JM. (2010). Drug-induced arrhythmias. *Critical Care Medicine*, **38**(6 Suppl.), S188–97.
3. Jones P, Dauger S, and Peters MJ. (2012). Bradycardia during critical care intubation: mechanisms, significance and atropine. *Archives of the Diseases of Childhood*, **97**, 139–44.
4. Alboni P, Gianfranchi L, and Brignole M. (2009). Treatment of persistent sinus bradycardia with intermittent symptoms: are guidelines clear? *Europace*, **11**, 562–64.
5. Tarditi DJ and Hollenberg SM. (2006). Cardiac arrhythmias in the intensive care unit. *Seminars in Respiratory and Critical Care Medicine*, **27**, 221–9.
6. Trohman RG, Kim MH, and Pinski SL. (2004). Cardiac pacing: the state of the art. *Lancet*, **364**, 1701–19.
7. Sherbino J, Verbeek PR, MacDonald RD, Sawadsky BV, McDonald AC, and Morrison LJ. (2006). Prehospital transcutaneous cardiac pacing for symptomatic bradycardia or bradyasystolic cardiac arrest: a systematic review. *Resuscitation*, **70**, 193–200.
8. Kaushik V, Leon AR, Forrester JS Jr, and Trohman RG. (2000). Bradyarrhythmias, temporary and permanent pacing. *Critical Care Medicine*, **28**(10 Suppl.), N121–8.

PART 5.9

Valvular problems

CHAPTER 158

Causes and diagnosis of valvular problems

Jason F. Deen and Karen K. Stout

Key points

- Significant aortic stenosis may present with angina pectoris, dyspnoea, or syncope.
- Acute aortic regurgitation usually arises as a consequence of infective endocarditis and, if severe, will most commonly result in cardiogenic shock and hypotension.
- Mitral stenosis is usually chronic in nature, but may manifest for the first time clinically with other forms of haemodynamic stress, such as pregnancy, amenia, fever, or atrial arrhythmia.
- Mitral regurgitation should be categorized to primary versus secondary causes to inform appropriate therapeutic options.
- Transthoracic echocardiography remains with imaging modality of choice for primary valve assessment.

Aortic stenosis

Aetiology and pathophysiology

Aortic stenosis (AS) is the most prevalent form of valvular heart disease and its prevalence increases with older age. Common aetiologies include calcific stenosis, congenital AS, including stenosis of a bicuspid aortic valve, and rheumatic heart disease. The pathophysiological endpoint is left ventricular outflow tract obstruction, with salient clinical manifestations of angina pectoris, syncope, and symptoms related to left ventricular failure (including dyspnoea, activity intolerance, pulmonary oedema, and orthopnoea) [1].

Calcific AS remains the most common cause in industrialized countries; approximately 25% of US adults have aortic sclerosis (early valve cusp calcification without significant outflow tract obstruction), while 2% have overt calcific AS (an advanced stage associated with a decreased functional valve orifice leading to left ventricular outflow tract obstruction) [2]. It is a manifestation of an ongoing systemic disease process of vascular osteoblastic activity, which begins within the valve tissue, and shares the histological features of atherosclerosis with inflammation and calcification. Risk factors for calcific AS are similar to atherosclerotic disease and include older age, male sex, tobacco use, hypertension, diabetes mellitus, and hyperlipidaemia. Just as with vascular calcification, hyperlipidaemia, in particular, has been identified as an inciting factor in cell signalling related to valvular calcification. Additionally, untoward genetics seem to play a role in developing the calcific phenotype [3,4].

Congenital AS represents a wide range of clinical manifestations with severe forms presenting in infancy. Bicuspid aortic valve is the most common form of congenital heart disease seen in adults, occurring in approximately 2% of the population, exhibiting a male predominance. Abnormal valve leaflet structure leads to more rapid progression to calcific AS as compared with tri-leaflet valves in the presence of traditional cardiovascular risk factors [5]. Furthermore, there are associations with aortic root and ascending aorta dilatation, which may predispose to aortic dissection that are independent of valve stenosis severity.

Although rare in industrialized countries, rheumatic heart disease may lead to AS. Isolated AS is uncommon, and is usually accompanied by mitral valve disease, as well as aortic regurgitation. Rheumatic aortic disease is distinguished from calcific aortic disease by the presence of commissural fusion.

AS leads to left ventricular outflow tract obstruction and produces an increased pressure load on the left ventricle. There is compensatory hypertrophy of the left ventricle, which may be explained by the law of Laplace, which states that wall stress of the ventricle is directly proportional to the pressure load, though inversely proportional to the wall thickness. As the ventricle becomes more hypertrophied, it is able to ameliorate the pressure load on the ventricle itself. This creates a physiological latency defined by increasing obstruction counteracted by increasing hypertrophy that, in turn preserves cardiac output. Unfortunately, the left ventricular hypertrophy is maladaptive, leading to diastolic dysfunction and impaired coronary flow reserve. Myocardial ischaemia occurs secondary to increased myocardial oxygen demand in the presence of decreased myocardial oxygen delivery and, if left untreated, leads to systolic dysfunction and eventual dilation [2]. The onset of the hallmark symptoms of severe AS—angina pectoris, syncope and heart failure—signifies an increased mortality risk [1].

Diagnosis

The characteristic murmur of AS is a systolic ejection murmur heard at the base of the heart in the right second intercostal space. It is usually harsh in quality with radiation to the carotid arteries. As the stenosis worsens, the peak of the crescendo-decrescendo murmur moves towards the second heart sound corresponding with a slowed, delayed carotid artery upstroke (*pulsus parvus et tardus*). The intensity of the murmur may decrease, while radiation may be extended toward the apex where a high-pitched vibratory murmur, akin to a paediatric Still's murmur, may be heard (Gallavardin

phenomenon). The A2 component of the second heart sound softens, leading to a single S2 and an S4 that may be auscultated. Palpation may reveal a thrill at the sternal notch and a displaced left ventricular apical impulse.

Electrocardiograms are usually non-diagnostic, but may show signs of left ventricular hypertrophy with ST and T wave abnormalities indicative of LV strain, as well as left atrial enlargement.

Chest radiography is usually normal with AS, but may show calcification of the aortic valve. Patients with bicuspid aortic valves may exhibit dilation of the ascending aorta. As AS progresses and left ventricular failure ensues, the cardiac silhouette enlarges and pulmonary oedema may be evident.

Transthoracic echocardiography remains the imaging modality of choice to assess AS. Information obtained includes valve structure, annular size, aortic valve area, transvalvular peak jet velocity, left ventricular systolic function, and the extent of left ventricular hypertrophy. Transvalvular gradients can be estimated using the velocity of flow through the valve orifice via the modified Bernoulli equation. More advanced diagnostics may be obtained to estimate valvular load, systemic arterial compliance, and overall left ventricular haemodynamic load. Exercise stress echocardiography is a useful adjunct to unmask findings that may be absent at rest [6].

Computed tomography angiography (CTA) provides anatomic detail of the aortic valve, left ventricle, and ascending aorta, which may be useful when the CTA is obtained as a method of studying the coronary arteries. The high radiation load, as well as the lack of flow-related parameters, makes CTA a poor choice for primary valve assessment [7].

Cardiovascular magnetic resonance imaging has become a useful adjunct to echocardiography in assessing aortic valve disease, particularly when information regarding the left ventricle, such as ventricular volumes and mass, is sought. Abnormalities in the left ventricular myocardium may be observed through the use of late-gadolinium techniques [8].

Aortic regurgitation

Aetiology and pathophysiology

Acute aortic regurgitation (AR) is differentiated from chronic AR as the former often results in unexpected haemodynamic compromise necessitating intensive care management. Infective endocarditis causes most acute AR, although it is less commonly caused by type A aortic dissection (usually in the setting of connective tissue disorders, bicuspid aortic valve, or atherosclerotic disease), blunt chest trauma, or a ruptured aortic valve leaflet fenestration. After aortic valve replacement, prosthetic valve regurgitation may occur after tearing or thrombosis of a valve leaflet. Perivalvular leaks may occur due to infection of the valve annulus after valve replacement [9].

Acute AR leads to a marked rise in left ventricular end-diastolic pressure due to the regurgitant volume. This pressure may be transmitted to the left atrium and pulmonary vascular bed leading to pulmonary oedema. The left ventricle is non-compliant and fails to dilate in response to its volume load. Cardiac output is therefore impaired due to a decreased stoke volume, while the pulse pressure narrows. Myocardial ischaemia may result due to decreased diastolic coronary pressure in the setting of high myocardial oxygen demand brought on by tachycardia and elevated end-diastolic pressure.

Diagnosis

The soft early diastolic murmur of acute AR is differentiated from chronic AR, which is a decrescendo murmur that is longer in duration and of higher pitch. Non-coaptation (non-apposition) of the aortic valve leaflets may lead to a soft A2 component of the second heart sound. Haemodynamically, patients with acute severe AR are usually tachycardiac and hypotensive. Tachypnoea and increased work of breathing accompanied by crackles on pulmonary auscultation are ominous signs. Differential pulses may be observed with AR due to aortic dissection.

Electrocardiography in acute AR usually shows sinus tachycardia, although non-specific ST segment and T wave changes indicative of left ventricular strain may be present. Ischaemic ST segment and T wave changes may be seen in primary ischaemia leading to AR, as well as haemodynamic coronary insufficiency.

Chest radiography usually shows pulmonary oedema without cardiomegaly unless the AR is chronic and associated with a dilated left ventricle. The mediastinum may be widened with aortic dissection.

If acute AR is suspected, urgent transthoracic echocardiography is indicated. TTE with provide information regarding valve anatomy, left ventricular size and function, as well as the anatomy of the proximal aorta. Severity of insufficiency may be delineated with colour flow Doppler examination of the regurgitant jet, as well as the distal aorta. TTE may determine aetiology, e.g. a valve vegetation consistent with endocarditis, a dilated aortic root or a bicuspid aortic valve. Transoesophageal echocardiography may be indicated with a non-diagnostic TTE study [10].

Computed tomography gives similar anatomic details regarding the aortic valve and root as echocardiography, although the lack of haemodynamic assessment capabilities and the radiation burden make it a poor choice for primary valve assessment. [7]. If aortic dissection is suspected, CT angiography is the diagnostic modality of choice.

While cardiac magnetic resonance imaging provides information regarding aortic regurgitant fraction, left ventricular size and function, as well as aortic root anatomy, this modality is more suited for comprehensive assessment of chronic AR, rather than acute AR [8].

Mitral stenosis

Aetiology and pathophysiology

Although measures are now well established to diagnose and treat *Streptococcal* pharyngitis and have reduced the incidence of mitral stenosis (MS), rheumatic disease, albeit rare, remains the leading cause of MS in industrialized countries. The rheumatic heart disease burden in developing countries remains a significant source of mortality and morbidity. Less common causes of MS include calcification of the mitral valve annulus associated with atherosclerosis, past infective endocarditis, underlying congenital abnormalities, underlying rheumatological or renal disease. Rheumatic heart disease causes inflammation of the mitral valve leaflets and supporting structures, and leads to thickening and scarring of the valve leaflets and chordea tendinae with valve leaflet fusion. Although the mitral valve is primarily affected, dysfunction of all other valves may be seen [11].

With progressive MS, a pressure gradient forms between the left atrium and left ventricle, leading to left atrial hypertension. The

increase in left atrial pressure causes an increased pressure load on the right ventricle. With severe MS, pulmonary hypertension occurs and may manifest as right ventricular failure with dyspnoea and exercise intolerance. MS is a slowly progressive disease with symptoms of activity intolerance, dyspnoea on exertion, paroxysmal nocturnal dyspnoea and orthopnoea occurring during a prolonged latent period. Atrial arrhythmias may be the initial presenting symptom, while others may become symptomatic after a period of haemodynamic stress, such as with fever, anaemia, hypovolaemia or pregnancy [12].

Diagnosis

Patients with severe MS often present with signs of heart failure, including pulmonary crackles, jugular venous distention, hepatomegaly, and lower extremity oedema. Cardiac examination reveals an accentuated first heart sound with an opening snap followed by a low-frequency diastolic rumble. In advanced disease, the first heart sound may become softer as the valve leaflets become more dysfunctional. There may be a right ventricular lift with underlying pulmonary hypertension. The timing of the second heart sound in relation to the opening snap may be a clue towards gauging severity of disease, with decreasing S2 to OS intervals indicating increasing left atrial pressure and worsening disease.

Electrocardiography may show left atrial enlargement with right ventricular hypertrophy seen in advanced disease. Underlying atrial fibrillation may be diagnosed if present.

Chest radiography may exhibit left atrial enlargement with enlargement of the main pulmonary arteries. Right ventricular enlargement is seen with advanced disease. Left atrial hypertension may be manifest as pulmonary oedema or effusions.

Transthoracic echocardiography (TTE) is the diagnostic modality of choice, providing information regarding valve leaflet anatomy that may differentiate between aetiologies of MS and amenability to percutaneous treatment. The mitral valve area can be calculated, which grades the severity of disease. Doppler examination provides the mitral transvalvular pressure gradient that estimates the pressure difference between left atrium and left ventricle. Left atrial dilation can be detected while right ventricular systolic pressure can be estimated with an adequate tricuspid regurgitation jet. Lastly, information regarding size and function of the left and right ventricles can be obtained [13].

CTA provides similar anatomic detail with regard to valve leaflet anatomy and chamber sizes. However, the lack of haemodynamic assessment capabilities and the radiation burden make it a poor choice for primary valve assessment [7].

Cardiac magnetic resonance imaging provides much of the same information as echocardiography including anatomic detail and some haemodynamic parameters. It may be a useful adjunct to echo to better visualize restricted mitral valve leaflets [8].

Mitral regurgitation

Aetiology and pathophysiology

Acute, as opposed to chronic, magnetic resonance (MR) may lead to haemodynamic compromise and pulmonary oedema necessitating ICU management. Acute MR is either due to 'primary' or 'secondary' causes. This useful classification guides initial treatment as the former are best treated surgically, while the latter may be amenable to early medical treatment. 'Primary' MR results from disruption of the mitral valve apparatus, either at the leaflet or supporting structures. Endocarditis or decelerating trauma may cause perforation or rupture of a valve leaflet, respectively. Underlying myxomatous disease may lead to chordal rupture. Papillary muscle rupture can occur with myocardial infarction. 'Secondary' MR is more often chronic than acute, and results from abnormalities of the left ventricle. Cardiomyopathy results in displacement of the papillary muscles and ischaemia may result in dyskinesis of the ventricular wall, both of which may prevent proper mitral valve closure. Occasionally, acute 'functional' MR may arise with myocardial infarction or acute heart failure exacerbations, such as rapidly progressing myocarditis or post-partum cardiomyopathy [9].

Acute MR results in a rapid increase in the volume load of the left atrium. The left atrial hypertension frequently leads to pulmonary oedema, although patients with a more compliant left atrium, such as those with chronic MR, may be more tolerant of the volume load. Left ventricular systolic function may be preserved or augmented due to an increase in preload conditions, although patients with underlying systolic dysfunction may be profoundly symptomatic.

Diagnosis

Acute MR causes a soft, early S1-coincident murmur as opposed to the holosystolic murmur heard in chronic MR due to the early equalization of left atrial and ventricular pressures. The patient is usually tachycardic. The first heart sound may be of decreased intensity. Pulmonary examination may reveal tachypnoea with crackles on pulmonary examination.

Electrocardiography may show sinus tachycardia with non-specific ST segment and T wave changes. Left atrial enlargement may be present. Ischaemic ST segment and T wave changes may be present if myocardial ischaemia is the aetiology of, or if the ischaemia is caused by, MR. Underlying atrial fibrillation may be diagnosed.

Chest radiography usually shows a normal cardiac silhouette with pulmonary oedema in acute MR. Left atrial and left ventricular enlargement is seen in chronic MR. If the regurgitant jet is directed toward a particular pulmonary vein, the oedema primarily will be seen in the draining lung segment, which may mimic a lobar pneumonia [14].

Transthoracic echocardiography provides the diagnosis of MR and can quantify its severity. Left ventricular size and function may be assessed as well. The presence of severe MR without compensatory left ventricular enlargement raises the suspicion of an acute process. The mechanism of regurgitation may be assessed, particularly with regard to an organic (i.e. due to a ruptured chordae or perforated leaflet) versus a functional cause (i.e. with underlying myocardial dysfunction). Right ventricular pressures may be estimated if an appropriate tricuspid regurgitant jet is present [15].

CTA is a poor choice to evaluate causes of acute MR, as aetiologies, such as ruptured chordae may be difficult to see. As with other forms of valve disease, the lack of haemodynamic data and the large radiation load make CTA a poor choice of primary assessment of MR [7].

Cardiac magnetic resonance imaging quantifies regurgitant and ventricular volumes, as well as ventricular function and may hint at an aetiology of mitral valve regurgitation. While not particularly suited for primary assessment of acute MR, it remains a useful adjunct to echocardiography in terms of assessment of chronic MR [8].

Prosthetic valve dysfunction

Surgical therapy is the primary treatment modality for severe heart valve lesions, and its superiority over medical treatment in haemodynamically important lesions is well documented. Prosthetic valve replacement is the most prevalent of surgical procedures to address heart valve problems, although the long-term survival after valve replacement is truncated, with a poorer prognosis for mitral valve replacement as compared with aortic valve replacement [16]. Prosthetic valves are either mechanical or bioprosthetic with patient age, anticoagulation issues, pre-operative condition, re-operation concerns, and patient preference informing the decision regarding the type of implant. The durability of mechanical valves with the need for life-long anticoagulation is contrasted with a bioprosthetic valve's exceedingly low risk of thromboembolic events in the setting of a shortened duration before valve deterioration. All prosthetic valves are at risk for structural valve deterioration, the time course of which is related to age at valve replacement surgery, with younger patients experiencing a shorter valve lifespan. Acute prosthetic valve dysfunction may lead to haemodynamic compromise necessitating ICU management. Notable aetiologies of acute prosthetic valve dysfunction include valve thrombosis, prosthetic valve endocarditis and perivalvular regurgitation [17]. Patients with prosthetic valves presenting to the ICU with haemodynamic abnormalities warrant transthoracic or transoesophageal echocardiography to assess prosthetic valve function.

References

1. Ross J Jr and Braunwald E. (1968). Aortic stenosis. *Circulation*, **38**(1 Suppl.), 61–7.
2. Carabello BA and Paulus WJ. (2009). Aortic stenosis *Lancet*, **373**, 956–66.
3. Rajamannan NM, Evans FJ, Aikawa E, et al. (2011). Calcific aortic valve disease: not simply a degenerative process. A review and agenda for research from the National Heart and Lung and Blood Institute Aortic Stenosis Working Group. Executive summary: calcific aortic valve disease—2011 update. *Circulation*, **124**, 1783–91.
4. Thanassoulis G, Campbell CY, Owens DS, et al. for the CHARGE Extracoronary Calcium Working Group. (2013). Genetic associations with valvular calcification and aortic stenosis. *New England Journal of Medicine*, **368**,503–12.
5. Michelena HI, Desjardins VA, Avierinos JF, et al. (2008). Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. *Circulation*, **117**, 2776–84.
6. Pibarot P and Dumesnil JG. (2012). Improving assessment of aortic stenosis. *Journal of the American College of Cardiology*, **60**, 169–80.
7. Chheda SV, Srichai MB, Donnino R, Kim DC, Lim RP, and Jacobs JE. (2010). Evaluation of the mitral and aortic valves With cardiac CT angiography. *Journal of Thoracic Imaging*, **25**, 76–85.
8. Myerson SG. (2012). Heart valve disease: investigation by cardiovascular magnetic resonance. *Journal of Cardiovascular Magnetic Resonance*, **14**, 7.
9. Stout KK. (2009). Acute valvular regurgitation. *Circulation*, **119**, 3232–41.
10. Evangelista A, Flachskampf FA, Erbel R, et al. (2010). Echocardiography in aortic diseases: EAE recommendations for clinical practice. *European Journal of Echocardiography*, **11**, 645–58.
11. Chandrashekhar Y, Westaby S, and Narula J. (2009). Mitral stenosis. *Lancet*, **374**, 1271–83.
12. Carabello BA. (2005). Modern management of mitral stenosis. *Circulation*, **112**, 432–7.
13. Baumgartner H. (2009). Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *European Journal of Echocardiography*, **10**, 1–25.
14. Morris PD, Warriner DR, and Channer KS (2013). Focal pulmonary oedema: an unusual presentation of acute mitral regurgitation. *Thorax*, **68**, 498.
15. Maganti K, Rigolin VH, Sarano ME, and Bonow RO. (2010). Valvular heart disease: diagnosis and management. *Mayo Clinic Proceedings*. **85**, 483–500.
16. Lindblom D, Lindblom U, Qvist J, and Lundström H. (1990). Long-term relative survival rates after heart valve replacement. *Journal of the American College of Cardiology*, **15**, 566–73.
17. Seiler C. (2004). Management and follow up of prosthetic heart valves. *Heart*, **90**, 818–24.

CHAPTER 159

Therapeutic strategy in valvular problems

Jason F. Deen and Karen K. Stout

Key points

- Medical management of aortic stenosis may be guided via the use of invasive haemodynamic monitoring, such as a Swan–Ganz catheter.
- Patients with severe symptomatic aortic stenosis with decreased left ventricular function may benefit from transcatheter aortic valve replacement if surgical aortic valve replacement is too high risk.
- Acute aortic regurgitation often leads to haemodynamic compromise and may be treated with afterload reduction along with inotropic support.
- Ideally, mitral stenosis is treated with percutaneous balloon valvuloplasty if the mitral valve anatomy is favourable.
- Chronic mitral regurgitation may be managed surgically or medically, depending on the aetiology of the valve incompetence, while acute severe mitral regurgitation most often requires surgery.

Aortic stenosis

For patients with severe aortic stenosis, surgical aortic valve replacement remains the definitive treatment. For those presenting with profound heart failure symptoms or cardiogenic shock, surgery remains the definitive treatment, but diuresis can be carefully performed. Close attention must be paid to the patient's volume status, as decreases in left ventricular preload may result in decreased cardiac output. Afterload reduction can be carefully pursued in select patients, but afterload reduction in patients with limited ability to augment stroke volume can precipitate haemodynamic collapse. Therefore, caution should be undertaken in medically managing what is inherently a mechanical abnormality of fixed, high afterload. Medical management, therefore, may be best guided via invasive hemodynamic monitoring [1]. Management of patients with low-flow/low-gradient aortic stenosis is complex. Those with diminished left ventricular systolic function due to increased afterload usually experience an improvement in left ventricular systolic function following surgery, while patients with decreased left ventricular systolic function due to fibrosis from myocardial ischaemia or cardiomyopathy are less like to benefit. Determining contractile reserve is useful here, and is defined as an increase in stroke volume >20% with inotrope (dobutamine) infusion [2]. Aortic valve replacement should be considered in low-flow/low-gradient aortic stenosis, particularly those with intact contractile reserve.

Aortic valve replacement should be offered to symptomatic patients with severe aortic stenosis in the absence of surgical contraindications. Patients with severe aortic stenosis, with or without symptoms, who are scheduled for coronary artery bypass grafting, should have an aortic valve replacement (AVR) at the time of surgery. Post-operative mortality for aortic valve replacement is approximately 4%, although the risk increases to 6.8% if the aortic valve replacement is combined with coronary artery bypass grafting [3]. Older age at time of surgery is not a contraindication, as surgical outcomes are similar between patients less than and greater than 80 years [4]. Surgical risk may be calculated through online tools from the Society of Thoracic Surgeons or the EuroSCORE. Symptomatic patients deemed inoperable or those patients with severely diminished left ventricular systolic function may benefit from transcatheter aortic valve replacement (TAVR) [5,6]. Aortic balloon valvuloplasty may be performed in haemodynamically unstable patients as a bridge to aortic valve replacement or TAVR, and is considered palliative when both surgery and TAVR are contraindicated [7].

Indications for surgical therapy

Severe aortic stenosis (AS) is defined by an aortic valve area <1.0 cm^2, mean transvalvular gradient >40 mmHg and peak jet velocity >4.0 m/sec. Patients with severe AS and symptoms related to aortic stenosis should undergo aortic valve replacement, either primarily or at the time of coronary artery bypass grafting. Asymptomatic patients with severe AS and decreased left ventricular systolic function (ejection fraction (EF) <50%), symptoms of AS on exercise testing, or who are undergoing coronary artery bypass grafting should undergo aortic valve replacement [7].

Aortic regurgitation

Acute aortic regurgitation (AR) is treated surgically with either valve replacement or valve repair. Pre-operative medical management is often necessary in haemodynamically unstable patients. Afterload reduction with vasodilators, such as nitroprusside, together with inotropic agents, may improve cardiac output. Associated ascending aortic dissection (type A) necessitates aortic root repair, although it may also require an additional aortic valve procedure to ensure competency if the aortic valve is congenitally abnormal or otherwise aneurysmal [8]. Surgery for chronic severe AR is

indicated when symptomatic or in the asymptomatic patient with diminished left ventricular systolic function (EF <50%). Severe AR should be addressed surgically with concomitant coronary artery bypass grafting or surgery on the ascending aorta irrespective of the absence of symptoms. Surgery should be considered in those patients with severe AR and normal left ventricular systolic function if the left ventricle is dilated (end-diastolic dimension >70 mm or end-systolic dimension >50 mm) [7].

Mitral stenosis

Severe symptomatic mitral stenosis (MS) is definitively treated by relieving the mechanical obstruction to flow into the left ventricle. This may be accomplished via balloon mitral valvuloplasty, surgical commissurotomy, or mitral valve replacement. Medical management may be necessary to treat associated pulmonary hypertension, pulmonary oedema, or atrial fibrillation. Atrial fibrillation with a rapid ventricular response unresponsive to medical therapies for rate control may be treated with direct cardioversion [9]. Factors that may exacerbate the symptoms of MS, such as volume overloading and anaemia should be corrected. Medical management, with diuresis and rate control to optimize diastolic filling, can significantly improve symptomatology.

Severe MS is defined as a mitral valve area <1.0 cm^2 with a transvalvular gradient >10 mmHg. Patients with symptomatic MS or a mitral valve area ≤1.5 cm^2 meet criteria for intervention. With favourable valve anatomy, percutaneous balloon mitral valvuloplasty is the treatment of choice as the mortality risk is less compared with open surgery. This is especially true if there are contraindications to surgery. A successful result, as defined by a valve area >1.5 cm^2 without significant mitral insufficiency, is achieved in the majority of cases. If there is a contraindication to balloon mitral valvuloplasty, including mitral valve area >1.5 cm^2, the presence of significant mitral regurgitation, left atrial thrombus, non-favourable valve anatomy or the presence of concomitant aortic valve disease, surgery is indicated [7]. Mitral valve replacement is performed more often than open commissurotomy with an operative mortality risk of 3–8% and correlates with the presence of pulmonary hypertension, underlying function status, age, and the presence of coronary artery disease [9].

Mitral regurgitation

Classification of acute mitral regurgitation (MR) etiology into subgroups of primary versus secondary informs therapeutic options. Primary MR, which results from disruption of the mitral valve apparatus either at the leaflet or supporting structure level, is treated surgically. Secondary MR is due to abnormalities in the left ventricle and is initially treated medically, with a default to surgery if medical options directed at the underlying pathophysiology fail. Patients with acute MR due to obstructive coronary artery disease and subsequent ischaemic cardiomyopathy require revascularization. In both organic and functional types of severe MR, initial medical stabilization plays a major role in an ICU setting. This may be accomplished by reducing afterload with vasodilatory agents (i.e. nitroprusside) along with inotropes, if cardiac output is compromised, and diuretics if pulmonary oedema is present. Intra-aortic balloon pumps may be used to acutely lower left ventricular afterload and are particularly useful in acute secondary mitral regurgitation due to myocardial ischaemia or cardiomyopathy [8].

When mitral valve surgery is undertaken, mitral valve repair, as opposed to valve replacement, results in lower short- and long-term mortality, while better preserving left ventricular function, but there is a higher incidence of recurrent regurgitation [7,10]. Factors favouring mitral valve replacement include underlying calcification of the valve leaflets and endocarditis, and mitral regurgitation. Surgery for secondary MR is riskier than surgery for primary MR and is associated with impaired survival, particularly in the setting of decreased left ventricular function [10]. For those patients in poor clinical condition who may have relative contraindications to surgery, including those with left ventricular dysfunction, percutaneous mitral valve repair is feasible, and is associated with a high rate of success and improvement in post-procedural left ventricular function [11]. Data, especially long-term, remain incomplete and the role of percutaneous intervention remains unclear.

References

1. Bonow RO, Carabello BA, Chatterjee K, et al. (2006). ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Valvular Heart Disease). http://content.onlinejacc.org/pdfaccess.ashx?ResourceID=2916596&PDFSource=13.
2. Monin JL, Que´re´ JP, Monchi M, et al. (2003). Low-gradient aortic stenosis, operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation*, **108**, 319–24.
3. Edwards FH, Peterson ED, Coombs LP, et al. (2001). Prediction of operative mortality after valve replacement surgery. *Journal of the American College of Cardiology*, **37**, 885–92.
4. Zapolanski A, Mak AW, Ferrari G, et al. (2012). Impact of New York Heart Association classification, advanced age and patient-prosthesis mismatch on outcomes in aortic valve replacement surgery. *Interactive Cardiovascular and Thoracic Surgery*, **15**, 371–6.
5. Thielmann M, Wendt D, Eggebrecht H, et al. (2009). Transcatheter aortic valve implantation in patients with very high risk for conventional aortic valve replacement. *Annals of Thoracic Surgery*, **88**, 1468–75.
6. Clavel MA, Webb JG, Rodés-Cabau J, et al. (2010). Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction. *Circulation*, **122**, 1928–36.
7. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC), European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, et al. (2012). Guidelines on the management of valvular heart disease (version 2012). *European Heart Journal*, **33**, 2451–96.
8. Stout KK. (2009). Acute valvular regurgitation. *Circulation*, **119**, 3232–41.
9. Carabello BA. (2005). Modern management of mitral stenosis. *Circulation*, **112**, 432–7.
10. Glower DD. (2012). Surgical approaches to mitral regurgitation. *Journal of the American College of Cardiology*, **60**, 1315–22.
11. Feldman T, Foster E, Glower DD, et al., for the EVEREST II Investigators. (2011). Percutaneous repair or surgery for mitral regurgitation. *New England Journal of Medicine*, **364**, 1395–406.

PART 5.10

Endocarditis

CHAPTER 160

Pathophysiology and causes of endocarditis

Franck Thuny and Didier Raoult

Key points

- Endocarditis is a fatal disease if not promptly diagnosed and treated.
- The pathophysiology is complex, and is based on a local prothrombogenic state of the endocardium and the capacity of some pathogens to adhere, colonize, and invade this altered endocardium.
- *Staphylococcus aureus* is the commonest cause of infective endocarditis.
- Blood cultures and echocardiography are the cornerstones of diagnosis, but can be negative in >10% of cases.
- Other microbiological, immunological, and imaging testing should be considered in difficult diagnostic situations.

Introduction

Endocarditis is defined as an inflammation of the endocardial surface of the heart. This may include heart valves, mural endocardium or the endocardium that covers implanted material, such as prosthetic valves, pacemaker/defibrillator leads, and catheters. Infective and non-infective-related causes must be distinguished (Box 160.1). In most cases, the inflammation is related to a bacterial or fungal infection with oral streptococci, group D streptococci, staphylococci and enterococci accounting for 85% of episodes. Infective endocarditis (IE) is a serious disease with an incidence ranging from 30 to 100 episodes/million patient-years [1]. From various portals of entry (e.g. oral, digestive, cutaneous) and a subsequent bacteraemia, pathogens can adhere and colonize intracardiac foreign material or adhere to previously damaged endocardium, due to numerous complex processes based on a unique host–pathogen interaction. Rarely, endocarditis can be related to non-infective causes, such as immunological or neoplastic.

Mortality is high, with more than one-third dying within a year of diagnosis from complications such as acute heart failure or emboli [2]. This disease still remains a diagnostic challenge, with many cases being identified and subsequently treated too late. Diagnosis of IE usually relies on the association between an infectious syndrome and recent endocardial involvement. Blood cultures and echocardiography are the main diagnostic procedures, but are negative in almost 30% of cases, requiring the use of more sophisticated techniques, including serological and molecular tests. Computed tomography, magnetic resonance imaging (MRI), and positron emission tomography are promising imaging modalities.

Improved understanding of its pathophysiology and the development of relevant diagnostic strategies enables accelerated identification and treatment, and thus an improved prognosis [3].

Aetiology

IE results in a complex pathogenesis involving many host-pathogen interactions. Oral streptococci, group D streptococci (e.g. *Streptococcus gallolyticus*), staphylococci, and enterococci are involved in 85% of episodes [1], with staphylococci accounting for 30% [1,4]. Oral streptococci are the major IE pathogens in the general population, while *Staphylococcus aureus* and coagulase-negative staphylococci are more often found in intravenous drug users, and in those with prosthetic valve or health care-related IE [4,5]. *Streptococcus gallolyticus* and enterococci are increasingly prevalent in the elderly, and often associated with colon tumours [6]. In 15% of cases no aetiology is found by blood culture [7]. Although often related to previous antibiotic therapy (commonly with streptococcal IE), a substantial number result from intracellular bacteria, fungi or other fastidious organisms (Box 160.1) [8].

Endocarditis can result from non-infective pathological conditions such as autoimmune disease and neoplasia (marantic endocarditis) [8,9]. Libman–Sacks endocarditis is the commonest cardiac manifestation of systemic lupus erythematosus, and is associated with primary or secondary antiphospholipid syndrome. Antiphospholipid antibodies, especially the IgG anticardiolipin and lupus anticoagulant, are involved in the pathogenesis of the disease by favouring formation of non-bacterial thrombotic vegetations [10]. Endocarditis has been described in other autoimmune conditions, such as rheumatoid arthritis. Immunological inflammation can be observed during rheumatic fever, where damage to endocardium, myocardium, and pericardium results from antibody cross-reactivity following *Streptococcus pyogenes* infection. Thrombotic sterile vegetations can be observed in the context of neoplasia (especially lung and pancreas) due to hypercoagulable states and, sometimes, with antiphospholipid antibodies. Loeffler's endocarditis is a form of restrictive cardiomyopathy with eosinophilic proliferation in endocardial and myocardial tissue. Finally, foreign material rejection or allergic phenomena may be a cause of non-infective porcine bioprosthetic valve endocarditis [9].

Box 160.1 Causes of endocarditis

Infective causes

'Standard' bacteria

- Oral (viridans) streptococci.
- *Streptococcus gallolyticus* (and other group D streptococci).
- *Streptococcus pneumonia.*
- *Streptococcus pyogenes.*
- Enterococci.
- *Staphylococcus aureus.*
- Coagulase negative staphylococci.
- Enterobacteriaceae.

Fastidious bacteria

- HACEK group.
- *Coxiella burnetii.*
- *Bartonella* spp.
- *Propionibacterium acnes.*
- *Tropheryma whipplei.*
- *Abiotrophia* ssp.
- *Mycoplasma* spp.
- *Legionella* spp.
- *Corynebacterium diphteriae.*
- *Listeria monocytogenes.*
- *Chlamydia* spp.
- *Finegoldia magna.*
- *Candida* spp.
- *Aspergillus* spp.

Virus (controversial)

Enterovirus.

Non-infective causes

- Acute rheumatic fever.
- Libman-Sacks endocarditis (antiphospholipid syndrome):
  - With systemic lupus.
  - With systemic lupus.
  - Without systemic lupus.
- Rheumatoid arthritis.
- Marantic endocarditis (neoplasia).
- Loeffler endocarditis.

HACEK, *Haemophilus* spp., *Actinobacillus* spp., *Cardiobacterium* spp., *Eikenella* spp., *Kingella* spp.

Pathophysiology

IE usually occurs on an endocardium with pre-existing lesions, or on intracardiac foreign material [2]. From various portals of entry (e.g. oral, digestive, cutaneous) and a subsequent bacteraemia, pathogens can adhere and colonize previously damaged endocardium due to numerous complex processes based on an unique host-pathogen interaction [11]. Severe life-threatening complications such as acute heart failure or embolic events can then occur (Fig. 160.1).

Underlying host lesions

The endocardium is normally resistant to infection. However, degenerative processes (fibrosis, calcifications), turbulent blood flow created by valvular or congenital heart diseases, and mechanical lesions secondary to material implantation can provoke endocardial damage. This results in exposure of the extracellular matrix, apoptosis, production of tissue factor, and then thrombus formation (non-bacterial vegetations). The presence of underlying endocardial damage may induce exposure of altered phospholipids (cardiolipin) on the outer membrane of endothelial cells, resulting in antiphospholipid antibody production by immune cells. Antiphospholipid antibodies may be involved in thrombus formation, even in the absence of autoimmune disease [12]. The formation of such non-bacterial thrombotic endocarditis may be a key event facilitating pathogen adherence and infection.

Alternatively, an endocardium free of previous lesions can form an adhesive surface to circulating virulent pathogens, such as *S. aureus*, due to expression of integrins by endothelial cells [13].

The role of bacteraemia

This has been studied in animals with catheter-induced, non-bacterial thrombotic endocarditis. Both the magnitude of bacteraemia and the pathogen's ability to attach to damaged valves are important. Bacteraemia occurs with invasive procedures, but also from routine daily activities, such as chewing, flossing, and tooth brushing. Accumulating numbers of circulating bacteria are greater after these activities than after an invasive puncture procedure. Such spontaneous low-grade, short duration, but repeated, bacteraemia may explain why most cases of IE are not preceded by invasive procedures. This questions the efficacy of single-dose antibiotic prophylaxis.

The host–pathogen interaction

During bacteraemia, some pathogens can adhere to components of the non-bacterial thrombotic vegetation or the inflamed endocardium. Fibrinogen, fibronectin or platelet proteins are recognized by adhesins located on the pathogen surface [5]. The predominance of Gram-positive pathogens can be explained by these organisms being the most equipped with these adhesins, collectively referred to as microbial surface component reacting with adhesive matrix molecules [5]. After adhesion, subsequent colonization and invasion of the endocardium maintain both inflammatory and coagulation processes, resulting in a vicious circle with the formation of infective vegetations in which the pathogens persist, multiply, and escape from the host defence systems. Consequently, the vegetations grow, a neo-angiogenesis process occurs and the valve tissue is destroyed, resulting ultimately in embolic events, abscess formation, and valve dysfunction [11]. An excessive host response

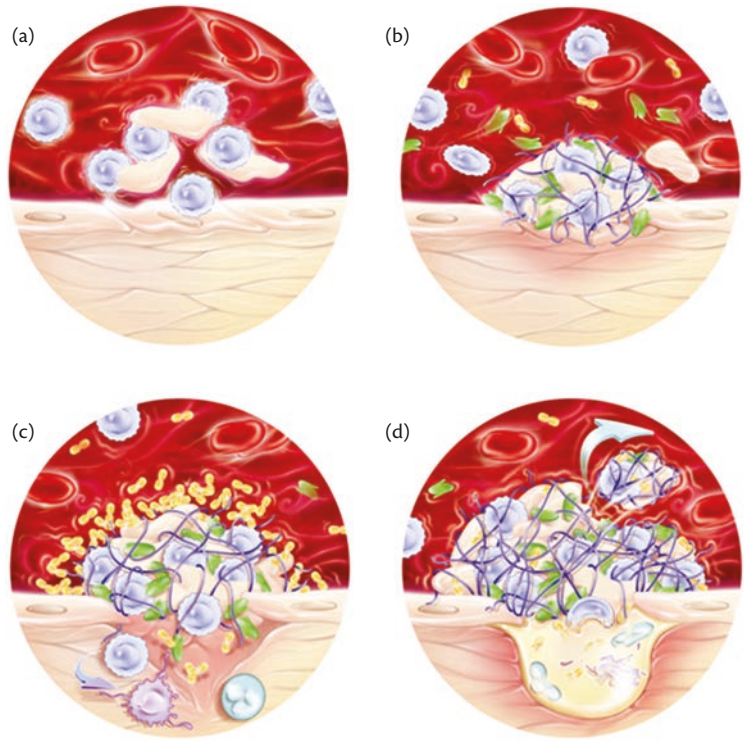


Fig. 160.1 Illustration of the infective endocarditis (IE) pathophysiology. The natural history of IE may be deconstructed into successive steps including cell apoptosis that may be promoted by blood turbulence in the vicinity of the valve lesion. (a) Procoagulant activity that results in fibrin and platelet deposition. (b) Bacterial colonization and chemoattraction of neutrophils increasing vegetation size. (c) Tissue remodelling and neoangiogenesis leading to the functional destruction of the valve (d). At this stage, the situation is irreversible and cardiac surgery is necessary.

may also be responsible for aggravation of lesions by secondary autoimmune effects, such as immune complex glomerulonephritis and vasculitis, but also an increasing risk of embolic events due to hypersecretion and activation of matrix metalloproteinases [14] and increased production of antiphospholipid antibodies (Fig. 160.1) [12].

Diagnosis

Evolution of diagnostic strategies

In cases carrying a high suspicion of IE, appropriate antibiotics must be started as soon as possible as delay has a negative effect on outcome. Efforts should be made to rapidly identify both patients with a likely diagnosis of IE and the causative pathogen to ensure that appropriate antibiotic therapy begins promptly.

Diagnosis usually relies on the association between an infectious syndrome and recent endocardial involvement. This is the cornerstone of the various classifications and scores, such as the Duke University criteria, proposed to facilitate the difficult diagnosis of this disease. In 2002, these criteria were further modified to include *Coxiella burnetii* serology as a new major criterion (Box 160.2) [15]. However, sensitivity is limited, especially at an early stage of the disease, in cases of negative blood culture and in the presence of prosthetic valve or pacemaker/defibrillator leads. New diagnostic strategies are emerging to improve pathogen identification when blood cultures are negative, and to demonstrate endocardial involvement when echocardiography is negative or doubtful. Polymerase chain reaction (PCR) techniques, immunohistochemistry, systematic serologies, antiphospholipid antibodies, MRI, and positron emission tomography-computed tomography (PET-CT) scans are promising tools that could be integrated into future diagnostic classifications (Fig. 160.2), as proposed by Raoult et al. for *Coxiella burnetii* endocarditis (Box 160.3) [16].

Clinical presentation

Although fever in a patient with a cardiac predisposition (heart valve disease, intracardiac materials, congenital heart disease) is the most frequent circumstance leading to diagnosis (almost 50% of cases [2]), clinical histories are highly variable (Box 160.4). Therefore, a high index of suspicion and low threshold for investigation are essential. Blood cultures and echocardiography still remain the cornerstones for diagnosis [6].

Microbiological investigations

The challenges are to rapidly identify the causative pathogen and the rare cases of non-infective endocarditis. In IE, blood cultures are negative in 2.5–31% of cases [7,8]. This often poses diagnostic and therapeutic issues. While culture-negative endocarditis is often related to previous antibiotic therapy, many result from infection with obligate intracellular bacteria, fungi, and fastidious pathogens whose isolation requires specialized culture techniques [8]. Appropriate antibiotic treatment is often delayed in such cases, potentially affecting outcomes.

To resolve these issues, some authors propose standardization of the timing and type of laboratory tests. This improves yields by systematically screening for all potential causes of IE [7]. The 'diagnostic

Box 160.2 Definition of infective endocarditis according to the proposed modified Duke criteria

Definite infective endocarditis

Pathological criteria

- **Micro-organisms**: demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen.

  Or

- **Pathological lesions**: vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis.

Clinical criteria

- Two major criteria; or
- One major criterion and three minor criteria; or
- Five minor criteria.

Possible infective endocarditis

- One major criterion and one minor criterion.
  Or
- Three minor criteria.

Rejected

- Firm alternate diagnosis explaining evidence of infective endocarditis.
- Resolution of infective endocarditis syndrome with antibiotic therapy for <4 days.
- No pathological evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 days.
- Does not meet criteria for possible infective endocarditis, as above.

Major criteria

Blood culture positive for IE

- **Typical micro-organisms consistent with IE from two separate blood cultures**: (Viridans streptococci, *Streptococcus bovis,* HACEK group, *Staphylococcus aureus*; or community-acquired enterococci, in the absence of a primary focus; or micro-organisms consistent with IE from persistently positive blood cultures, defined as follows: at least two positive cultures of blood samples drawn >12 hours apart; or all of three or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 hour apart).
- Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titre >1:800.

Evidence of endocardial involvement

- Echocardiogram positive for IE defined as follows:
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or
  - Abscess; or
  - New partial dehiscence of prosthetic valve or new valvular regurgitation (worsening or changing of pre-existing murmur not sufficient).

Minor criteria

- Predisposition, predisposing heart condition or injection drug use.
- Fever, temperature >38°C.
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
- **Immunological phenomena**: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
- **Microbiological evidence**: positive blood culture, but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

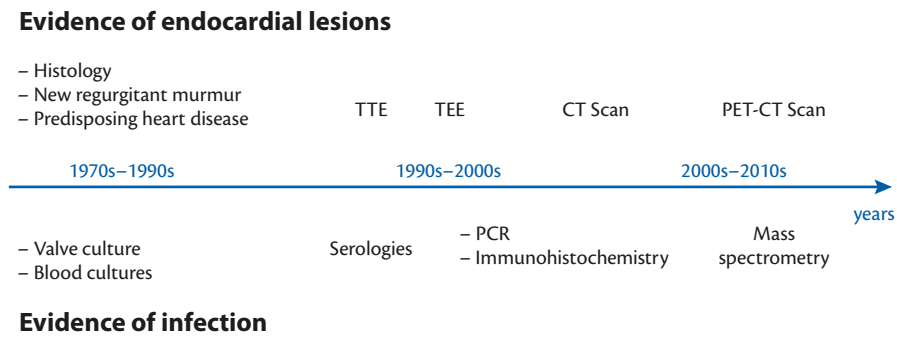


Fig. 160.2 Evolution of diagnostic methods to diagnose infective endocarditis.
TTE, transthoracic echocardiography; TEE, trans-oesophageal echocardiography; CT, computed tomography; PET, positron emission tomography.

kit', composed of three units, can be performed within 2 hours for every patient with suspected IE. The first, performed immediately, includes a set of two blood culture bottles, for aerobic and anaerobic cultures, and a tube to collect a serum sample for detection of rheumatoid factor and estimation of specific antibodies directed against *Coxiella burnetii, Legionella pneumophila, Bartonella, Brucella, Mycoplasma*, and *Aspergillus* spp. The second and third units each contain a set of two blood culture bottles to be used 2 hours after the first. The results of these diagnostic tests can be obtained soon after admission, thus shortening the time to institution of a specific therapy. Using this approach, clinicians would not have to defer serological testing until blood cultures are shown to be negative.

Box 160.3 Definition of Q fever endocarditis, adapted from Raoult D. Chronic Q fever: expert opinion versus literature analysis and consensus

Definite criterion

Positive culture, PCR, or immunochemistry of a cardiac valve.

Major criteria

- Microbiology: positive culture or PCR of the blood or an emboli or serology with IgGI antibodies ≥6400.
- Evidence of endocardial involvement:
  - *Echocardiogram positive for IE*: oscillating intra-cardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or abscess; or new partial dehiscence of prosthetic valve; or new valvular regurgitation (worsening or changing of pre-existing murmur not sufficient).
  - PET-scan showing a specific valve fixation and mycotic aneurism.

Minor criteria

- Predisposing heart condition (know or found on echography).
- Fever, temperature > 38°.
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm (see PET-scan), intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
- **Immunological phenomena**: glomerulonephritis, Osler's nodes, Roth's spots, or rheumatoid factor.
- **Serological evidence**: IgGI antibodies ≥800 <6400.

Diagnosis definite

- 1A criterion.
- 2B criteria.
- 1B criterion, and 3C criteria (including one microbiology evidence, and cardiac predisposition).

Diagnosis possible

- 1B criterion, 2C criteria (including 1 microbiology evidence, and cardiac predisposition).
- 3C criteria (including positive serology, and cardiac predisposition).

Box 160.4 Clinical presentation of IE

IE must be suspected in the following situations

- New regurgitant heart murmur.
- Embolic events of unknown origin.
- Sepsis of unknown origin (especially if associated with IE causative organism).
- **Fever**: the most frequent sign of IE. Should be suspected if fever is associated with:
  - Intracardiac prosthetic material (e.g. prosthetic valve, pacemaker, implantable defibrillator, surgical baffle/conduit.
  - Previous history of IE.
  - Previous valvular or congenital heart disease.
  - Other predisposition for IE (e.g. immunocompromised state, IVDA).
  - Predisposition and recent intervention with associated bacteraemia.
  - Evidence of congestive heart failure.
  - New conduction disturbance.
  - Positive blood cultures with typical IE causative organism or positive serology for chronic Q fever.
  - **Vascular or immunological phenomena**: embolic event, Roth spots, splinter haemorrhages, Janeway lesions, Osler's nodes.
  - Focal or non-specific neurological symptoms and signs.
  - Evidence of pulmonary embolism/infiltration (right-sided IE).
  - Peripheral abscesses (renal, splenic, cerebral vertebral) of unknown cause.

Reproduced from Habib G et al., 'Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC)', *European Heart Journal*, 2009, 30, 19, pp. 2369–2413, by permission of Oxford University Press © European Society of Cardiology, HYPERLINK "http://www.escardio.org/guidelines" www.escardio.org/guidelines.

Causative pathogens can also be identified by other means, such as cultures from valve tissue. However, pathogen detection often poses a challenge for pathologists. It can be done by non-specific histochemical stains or immunohistochemical analyses. As specific antibodies are often not available, another method termed auto-immunohistochemistry, which uses the patient's own serum, has been described for detection of micro-organisms in valve specimens.

The rapid and reliable detection of pathogens by PCR has been validated in valve tissue from patients undergoing surgery for IE. Molecular pathogen detection in blood using pathogen-specific or broad-range PCR assays for bacteria and fungi is also promising. However, cautious interpretation is crucial, because of the risk of interfering contamination (false positives). The clinical context must also be considered. These advanced methods can be integrated into a standardized multimodal strategy that allows better identification of the causes of blood-culture-negative endocarditis (Fig. 160.3) [8].

Imaging investigations

Echocardiography

Echocardiography can accurately detect endocardial involvement in IE, and must be done rapidly and repeated weekly as soon as the condition is suspected. Transthoracic echocardiography (TTE) should be used initially as a normal scan in low-risk patients provides a rapid, non-invasive confirmation that the diagnosis is unlikely. TTE is superior to transoesophageal echocardiography (TEE) for detecting anterior cardiac abscesses and for haemodynamic assessment of valvular dysfunction. Because of its higher sensitivity and specificity, TEE is recommended in cases of:

- A negative TTE associated with high clinical suspicion.
- Poor TTE quality.
- The presence of prosthetic valves or intracardiac device.
- A positive TTE [6].

The identification of vegetations, abscess, valvular perforation, or new prosthetic-valve dehiscence will confirm the diagnosis in most, though not all, cases. Diagnosis may be particularly challenging in patients with intracardiac devices, a valvular prosthesis, pre-existing severe lesions, or very small or no vegetations. An erroneous diagnosis of IE may occur in several situations; for example, differentiating between vegetations and thrombi, prolapsed cusp, cardiac tumours (myxoma or fibroelastoma), myxomatous changes, Lambl's excrescences, or strands. Innovations in imaging techniques are emerging to resolve these issues, e.g. multislice CT, PET, molecular imaging and MRI [3].

Other imaging modalities

Other imaging modalities can assist in difficult diagnosis or in therapeutic decision-making.

Computed tomography (CT) scan offers rapid imaging of the heart and other organs, thus identifying both cardiac lesions and any extracardiac complications that may modify the therapeutic strategy such as emboli, infectious aneurysms, haemorrhage and septic metastases. Moreover, it provides an anatomical assessment of the coronary bed, which is important in preoperative evaluation. CT appears useful in cases of inconclusive echocardiographic studies, especially perivalvular (abscess and pseudoaneurysms) involvement [17]. Contrast products should be used cautiously in patients with renal failure or haemodynamic instability because of the risk of worsening renal impairment in combination with antibiotic nephrotoxicity. Specific recommendations are needed to clearly define appropriate situations where contrast should be used.

Although multiple case reports demonstrate how MRI can identify valvular and perivalvular damage, the identification of silent cerebral complications appears to be its main utility. Systematic MRI detected subclinical cerebrovascular complications in about 50% of patients, and this may modify disease management [18].

Preliminary results have shown much promise for PET-CT scans in the setting of pacemaker/defibrillator leads and prosthetic valve IE [19]. This imaging modality enables measurement of metabolic activity within an organ obtained from the emission of positrons following disintegration of the injected radioactive product. It can identify inflammatory and infectious processes as the inflammatory cells have significant fluorodeoxyglucose (FDG) uptake.

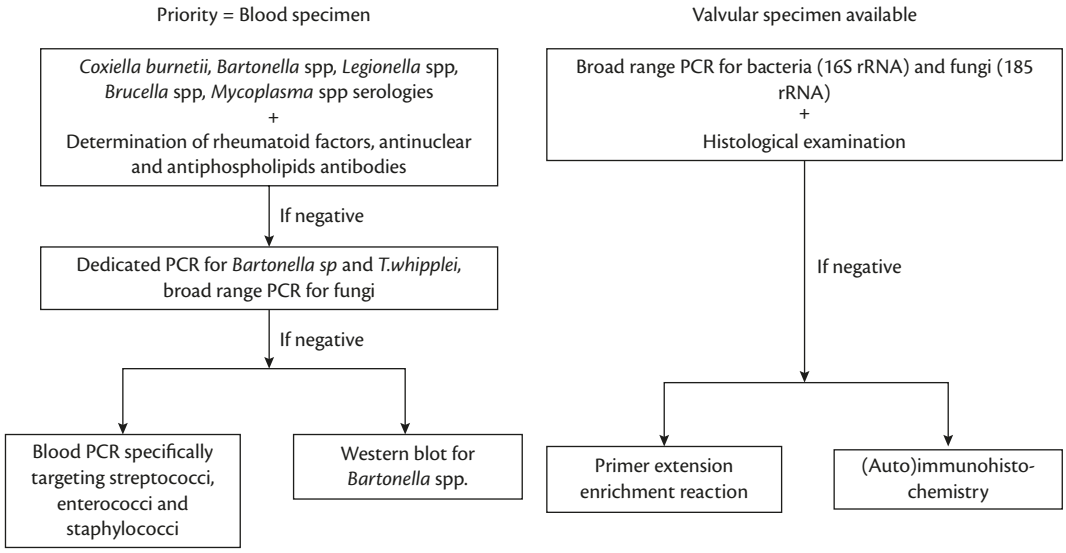


Fig. 160.3 Diagnostic tests applied to clinical specimens for identification of the causative agents of blood culture–negative endocarditis.
Adapted from Fournier PE et al., 'Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases', Clinical Infectious Diseases, 2010, 51, 2, pp. 131–408, by permission of Oxford University Press and Infectious Diseases Society of America.

Fluorine-18 fluorodeoxyglucose (18F-FDG) PET-CT may detect periprosthetic valve abscesses when initial TTE and TEE studies are normal or of doubtful significance (Fig. 160.4). A recent study showed that the implementation of a positive PET-CT as a major criterion in the modified Duke classification significantly increases its sensitivity in cases of suspicion of prosthetic valve IE [20]. Moreover, it may reveal the source of infection, e.g. a neoplasm such as bowel cancer. At present, 18F-FDG PET-CT is being evaluated for its ability to detect peripheral emboli and to diagnose implantable electronic device infections.

Gallium-67, indium-111 or technecium-99m-HMPAO labelled-leucocyte scintigraphy is another option for imaging

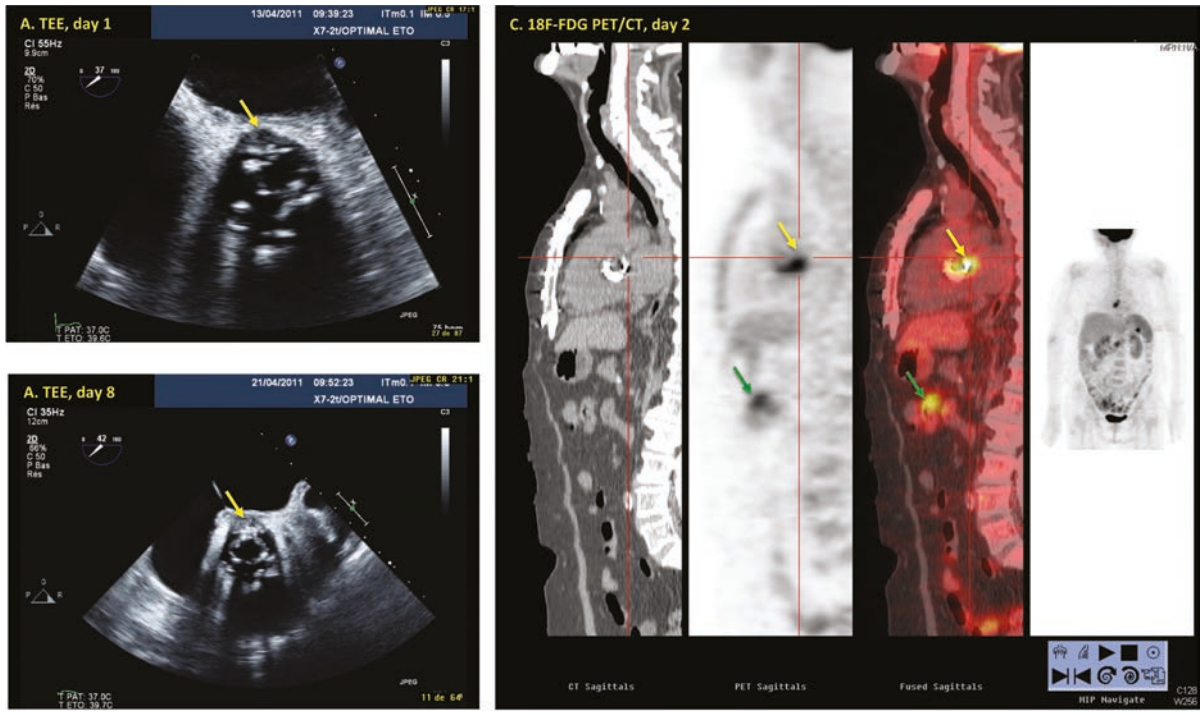


Fig. 160.4 Results of echocardiographic studies and 18F-FDG PET-CT in a case of suspicion of aortic bioprosthetic valve infective endocarditis. The first TEE (a) showed a small doubtful thickening around the aortic bioprosthetic annulus (yellow arrow) in a patient with fever and negative blood cultures. The second TEE (b), performed 8 days after, showed the development of a periprosthetic abscess (yellow arrow). The 18F-FDG PET-CT performed the day after the first TEE showed a hyperfixation around the aortic prosthesis (c, yellow arrow). The patient underwent urgent valve surgery, which confirmed the abscess. Of note, colonic hyperfixation was shown by18F-FDG PET-CT (green arrow), which reveals a polyp at subsequent colonoscopy.

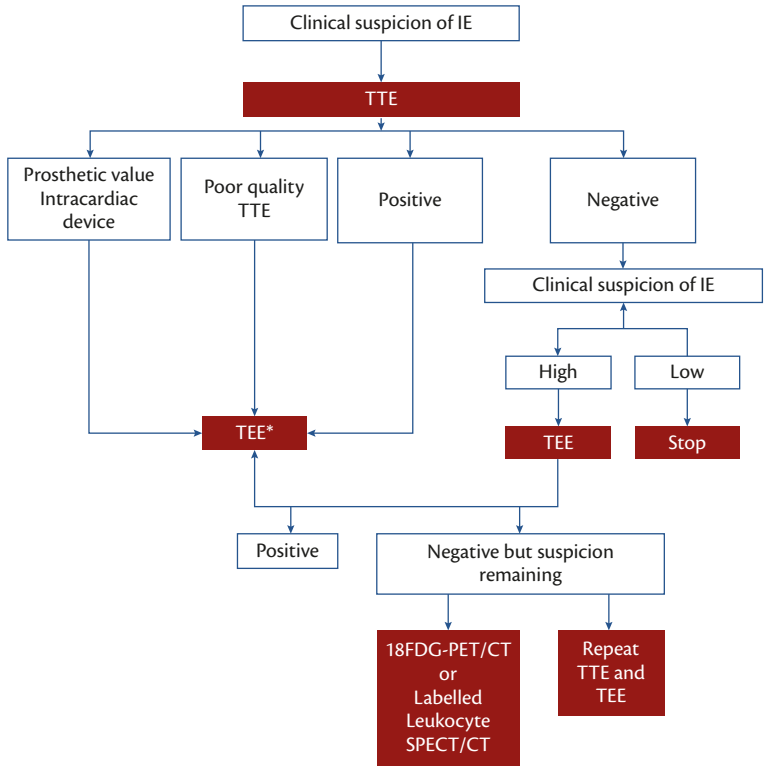


Fig. 160.5 Indications for cardiac imaging in suspected infective endocarditis.
*TEE is not mandatory in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings.
IE, infective endocarditis; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

infection, both with or without incorporation with CT images. Unlike ^{18}F-FDG PET/CT this method is more specific for infection, but is more time-consuming (24 hours). Indications for cardiac imaging are summarized in Fig. 160.5.

References

1. Selton-Suty C, Celard M, Le Moing V, et al. (2012). Preeminence of Staphylococcus aureus in infective endocarditis: a 1-year population-based survey. *Clinical Infectious Diseases*, **54**, 1230–9.
2. Thuny F, Di Salvo G, Belliard O, et al. (2005). Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. *Circulation*, **112**, 69–75.
3. Thuny F, Grisoli D, Collart F, Habib G, and Raoult D. (2012). Management of infective endocarditis: challenges and perspectives. *Lancet*, **379**, 965–75.
4. Fowler VG, Jr, Miro JM, Hoen B, et al. (2005). *Staphylococcus aureus* endocarditis: a consequence of medical progress. *Journal of the American Medical Association*, **293**, 3012–21.
5. Que YA and Moreillon P. (2011). Infective endocarditis. *Nature Reviews Cardiology*, **8**, 322–36.
6. Habib G, Hoen B, Tornos P, et al. (2009). Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *European Heart Journal*, **30**, 2369–413.
7. Raoult D, Casalta JP, Richet H, et al. (2005). Contribution of systematic serological testing in diagnosis of infective endocarditis. *Journal of Clinical Microbiology*, **43**, 5238–42.
8. Fournier PE, Thuny F, Richet H, et al. (2010). Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. *Clinical Infectious Diseases*, **51**, 131–40.
9. Fournier PE, Thuny F, Lepidi H, et al. (2011). A deadly aversion to pork. *Lancet*, **377**, 1542.
10. Zuily S, Regnault V, Selton-Suty C, et al. (2011). Increased risk for heart valve disease associated with antiphospholipid antibodies in patients with systemic lupus erythematosus: meta-analysis of echocardiographic studies. *Circulation*, **124**, 215–24.
11. Benoit M, Thuny F, Le Priol Y, et al. (2010). The transcriptional programme of human heart valves reveals the natural history of infective endocarditis. *PLoS One*, **5**, e8939.
12. Kupferwasser LI, Hafner G, Mohr-Kahaly S, Erbel R, Meyer J, and Darius H. (1999). The presence of infection-related antiphospholipid antibodies in infective endocarditis determines a major risk factor for embolic events. *Journal of the American College of Cardiology*, **33**, 1365–71.
13. Que YA, Haefliger JA, Piroth L, et al. (2005). Fibrinogen and fibronectin binding cooperate for valve infection and invasion in *Staphylococcus aureus* experimental endocarditis. *Journal of Experimental Medicine*, **201**, 1627–35.
14. Thuny F, Habib G, Le Dolley Y, et al. (2011). Circulating matrix metalloproteinases in infective endocarditis: a possible marker of the embolic risk. *PloS one*, **6**, e18830.
15. Li JS, Sexton DJ, Mick N, et al. (2000). Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clinical Infectious Diseases*, **30**, 633–8.
16. Raoult D. (2012). Chronic Q fever: expert opinion versus literature analysis and consensus. *Journal of Infection*, **65**, 102–8.
17. Feuchtner GM, Stolzmann P, Dichtl W, et al. (2009). Multislice computed tomography in infective endocarditis: comparison with transesophageal echocardiography and intraoperative findings. *Journal of the American College of Cardiology*, **53**, 436–44.
18. Duval X, Iung B, Klein I, et al. (2010). Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis: a prospective study. *Annals of Internal Medicine*, **152**, 497–504.

19. Sarrazin JF, Philippon F, Tessier M, et al. (2012). Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. *Journal of the American College of Cardiology*, **59**, 1616–25.

20. Saby L, Laas O, Habib G, et al. (2013) Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. *Journal of the American College of Cardiology,* **61**, 2374–82.

CHAPTER 161

Prevention and treatment of endocarditis

Dominique Grisoli and Didier Raoult

Key points

- Data supporting antibiotic prophylaxis for infective endocarditis (IE) are poor and benefits are hypothetical. Nevertheless, in order to avoid medico-legal issues, physicians should follow recommendations provided by learned societies from their countries.
- General preventive measures are crucial. Invasive procedures, especially intravenous catheterization, should be restricted to the minimum in patients with predisposing cardiac conditions.
- IE is one of the deadliest infectious diseases, and its treatment must be undertaken in reference centres in a standardized and multidisciplinary manner.
- IE has become a 'surgical disease' so dedicated surgeons should be involved in therapeutic discussions from the very beginning. When indicated, surgery has to be performed without delay. Most deaths from IE result from complications that constitute definite surgical indications.
- Patients with severe symptoms or perivalvular damages are at risk of sudden death and should be monitored in critical care, while awaiting surgery.

Introduction

Initially always lethal, the prognosis of infective endocarditis (IE) has been revolutionized by antibacterial therapy and valve surgery. Nevertheless, it remains one of the deadliest infectious diseases, with ≥30% of patients dying within a year of diagnosis [1]. Its incidence has also remained stable at 25–50 cases per million per year [2].

IE results predominantly from a combination of bacteraemia and a predisposing cardiac condition including endocardial lesions and/or intracardiac foreign material. While antibiotic prophylaxis is recommended by various learned societies to cover health care procedures with the potential of causing bacteraemia in at-risk patients, there is no evidence to support this strategy. Even though the benefits are hypothetical, national guidelines should still be followed to avoid medico-legal issues. General preventive measures, such as education of clinicians and at-risk patients appear to be more crucial. Invasive procedures, especially intravenous (iv) catheterization, should be kept to the minimum possible.

The severity of IE mandates a multidisciplinary and standardized approach to treatment, with involvement of dedicated surgeons within specialist centres. Standardized antibiotic protocols have produced dramatic reductions in hospital and 1-year mortality in reference centres. Most deaths now result from complications that constitute definite surgical indications, so optimization of surgical management and avoidance of delay will clearly improve prognosis. This disease has now entered an 'early surgery' era, with a more aggressive surgical approach showing promising results [3].

Conditions such as septic shock, sudden death, and vancomycin-resistant staphylococcal endocarditis still constitute therapeutic and research challenges, and justify an important role for specialist centres.

Prevention

Existing evidence

Prophylaxis aims at preventing bacteria from growing on endocardial lesions in patients with known predisposing cardiac conditions. It is based on screening and treatment of potential entry sites for organisms, and on antibiotic prophylaxis given before health care procedures that carry various rates of induced bacteraemia.

Surprisingly, no strong evidence supports the use of antibiotic prophylaxis. Recommendations are mainly based on experimental studies using transient high-grade bacteraemia to reproduce the potential effects of a dental procedure [4]. However, everyday actions, such as chewing or tooth brushing may also cause low-grade bacteraemia [5], while cumulative everyday bacteraemia over 1 year was estimated at 6 million times higher than bacteraemia following dental extraction. As underlined by a recent Cochrane review of antibiotic prophylaxis against IE in dentistry [6], only a few case-control studies exist, of which only one could be included in their review, with no significant protective effect being shown.

Furthermore, in large observational studies, only a minority of IE cases was secondary to medical procedures [7]. It is unlikely that new data will be provided in the near future. Indeed, because of the low incidence of this disease, a randomized controlled trial would need a huge number of patients, and would probably cause legal and ethical issues. Despite low reported rates of hypersensitivity and anaphylaxis, any benefit from antibiotic prophylaxis must also be balanced against potential adverse effects. Of note, the extensive use of antibiotics is responsible for the development of resistant bacteria, although the impact of single doses is uncertain.

Table 161.1 Classification of PCC according to the risk of developing infective endocarditis

High risk PCC	Class[a]	Level[b]
Valvular prostheses (mechanical, bioprosthese, homograft)	IIa	C
History of infective endocarditis	IIa	C
Surgically constructed pulmonary-systemic shunts	IIa	C
Non-operated cyanotic congenital heart disease	IIa	C
Cardiac transplantation recipients who develop cardiac valvulopathy*		
Moderate/lower risk PCC		
Acquired valvular dysfunction	III	C
Mitral valve prolapse with regurgitation and/or thickened leaflets	III	C
Other congenital cardiac disease (except ostium secondum ASD)	III	C
Hypertrophic cardiomyopathy	III	C
Bicuspid aortic valve†	III	C

*In the 2007 AHA recommendations [11]; †In the 2006 BSAC recommendations [10].

[a]Class of recommendation; [b]level of evidence.

PCC, predisposing cardiac condition; ASD, atrial septal defect.

Data from Gould FK et al., 'Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy', *Journal of Antimicrobial Chemotherapy*, 2006, 57, pp. 1035–1042; and Wilson W et al., 'Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group', *Circulation*, 2007, 116, pp. 1736–1754.

Recommendations

Antibiotic prophylaxis has been recommended since 1955. Recurrent updates have since been published by numerous national and international societies. Over the last decade, and influenced by extensive literature reviews that highlight the lack of evidence supporting antibiotic prophylaxis for IE [6], there has been a noticeable change, with a major trend to restricting use to highest-risk patients and procedures. This began with the 2002 French recommendations [8], and climaxed with the 2008 National Institute for Health and Clinical Excellence (NICE) guidance, where no prophylaxis was recommended [9]. Although the same trend can generally be noted elsewhere, considerable variation still exists.

The classification of predisposing cardiac conditions according to the risk of developing IE is detailed in Table 161.1, while Tables 161.2 and 161.3 provide indications for prophylaxis in the setting of dental and non-dental procedures according to recent guidelines [8–12]. Recommendations concerning choices of drugs, doses, and routes of administration for dental and non-dental procedures are summarized in Tables 161.4, 161.5, 161.6, and 161.7.

Our recommendations

Despite the absence of evidence supporting the use of prophylaxis for IE in at-risk patients, malpractice claims are not uncommon, especially in the United States, from patients who developed endocarditis after dental care for which they did not receive prophylaxis. In one study reviewing 319 legal cases from various countries, 83 (26%) were successful in legally associating a dental procedure to the onset of IE [13]. However, the most recent guidelines are highly disparate between the different learned societies (see Tables 161.8 and 161.9 for guidance in interpreting these guidelines). Therefore, following national guidelines where practiced is advised, mainly to avoid medico-legal issues.

While data supporting current recommendations are poor, and the benefits of prophylaxis hypothetical, the education of at-risk patients is crucial. General preventive measures must be highlighted. Early identification and treatment of potential sources of endocarditis are mandatory. Patients with predisposing cardiac conditions should be urged to consult their physicians about fever or other lasting symptoms. Physicians should also be aware of the importance of blood cultures before any antibiotic prescription in this setting. Because of the suspected major role of everyday bacteraemia in IE [5], the need for good oral hygiene and frequent dental assessments are critical. Finally, the absolute necessity to limit

Table 161.2 Indications for endocarditis prophylaxis in the setting of dental procedures

	Dental procedures	**Predisposing cardiac condition**	
		High risk	**Moderate risk**
French (2002) [8]	Several dental procedures (dental extraction, scaling …)	Prophylaxis recommended	Prophylaxis optional
BSAC (2006) [10]	All dental procedures involving dentogingival manipulation or endodontics	Prophylaxis recommended	Not recommended
AHA (2007) [11]	All dental procedures involving manipulation of gingival tissue, or the peri-apical region of teeth, or perforation of the oral mucosa	Prophylaxis recommended	Not recommended
NICE (2008) [9]	All dental procedures	Not recommended	Not recommended
ESC (2009) [12]	Only dental procedures requiring manipulation of the gingival, or peri-apical region of the teeth, or perforation of the oral mucosa	Prophylaxis recommended	Not recommended

BSAC, British Society for Antimicrobial Chemotherapy; AHA, American Heart Association; NICE, National Institute for Health and Clinical Excellence; ESC, European Society of Cardiology.

Data from various sources. See references.

Table 161.3 Indications for endocarditis prophylaxis in the setting of non-dental procedures

	Procedures	Predisposing cardiac condition	
		High risk	Moderate risk
French (2002) [8]	Several procedures: e.g. colonoscopy, etc.	'Clinician's best judgment'	
	Depending on the procedure	Recommended or optional	Optional or not recommended
BSAC (2006) [10]	Several procedures: e.g. oesophageal laser therapy, cystoscopy	Prophylaxis recommended	Prophylaxis recommended
AHA (2007) [11]	Respiratory tract procedure involving incision or biopsy of the respiratory mucosa	Prophylaxis recommended	Not recommended
	Respiratory tract procedure without incision of the respiratory mucosa	Not recommended	Not recommended
	Gastrointestinal and genitourinary tract procedures	Not recommended	Not recommended
NICE (2008) [9]	Respiratory tract, gastrointestinal, genitourinary, dermatological, or musculoskeletal procedures	Not recommended	Not recommended
ESC (2009) [12]	Respiratory tract, gastrointestinal, genitourinary, dermatological, or musculoskeletal procedures	Not recommended	Not recommended

BSAC, British Society for Antimicrobial Chemotherapy; AHA, American Heart Association; NICE, National Institute for Health and Clinical Excellence; ESC, European Society of Cardiology.
Data from various sources. See references.

Table 161.4 Endocarditis prophylaxis: antibiotic regimens for dental procedures in adults

		1 hour before procedure (po)	Before procedure or at induction of anaesthesia (iv)
French (2002) [8]		Amoxicillin 3 g	Amoxicillin (2 g) (6 hours later: 1 g po)
	If allergic to β-lactam	Pristinamycin (1 g) *or* Clindamycin (600 mg)	Vancomycin (1 g) *or* Teicoplanin (400 mg)
BSAC (2006) [10]		Amoxicillin (3 g)	Amoxicillin (1 g)
	If allergic to β-lactam	Clindamycin (600 mg) *or* Azithromycin (500 mg)	Clindamycin (300 mg)
AHA (2007) [11]		Amoxicillin (2 g)	Ampicillin (2 g) *or* Cephazolin/Ceftriaxone (1 g)
	If allergic to β-lactam	Clindamycin (600 mg), *or* Azithromycin (500 mg), *or* Cephalexin (2 g)	Clindamycin (600 mg)
ESC (2009) [12]		Amoxicillin (2 g)	Ampicillin (2 g)
	If allergic to β-lactam	Clindamycin (600 mg)	Clindamycin (600 mg)

po, oral antibiotics; iv, intravenous regimens for people under general anaesthesia or unable to swallow.
Data from various sources. See references.

invasive procedures should also be highlighted. Indeed, the use of iv catheters should be dramatically restricted in both frequency and duration in patients with intracardiac devices to reduce the risk of nosocomial bacteraemia and, therefore, health care-induced IE. To sum up, '*primum non nocere*'.

Treatment

In our tertiary care centre, diagnostic strategy was standardized in 1994, and therapeutic protocols in 2002, using a very limited number of antimicrobial agents. The implementation of this standardized therapeutic protocol has been associated with a reduction in hospital mortality from 12.7% to 4.4%, and overall 1-year mortality from 18.5% to 8.2% [14].

Antibiotics

For suspected or confirmed IE, empiric antibiotic therapy should be promptly initiated after microbiological sampling. This should be subsequently modified according to laboratory results. Early antibiotic therapy dramatically reduces morbidity and mortality [15]. In our tertiary care centre, this is started within 2 hours of admission in patients with a high suspicion of IE. We use a standardized diagnostic kit that limits the number of blood cultures taken over 2 hours and enables, through serological testing, identification of the major organisms responsible for blood culture-negative endocarditis (BCNE). Unlike prophylaxis, guidelines for antimicrobial therapy are consensual between societies [12, 16] and supported by a strong evidence base.

General principles of antibiotics in IE

The recommended duration of antibiotic therapy begins on the first day of effective treatment, i.e. the first day on which blood cultures are negative. For BCNE, counting of days should begin on the first day of clinical efficacy with no pyrexia. For prosthetic valve endocarditis (PVE), the antibiotic duration should be longer (at least 6 weeks) than for native valve endocarditis (NVE). When NVE requires prosthetic valve replacement, the post-operative antibiotic regimen should be as for NVE [12]. Post-operatively, if the valve cultures are positive, a full course of antibiotic therapy should be restarted.

Table 161.5 Endocarditis prophylaxis: antibiotic regimens for dental procedures in children

		1 hour before procedure (po)	Before procedure or at induction of anaesthesia (iv)
French (2002) [8]		Amoxicillin (75 mg/kg)	Amoxicillin (50 mg/kg) (6 hours later: 25 mg/kg po)
	If allergic to β-lactam	Pristinamycin (25 mg/kg) *or* clindamycin (15 mg/kg)	Vancomycin (20 mg/kg) (max. 1 g)
BSAC (2006) [10]		*<5 years:* Amoxicillin (750 mg) *5–10 years:* Amoxicillin (1.5 g)	*<5 years:* Amoxicillin (250 mg) *5–10 years:* Amoxicillin (500 mg)
	If allergic to β-lactam	*<5 years:* Clindamycin (150 mg) *5–10 years:* Clindamycin (300 mg) *or* *<5 years:* Azithromycin (200 mg) *5–10 years:* Azithromycin (300 mg)	*<5 years:* Clindamycin (75 mg) *5–10 years:* Clindamycin (150 mg)
AHA (2007) [11]		Amoxicillin (50 mg/kg)	Ampicillin (50 mg/kg) *or* Cephazolin/Ceftriaxone (50 mg/kg)
	If allergic to β-lactam	Clindamycin (20 mg/kg), *or* Azithromycin (15 mg/kg), *or* Cephalexin (50 mg/kg)	Clindamycin (20 mg/kg)
ESC (2009) [12]		Amoxicillin (50 mg/kg)	Ampicillin (50 mg/kg)
	If allergic to β-lactam	Clindamycin (20 mg/kg)	Clindamycin (20 mg/kg)

po, oral antibiotics; iv, intravenous regimens for people under general anaesthesia or unable to swallow.

Data from various sources. See references.

Table 161.6 Endocarditis prophylaxis: antibiotic regimens for non-dental procedures in adults

		Before procedure or at induction of anaesthesia (iv)
French (2002) [8]		Amoxicillin (2 g), then Gentamicin (1.5 mg/kg) (6 hours later: 1 g po)
	If allergic to β-lactam	Vancomycin (1 g), *or* Teicoplanin (400 mg), then Gentamicin (1.5 mg/kg)
BSAC (2006) [10]		Amoxicillin (1 g), then Gentamicin (1.5 mg/kg)
	If allergic to β-lactam	Teicoplanin (400 mg), then Gentamicin (1.5 mg/kg)
AHA (2007) [11]		Amoxicillin (only for respiratory tract procedures involving incision of the respiratory mucosa)
	If allergic to β-lactam	Vancomycin (only for respiratory tract procedures involving incision of the respiratory mucosa)
ESC (2009) [12]		None
	If allergic to β-lactam	None

po, oral antibiotics; iv, intravenous regimens for people under general anaesthesia or unable to swallow.

Data from various sources. See references.

Table 161.7 Endocarditis prophylaxis: antibiotic regimens for non-dental procedures in children

		Before procedure or at induction of anaesthesia (iv)
French (2002)		Amoxicillin (50 mg/kg), then Gentamicin (2 mg/kg) (max. 80 mg) (6 hours later: Amoxicillin (25 mg/kg) orally)
	If allergic to β-lactam	Vancomycin (20 mg/kg) (max 1 g), then Gentamicin (2 mg/kg)
BSAC (2006)		Amoxicillin (<5 years: 250 mg; 5–10 years: 500 mg), then Gentamicin (1.5 mg/kg)
	If allergic to β-lactam	Teicoplanin (6 mg/kg), then Gentamicin (1.5 mg/kg)
AHA (2007)		Ampicillin (50 mg/kg), *or* cefazolin/ceftriaxone (50 mg/kg) (only for respiratory tract procedures involving incision of the respiratory mucosa)
	If allergic to β-lactam	Clindamycin (20 mg/kg) (only for respiratory tract procedures involving incision of the respiratory mucosa)
ESC (2009)		None
	If allergic to β-lactam	None

po, oral antibiotics; iv, intravenous regimens for people under general anaesthesia or unable to swallow.

Data from various sources. See references.

Table 161.8 Classes of recommendations

Class of recommendation	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful

Adapted with kind permission from Agency for Healthcare Research and Quality (previously Agency for Health Care Policy and Research), AHCPR Clinical Practice Guidelines, '1. Acute Pain Management' (Feb. 1992) and '9. Management of Cancer Pain' (March 1994), available from http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/archive.html (select "Clinical Guides").

Table 161.9 Levels of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Adapted with kind permission from Agency for Healthcare Research and Quality (previously Agency for Health Care Policy and Research), AHCPR Clinical Practice Guidelines, '1. Acute Pain Management' (Feb. 1992) and '9. Management of Cancer Pain' (March 1994), available from http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/archive.html (select "Clinical Guides").

Empirical antibiotic therapy

Our empirical antibiotic protocol (Table 161.10) combines amoxicillin with gentamicin for community-acquired IE. For nosocomial IE (cardiac surgery or pacemaker within the last 12 months, and right-sided IE), a combination of vancomycin with gentamicin and rifampicin is used [14].

Antibiotic regimens when a micro-organism has been identified

- **Common organisms:** for the most common organisms (*Streptococcus*, *Staphylococcus*, and *Enterococcus* spp.), Table 161.11 details our adaptations of the antibiotic regimens advised by the latest recommendations [12].
- **Rare organisms:**
  - *Non-HACEK Gram-negative bacterial IE*—rare and severe, this requires involvement of a specialized infectious disease team. Early surgery is often required and the antibiotic treatment includes long-term (≥6 weeks) combinations of β-lactams and aminoglycosides, sometimes with additional quinolones or cotrimoxazole.
  - *Fungal IE*—carrying high rates of mortality (>50%), this pathology predominantly affects prosthetic valves, and/or occurs in immunocompromised patients or iv drug abusers. Fungi, mainly *Candida* and *Aspergillus* spp., are the most frequent pathogens involved in post-operative BCNE. Treatment includes valve replacement and amphotericin B with or without azoles. Long-term oral treatment with azoles is often required, sometimes for life.
  - *Fastidious micro-organisms IE*—Table 161.12 summarizes proposed regimens for fastidious micro-organisms [12]. However, no strong evidence base supports these therapeutic strategies.

BCNE

Representing 2.5–31% of all cases of endocarditis, these are both diagnostically and therapeutically challenging, and should be managed by infectious disease specialists. Although often related to previous antibiotic therapy, or to issues in sampling and diagnosis, an important proportion of BCNE is attributable to fastidious pathogens, obligate intracellular bacteria, and fungi.

When the causal micro-organism has been identified, antibiotic therapy is rarely a concern. Indeed, relapses are very rare unless an indicated surgical treatment could not be performed. A 7-year relapse rate ≤5% was reported in a series including BCNE patients [17].

Antibiotic resistance issues concern very few patients with IE. The emergence of meticillin-resistant *Staphylococci* has not resulted in a higher mortality from *S. aureus* IE because of the introduction of vancomycin in 1958. Surprisingly, half a century later, this drug is still the antibiotic of choice in this setting [12,16], although some vancomycin-resistant strains have been recently identified.

Surgery

Indications

Since the first reported success in 1965, the role of surgery in active IE has gradually expanded, especially over the last decade. The latest guidelines recommend surgical treatment for complicated left-sided endocarditis [12,16]. Indications for surgical management of IE are

Table 161.10 Empirical antibiotic regimens before micro-organism identification

Medical history	Drugs (no β-lactam intolerance)	Drugs (β-lactam intolerance)	Duration (weeks)
Native valve	Amoxicillin[a]	Vancomycin[c]	4–6
	+ Gentamicin[b]	+ Gentamicin[b]	4–6
Prosthetic valve > 1 year	Amoxicillin[a]	Vancomycin[c]	6
	+ Gentamicin[b]	+ Gentamicin[b]	6
Prosthetic valve < 1 year	Vancomycin[c]		6
	+ Gentamicin[b]		2
	+ Rifampicin[d]		6
Early PVE after cardiac surgery	Vancomycin[c]		6
	+ Gentamicin[b]		2
	+ Amphoteracin B		4–6

[a] 100–200 mg/kg/day iv in 4–6 doses. [b] 3 mg/kg/day iv or im in one dose, renal function and serum gentamicin concentrations should be monitored once a week, pre-dose (trough) concentrations should be <1 mg/L and post-dose (1 hour after injection) serum concentrations should be around 10–12 mg/L. [c] 30 mg/kg/day iv in two doses, serum vancomycin concentrations should achieve 25–30 mg/L at predose levels. [d] 1200 mg/day iv or po in two doses.

PVE, prosthetic valve endocarditis.

Table 161.11 Antibiotic regimens after micro-organism identification

Micro-organisms	Drugs (no β-lactam intolerance)	Drugs (β-lactam intolerance)	Duration (weeks)
Streptococcus spp.	Amoxicillin[a]	Vancomycin[c]	4–6
HACEK-related species	+ Gentamicin[b]	+ Gentamicin[b]	2
Enterococcus spp.	Amoxicillin[a]	Vancomycin[c]	6
	+ Gentamicin[b]	+ Gentamicin[b]	6
Staphylococcus species (methicillin-susceptible)	Oxacillin[d]	Vancomycin[c]	4–6
	+ Gentamicin[b]	+ Gentamicin[b]	5 days*
	+ Rifampicin if PVE[e]	+ Rifampicin if PVE[e]	4–6
Staphylococcus spp. (methicillin-resistant)	Vancomycin[c]		4–6
	+ Gentamicin[b]		5 days*
	+ Rifampicin if PVE[e]		4–6
Coxiella burnetii	Doxycycline[f]		18 months†
	+ Hydroxychloroquine[g]		18 months†

[a] 100–200 mg/kg/day iv in 4–6 doses. [b] 3 mg/kg/day iv or im in one dose, to be monitored as in Table 161.10. [c] 30 mg/kg/day iv in two doses, to be monitored as in Table 161.10. [d] 12 g/day iv in 4–6 doses. [e] 1200 mg/day iv or po in two doses. [f] 200 mg/24 hours po. [g] 200–600 mg/24 hours po.

*2 weeks if PVE. †24 months if PVE.

PVE, prosthetic valve endocarditis.

detailed in Table 161.13 [12]. Whereas American and European guidelines are consensual in situations of congestive heart failure or uncontrolled infection, they still remain controversial regarding embolic risk, with European guidelines being more surgically aggressive [12,16].

These guidelines are, however, largely based on observational studies or expert opinion. We recently published a systematic review showing a significant inverse correlation between rates of early surgery and in-hospital mortality [2]. Moreover, a recent randomized controlled trial, comparing early surgery and conventional treatment in patients with IE and large vegetations (>10 mm), showed significant reductions in death and embolic events in the early surgery group [3]. Therefore, management of complicated IE has clearly entered the era of early surgery.

Principles of surgery

The main objectives are eradication of all infected tissue for infection control and reconstruction of cardiac morphology.

The type of prosthesis (mechanical or bioprosthetic) used to replace the infected valve has no prognostic impact. However, whenever possible, valvular repair techniques offer better outcomes than prosthetic valve replacement, especially for the mitral valve, with a lower risk of relapse [18].

Valvular and perivalvular damages can be extreme in IE, and surgical management often requires particular surgical techniques

Table 161.12 Antibiotic regimens for fastidious organisms

Micro-organisms	Antibiotic therapy	Treatment duration/outcome
Brucella spp.	Doxycycline (200 mg/24 hours) po + Cotrimoxazole (960 mg/12 hours) po + Rifampicin (300–600 mg/24 hours) po	◆ 3 months *Success*: antibody titre < 1:60
Coxiella burnetii (agent of Q fever)	Doxycycline (200 mg/24 hours) + Hydroxychloroquine (200–600 mg/24 hours) po	18 months for NVE 24 months for PVE *Success at 1 year*: 4-times decrease of phase I IgG and IgA + disappearance of phase II IgM
Bartonella spp.	Ceftriaxone (2 g/24 hours) iv or Doxycycline (200 mg/24 hours) po + Gentamicin (3 mg/24 hours) or Netilmicin iv	6 weeks 3 weeks *Success*: >90%
Legionella spp.	Erythromycin (3 g/24 hours) iv for 2 weeks then po for 4 weeks + Rifampicin (300–1200 mg/24 hours) or Ciprofloxacin po	6 weeks 6 weeks (optimal treatment unknown)
Mycoplasma	Newer fluoroquinolones	> 6 months (optimal treatment unknown)
Tropheryma whipplei	Ceftriaxone iv 2 weeks, then Trimethoprim-sulphamethoxazole 1 year	Long-term treatment Optimal treatment unknown

Data from Habib G et al., 'Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC)', *European Heart Journal*, 2009, **30**(19), pp. 2369–413.

Table 161.13 Indications for surgical management of infective endocarditis

Indication	Timing[a]	Class	Level of evidence
Heart failure			
Aortic or mitral severe acute regurgitation, obstruction, or fistula with refractory pulmonary oedema or cardiogenic shock	Emergent	I	B
Aortic or mitral severe acute regurgitation or obstruction with persisting heart failure or echo signs of poor tolerance	Urgent	I	B
Aortic or mitral severe regurgitation or severe prosthetic dehiscence with no heart failure	Elective	IIa	B
Right heart failure due to severe tricuspid regurgitation with poor response to diuretics	Urgent/elective	IIa	C
Uncontrolled infection			
Locally: abscess, false aneurysm, fistula, enlarging vegetation	Urgent	I	B
Persisting fever and positive blood cultures >7–10 days	Urgent	I	B
Fungi or multiresistant organisms	Urgent/elective	I	B
PVE[b] due to staphylococci or Gram-negative bacteria	Urgent/elective	IIa	C
Prevention of embolism			
Aortic/mitral large vegetations (>10 mm) following embolic(s) event(s) despite appropriate antibiotic therapy	Urgent	I	B
Aortic/mitral large vegetations (>10 mm) and other predictors of complicated course	Urgent	I	C
Aortic/mitral isolated very large vegetations (>15 mm)[c]	Urgent	IIb	C
Persistent tricuspid valve vegetations >20 mm after recurrent pulmonary emboli	Urgent/elective	IIa	C

[a] Emergent surgery = within 24 hours. Urgent surgery, within a few days. Elective surgery, after at least 1 or 2 weeks of antibiotic therapy.

[b] PVE, prosthetic valve endocarditis.

[c] Surgery might be preferred if valve repair is feasible.

Adapted from Habib G et al., 'Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC)', *European Heart Journal*, 2009, **30**(19), pp. 2369–413, by permission of Oxford University Press © European Society of Cardiology, www.escardio.org/guidelines.

and skills. Thus, severe cases should be referred to specialized departments (1).

Therapeutic challenges

IE still carries high mortality rates, namely ≥20% at 1 year [2]. Most deaths relate to complications that constitute definite surgical indications [12], e.g. heart failure, embolic events, and uncontrolled infection [2]. Thus, optimization of surgical approach in such patients constitutes the clearest opportunity to reduce mortality rates [2,3]. However, several other conditions still remain matters of concern, especially septic shock, sudden death, and vancomycin-resistant staphylococcal IE.

Septic shock

Septic shock has been constantly associated with a poor prognosis for IE. We found 15 of 37 in-hospital deaths were secondary to multi-organ failure/septic shock [1]. Predictors include diabetes mellitus, *Staphylococcus aureus* infection, acute renal failure, supraventricular tachycardia, vegetation size >15 mm and signs of persistent infection [19]. Mechanisms leading from local infection to multi-organ failure and shock are not clearly understood. Indeed, the amount of blood-circulating bacteria has not been correlated with the risk of developing septic shock. Therefore, bacterial toxins and host inflammatory mediators are likely to play a major role in the occurrence of this disastrous situation. In this setting, we are currently evaluating the benefit of combining clindamycin and vancomycin.

Sudden death

We found sudden death (SD) occurred in 2.7% of patients at 6 months during or after conservative management, most dying during the first hospitalization. Identified risk factors were diabetes, signs of heart failure at admission, and a high comorbidity index [20]. These findings underline the importance of performing surgery without delay even if heart failure symptoms have responded well to medical treatment, considering the risk of sudden worsening. Indeed, in our series, 4 of 10 patients who experienced sudden death were awaiting surgery [20]. ICU monitoring is obviously mandatory for patients with severe symptoms or perivalvular damage.

Vancomycin-resistant staphylococci

Vancomycin-resistant staphylococci have recently emerged, with the occurrence of persistent bacteraemia despite appropriate antibiotic regimens. Strains with various degrees of vancomycin resistance have been isolated. New drugs have been proposed (e.g. teicoplanin, linezolid, daptomycin), but strong evidence of efficacy are still missing. We are currently evaluating the combination of cotrimoxazole with clindamycin in this challenging situation. The involvement of a dedicated infectious diseases team in such cases is mandatory.

Conclusion

IE remains one of the deadliest infectious diseases. Management must be undertaken in a standardized manner to shorten delays in diagnosis, risk stratification, and treatment. The rapid performance of surgery, when indicated, appears to be key in reducing mortality. This global approach is only possible in multidisciplinary reference centres that include an experienced surgical team.

References

1. Thuny F, Di Salvo G, Belliard O, et al. (2005). Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. *Circulation*, **112**, 69–75.
2. Thuny F, Grisoli D, Collart F, Habib G, and Raoult D. (2012). Management of infective endocarditis: challenges and perspectives. *Lancet*, **379**, 965–75.
3. Kang DH, Kim YJ, Kim SH, et al. (2012). Early surgery versus conventional treatment for infective endocarditis. *New England Journal of Medicine*, **366**, 2466–73.
4. Moreillon P, Wilson WR, Leclercq R, and Entenza JM. (2007). Single-dose oral amoxicillin or linezolid for prophylaxis of experimental endocarditis due to vancomycin-susceptible and vancomycin-resistant *Enterococcus faecalis*. *Antimicrobial Agents and Chemotherapy*, **51**, 1661–5.
5. Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, and Bahrani-Mougeot FK. (2008). Bacteremia associated with toothbrushing and dental extraction. *Circulation*, **117**, 3118–25.
6. Oliver R, Roberts GJ, Hooper L, and Worthington HV. (2008). Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. *Cochrane Database of Systematic Reviews* **4**, CD003813.
7. Duval X, Alla F, Hoen B, et al. (2006). Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. *Clinical Infectious Diseases*, **42**, e102–7.
8. Danchin N, Duval X, and Leport C. (2005). Prophylaxis of infective endocarditis: French recommendations 2002. *Heart*, **91**, 715–18.
9. Centre for Clinical Practice at NICE (UK) (2008). *Prophylaxis Against Infective Endocarditis: Antimicrobial Prophylaxis Against Infective Endocarditis in Adults and Children Undergoing Interventional Procedures.* London: NICE.
10. Gould FK, Elliott TS, Foweraker J, et al. (2006). Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy. *Journal of Antimicrobial Chemotherapy*, **57**, 1035–42.
11. Wilson W, Taubert KA, Gewitz M, et al. (2007). Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*, **116**, 1736–54.
12. Habib G, Hoen B, Tornos P, et al. (2009). Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *European Heart Journal*, **30**, 2369–413.
13. Martin MV, Longman LP, Forde MP, and Butterworth ML. (2007). Infective endocarditis and dentistry: the legal basis for an association. *British Dental Journal*, **203**, E1.
14. Botelho-Nevers E, Thuny F, Casalta JP, et al. (2009). Dramatic reduction in infective endocarditis-related mortality with a management-based approach. *Archives of Internal Medicine*, **169**, 1290–8.
15. Fernandez-Hidalgo N, Almirante B, Tornos P, et al. (2011). Prognosis of left-sided infective endocarditis in patients transferred to a tertiary-care hospital--prospective analysis of referral bias and influence of inadequate antimicrobial treatment. *Clinical Microbiology and Infection*, **17**, 769–75.
16. Baddour LM, Wilson WR, Bayer AS, et al. (2005). Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical

Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association. *Circulation*, **111**, e394–434.
17. Thuny F, Giorgi R, Habachi R, et al. (2012). Excess mortality and morbidity in patients surviving infective endocarditis. *American Heart Journal*, **164**, 94–101.
18. Feringa HH, Shaw LJ, Poldermans D, et al. (2007). Mitral valve repair and replacement in endocarditis: a systematic review of literature. *Annals of Thoracic Surgery*, **83**, 564–70.
19. Olmos C, Vilacosta I, Fernandez C, et al. (2013). Contemporary epidemiology and prognosis of septic shock in infective endocarditis. *European Heart Journal*, **34**, 1999–2006.
20. Thuny F, Hubert S, Tribouilloy C, et al. (2013). Sudden death in patients with infective endocarditis: findings from a large cohort study. *International Journal of Cardiology*, **162**, 129–32.

PART 5.11

Severe hypertension

CHAPTER 162

Pathophysiology and causes of severe hypertension

Jerrold H. Levy and David Faraoni

Key points

- Endothelial and vascular circulatory interactions are critical parts of normal vascular control of blood pressure.
- The pathophysiology of hypertension is complex and depends on patient-related factors, genetics, and multiple factors that interact at cellular and organ levels.
- Of these factors, vascular endothelial and circulatory dysfunction with loss of endothelial-derived relaxing factors, such as nitric oxide and prostacyclin, are critical lesions.
- In certain patients, other factors may contribute to hypertension, including the renin-angiotensin system, mediators, but also hyperdynamic hypertension in young critically-ill patients.
- Despite the complex pathophysiological responses, therapy should be multimodal and often requires targeting of several different receptors or mediators to control hypertension that may often be resistant to therapy in critically-ill patients.

Introduction

Hypertension affects multiple groups of patients characterized by different clinical presentations and a spectrum of potential causes. The pathophysiology is complex and multifactorial. Although most patients are labelled 'essential hypertension', multiple mechanisms are involved in blood pressure regulation. Factors that influence blood pressure homeostasis include endothelial function, the renin-angiotensin system, and the sympathetic nervous system. In elderly patients, hypertension is common as the vascular system and arterial stiffness also contribute. Other important factors include inflammatory processes as part of systemic diseases, including atherosclerosis that may contribute to renal and vascular injury. Hypertension is also associated with metabolic disturbances including dyslipidaemia that manifests in obese patients who also have insulin resistance. These different pathways all represent potential targets for treatment, but also increase the challenge of multimodal pathophysiology.

The normal vascular endothelium regulates vascular tone and structure, and is critical to maintain vascular patency by its anticoagulant properties. Vascular tone is maintained by the release of both vasodilator and constrictor mediators. Vasodilation is a critical aspect of endothelial function; an essential endothelial-derived relaxing factor is nitric oxide [1]. Other endothelium-derived or modulated vasodilators include prostacyclin and bradykinin. Endothelial and inflammatory dysfunction may also contribute to vascular dysfunction, and act synergistically, increasing atherosclerosis and further endothelial dysfunction. Oxidative stress, defined as a substantial increase in the level of reactive oxygen species (ROS), also contributes to hypertensive pathophysiology and cellular injury. Free radicals may also reduce nitric oxide availability. Because of the multiple factors involved, this review discusses different mechanisms as part of the multiple pathophysiological causes of hypertension, especially in the critically ill.

Understanding the risk

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) classified blood pressure as normal, prehypertension, and stages 1 and 2 hypertension [2]. Prehypertension (formally known as 'high normal' BP) is also associated with increased cardiovascular morbidity and mortality, as well as subclinical atherosclerosis and target-organ damage. The recently published executive summary of the JNC-8 guidelines [3] did not alter these definitions, but defined thresholds for pharmacological treatment and updated some treatment goals for specific populations based on new evidence review. Moreover, some patients will be admitted to intensive care units (ICUs) with hypertensive crises that require a specific understanding of the underlying mechanisms to guide therapeutic approaches.

Blood pressure determinants as causes of hypertension

Blood pressure is the product of cardiac output and systemic vascular resistance. Hypertensive patients may have a normal cardiac output, but increased peripheral vascular resistance due to multiple aetiologies. Systemic vascular resistance is determined by small arterioles that play a critical role in vascular tone and its regulation, and may be sensitive to multiple mediators that are part of normal physiological and pathophysiological responses. The role of L-type calcium channels in vascular smooth muscle cells is important for regulation of vascular tone by modifying intracellular calcium concentrations. Ongoing sympathetic activation may produce prolonged smooth muscle constriction inducing structural changes with thickening of the arteriolar vessel walls. This is possibly mediated by angiotensin leading to an irreversible rise in peripheral

resistance. Acutely, however, in the ICU setting, patients suffering major injury may be hyperdynamic with increased cardiac output due to sympathetic hyperactivity. The increased sympathetic tone may also increase systemic arteriolar resistance further contributing to hypertension. The renin-angiotensin system may contribute in part to this sympathetic hyperactivity.

Renin-angiotensin system

The renin-angiotensin system is an important mechanism for regulating blood pressure. Renin is stored in the juxtaglomerular apparatus of the kidney. It is secreted to convert angiotensinogen to angiotensin I following decreased glomerular perfusion, or in response to sympathetic nervous system stimulation. In turn, angiotensin I is rapidly converted to angiotensin II by a lung endothelial kininase (angiotensin-converting enzyme (ACE)). Angiotensin II is a potent vasoconstrictor that contributes to hypertension, but also stimulates aldosterone release from the zona glomerulosa of the adrenal gland. Aldosterone is an important autocoid that causes sodium and water retention, further increasing hypertension. Of note, the renin-angiotensin system is a critical target for multiple pharmacological agents used to treat hypertension and heart failure, including ACE inhibitors, angiotensin II, and aldosterone antagonists. By inhibiting kininase, ACE inhibitors also increase generation of bradykinin from high molecular weight kininogen, which is also responsible for secondary angioedema and cough. Despite the critical role of the renin-angiotensin system in blood pressure regulation, many hypertensive patients have low levels of renin and angiotensin II.

Autonomic nervous system

Sympathetic activation leads to release of norepinephrine, and stimulates both α_1 and β_1 receptors. Stimulation of α_1 receptors activates membrane phospholipase-C which, in turn hydrolyses phosphatidylinositol-4,5-diphosphate and leads to the generation of two second messengers—diacylglycerol and inositol triphosphate. Both these second messengers increase cytosolic Ca^{2+} by different mechanisms, including facilitating release of calcium from the sarcoplasmic reticulum, and potentially increasing calcium sensitivity of the contractile proteins in vascular smooth muscle. As a consequence, stimulation of the sympathetic nervous system can cause arteriolar constriction. Activation of β_1 receptors increases heart rate and contractility, thereby increasing cardiac output. Activation of the autonomic nervous system is thus important in maintaining normal blood pressure. However, following stress and other mechanisms of activation, it may also produce hypertension.

Patients who increase their cardiac output following exercise have a normal compensatory drop in vascular resistance due to endothelial activation associated with increased flow, especially in patients with normal vascular endothelial function. Endothelial activation causes release of NO and prostaglandins that stimulate vascular smooth muscles to relax, and hence cause vasodilation. Elderly patients with vascular and circulatory dysfunction may not drop their blood pressure in response to exercise. Overall, blood pressure changes and the potential to develop hypertension, especially in a critically-ill patient, is determined by complex interactions among many of the factors described including the autonomic nervous system, renin-angiotensin system, circulating intravascular volume, endothelial function, and multiple mediators, which may or may not be released.

Endothelial function

The endothelium is a monolayer of cells that lines the vasculature, and is strategically placed to oversee and regulate critical homeostatic and haemostatic functions. The endothelium directly interfaces with blood flow and responds by releasing or modifying a multitude of factors that regulate vasomotor function, haemostasis, and inflammatory processes. Following increased flow, the related shear stress releases vasodilatory mediators (nitric oxide (NO) and prostacyclin) producing both vascular relaxation and vasodilation, but also inhibits platelet and inflammatory cell activation. For normal endothelial function, critical processes include the important antiproliferative and antithrombotic molecules, NO, and prostacyclin [4]. Nitric oxide is a vasodilator agent that inhibits platelet aggregation, monocyte adhesion to endothelial cells, and abnormal smooth muscle cell proliferation. Thus, NO has a critical role as an important 'anti-atherogenic' moiety [4].

Endothelial dysfunction is often defined as the inability of the endothelium to release NO (and, by implication, to protect against atherogenesis). The critical role of endothelium-dependent and also smooth muscle-dependent vasomotor properties of the vasculature in hypertension highlights another important concept in cardiovascular pathophysiology. Vascular and circulatory functions may play a very important role in determining cardiovascular risk [4]. Vessel function (particularly the propensity for vessels to constrict, rather than dilate during conditions of physical and/or mental stress) appears to confer important risk in the pathophysiology of acute vascular events [5]. Consistent with this suggested importance of vascular function in risk determination, many studies have now been published correlating endothelial function measurements with prospectively determined risk of cardiovascular events during follow-up [6].

Most studies examining in vivo endothelial function have measured endothelium-dependent dilatation, in large part because techniques have been developed to assess this particular aspect of endothelial physiology. However, the endothelium has a multiplicity of functions beyond regulation of vessel tone, as previously noted. Thus, articles reporting 'endothelial function' and 'dysfunction' on the basis of the measurement of endothelium-dependent dilatation give insights into only one aspect of endothelial physiology, albeit an important one. To date, little work has evaluated whether the various endothelial functions correlate with each other in disease states (for example, how impaired endothelium-dependent dilatation, regulation of endothelial cell adhesion molecule expression, and release of key haemostatic regulatory molecules relate to one another).

Vasoactive substances

Many vasoactive mediators alter both intravascular volume regulation and vascular tone as part of normal blood pressure maintenance, but their role in essential hypertension is not well known. Rare events such as a pheochromocytoma, a catecholamine-secreting tumour derived from chromaffin cells, causes excessive catecholamine secretion, and may generate life-threatening hypertensive crises and/or cardiac arrhythmias.

The endothelium also produces vasoconstrictor substances such as endothelin, which is perhaps the most potent endogenous

vasoconstrictor, and angiotensin II [1]. Angiotensin II is a potent vasoconstrictor, but also stimulates endothelin production. Endothelin and angiotensin II promote proliferation of smooth muscle cells and thereby contribute to the formation of plaque. Activated macrophages and vascular smooth muscle cells, characteristic cellular components of atherosclerotic plaque, produce large amounts of endothelin that also activates local renin-angiotensin systems [1].

Atrial natriuretic peptide (ANP) is a hormone secreted from the heart atria in response to increased blood volume. ANP increases sodium and water excretion from the kidney as a sort of natural diuretic. A defect in this system may cause fluid retention and hypertension. Sodium transport across vascular smooth muscle cell walls is also thought to influence blood pressure via its interrelation with calcium transport.

Diabetes and hypertension

Several risk factors are associated with hypertension, including obesity, glucose intolerance, diabetes mellitus, and hyperlipidaemia as part of a final common pathway to cause raised blood pressure and vascular damage. Some non-obese hypertensive patients can display insulin resistance. Vascular endothelial and circulatory dysfunctions are major mechanisms involved in the association between hypertension and diabetes, while the two conditions are linked with cardiovascular disease, stroke, and progression of renal disease. Of note, JNC 7 and 8 recommendations are consistent with guidelines from the American Diabetes Association that recommends rigorous blood pressure control to reduce the progression of diabetic nephropathy to end-stage renal disease.

Genetic factors

Recent findings suggest that the onset of prehypertension may be, at least in part, genetically determined [7]. Genetic abnormalities associated with hypertension include rare syndromes, such as mineralocorticoid-remediable aldosteronism, mineralocorticoid excess, and pseudohypoaldosteronism. Other genetic mutations may contribute to hypertension in the general population. Genetic association studies have identified polymorphisms in specific genes, such as those encoding for angiotensinogen and adrenergic receptors. Again, these are rare events in the general population and beyond the scope of this review.

Pregnancy and hypertension

Approximately 10% of all pregnancies are complicated by hypertension, with eclampsia and pre-eclampsia accounting for approximately half. The clinical manifestations of preeclampsia are hypertension and proteinuria with or without co-existing systemic abnormalities. Eclampsia is a life-threatening condition, similar to hypertensive emergencies. Overall, pre-eclampsia is characterized by endothelial dysfunction, and may be a contributor to future cardiovascular diseases. Underlying mechanisms include endothelial and circulatory dysfunction that occur in a complex milieu of other influencing factors, such as maternal immunological intolerance, placental issues, genetics, environmental factors, and vascular and inflammatory changes similar those that produce atherosclerotic vascular disease.

Hypercoagulability

Hypertensive patients have multiple vascular abnormalities that include endothelial dysfunction, atheromatous injury and/or plaque formation, and vessel wall abnormalities that may also occur as part of the ageing process. Endothelial function is critical for inhibiting thrombosis, promoting anticoagulation, and fibrinolysis. In hypertensive patients, especially in hypertensive emergencies, endothelial dysfunction further contributes to arterial wall injury. The endothelium is critical in maintaining vascular patency by providing a multitude of anticoagulant, antiplatelet, and fibrinolytic properties. Endothelium-derived relaxing factors including NO and prostacyclin also inhibit platelet aggregation. The endothelium also catalyses the formation of bradykinin that further stimulates release of NO, prostacyclin, and tissue plasminogen activator (t-PA), modulating a critical role in fibrinolysis [1].

Hypertension and hypertensive crisis may further damage the endothelium and increase endothelial permeability, platelet aggregation, leukocyte adhesion, and cytokine generation [1]. Thrombomodulin, another important vascular endothelial receptor, binds to thrombin to scavenge this important procoagulant mediator. As part of this thrombin–thrombomodulin complex activation, the endothelium is further activated releasing NO, prostacyclin, tPA and activated protein C that, along with its cofactor protein S, degrades FVa and FVIIIa, blocking amplification of the coagulation system and thus limiting further thrombin formation [1]. In summary, hypertension promotes hypercoagulability by causing further injury to vascular endothelial function.

Identifiable causes of hypertension

Despite the complex pathophysiology of hypertension, some identifiable aetiologies or associated syndromes commonly present in an ICU setting (Box 162.1). Some are reversible, such as fluid overload associated with renal failure, while others may require targeted therapy of the underlying disease. Regardless of cause, management of blood pressure, especially in patients who are symptomatic (as in hypertensive crises) is critical. Other important causes of hypertensive crises are listed in Box 162.2.

Box 162.1 Identifiable causes of hypertension

- Chronic kidney disease.
- Coarctation of the aorta.
- Cushing's syndrome.
- Drug-induced.
- Obstructive uropathy.
- Pheochromocytoma.
- Primary aldosteronism/mineralocorticoid excess.
- Renovascular hypertension.
- Sleep apnoea.
- Thyroid or parathyroid disease.

Box 162.2 Causes of hypertensive emergencies

- Acute renal failure/injury.
- Antihypertensive withdrawal.
- Autonomic hyperreactivity.
- Cushing's syndrome.
- Drug interactions with monoamine-oxidase inhibitors (tyramine), amphetamines.
- **Drugs**: cocaine, sympathomimetics.
- Eclampsia.
- Guillain-Barré syndrome.
- Head injury, intracranial hypertension.
- Pheochromocytoma.
- Pregnancy.
- Renal artery stenosis.
- Renovascular disease.
- Vasculitis.

Resistant hypertension

In an ICU setting, despite therapy, resistant hypertension can occur even in patients who do not present with hypertensive crises. Resistant hypertension may reflect the severity of vascular and endothelial dysfunction, and may be analogous to patients with pulmonary hypertension who progress to end-stage disease with increased cardiovascular morbidity and mortality. Multiple factors may contribute to resistant hypertension, including increased sympathetic activity, insulin resistance, endothelial dysfunction, chemoreceptors, and baroreceptor dysregulation [8]. Managing patients with resistant hypertension, especially with hypertensive crises, may require targeting of multiple receptors including L-type calcium channels with dihydropyridine calcium channel blockers, β and α-adrenergic receptors with dual sympathetic blocking agents such as labetalol, and central-acting sympatholytic agents like clonidine, an α_2 adrenergic agonist that inhibits synaptic release of neurotransmitters.

References

1. Davignon J and Ganz P. (2004). Role of endothelial dysfunction in atherosclerosis. *Circulation*, **109**(23 Suppl. 1), III27–32.
2. Chobanian AV, Bakris GL, Black HR, et al. (2003). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Journal of the American Medical Association*, **289**, 2560–72.
3. James PA, Oparil S, Carter BL, et al. (2014). 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *Journal of the American Medical Association*, **311**, 507–20.
4. Celermajer DS. (2008). Reliable endothelial function testing: at our fingertips? *Circulation*, **117**, 2428–30.
5. Lerman A and Zeiher AM. (2005). Endothelial function: cardiac events. *Circulation*, **111**, 363–8.
6. Deanfield JE, Halcox JP, and Rabelink TJ. (2007). Endothelial function and dysfunction: testing and clinical relevance. *Circulation*, **115**, 1285–95.
7. Davis JT, Rao F, Naqshbandi D, et al. (2012). Autonomic and hemodynamic origins of pre-hypertension: central role of heredity. *Journal of the American College of Cardiology*, **59**, 2206–16.
8. Isso JL, Sica SA, and Black HR (eds) (2008). *Hypertension Primer*, American Heart Series, 4 edn. Philadelphia, PA: Lippincott Williams & Williams.

CHAPTER 163

Management of severe hypertension in the ICU

Jerrold H. Levy

Key points

- Hypertensive emergencies are characterized by acute end-organ dysfunction and require immediate intervention to reduce the blood pressure (BP) and include acute cardiopulmonary/neurological dysfunction.
- The degree of BP reduction depends on the clinical situation, as acute reduction of BP may also cause acute organ dysfunction.
- Acute changes in BP require acute interventions, while chronic hypertension should usually be treated with oral therapy.
- Intravenous dihydropyridine agents provide reliable and predictable acute BP management, and have increasingly replaced nitroprusside as a parenteral agent for hypertensive emergencies.
- Patients who are hypertensive and tachycardic may benefit from agents such as labetalol that have beta- and alpha-adrenergic blocking effects.

Clinical evaluation

The clinical evaluation of a hypertensive patient requires determining whether acute organ dysfunction is present in order to confirm a hypertensive emergency. As in any emergency, immediate therapy is necessary, while additional information including history, physical examination, and laboratory information can be obtained after therapy is initiated. According to the most recent guidelines of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), patients with a hypertensive emergency should be admitted to an ICU for continuous monitoring of BP and treatment with an appropriate agent [1].

Goal of therapy in hypertensive emergencies

The initial goal of therapy is to reduce mean arterial BP by no more than 15% ((diastolic 110 mmHg) within minutes to 1 hour). Complications may result from aggressive reduction, especially with overshoot hypotension due to dysfunctional cerebral autoregulation. The use of rapid-acting and titratable agents is critical. Once the BP is stable, it should then be reduced to 160/100–110 mmHg within the next 2–6 hours. Significant drops in BP should be avoided to prevent cerebral, renal, and/or coronary ischaemia. Furthermore, special considerations should be taken when treating specific causes of acute hypertension, such as aortic dissection, acute cerebral haemorrhage, sympathetic crisis, and post-operative hypertension. For example, in aortic dissection, rapid titration and BP control are essential in order to stabilize patients for surgery [2,3].

Hypertensive urgencies

Hypertensive urgencies are common presentations, and may present with exceedingly high blood pressures, but without symptomatic manifestations. Therapy often involves (re-)starting oral medications. When treating hypertension in this setting, avoiding overshoot is critical, with the goal of reducing, but not necessarily normalizing BP.

Uncomplicated severe hypertension

Patients often present with asymptomatic hypertension that may be related to acute conditions, such as pain due to injury (e.g. bone fracture), anxiety, withdrawal symptoms, or, in young patients, hyperdynamic physiological responses following injury. This is commonplace in the ICU; patients following major surgical procedures may be hypertensive during weaning from mechanical ventilation, or in the initial post-operative period. In these circumstances, it is critical to treat any pain and/or underlying disorder. Again, in these circumstances, avoiding overshoot hypotension with multimodal therapy is important.

Pharmacological principles of therapy

Pharmacological therapy is used to treat hypertensive crises, urgencies, and chronic hypertension and includes:

- α1-adrenergic receptor blockade, ganglionic blockade and calcium channel blockade.
- Stimulation of central α2-adrenergic receptors, dopamine1-adrenergic receptors, or vascular guanylate cyclase and adenylate cyclase.
- Inhibition of phosphodiesterase enzymes.
- Inhibition of angiotensin-converting enzymes
- β-blockade [4].

Decreasing sympathetic tone decreases blood pressure by decreasing myocardial contractility and heart rate, thus altering cardiac output. It is an important therapeutic approach in the hyperdynamic

patient with hypertension and tachycardia. As a spectrum of different drugs can produce vasodilation and/or treat hypertension, the various potential pharmacological approaches to vasodilation will be described in the following section (see Table 163.1).

Mechanisms of vasodilation

Vascular tone is regulated by the flux of calcium in and out of vascular smooth muscle. Hence, calcium channel blockade produces vasodilation by decreasing calcium entry. Increasing cyclic nucleotides -adenosine-3',5'-monophosphate (cyclic AMP) or guanine-3',5'-monophosphate (cyclic GMP)—in vascular smooth muscle facilitates calcium uptake by intracellular storage sites, thus decreasing the calcium available for contraction. The net effect of increasing calcium uptake is to produce vascular smooth muscle relaxation and, hence, vasodilation. Prostaglandins stimulate vascular adenylate cyclase to increase cyclic AMP and produce pulmonary and systemic vasodilation. Phosphodiesterase inhibitors block the breakdown of cyclic nucleotides and can also produce vasodilation.

Nitrovasodilators: glyceryl trinitrate and nitroprusside

Nitrates and sodium nitroprusside generate nitric oxide (NO) which, in turn, activates guanylyl cyclase to generate cyclic GMP that ultimately produces vascular relaxation [5]. Any nitrovasodilator must be converted to NO, where nitrogen is in a +2 oxidation state. For nitroprusside, this is easily accomplished as the nitrogen is in a +3 oxidation state, with the NO molecule bound to the charged iron molecule in an unstable manner. Thus, nitroprusside readily donates its NO moiety. However, for glyceryl trinitrate, nitrogen exists in a +5 oxidation state. This must undergo several metabolic transformations before conversion to an active molecule. The reason that glyceryl trinitrate does not produce coronary steal compared with nitroprusside is that the small intracoronary resistance vessels lack the metabolic transformation pathway required to convert glyceryl trinitrate into NO. Importantly, nitroprusside and glyceryl trinitrate both produce venodilation and this contributes significantly to the labile haemodynamic state, especially in hypertensive patients. Tremendous fluctuations in blood pressure may be seen when sodium nitroprusside is started for the treatment of hypertension in the immediate post-operative period. In the hypertensive patient, intravenous (iv) volume administration is often employed to allow nitroprusside to be safely infused due to the relative intravascular hypovolaemia. Nitroprusside is 44% cyanide by weight so cyanide toxicity can occur, producing coronary vasodilation and coronary steal [5].

Intravenous dihydropyridine calcium channel blockers

These agents are increasingly used in critically-ill patients for their specific arterial vasodilating effect. They differ from antiarrhythmic agents such as diltiazem that will also produce AV nodal blockade.

Table 163.1 Currently available IV antihypertensive agents

Agent	Onset/duration	Elimination half-life	Adverse events	Cautions/concerns
Enalaprilat	<15 min/12–24 hours	11 hours	Precipitous fall in BP in high-renin states, headache, cough, renal failure, hyperkalaemia, angioedema	Avoid in acute MI, long duration of action
Esmolol	1–2 min/10–30 min	2–9 min	Heart block, hypotension, nausea, bronchospasm, overt heart failure, cardiogenic shock	Reduces cardiac output, which may impair organ perfusion
Fenoldopam	5–15 min/ 30 min–4 hours	5 min	Tachycardia, headache, nausea, dizziness, flushing, hypotension, increased intra-ocular pressure	Caution with glaucoma
Hydralazine	10–20 min/1–4 hours	1 hour	Marked hypotension, tachycardia, flushing	Avoid in aortic dissection, MI, severe renal disease. Prolonged and unpredictable effects. Difficult to titrate
Labetalol	<5 min/3–6 hours	5.5 hours	Bradycardia (heart block), overt heart failure, cardiogenic shock, oedema, nausea, vomiting	Avoid in acute heart failure. Severe bradycardia. Heart block, asthma
Nicardipine	5–10 min/ 15 min–4 h	44.8 min	Tachycardia, headache, nausea, flushing, thrombophlebitis, hypotension, vomiting	Avoid in acute heart failure; caution with coronary ischemia; long duration of action
Glyceryl trinitrate	2–5 min/ 5–10 min	1-4 min	Flushing, headache, vomiting, hypotension, methaemoglobinaemia, decreased arterial resistance, reflex tachycardia	Reduction in preload and cardiac output undesirable in patients with compromised renal and cerebral perfusion
Sodium nitroprusside	Immediate/2–3 min	2–3 min	Nausea, muscle twitching, sweating, thiocyanate and cyanide intoxication, hypotension	Increases intracranial pressure. May reduce coronary perfusion pressure (coronary 'steal'). Cyanide toxicity
Clevidipine	2–4 min 5–15 min	1 min	Headache, nausea, vomiting	Lipid suspension, no preservative. Avoid with soy allergy, defective lipid metabolism

BP, blood pressure; MI, myocardial infarction.

Dihydropyridine calcium channel blockers (DHP CCBs) available for parenteral administration in the USA and some other countries include nicardipine and clevidipine [6]. DHP CCBs produce vasodilation by high affinity binding to L-type calcium channels, decreasing calcium entry into vascular smooth muscle. DHP CCBs are arterial-specific agents that primarily affect resistance arteries, resulting in a more or less generalized vasodilatation in the renal, cerebral, and coronary vascular beds. They have minimal direct negative effects on cardiac contractility or conduction, and usually do not result in reflex tachycardia during prolonged antihypertensive treatment. Calcium channel blockers (CCBs) have minimal effects on venous smooth muscle, probably due to the relatively low density of L-type calcium channels present in the vascular capacitance bed, and do not affect cardiac filling pressure and preload. As a result, cardiac output often increases when a CCB is administered to treat hypertension.

DHP CCBs are direct arterial vasodilators. Nifedipine was the first such agent, followed by second generation water-soluble agents that are also available in iv form including isradipine and nicardipine, and the third generation, ultrashort-acting agent clevidipine. Nicardipine produces arterial vasodilation without any effects on the vascular capacitance bed, no effects on atrioventricular nodal conduction, and no depression of ventricular function (i.e. contractility). DHP CCBs have significant vasodilatory properties and preferentially dilate coronary, cerebral, and skeletal muscle vasculature, without impairment of atrioventricular conduction or myocardial contractility.

Dopaminergic receptor agonists (fenoldopam)

Fenoldopam is a selective agonist to peripheral dopaminergic DA_1-receptors, producing vasodilatation, increasing renal perfusion, and enhancing natriuresis. Fenoldopam has a short duration of action with an elimination half-life of <10 minutes. In doses of 0.1–1.5 mcg/kg/min, fenoldopam reduced both systolic and diastolic BP, but also increased heart rate. There were no significant differences in plasma levels of adrenaline, noradrenaline, or dopamine in the fenoldopam patients. Because of a unique mechanism of action, fenoldopam may have advantages in selected subsets of patients.

Pharmacokinetic principles of vasoactive therapy in the ICU

Pharmacokinetic considerations are important for dosing vasoactive drugs in the ICU. Drugs often reach a therapeutic level after approximately three half-lives from initiating an infusion. For short-acting drugs like nitroprusside or glyceryl trinitrate whose half-lives are only several minutes, stable plasma concentrations are achieved soon (<10 minutes) after beginning a constant-rate infusion. Based on this short half-life, the drug can be efficiently titrated by just changing the infusion rate. Dosing strategies for other agents may be less straightforward. Many drugs behave pharmacokinetically as if the body consists of two or three compartments. With iv use, the drug is administered into a central compartment, from which it is either eliminated by metabolic processes, or distributed into one or two peripheral compartments. The central compartment can be identified with blood volume and organs that rapidly equilibrate with the circulation. In general, the effect of the drug is proportional to its concentration in the central compartment. The peripheral compartments can be identified with less rapidly equilibrating tissues. In most cases, the elimination process is slow in comparison to the rate at which the drug distributes from the central into the peripheral compartments. Thus, to establish effective plasma levels of the drug, one must initially give enough to compensate for the loss of drug from the central compartment by both distribution and elimination. As the peripheral compartments 'fill up' with drug, the rate of drug administration can be decreased to the point of simply matching the rate at which the drug is eliminated by metabolism. Practically, this usually means that the drug is administered by continuous infusion with the rate decreasing in stepwise fashion. However, in some circumstances, where a rapid therapeutic effect is needed, the drug should be administered as an initial loading bolus dose with concomitant institution of a continuous steady-state infusion. Esmolol and nicardipine are example of these types of drugs.

Nicardipine, a dihydropyridine derivative calcium channel blocker, has several important pharmacodynamic properties, including its arteriolar selectivity and lack of effects on the vascular capacitance bed. However, its pharmacokinetic profile, based on preliminary data, indicates that effective administration will require variable rate infusions, decreasing in stepwise fashion [7]. In a comparison with sodium nitroprusside in the treatment of perioperative hypertension, the effectiveness of dosing nicardipine in this manner has been demonstrated, with control of hypertension achieved in 14 minutes. If even more rapid control is essential, a dosing strategy consisting of a loading bolus or rapid infusion dose with constant rate infusion may be more efficient [8].

Transitioning/weaning from intravenous to oral therapy for hypertension

Patients should be rapidly transitioned to oral from iv therapy as soon as possible due to cost and ability to transfer to a general ward. This can often occur by restarting preoperative antihypertensive agents, or starting new oral agents. Patients receiving iv DHP CCBs can be readily transitioned to oral agents, such as amlodipine, nicardipine, or nifedipine. Furthermore, if patients were receiving higher doses of DHP CCBs to control BP, then iv β-blockers (e.g. metoprolol or labetalol) are often administered if the patient is tachycardic in order to control heart rate. In post-operative hypertension, patients often have transient and self-limiting hypertension that only may require therapy until extubation. Steps should be taken to identify barriers to transitioning patients to oral therapy. For patients requiring extended anti-hypertensive therapy beyond the immediate post-operative period, β-blocking agents are often ineffective monotherapy. Patients who require continuous infusions of iv DHP CCBs will likely require combination oral therapy utilizing medications with different mechanisms of action. Finally, patients with renal failure and fluid overload, may sometimes have their hypertensive emergency completely treated by appropriate dialysis and fluid removal.

JNC-8 guidelines and what's new

The new guidelines [1] have modified goals for chronic BP management; in hypertensive persons ≥60 years the BP should be targeted <150/90 mmHg, while in those aged 30–59 years a diastolic goal <90 mmHg should be sought. The Panel felt there was

insufficient evidence in hypertensive persons <60 years to recommend a systolic goal, or a diastolic goal in those <30 years so, based on expert opinion, they recommended a BP target <140/90 mmHg for these groups. The same thresholds and goals as for hypertensive patients <60 years were also recommended for diabetics and those with non-diabetic chronic kidney disease. They suggested drug treatment should be initiated with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, CCB, or thiazide diuretic in non-black hypertensives, including diabetics. In black hypertensives (including diabetics), a calcium channel blocker or thiazide-type diuretic was recommended as initial therapy. Importantly, the Panel stressed that their recommendations are not a substitute for clinical judgment. Decisions about care should be carefully considered, and take into account both clinical characteristics and circumstances of the individual patient.

References

1. James PA, Oparil S, Carter BL, et al. (2014). 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *Journal of the American Medical Association*, **311**, 507–20.
2. Marik PE and Varon J. (2007). Hypertensive crises: challenges and management. *Chest*, **131**, 1949–62.
3. Varon J. (2007). Diagnosis and management of labile blood pressure during acute cerebrovascular accidents and other hypertensive crises. *American Journal of Emergency Medicine*, **25**, 949–59.
4. Levy JH. (1993). The ideal agent for perioperative hypertension and potential cytoprotective effects. *Acta Anaesthesiologica Scandinavica*, 99(Suppl.), 20–5.
5. Harrison DG and Bates JN. (1993). The nitrovasodilators. New ideas about old drugs. *Circulation*, **87**, 1461–7.
6. Pollack CV, Varon J, Garrison NA, Ebrahimi R, Dunbar L, and Peacock WF, 4th. (2009). Clevidipine, an intravenous dihydropyridine calcium channel blocker, is safe and effective for the treatment of patients with acute severe hypertension. *Annals of Emergency Medicine*, **53**, 329–38.
7. Peacock WF, 4th, Hilleman DE, Levy PD, Rhoney DH, and Varon J. (2012). A systematic review of nicardipine vs labetalol for the management of hypertensive crises. *American Journal of Emergency Medicine*, **30**, 981–93.
8. Halpern NA, Goldberg M, Neely C, et al. (1992). Postoperative hypertension: a multicenter, prospective, randomized comparison between intravenous nicardipine and sodium nitroprusside. *Critical Care Medicine*, **20**, 1637–43.

PART 5.12

Severe capillary leak

CHAPTER 164

Pathophysiology of severe capillary leak

Anatole Harrois and Jacques Duranteau

Key points

- Severe capillary leak plays an important role in the pathogenesis of sepsis, acute lung injury, and shock syndromes.
- Tissue oedema can impair tissue oxygenation and likely contributes to organ dysfunction.
- Microvascular permeability is mainly regulated by four components—the glycocalyx, endothelial cell–cell junctions (adherens junctions and tight junctions), transcellular transport across the endothelium (caveolae and vesiculo-vacuolar organelles) and endothelial–associated cells.
- Inflammatory mediators such as cytokines, endotoxin, microbial compounds, angiogenic (e.g. vascular endothelial growth factor) and pro-coagulant (e.g. thrombin) factors increase microvascular permeability by weakening endothelial junctions.
- An understanding of the pathogenesis of microvascular permeability may lead to new therapies targeting the microvascular barrier in sepsis and acute lung injury.

Introduction

Severe capillary leak is an important factor in the pathogenesis of many inflammatory syndromes, including sepsis and acute respiratory distress syndrome (ARDS). Microvascular leak is caused by an increase in endothelial permeability. The microvascular barrier consists of an endothelial cell monolayer comprised of endothelial cells, associated endothelial cell–cell junctions, and extracellular components, and the glycocalyx. The microvascular barrier functions as an interface between circulating blood and surrounding tissues by controlling the exchange of fluid, metabolic compounds and cells from the circulation into the tissues. Inflammatory mediators such as cytokines, endotoxin, microbial compounds, reactive oxygen species, angiogenic (e.g. vascular endothelial growth factor (VEGF)) or pro-coagulant (e.g. thrombin) factors increase vascular permeability by destabilizing endothelial junctions. This then results in tissue oedema with potential harmful effects on tissue oxygenation, probably contributing to organ dysfunction. Tissue oedema could impair tissue oxygenation by increasing the distance required for the diffusion of oxygen to the cells and by decreasing microvascular perfusion due to increases in interstitial pressure.

Microvascular permeability

Microvascular permeability differs between organs. Microvascular barrier can be physiologically leaky with a high permeability for macromolecules, as in endocrine glands, or for fluid, as in the kidney and liver. In contrast, the microvascular barrier can be highly selective with a low permeability and high transendothelial resistance as observed in the blood brain barrier [1].

Microvascular permeability is mainly regulated by four components (Fig. 164.1):

- The glycocalyx.
- Endothelial cell–cell junctions (adherens junctions and tight junctions), i.e. paracellular permeability.
- Transcellular transport across the endothelium (caveolae and vesiculo-vacuolar organelles, VVOs), i.e. transcellular permeability.
- Endothelial–associated cells associated with capillaries in the 'vascular unit' e.g. pericytes, alveolar epithelial cells, smooth muscle cells and macrophages [2–4].

Appropriate regulation of these components maintains a low and selective permeability to fluid and solutes under normal physiological conditions. The strength of the endothelial barrier results from a balance between stabilizing and destabilizing signals, allowing the vascular system to adapt to physiological needs.

The glycocalyx

The glycocalyx is a thin gel-like layer of glycoproteins and polysaccharides that covers the luminal surface of the microvascular endothelium with an estimated thickness ranging from 150–500 nm [5,6]. The glycocalyx serves as a vascular permeability barrier, a mechanotransducer of flow-induced shear stress to endothelial cells, and a regulator of leukocyte-endothelial interactions.

The major components of the glycocalyx are proteoglycans (transmembrane syndecans, membrane-bound glypicans, and matrix-localized perlecans) and glycosaminoglycans (GAGs). Glycosaminoglycans are linked to endothelial membrane-bound proteoglycans, which link the glycocalyx to the actin cytoskeleton. The majority of GAG sidechains are heparin sulphate, chondroitin/dermatan sulphate, and hyaluronic acid or hyaluronan. These constituents form a negatively-charged network that can rebuff blood cells and select plasma components according to their electrostatic

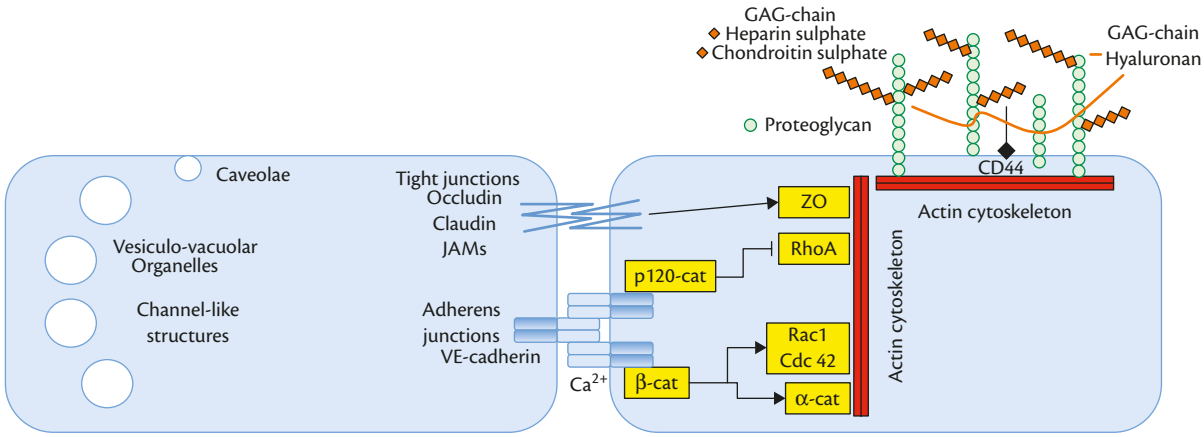


Fig. 164.1 Schematic representation of the components involved in the regulation of microvascular permeability.
Cat, catenin; ZO, zona occludens proteins; GAG, glycosaminoglycan.

charge. The glycocalyx is a dynamic structure that is highly dependent upon the local micro-environment (local ionic strength) and pH. Endothelial cells also regulate the biosynthesis of new glycosaminoglycans to allow adaptations to changes in the local environment, such as shear stress and local pH. The structure of the glycocalyx has an underlying three-dimensional fibrous meshwork with a characteristic spacing of 20 nm in all directions [7]. Such spacing can act as a molecular filter for plasma proteins, and control filtration, both when the endothelium is continuous and when it is fenestrated.

Paracellular permeability

The endothelial junctions consist of adherens, tight, and gap junctions. Adherens junctions (AJs) are found in all microvascular beds, whereas tight junctions (TJs) are mainly expressed in the blood–brain barrier and the blood retinal barrier. Gap junctions form channels between adjacent endothelial cells, and allow diffusion of water, ions, and other small molecules with transmission of signals within the contiguous monolayer of cells.

AJs are mainly made by calcium-dependent vascular endothelial cadherin proteins (VE-cadherin). VE-cadherin forms interactions between adjacent endothelial cells by their extracellular domains in a calcium-dependent manner. The intracellular domain of VE-cadherin is connected to the actin cytoskeleton via a family of catenins (α-, β-, γ-, and p120-catenins) [1]. VE-cadherins not only serve as a structural linkage between endothelial cells, but are also involved in intracellular signalling and in the control of cell–cell communications. The stability of VE-cadherin complexes is regulated by phosphorylation, which induces its internalization and disrupts barrier integrity, thus resulting in vascular permeability. VE-cadherins play a key role in the communication between adherens and tight junctions, as well as supporting and stabilizing the tight junctions. For example, VE-cadherin can transmit shear stress signals to tight junction occludin through engagement of Tiam1/Rac1, thereby leading to barrier stabilization [8].

Catenins play a critical role in stabilizing the VE-cadherin–catenin–cytoskeleton system that is undergoing constant remodelling. The cytoplasmic domain of VE-cadherin interacts with β-, γ-, and p120-catenins through its cytoplasmic domain. The α-/β-catenin interaction induces cell–cell adhesion through an interaction with actin and formation of cortical actin bundles. In addition, β-catenin and γ-catenin (plakoglobin) prevent VE-cadherin proteolysis. Finally, β-catenin and 120-catenin modulate the actin cytoskeleton by way of RhoGTPase activation (p190RhoGAP, Rac1, Cdc42, RhoA).

Tight junctions are composed of three types of transmembrane proteins—occludin, claudin and junctional adhesion molecules (JAM) [9]. These proteins are connected to the actin cytoskeleton via zona occludens proteins (ZO-1, ZO-2) and α-catenin. Similar to adherens junctions, phosphorylation of both tight junction proteins and their intracellular partners regulate endothelial cell–cell junctions and vascular permeability.

It is essential to understand that adherens and tight junctions not only have a function of linking endothelial cells, but serve also as signalling molecules through their interaction with the actin cytoskeleton for the regulation of cell polarity, cellular movement, and fluid sensing. Another major point is the fact that endothelial-associated cells, which form with capillaries the 'vascular unit', contribute to stabilization of the endothelial barrier. For example, pericytes and alveolar epithelial cells (alveolar-capillary membrane) can markedly attenuate microvascular hyperpermeability by controlling pro-permeability signals [10].

Transcellular permeability

This mechanism involves vesicle-mediated endocytosis at the endothelial luminal membrane, followed by transcytosis across the cell, and exocytosis at the basolateral membrane. Transcellular permeability is an energy-dependent process involving caveolae and clusters of interconnected VVOs that form channel-like structures of diameter = 80–200 nm. Caveolae are 60–80 nm diameter pits that are seen in the endothelium membrane, and as free vesicles within the cytoplasm.

Formation of caveolae at the membrane of the endothelium implies inclusion of caveolin-1 (Cav-1), a structural protein of caveolae, into membrane lipid microdomains enriched with cholesterol and sphingolipids. There are two caveolin isoforms in endothelial cells, caveolin-1 and 2, but only Cav-1 exclusively regulates caveolae formation and transcytosis. Caveolae are involved in several functions including endocytosis, transcytosis, potocytosis, lipid regulation, calcium signalling, and in diverse signalling pathways.

Caveolae may mediate transcellular transport of molecules such as albumin, iron-transferrin, insulin, low-density lipoproteins, and chemokines. The transport of albumin by caveolae is crucial for regulation of transendothelial oncotic pressure and is crucial for fluid balance across the endothelium.

VVOs consist of clusters of 1–2 μm vesicles or vacuoles. Unlike caveolae, VVOs are sessile structures that can assemble into transcellular membranous channels. These channels open into the luminal, abluminal, or lateral endothelial cell surfaces. The channel-forming VVOs provide a transcellular permeability pathway to macromolecules. Further data are needed to clarify their function in the control of microvascular permeability.

Capillary leak during sepsis and the acute respiratory distress syndrome

As illustrated in Fig. 164.2, during sepsis or ARDS, increased microvascular leak occurs due to loss of intercellular junctional integrity, remodelling of the cellular cytoskeleton, or endothelial apoptosis or damage. Inflammatory mediators such as cytokines, endotoxin, microbial compounds, angiogenic (e.g. VEGF) and pro-coagulant (e.g. thrombin) factors increase microvascular permeability by weakening endothelial junctions. The most common effects reported with these mediators are alterations of the glycocalyx, endothelial junctions (especially phosphorylation of constituents of AJs with VE-cadherin internalization), and activation of actomyosin contractility causing interendothelial gaps (Fig. 164.2).

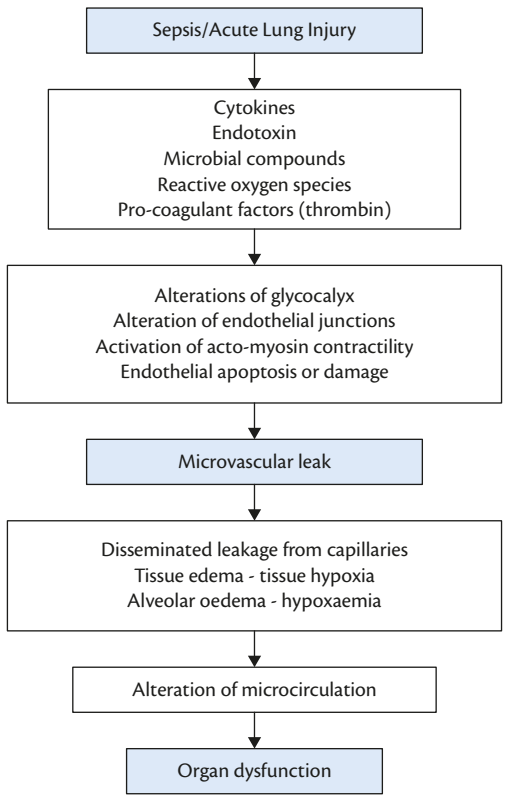


Fig. 164.2 Schematic representation of causes and consequences of microvascular leak in sepsis and ARDS.

These processes facilitate the migration of immune cells, antibody, and other substances to sites of microbial invasion. However, excessive release of inflammatory mediators into the circulation could paradoxically injure organs by triggering a disseminated leakage from capillaries, inducing uncontrolled fluid extravasation and tissue oedema. Accumulation of interstitial fluid is detrimental to tissue oxygenation and organ function as oedema increases the diffusion distance for oxygen and nutrients, and compresses capillaries by increasing the interstitial pressure in organs with non-expendable interstitial volumes (kidney, brain, muscle). In addition, oedema in the lungs leads to alveolar flooding and hypoxaemia. Microvascular leak is a major cause underlying the generalized alteration of the microcirculation induced by sepsis. For example, peritonitis induces not only intestinal capillary leak, but also alterations within the microvascular pulmonary microcirculation with increases in the number of stationary leukocytes and protein leak into the pulmonary alveoli [11].

The loss of endothelial barrier function and the resultant capillary leak appears to be a key factor underlying multiple organ dysfunction (MOD). This has been demonstrated in several models of sepsis using different strategies to prevent capillary leak [12–15]. Xu et al. [13] used transgenic mice that selectively overexpress the NF-κB inhibitor I-κBα on endothelium. They reported that this selective prevention of endothelial activation and capillary leak could avoid the resultant sepsis-induced MOD. London et al. [14] found that reduction of capillary leak by a recombinant Slit2N fragment improved survival in animal models of endotoxin, polymicrobial sepsis, and H5N1 influenza. They identified the Slit-induced signalling pathway as a modulator of vascular stability that can strengthen endothelial cell–cell interactions through inhibition of VEGF in a process dependent on the endothelial-specific receptor Robo4.

As previously mentioned, sepsis induces an alteration of the glycocalyx. In humans, endotoxin administration led to alterations of the endothelial glycocalyx illustrated by a profound reduction in microvascular glycocalyx thickness (polarization spectroscopy imaging of sublingual microcirculation) with a significant rise in circulating hyaluronan levels [16]. This abnormality has been confirmed in septic patients with high levels of glycocalyx markers (syndecan-1, heparan sulphate) correlating with disease severity and mortality [17–19].

Conclusion

Capillary leak contributes to organ dysfunction in sepsis and ARDS. An understanding of the pathogenesis of microvascular permeability may lead to new therapies targeting the microvascular barrier in sepsis and ARDS.

References

1. Yuan SY and Rigor RR. (2010). *Regulation of Endothelial Barrier Function.* San Rafael, CA: Morgan & Claypool Life Sciences.
2. Goddard LM and Iruela-Arispe ML. (2013). Cellular and molecular regulation of vascular permeability. *Thrombosis and Haemostasis*, **109**, 407–15.
3. Curry FR and Adamson RH. (2013). Tonic regulation of vascular permeability. *Acta Physiologica*, **207**, 628–49.
4. Komarova Y and Malik AB. (2010). Regulation of endothelial permeability via paracellular and transcellular transport pathways. *Annual Review of Physiology*, **72**, 463–93.

5. Weinbaum S, Tarbell JM, and Damiano ER. (2007). The structure and function of the endothelial glycocalyx layer. *Annual Review of Biomedical Engineering*, **9**, 121–67.
6. Lipowsky HH. (2012). The endothelial glycocalyx as a barrier to leukocyte adhesion and its mediation by extracellular proteases. *Annual Review of Biomedical Engineering*, **40**, 840–8.
7. Squire JM, Chew M, Nneji G, Neal C, Barry J, and Michel C. (2001). Quasi-periodic substructure in the microvessel endothelial glycocalyx: a possible explanation for molecular filtering? *Journal of Structural Biology*, **136**, 239–55.
8. Walsh TG, Murphy RP, Fitzpatrick P, et al. (2011). Stabilization of brain microvascular endothelial barrier function by shear stress involves VE-cadherin signaling leading to modulation of pTyr-occludin levels. *Journal of Cellular Physiology*, **226**, 3053–63.
9. Harhaj NS and Antonetti DA. (2004). Regulation of tight junctions and loss of barrier function in pathophysiology. *International Journal of Biochemistry and Cell Biology*, **36**, 1206–37.
10. Wang L, Taneja R, Wang W, et al. (2013). Human alveolar epithelial cells attenuate pulmonary microvascular endothelial cell permeability under septic conditions. *PLoS One*, **8**, e55311.
11. McCormack DG, Mehta S, Tyml K, Scott JA, Potter R, and Rohan M. (2000). Pulmonary microvascular changes during sepsis: evaluation using intravital videomicroscopy. *Microvascular Research*, **60**, 131–40.
12. Ye X, Ding J, Zhou X, Chen G, and Liu SF. (2008). Divergent roles of endothelial NF-kappaB in multiple organ injury and bacterial clearance in mouse models of sepsis. *Journal of Experimental Medicine*, **205**, 1303–15.
13. Xu H, Ye X, Steinberg H, and Liu SF. (2010). Selective blockade of endothelial NF-Î°B pathway differentially affects systemic inflammation and multiple organ dysfunction and injury in septic mice. *Journal of Pathology*, **220**, 490–8.
14. London NR, Zhu W, Bozza FA, et al. (2010). Targeting Robo4-dependent Slit signaling to survive the cytokine storm in sepsis and influenza. *Science Translational Medicine*, **2**, 23ra19.
15. Szczepaniak WS, Zhang Y, Hagerty S, et al. (2008). Sphingosine 1-phosphate rescues canine LPS-induced acute lung injury and alters systemic inflammatory cytokine production in vivo. *Translational Research*, **152**, 213–24.
16. Nieuwdorp M, Meuwese MC, Mooij HL, et al. (2009). Tumor necrosis factor-alpha inhibition protects against endotoxin-induced endothelial glycocalyx perturbation. *Atherosclerosis*, **202**, 296–303.
17. Sallisalmi M, Tenhunen J, Yang R, Oksala N, and Pettila V. (2012). Vascular adhesion protein-1 and syndecan-1 in septic shock. *Acta Anesthesiologica Scandinavica*, **56**, 316–22.
18. Nelson A, Berkestedt I, Schmidtchen A, Ljunggren L, and Bodelsson M. (2008). Increased levels of glycosaminoglycans during septic shock: relation to mortality and the antibacterial actions of plasma. *Shock*, **30**, 623–7.
19. Steppan J, Hofer S, Funke B, et al. (2011). Sepsis and major abdominal surgery lead to flaking of the endothelial glycocalyx. *Journal of Surgical Research*, **165**, 136–41.

CHAPTER 165

Management of acute non-cardiogenic pulmonary oedema

Sébastien Tanaka and Jacques Duranteau

Key points

- Severe capillary leak is an important factor in the pathogenesis of organ dysfunction following inflammatory syndromes such as sepsis-induced acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).
- The Surviving Sepsis Campaign recommends a conservative, rather than liberal fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion.
- There is no evidence to recommend the use of diuretics to prevent tissue oedema.
- Several therapeutic options that restore microvascular permeability have been investigated in preclinical sepsis models.
- The challenge is now to proceed into carefully designed clinical trials.

Introduction

Microvascular leak caused by an increase in endothelial permeability plays an important role in the pathogenesis of many inflammatory syndromes, such as sepsis, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The resulting tissue oedema impairs tissue oxygenation, thereby contributing to organ dysfunction. It would thus appear rational to prevent, ameliorate, or reverse excessive capillary leak. Several interventions in current practice are designed to maintain intravascular colloid osmotic pressure, reduce capillary leak, or reduce extravascular water. The evidence base underlying these will be reviewed. In addition, there are novel targeted strategies specifically designed to reduce capillary leak with encouraging preclinical data. The challenge is now to prove the clinical effectiveness of these strategies with carefully designed clinical trials.

Current therapeutic options

Fluid management

Fluid resuscitation is one of the first line treatments in septic patient management. However, the risk of excessive fluid administration is now well demonstrated. This risk is particularly apparent in patients with ARDS where a positive fluid balance was associated with worse outcomes and was an independent indicator of mortality [1]. Thus, the challenge for the physician is to find a good balance between intravascular volume restoration and tissue oxygenation, without inducing fluid overload and worsening lung injury. However, the strict application of a fluid-restrictive strategy is not always possible because of haemodynamic instability. Only a few prospective studies have evaluated the effects of a conservative fluid strategy, reporting that a fluid restriction strategy can improve oxygenation and increase the number of ventilator-free days [2,3]. Fluid restriction was variably associated with diuretic treatment and vasopressor use, but the study design did not allow an assessment of their impact on mortality. The Surviving Sepsis Campaign recommends a conservative, rather than liberal fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion [4]. Thus, it is crucial to titrate fluid resuscitation to prevent or minimize extravascular lung water. Assessment of pulmonary permeability by transpulmonary thermodilution with monitoring of extravascular lung water (EVLW) could be an interesting tool to manage fluid resuscitation in ARDS.

The choice of fluid to minimize capillary leak remains a matter of significant controversy. It would make sense to increase plasma oncotic pressure to limit the formation of oedema, particularly for septic patients in whom haemodilution and catabolism would reduce plasma protein levels. Experimental studies have demonstrated a beneficial effect of albumin on pulmonary inflammation with a decrease in capillary permeability [5]. In ARDS patients, a moderate improvement of oxygenation was observed when albumin was combined with diuretics compared with diuretic treatment alone [6]. However, no differences in mortality or the numbers of days spent on mechanical ventilation, in intensive care unit (ICU) or in hospital, were observed in the SAFE study comparing albumin 4% and crystalloid administration [7].

Diuretics

Given that relatively few studies have focused on the use of diuretics in ALI/ARDS, there is no evidence to recommend their use to prevent tissue oedema. In a canine oleic acid model of ARDS, furosemide improved the PaO_2/FiO_2 ratio, reduced lung injury, and the level of PEEP [8]. Septic patients with ARDS treated with furosemide alone developed more vascular dysfunction than those

treated with both furosemide and albumin [6]. Patients with ALI randomized to receive a conservative fluid strategy, in which an improvement of lung function was observed, received more diuretics than the liberal fluid strategy group [3]. In the same cohort of patients, diuretic therapy given post-acute kidney injury was associated with an increase in 60-day patient survival [9].

Vasopressin

Low-dose vasopressin (AVP) was recently proposed as a pharmacological approach to decrease capillary leak in ALI. The rationale is that excessive nitric oxide (NO) production accounts for the increased vascular leakage and that vasopressin can limit this excessive NO production. In an established ovine model of ALI, low-dose AVP infusion could attenuate pulmonary dysfunction, shunt fraction, nitrosamine stress, and oedema formation [10]. However, clinical studies are needed to confirm benefit.

Novel therapeutic options

A variety of other therapeutic options to restore microvascular permeability have been investigated in pre-clinical sepsis models. However, the challenge is now to prove their effectiveness in patients with ALI/ARDS and sepsis in carefully designed clinical trials.

Sphingosine-1-phosphate and S1P agonists

Sphingosine-1-phosphate (S1P) is formed in intracellular compartment by phosphorylation of sphingosine and acts on five specific G protein-coupled receptors (S1P receptors S1PR1-5). S1PR1 activation enhances cadherin expression, stabilizes the endothelial cytoskeleton, and counteracts VEGF-induced VE-cadherin internalization and thrombin-activated PAR-1 signalling. Clinical studies suggest that low plasma S1P levels may have an impact on vascular leakage and mortality in malaria and sepsis [11,12]. In endotoxin-induced acute lung injury models, leak and lung injury could be decreased by treatment with FTY720 (an S1P analogue) or S1P. S1PR3 was recently shown to promote lipopolysaccharide (LPS)-induced vascular leakage, while elevated plasma concentrations were associated with an increased mortality in patients with sepsis or ALI [13]. S1PR3 could thus also be a potential therapeutic target.

Angiopoietin (Angpt)-tie pathway

Angiopoietin-1 (Angpt-1) and Angpt-2 are ligands for the endothelial-specific receptor tyrosine kinase Tie2. Angpt-1 is secreted by peri-endothelial cells and promotes vascular endothelial cell survival and endothelial cell adhesion, while inhibiting endothelial permeability in response to VEGF or thrombin. Angpt-2 is synthesized in endothelium and is the natural antagonist of Angpt-1. Angpt-2, by interfering with Angpt-1, leads to endothelial barrier destabilization, endothelial cell activation, and vascular inflammation. In sepsis and ARDS, the Angpt-1/Tie2 axis is suppressed with a concomitant increase in circulating Angpt-2 [14]. Circulating Angpt-2 is associated with pulmonary permeability oedema, and the occurrence and severity of ARDS [15]. A greater reduction in plasma Angpt-2 levels over time has been reported when a conservative fluid strategy was applied to ARDS patients compared to a liberal strategy [15]. Induction of Angpt-2 precedes adverse outcomes, while circulating Angpt-2 levels or a high Angpt-2/Angpt-1 ratio could predict the development of sepsis and shock [16]. Preclinical studies have demonstrated benefits through modulating the Angpt–Tie-2 axis using recombinant Angpt-1, the Angpt-1 agonist (vasculotide), or antibodies specific for Angpt-2 [16]. Furthermore, genetic variants in the Angpt-2 gene are associated with an increased risk of ARDS [16]. Modulation of the Angpt–Tie-2 axis appears to be a particularly strong concept for future clinical trials.

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) has been proposed to be a pivotal factor underlying sepsis-related microvascular leak. Numerous reports also suggest a pathological role in ARDS. Through binding with endothelial VEGF receptors (VEGFR1–3), VEGF can increase microvascular permeability by several mechanisms, including VE-cadherin internalization via the VEGFR2-Src-VE-cadherin signaling pathway and cytoskeletal rearrangement. Anti-VEGF therapies may limit sepsis-related microvascular leak. However, the function of VEGF is highly complex, with both protective and pathological effects, so a VEGF-targeted therapeutic agent remains controversial. A neutralizing anti-VEGF antibody (bevacizumab) is at present under consideration for patients in septic shock.

Atrial natriuretic peptide

In a murine model, atrial natriuretic peptide (ANP) significantly decreased endotoxin-induced lung vascular leak through effects on PAK1 (p21-activated kinase)-dependent signalling, leading to EC barrier enhancement [17]. PAK1 is a cytoskeletal Rac effector involved in cortical actin rearrangement and regulation of actin polymerization. The authors also reported that ANP knockout mice developed more severe endotoxin-induced lung injury [17]. In ARDS patients, an infusion of ANP given over 1 hour did not improve pulmonary gas exchange [18]. However, a longer infusion (24 hours) improved the PaO_2/FiO_2 ratio and thoracic compliance with a decrease in pulmonary shunt. The potential clinical role for ANP in ARDS merits further investigation.

Slit2N-robo4 pathway

London et al. identified the Slit-induced signaling pathway as a modulator of vascular stability that can strengthen adherens junctions through an increased expression of VE-cadherin and an inhibition of VEGF-induced vascular hyperpermeability [19]. This was demonstrated in animal models of endotoxin-induced acute lung injury, caecal ligation and puncture, and H5N1 influenza. The Slit2N-Robo4 pathway could also repress enodotoxin-induced endothelial inflammation by inhibiting the Pyk2–NF-kB pathway. Therefore, modulation of the Slit2N- Robo4 pathway may represent another promising therapeutic option to restore microvascular permeability and prevent sepsis-induced organ injury.

Fibrinopeptide $B\beta_{15–42}$

Fibrinopeptide $B\beta_{15-42}$ is released from fibrin following thrombin-induced fibrin formation. This peptide, also called FX06, can be used as an index of fibrinolytic activity. FX06 reduced capillary leakage in three models of capillary leak (Dengue shock, endotoxin shock, endotoxin pneumonitis) [20]. Its protective effect appears related to its binding to VE-cadherin, stabilization of inter-endothelial junctions, and anti-inflammatory effects.

Conclusion

Capillary leak contributes to organ dysfunction in sepsis and ARDS. A number of interventions in current practice are designed to

maintain intravascular colloid osmotic pressure, reduce capillary leak, or reduce extravascular water. A conservative, rather than liberal fluid strategy is recommended. Preclinical studies suggest that preventing microvascular leak may represent a viable therapeutic strategy to decrease organ dysfunction. Therapeutic agents that stabilize the glycocalyx might also prevent inflammation-induced organ failure. The challenge is now to proceed into carefully designed clinical trials.

References

1. Sakr Y, Vincent JL, Reinhart K, et al. (2005). High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. *Chest*, **128**, 3098–108.
2. Mitchell JP, Schuller D, Calandrino FS, and Schuster DP. (1992). Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *American Review of Respiratory Disease*, **145**, 990–8.
3. Wiedemann HP, Wheeler AP, Bernard GR, et al. (2006). Comparison of two fluid-management strategies in acute lung injury. *New England Journal of Medicine*, **354**, 2564–75.
4. Dellinger RP, Levy MM, Rhodes A, et al. (2013). Surviving Sepsis Campaign Guidelines Committee including the Pediatric S. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine*, **41**, 580–637.
5. Zhang H, Voglis S, Kim CH, and Slutsky AS. (2003). Effects of albumin and Ringer's lactate on production of lung cytokines and hydrogen peroxide after resuscitated hemorrhage and endotoxemia in rats. *Critical Care Medicine*, **31**, 1515–22.
6. Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, and Bernard GR. (2005). A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Critical Care Medicine*, **33**, 1681–7.
7. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, and Norton R. (2004). A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *New England Journal of Medicine*, **350**, 2247–56.
8. Reising CA, Chendrasekhar A, Wall PL, Paradise NF, Timberlake GA, and Moorman DW. (1999). Continuous dose furosemide as a therapeutic approach to acute respiratory distress syndrome (ARDS). *Journal of Surgical Research*, **82**, 56–60.
9. Grams ME, Estrella MM, Coresh J, Brower RG, and Liu KD. Fluid balance, diuretic use, and mortality in acute kidney injury. *Clinical Journal of the American Society of Nephrology*, **6**, 966–73.
10. Westphal M, Rehberg S, Maybauer MO, et al. (2011). Cardiopulmonary effects of low-dose arginine vasopressin in ovine acute lung injury. *Critical Care Medicine*, **39**, 357–63.
11. Kumaraswamy SB, Linder A, Akesson P, and Dahlback B. (2012). Decreased plasma concentrations of apolipoprotein M in sepsis and systemic inflammatory response syndromes. *Critical Care*, **16**, R60.
12. Finney CA, Hawkes CA, Kain DC, et al. (2011). S1P is associated with protection in human and experimental cerebral malaria. *Molecular Medicine*, **17**, 717–25.
13. Sun X, Singleton PA, Letsiou E, et al. (2012). Sphingosine-1-phosphate receptor-3 is a novel biomarker in acute lung injury. *American Journal of Respiratory Cell and Molecular Biology*, **47**, 628–36.
14. Parikh SM. (2013). Dysregulation of the angiopoietin-Tie-2 axis in sepsis and ARDS. *Virulence*, **4**, 517–24.
15. Calfee CS, Gallagher D, Abbott J, Thompson BT, and Matthay MA, for the ARDSNET Network. (2012) Plasma angiopoietin-2 in clinical acute lung injury: prognostic and pathogenetic significance. *Critical Care Medicine*, **40**, 1731–7.
16. David S, Mukherjee A, Ghosh CC, et al. (2012). Angiopoietin-2 may contribute to multiple organ dysfunction and death in sepsis. *Critical Care Medicine*, **40**, 3034–41.
17. Birukova AA, Xing J, Fu P, et al. (2010). Atrial natriuretic peptide attenuates LPS-induced lung vascular leak: role of PAK1. *American Journal of Physiology - Lung Cellular and Molecular Physiology*, **299**, L652–63.
18. Bindels AJ, van der Hoeven JG, Groeneveld PH, Frolich M, and Meinders AE. (2001). Atrial natriuretic peptide infusion and nitric oxide inhalation in patients with acute respiratory distress syndrome. *Critical Care*, **5**, 151–7.
19. London NR, Zhu W, Bozza FA, et al. Targeting Robo4-dependent Slit signaling to survive the cytokine storm in sepsis and influenza. *Science Translational Medicine*, **2**, 23ra19.
20. Groger M, Pasteiner W, Ignatyev G, et al. (2009). Peptide Bbeta(15-42) preserves endothelial barrier function in shock. *PloS One*, **4**, e5391.

PART 5.13

Pericardial tamponade

CHAPTER 166

Pathophysiology and causes of pericardial tamponade

John R. Schairer and Steven J. Keteyian

Key points

- Cardiac tamponade is a shock state resulting from the accumulation of blood or fluid in the pericardial space, which limits ventricular filling resulting in a decreased stroke volume and cardiac output.
- Cardiac tamponade is a continuum and not an all-or-nothing diagnosis.
- A rapidly accumulating pericardial effusion can become haemodynamically significant with smaller volumes versus a pericardial effusion that occurs gradually over time.
- Echocardiography is the cornerstone of the work-up of pericardial effusion, providing diagnostic, prognostic, and therapeutic information. Computed tomography and magnetic resonance imaging can also be helpful.
- Comorbid conditions that may affect the pathophysiology of cardiac tamponade and, secondarily, the signs of cardiac tamponade need to be considered when entertaining a diagnosis of cardiac tamponade.

Introduction

Pericardial disease leading to pericardial effusion (PEF) is a common condition encountered by the clinician in day-to-day practice. The most common causes are viral infections, metastatic cancer, renal disease, and bleeding disorders, such as aortic dissection and trauma. If the effusion becomes large enough it can cause haemodynamic compromise or shock, resulting in the clinical condition of cardiac tamponade. Importantly, tamponade is not an all-or-nothing diagnosis, but instead should be viewed along a continuum of progressively worsening haemodynamics.

Epidemiology and aetiology of pericardial effusion

Inflammation of the pericardium or pericarditis is reported in 5% of patients admitted to the emergency department for work-up of chest pain, and in 1% of autopsy studies [1]. The most common cause of pericarditis (80–90%), and thus PEF, is viral infection [2]. Factors associated with increased risk for recurrent pericarditis, tamponade, or pericardial constriction are female gender, fever >38°C, subacute onset (symptoms developing over a period of several days to weeks), large effusion or tamponade, and use of non-steroidal anti-inflammatory agents [3]. Conditions associated with a high incidence of progression to tamponade are neoplasm with metastasis to the pericardium, renal disease, and disorders giving rise to bleeding into the pericardial space, such as aortic dissection and penetrating wounds. Up to one-third of patients with an asymptomatic large PEF eventually developed tamponade [4,5]. Echocardiography, computed tomography, and magnetic resonance imaging (MRI) provide important information in the diagnostic work-up and management of PEF. However, PEF as reported by computed tomography tends to be larger than reported by echocardiography. Echocardiography is considered the more accurate measurement.

Pathophysiology

Intrapericardial and intrathoracic pressures are normally equal and vary with respiration. With inspiration, intrathoracic pressure decreases causing an increased flow into the right side of the heart and a decrease in flow from pulmonary veins into the left side. During expiration the process is reversed. As a result of these respiratory fluctuations in flow, chamber size, intracardiac pressures, vascular pressures, and stroke volume also fluctuate.

The pericardium is composed of parietal and visceral layers. The visceral layer, when inflamed, forms an increased amount of PEF. In situations of gradual accumulation of PEF, such as in malignancy and chronic kidney disease, the pericardium has time to stretch and the effusion can become as large as 2 L without causing haemodynamic compromise. When PEF accumulates rapidly, e.g. with chamber perforation or aortic dissection, the pericardium does not have time to stretch and a PEF as small as 150 mL can lead to tamponade.

As the size of the PEF increases, pressure in the pericardial space also increases. The haemodynamic consequence is a limitation in cardiac filling, similar to diastolic dysfunction. In tamponade, the ventricles no longer fill against the diastolic pressures of the individual chamber, but rather against the common pressure of the intrapericardial space. When the limits of pericardial stretch are reached, the total intrapericardial volume becomes fixed. Any additional increase in PEF results in either a decrease in heart size or if one chamber increases in size during the respiratory cycle, the other chamber must decrease. The normal reciprocal changes in flow and chamber size during respiration become exaggerated; this is referred to as ventricular interdependence. As the right ventricle is a thin-walled structure, it is more susceptible to changes in pressure and volume than the left ventricle. Ventricular interdependence is

the explanation for exaggerated respiratory variation in flows across the four cardiac valves, and the exaggerated respiratory variation in systolic BP known as pulsus paradoxus.

Reddy et al. [6,7] described the haemodynamics of PEF and tamponade. They measured intracardiac, intrapericardial, and arterial pressures, and cardiac output in patients with tamponade before, during, and after pericardiocentesis. Baseline haemodynamics revealed equalization of right atrial (RA), intrapericardial, pulmonary capillary, and left atrial pressures at 16 mmHg or higher. They divided the haemodynamics of an enlarging pericardial effusion into three phases of increasing haemodynamic compromise, beginning with little compromise (Phase 1) and culminating in tamponade with cardiogenic shock (Phase 3; Fig. 166.1). As the abnormal haemodynamics evolve over three phases, tamponade should not be considered as an all-or-nothing diagnosis, but rather a continuum.

Clinical findings in PEF and CT

Phase 1: the early phase of fluid accumulation

The increased fluid within the pericardial space causes a gradual increase in intrapericardial pressure, resulting in an increase in both right ventricle (RV) and left ventricle (LV) filling pressures. At the end of Phase 1, RV filling pressure and intrapericardial pressure are equal at approximately 10 mmHg, there is a small decrease in cardiac output, and arterial pressure decreases slightly during inspiration, although values are still within the normal range. LV filling pressure is still slightly higher than pericardial pressure. The main finding of Phase 1 is an enlarged cardiac silhouette on imaging studies.

Phase 2: pre-tamponade

Here, intrapericardial, right and left atrial pressures continue to increase. The rising intrapericardial pressure causes cardiac chambers to decrease in size and, secondarily, cardiac output to decrease, but there are no signs of shock. Many of the echocardiographic and clinical signs of tamponade may become apparent, although classically they are found in Phase 3. There is a further decrease in arterial pressure during inspiration, approaching the 10 mmHg value that is consistent with pulsus paradoxus. Recognizing Phase 2 is important as it enables prediction of impending tamponade and intervention before the patient goes into shock.

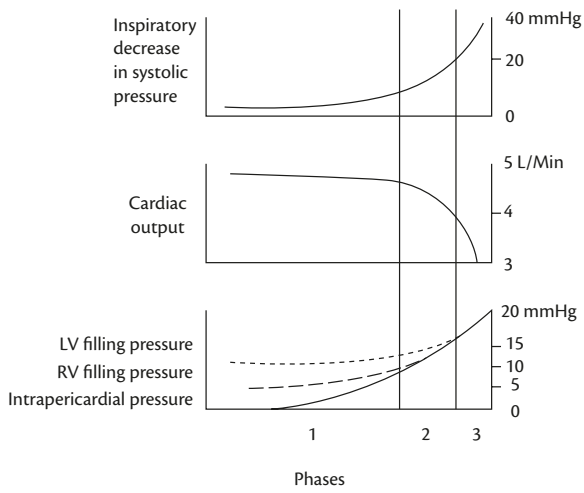


Fig. 166.1 Pathophysiology of cardiac tamponade. Phase 1: Intrapericardial pressure < RA pressure < LV filling pressure. Phase 2: begins with equalization of pericardial and RA pressures. Phase 3: begins with equalization of intrapericardial, RA, and LV filling pressures.

RA, right atrium; LV, left ventricle.

Reproduced from Schairer JR et al., 'A systematic approach to evaluation of pericardial effusion and cardiac tamponade', *Cardiology in Review*, **19**(5), pp. 233–8, copyright 2011, with permission from Wolters Kluwer Health.

Phase 3: cardiac tamponade

Intrapericardial, right and left atrial pressures equalize at ≥16 mmHg. Increases in intrapericardial pressures >16 mmHg cause a further drop in cardiac output. The inspiratory fall in arterial pressure is now ≥10 mmHg, cardiac chamber size is decreased and circulatory collapse occurs; cardiogenic shock or tamponade ensues. The signs of tamponade are usually present during this phase. Pulsus paradoxus is the *sine qua non* of Phase 3 with an inspiratory drop of systolic pressure >10 mmHg. Although pulsus paradoxus was originally thought to occur only if there was equalization of pressures (i.e. Phase 3), a few patients demonstrate this finding during Phase 2. Finally, it is important to recognize that pulsus paradoxsus may not always be present in tamponade and can also be seen in other disease processes (Box 166.1).

Echocardiography and Doppler in PEF and CT

Echocardiographic evaluation of PEF

Echocardiography is the diagnostic cornerstone of PEF and its complication, tamponade. A major role of echocardiography is

Box 166.1 Comorbid conditions affecting pulsus paradoxus

Conditions in which pulsus paradoxus may be present without tamponade

- Obesity.
- Asthma/chronic obstructive pulmonary disease.
- RV infarction.
- Pulmonary embolism.
- Effusive-constrictive tamponade.
- Heart failure.
- Constriction (rare).

Conditions in which pulsus paradoxus may be absent with tamponade

- Atrial septal defect.
- RV hypertrophy without pulmonary hypertension.
- Shock and severe tamponade.
- Increased LV filling pressures and diastolic stiffness.
- Local pericardial adhesions.
- Positive pressure ventilation.
- Aortic regurgitation.

Reproduced from Schairer JR et al., 'A systematic approach to evaluation of pericardial effusion and cardiac tamponade', *Cardiology in Review*, **19**(5), pp. 233–8, copyright 2011, with permission from Wolters Kluwer Health.

Table 166.1 Estimation of RA pressure using IVC

Inferior vena cava diameter	Decrease in diameter with respiration or 'sniff' test	RA pressure (mean) mmHg
Normal (≤2.1cm)	>50%	0–5 [3]
Normal (≤2.1cm)	<50%	5–10 [9]
Dilated (>2.1cm)	>50%	5–10 (8)
Dilated (>2.1cm)	<50%	>15

Reproduced from Schairer JR et al., 'A systematic approach to evaluation of pericardial effusion and cardiac tamponade', *Cardiology in Review*, 19, 5, pp. 233–238, copyright 2011, with permission from Wolters Kluwer Health

determining the presence, size, and location of the PEF. PEF size is designated 'physiological' (25–50 mL) if there is no separation of epicardium and pericardium during end-diastole, 'small' (<100 mL) if the echocardiographic-free space is ≤10 mm, 'moderate' (100–500 mL) if the echocardiographic-free space is between 10–20 mm, and 'large' (>500 mL) if the echocardiographic-free space is ≥20 mm. Measurements should be performed at end-diastole. The distribution of the PEF can be either circumferential or loculated.

The first haemodynamic change to occur with an enlarging PEF is an increase in RA pressure manifested clinically as jugular venous distention, or echocardiographically as inferior vena cava (IVC) dilatation. As RA pressure increases, IVC size increases and its response to respiration decreases until, at an RA pressure of ≥15 mmHg, the IVC is dilated and does not change size with respiration; this is termed IVC plethora (Table 166.1). The sensitivity of IVC plethora for tamponade is 97%, while the specificity is somewhat lower at 66%. Without IVC plethora, tamponade is unlikely.

Doppler evaluation in CT

Appleton et al. [8] described changes in E-wave velocity with respiration across the mitral and tricuspid valves comparing normal subjects, patients with large PEF, and those with tamponade. The normal respiratory variation across the mitral and tricuspid valves is ≤15 and ≤25%, respectively. In general, variations in E-wave velocities during respiration across the mitral and tricuspid valves that are greater than 25 and 50%, respectively, indicate tamponade.

When evaluating respiratory changes in PEF and suspected tamponade, other disease states demonstrating an increase in respiratory flow variation across the valves should also be considered, e.g. chronic obstructive lung disease, pericardial constriction, severe tricuspid regurgitation and RV dysfunction.

Echocardiographic evaluation of tamponade

Because of the increased pressure in the pericardial space in tamponade, there is a reduced size of the RV chamber, RV collapse during diastole, or RA inversion during systole. RV collapse occurs during diastole because pericardial pressure exceeds RV early diastolic pressure (Fig 166.2).

RV chamber size in tamponade achieves its smallest dimension after the onset of the E-wave of the mitral valve and after closure of

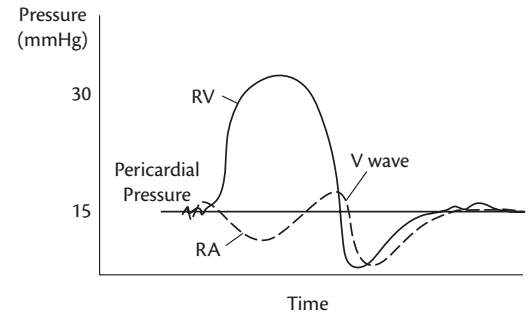


Fig 166.2 Pathophysiology of right ventricular (RV) and right atrial (RA) collapse. Pericardial pressure exceeds RA and RV pressure causing collapse. The y-descent of the v-wave also becomes less prominent.
Reproduced from Schairer JR et al., 'A systematic approach to evaluation of pericardial effusion and cardiac tamponade', *Cardiology in Review*, **19**(5), pp. 233–8, copyright 2011, with permission from Wolters Kluwer Health.

the aortic valve (i.e. during diastole), when the RV should be dilating [9]. RV diastolic collapse involves the free wall of the RV outflow tract (Fig. 166.3). RV collapse is present in patients who did not have clinical tamponade but did have moderate-to-large PEF. This suggests that RV collapse may be a very early sign of tamponade. In all cases the abnormal motion reverts back to normal after drainage of the PEF. Because of the RV collapse in early diastole, passive RV filling becomes less important; filling now depends almost exclusively on atrial contraction. RV collapse was associated with an approximate 20% decrease in cardiac output [10].

Increased pericardial pressure also causes RA collapse or inversion (Fig. 166.2) [11]. The percentage of the cardiac cycle that RA inversion occupies is termed the RA inversion time index. An index ≥0.34 yielded 94% sensitivity, 100% specificity, predictive value of 100%, and accuracy of 97%. The index is believed to be the most sensitive finding for tamponade. The absence of sinus rhythm does not preclude the use of RA collapse to make the diagnosis of tamponade. Increased intrapericardial pressure also explains the loss of the y-decent of the V-wave in the jugular pulse, while the x-descent of the A-wave of the RA waveform is preserved (Fig. 166.2).

False-negative and false-positive findings occur for both RA and RV collapse. False negatives occur in patients with elevated right heart pressures or RV hypertrophy, both of which counter the increased pericardial pressures. One cause of diastolic collapse unrelated to CT is a large pleural effusion.

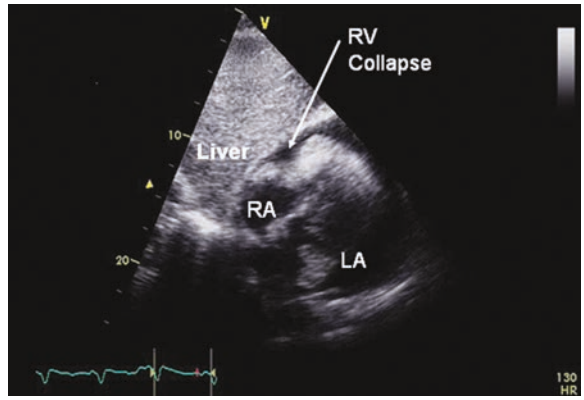


Fig. 166.3 2D-echo demonstrating RV collapse.

Diagnosis of tamponade: detection before haemodynamic embarrassment

Findings can begin during Phase 2 when pericardial pressure is increased, but there is no haemodynamic collapse. Some patients with a large PEF may have variations in flow velocity across the AV valves that exceed normal values, but are not large enough to meet the criteria for tamponade [8]. With pericardiocentesis, these flow velocities return to normal, suggesting a pretamponade state. Just as tamponade is not an all-or-nothing pathological process, the echocardiographic signs should not be viewed as present or absent, but rather as part of a continuum the clinician follows over the course of the disorder. In a haemodynamically stable patient, the development of an 8 mmHg pulsus paradoxus or a respiratory variation across the mitral valve of only 20% may signal impending tamponade, allowing intervention before the patient goes into shock.

Tamponade in the absence of supportive symptoms

If a large PEF or tamponade is suspected, the patient should be initially evaluated for comorbid conditions that may cause false-positive or false-negative findings. A frequently encountered clinical scenario of altered physiology obscuring signs of tamponade is mechanical ventilation. Instead of being negative, intrathoracic pressure during inspiration is now positive, and even more positive than during expiration. Doppler recordings of flow across the tricuspid valve are now greater in expiration, while flow across the mitral valve is greater with inspiration; both are attenuated throughout the respiratory cycle. Also, if the patient is ventilated because of lung disease, they may have pulmonary hypertension and may not demonstrate RA or RV collapse even in the presence of tamponade. The IVC may be dilated due to pulmonary hypertension, RV failure, or tamponade. Other conditions affects signs of tamponade include hypertensive heart disease, volume status, loculated effusions, atrial septal defects, and aortic insufficiency.

Conclusion

PEF and tamponade are not uncommon in patients with both acute and chronic illnesses. Echocardiography is an important tool for identifying the presence of PEF and its haemodynamic consequences. Cardiac tamponade is a continuum and not an all-or-nothing diagnosis. Its diagnosis should be made with the full understanding of the cause of the pericardial disease, and any comorbid conditions that may affect interpretation of the signs.

Acknowledgements

Special thanks to Lishwan Kidd and JoAnn Krzeminski for their help in preparing this manuscript.

References

1. Launberg J, Fruengaard P, Hesse B, Jorgensen F, Elsborg L, and Petri A. (1996). Long-term risk of death, cardiac events and recurrent chest pain in patients with acute chest pain of different origin. *Cardiology*, **87**, 60–6.
2. Maisch B, Seferovic PM, Ristic AD, et al. (2004). Guidelines on the diagnosis and management of pericardial diseases executive summary; The Task force on the diagnosis and management of pericardial diseases of the European society of cardiology. *European Heart Journal*, **25**, 587–610.
3. Imazio M. (2007). Indicators of poor prognosis of acute pericarditis. *Circulation*, **115**, 2739–44.
4. Reinmuller R and Titling R. (1990). MR and CT for detection of cardiac tumors. *Thoracic Cardiovascular Surgery*, **38**(Suppl. 2), 168–72.
5. Sagrista-Sauleda J, Angel J, Permanyer-Miralda G, and Soler-Soler J. (1999). Long-term follow-up of idiopathic chronic pericardial effusion. *New England Journal of Medicine*, **341**, 2054–9.
6. Reddy PS, Curtiss EI, O'Toole JD, and Shaver JA. (1978). Cardiac tamponade: hemodynamic observations in man. *Circulation*, **58**, 265–72.
7. Reddy PS and Curtiss EI. (1990). Cardiac tamponade. *Cardiology Clinics*, **8**, 627.
8. Appleton CP, Hatle LK, and Popp RL. (1988). Cardiac tamponade and pericardial effusion: respiratory variation in transvalvular flow velocities studied by Doppler echocardiography. *Journal of the American College of Cardiology*, **11**, 1020–30.
9. Armstrong WF, Schilt BF, Helper DJ, Dillon JC, and Feigenbaum H. (1982). Diastolic collapse of the right ventricle with cardiac tamponade: an echocardiographic study. *Circulation*, **65**, 1491–6.
10. Leimgruber PP, Klopfenstein HS, Wann LS, and Brooks HL. (1983). The hemodynamic derangement associated with right ventricular diastolic collapse in cardiac tamponade: an experimental echocardiographic study. *Circulation*, **68**, 612–20.
11. Gillam LD, Guyer DE, Gibson TC, King ME, Marshall JE, and Weyman AE. (1983). Hydrodynamic compression of the right atrium: a new echocardiographic sign of cardiac tamponade. *Circulation*, **68**, 294–301.
12. Schairer JR, Biswas S, Keteyian SJ, and Ananthasubramaniam K. (2011). A systematic approach to evaluation of pericardial effusion and cardiac tamponade. *Cardiology in Reviews*, **19**, 233–8.

CHAPTER 167

Management of pericardial tamponade

Santanu Biswas and John J. Frank

Key points

- Haemodynamically unstable cardiac tamponade is a medical emergency, and definitive therapy is usually fluid removal. However, in a select group of clinically stable patients, treatment of the underlying cause may resolve the effusion.
- Assessing the underlying aetiology is important in selecting the proper management strategy, such as for aortic dissection or trauma where surgical management is favoured.
- Aggressive fluid resuscitation is the standard of care for haemodynamic support. The role of other vasoactive agents remains controversial, but inotropes appear to have a theoretical benefit.
- Both pericardiocentesis and surgical approaches are well-established techniques. In most cases, pericardiocentesis remains a first-line procedure due to its safety, speed, and wide availability.
- Whenever possible, pericardiocentesis should be performed with imaging guidance. Exceptions to the case include immediate life-threatening situations.

Introduction

The definitive treatment for cardiac tamponade is fluid removal. However, timing requires a clinical assessment of a patient's stability, rather than the use of any specific finding on echocardiography. If the patient is stable, a case may be made for careful haemodynamic monitoring and serial echocardiography [1]. However, in the unstable patient, urgent aspiration of the pericardial fluid is recommended. Once the decision has been made, the many management aspects to consider include treatment of the underlying cause, the method of haemodynamic support, the actual strategy for fluid removal, and finally, post-procedural care.

Treatment of the underlying cause

Table 167.1 lists various causes of pericardial effusions. While pericarditis is the most common cause for pericardial disease [2], the commonest causes of an effusion leading to clinical tamponade, and its subsequent fluid removal are malignancy and procedure-related perforations [3]. In such cases, pericardiocentesis or surgical fluid removal may be the treatment of choice. In other cases, patients with subclinical tamponade may be managed by addressing the underlying cause, which may subsequently resolve the effusion and avoid the need for an invasive procedure. For example, a large effusion resulting from uraemia usually responds well to dialysis [2]. Such a strategy may be especially attractive in the setting of relative contraindications to pericardiocentesis (e.g. anticoagulation has not been withdrawn). In addition, addressing the causative aetiology usually limits recurrence of effusion.

Supportive measures

Once the decision has been made to pursue drainage, there is often a delay resulting from mobilization of the necessary personnel and equipment. During this time, measures should be taken to support tissue perfusion. The most widely-accepted management strategy is aggressive fluid resuscitation. The usual rationale is that fluids expand intravascular volume, helping to maintain venous pressure above pericardial pressure and thereby continuing to promote circulation [4]. Fluid resuscitation may be beneficial only up to a point, after which, fluids may actually aggravate tamponade [5]. This seemingly counter-intuitive effect is thought to be due to the rapid increase in left ventricular (LV) diastolic pressure against a pericardial sac that is already constrained by the effusion. The increased LV diastolic pressure is transmitted to the pericardium that, in turn, further increases pericardial pressure and then causes RV collapse earlier than would be otherwise observed.

In addition to fluids, various vasopressors, vasodilators, and inotropes may have some theoretical benefit. Human studies are sparse, but animal studies suggest a role for inotropes such as dobutamine and isoprenaline [6,7], as these were shown to preserve cardiac output while counteracting the increased systemic vascular resistance that occurs in tamponade. Studies examining hydralazine and nitroprusside report mixed results [6,8].

If circulatory collapse does occur, then immediate blind pericardiocentesis should be performed as there is no effective medical therapy. Supportive measures, such as chest compressions [9] and mechanical ventilation do little to maintain circulation, and may even be harmful, especially with positive pressure ventilation [10].

In summary, fluid resuscitation remains the standard of care for haemodynamic support in tamponade, but the primary benefit appears to be in hypovolaemic states. Regarding inotropes, the clinical relevance of these agents in humans remains unclear [9].

Table 167.1 Causes of pericardial effusions

Category	Examples
Pericarditis	Viral, bacterial, tuberculosis, autoimmune, idiopathic, post-operative, post-radiation
Trauma	Penetrating injury, blunt trauma, post-surgical
Malignancy	Primary malignancies, metastases to the pericardium, local invasive
Sodium and water retention	Congestive heart failure, nephrotic syndrome, hepatic cirrhosis
Other	Chylopericardium, myxoedema
Idiopathic	

Management strategies

Drainage techniques may be broadly grouped into percutaneous or surgical with many variations in each category (see Table 167.2). Aspects to consider in deciding the proper fluid removal strategy include attention to the suspected aetiology, relative contraindications, and the likelihood of recurrence. For example, in chest trauma either from blunt injury or a penetrating wound, an open surgical approach is recommended given the high likelihood of other unpredictable and potentially catastrophic injuries [11]. Surgery is also favoured over pericardiocentesis in tamponade occurring in the setting of a proximal aortic dissection. Here, the stiff pericardial sac is thought to limit additional blood loss. In such cases, pericardiocentesis may destabilize these patients [12].

Table 167.2 Procedures to remove pericardial effusions

	Comments
Percutaneous	
Blind pericardiocentesis	Should be done only in an emergency
Echocardiography-guided pericardiocentesis	May be done at bedside. Needle entry site can be adjusted to the location of maximal fluid location
Fluoroscopy-guided pericardiocentesis	Needs a room with fluoroscopy capabilities and associated personnel
Pericardiocentesis with intrapericardial sclerosis	Reserved for recurrent malignant effusions
Pericardiocentesis with balloon pericardiotomy	Requires fluoroscopic guidance.
Surgical	
Subxiphoid pericardial window	May be performed with local or general anaesthesia. Decreases effusion recurrence compared with pericardiocentesis, but long-term mortality data are unavailable
Video-assisted thoracoscopic pericardiectomy	Requires general anaesthesia. Usually reserved for effusive-constrictive disease
Pericardioperitoneal shunt	May be performed with local or general anaesthesia
Pericardiectomy	Requires general anaesthesia. Relatively high morbidity procedure

In most other instances, pericardiocentesis is an acceptable first-line strategy given its speed, ease of use, and relative safety. Pericardiocentesis may be performed blind without imaging guidance, however complication rates (5–35%) may be unacceptably high [13]. As a result, either ultrasound or fluoroscopic guidance is recommended. Pericardiocentesis with fluoroscopy usually requires access to a room with fluoroscopic capabilities, haemodynamic monitoring, and support personnel to operate the equipment and monitor the patient. On the other hand, echocardiography-guided pericardiocentesis may be performed at the bedside if needed.

The most common approach for pericardial access is subxiphoid, especially if the procedure is being performed either blindly or with fluoroscopic guidance. With echocardiography, the access site is adapted to the location of the pericardial effusion. The optimum needle entry site is chosen to maximize distance between the myocardium and pericardium and maximize the distance between the needle entry site and other vital organs, such as liver and lungs. Alternative entry sites are often used, as demonstrated in a 20-year case series of echocardiographically-guided pericardiocentesis where the chest wall was favoured over the subxiphoid region in 79% of cases [3].

Pericardiocentesis has been shown to be very safe, with echocardiographic- and fluoroscopically-guided case series reporting total complication rates of 4.7% [3] and 3.7% [14], respectively. The incidence of cardiac perforation was equally low at less than 1%.

Effusion recurrence is a concern; Rafique et al. [15] reported a recurrence rate of 52%. However, recurrence was significantly decreased (12%) when a catheter was left in the pericardial space until drainage decreased to <100 mL over a 24-hour period. The probability of fluid re-accumulation is heavily influenced by the underlying cause. For example, a malignant effusion has a higher likelihood of recurrence whereas an effusion related to inadvertent cardiac perforation in a catheter-based procedure is expected to be self-limiting.

Pericardial sclerosis can be used, especially in malignant effusions, to decrease effusion recurrence. Sclerosing agents (e.g. tetracycline, doxycycline, bleomycin, cisplatin, thioTEPA) scar the pericardium and prevent the visceral pericardium from secreting additional fluid. Success rates are greatly affected by the nature of the malignancy; however, given the generally poor prognosis of this population, long-term data are usually unavailable. Nevertheless, a retrospective review comparing pericardial sclerosis versus surgical pericardial window reported similar recurrence rates (13 and 14%, respectively) [16].

Another modification to the traditional pericardiocentesis is balloon pericardiotomy with the pericardium being accessed from the subxiphoid region. Initially, pericardiocentesis is performed in the usual fashion, but the initial catheter is then exchanged over a guide wire for a balloon-tipped catheter filled with iodinated contrast. The catheter is advanced, under fluoroscopic guidance, until it straddles the pericardial sac. Once proper positioning is confirmed, the balloon is inflated to create the window. While the procedural success and freedom from short-term recurrence is high, long-term success rates cannot be evaluated given the overall poor prognosis due to the underlying disease [17].

Various surgical techniques are described for the management of pericardial effusions; creation of a pericardial window through a subxiphoid incision is the commonest method used. This procedure is relatively quick, safe, and can even be performed under local anaesthesia [18]. Regarding overall efficacy, a study comparing populations receiving a subxiphoid pericardial window

versus pericardiocentesis showed decreased effusion recurrence (4.6 versus 16.5%, respectively); however, the no survival benefit was shown, likely due to the poor prognosis of the underlying cause [19].

Other relatively minor surgical options include video-assisted thorascopic pericardectomy and the creation of a pericardioperitoneal shunt. Video-assisted thorascopic pericardiectomy is usually used in the setting of effusive-constrictive disease. The use of a video camera allows good visualization of the pericardium and safe pericardial resection; however, the procedure does require use of general anaesthesia. The pericardio-peritoneal shunt is a recently described procedure that may be performed under general or local anaesthesia. The procedure appears to be safe and effective, but larger case series or comparative studies are lacking.

The most aggressive surgical method is pericardiectomy, which is usually reserved for refractory constrictive pericarditis. Various approaches may be used including subxiphoid, left anterior thoracotomy, median sternotomy, and bilateral anterior thoracotomy. The subxiphoid approach carries with it the lowest risk of complications, but also suffers from a higher probability of recurrence. The other approaches have higher morbidity rates, but permit a wider area of pericardial resection, which directly affects effusion recurrence [20].

Post-procedure care

After the initial procedure has been completed, the patient should be transferred to a unit not only experienced with recognizing cardiac tamponade, but also experienced in managing drain catheters. If a catheter is left in the pericardium, there is no official guideline as to how long it should remain, although some experts suggest that the catheter may be removed once the quantity of fluid drained is <50 mL in a 24-hour period [9]. Given the high likelihood of recurrence and the emergent nature of cardiac tamponade, the unit personnel should not only be familiar with catheter maintenance protocols, but also have ready access to pericardiocentesis equipment should the need arise to perform a repeat procedure. In addition, the unit should continue to observe for complications that either were not immediately apparent during the procedure or were the result of the procedure itself. Examples include inadvertent arterial puncture and purulent pericarditis. Finally, it should be emphasized that overall mortality is primarily influenced by the underlying disease and treatment should be guided accordingly once a cause has been established.

Conclusion

As cardiac tamponade is a medical emergency, prompt recognition is the key to successful management. Aggressive fluid resuscitation remains the clinical standard for medical treatment, although fluid removal is the ultimate goal. However, there are important differences among the approaches for fluid removal, pericardiocentesis with either echocardiographic or fluoroscopic guidance should be used as the initial procedure for the majority of cases. Finally, it should be emphasized that overall mortality is primarily influenced by the underlying disease; treatment should be guided accordingly once a cause has been established.

Acknowledgements

Special thanks to JoAnn Krzeminski in preparation of this manuscript.

References

1. Wei J, Yang HS, Tsai SK, et al. (2011). Emergent bedside real-time three-dimensional transesophageal echocardiography in a patient with cardiac arrest following a caesarean section. *European Journal of Echocardiography*, **12**, E16.
2. Maisch B, Seferovic PM, Ristic AD, et al. (2004). Guidelines on the diagnosis and management of pericardial diseases executive summary; The Task force on the diagnosis and management of pericardial diseases of the European society of cardiology. *European Heart Journal*, **25**, 587–610.
3. Tsang TS, Enriquez-Sarano M, Freeman WK, et al. (2002).Consecutive 1127 therapeutic echocardiographically guided pericardiocenteses: clinical profile, practice patterns, and outcomes spanning 21 years. *Mayo Clinic Proceedings*, **77**, 429–36.
4. Cooper FW, Stead EA, and Warren JV. (1944). The beneficial effect of intravenous infusions in acute pericardial tamponade. *Annals of Surgery*, **120**, 822–5.
5. Cogswell TL, Bernath GA, Keelan MH Jr, Wann LS, and Klopfenstein HS. (1986). The shift in the relationship between intrapericardial fluid pressure and volume induced by acute left ventricular pressure overload during cardiac tamponade. *Circulation*, **74**, 173–80.
6. Millard RW, Fowler NO, and Gabel M. (1983). Hemodynamic and regional blood flow distribution responses to dextran, hydralazine, isoproterenol and amrinone during experimental cardiac tamponade. *Journal of the American College of Cardiology*, **1**, 1461–70.
7. Hoit BD, Gabel M, and Fowler NO. (1990). Hemodynamic efficacy of rapid saline infusion and dobutamine versus saline infusion alone in a model of cardiac rupture. *Journal of the American College of Cardiology*, **16**, 1745–9.
8. Fowler NO, Gabel M, and Holmes JC. (1978). Hemodynamic effects of nitroprusside and hydralazine in experimental cardiac tamponade. *Circulation*, **57**, 563–7.
9. Spodick DH. (2003). Acute cardiac tamponade. *New England Journal of Medicine*, **349**, 684–90.
10. Moller CT, Schoonbee CG, and Rosendorff C. (1979). Haemodynamics of cardiac tamponade during various modes of ventilation. *British Journal of Anaesthesia*, **51**, 409–15.
11. Blatchford JW, 3rd and Anderson RW. (1985). The evolution of the management of penetrating wounds of the heart. *Annals of Surgery*, **202**, 615–23.
12. Isselbacher EM, Cigarroa JE, and Eagle KA. (1994). Cardiac tamponade complicating proximal aortic dissection. Is pericardiocentesis harmful? *Circulation*, **90**, 2375–8.
13. Wong B, Murphy J, Chang CJ, Hassenein K, and Dunn M. (1979). The risk of pericardiocentesis. *American Journal of Cardiology*, **4**, 1110–14.
14. Duvernoy O, Borowiec J, Helmius G, and Erikson U. (1992). Complications of percutaneous pericardiocentesis under fluoroscopic guidance. *Acta Radiologica*, **33**, 309–13.
15. Rafique AM, Patel N, Biner S, et al. (2011). Frequency of recurrence of pericardial tamponade in patients with extended versus nonextended pericardial catheter drainage. *American Journal of Cardiology*, **108**, 1820–5.
16. Girardi LN, Ginsberg RJ, and Burt ME. (1997). Pericardiocentesis and intrapericardial sclerosis: effective therapy for malignant pericardial effusions. *Annals of Thoracic Surgery*, **64**, 1422–7.
17. Ziskind AA, Pearce AC, Lemmon CC, et al. (1993). Percutaneous balloon pericardiotomy for the treatment of cardiac tamponade and large pericardial effusions: description of technique and report of the first 50 cases. *Journal of the American College of Cardiology*, **21**, 1–5.
18. Chen EP and Miller JI. (2002). Modern approaches and use of surgical treatment for pericardial disease. *Current Cardiology Reports*, **4**, 41–6.
19. McDonald JM, Meyers BF, Guthrie TJ, Battafarano RJ, Cooper JD, and Patterson GA. (2003). Comparison of open subxiphoid pericardial drainage with percutaneous catheter drainage for symptomatic pericardial effusion. *Annals of Thoracic Surgery*, **76**, 811–15.
20. Piehler JM, Pluth JR, Schaff HV, Danielson GK, Orszulak TA, and Puga FJ. (1985). Surgical management of effusive pericardial disease. Influence of extent of pericardial resection on clinical course. *Journal of Thoracic and Cardiovascular Surgery*, **90**, 506–16.

PART 5.14

Pulmonary hypertension

CHAPTER 168

Pathophysiology and causes of pulmonary hypertension

Laura Price and S. John Wort

Key points

- Pulmonary hypertension (PH) in the critically ill may reflect an acute cause and/or an exacerbation of pre-existing PH, and is probably under-diagnosed.
- The presence of right ventricular (RV) dysfunction and failure is universally an adverse prognostic feature. In cases of severe, PH, associated 'PH crises' and severe RV failure may progress rapidly to cardiovascular collapse. This is especially the case in RV 'afterload mismatch', when a normal RV is exposed to a sudden increase in afterload, such as following a massive pulmonary embolism (PE) or after heart transplantation.
- Acute *de novo* causes of PH include those relating to acute lung injury, sepsis, and acute PE. Post-operative PH is not an infrequent problem and has many contributing factors. The most prevalent cause of PH on ICU is likely to relate to left-sided heart disease with raised filling pressures ('group 2' PH), which may often co-exist with other causes.
- Patients with pre-existing pulmonary arterial hypertension may require intensive care unit (ICU) management to manage severe RV failure (due to disease progression, intercurrent illness, or post-operatively). This is a very high-risk patient group with an ICU mortality of up to 50%.
- Several general physiological challenges in the critical care environment are recognized to increase pulmonary vascular resistance and/or worsen RV function, including the effects of positive-pressure ventilation, hypoxaemia, and acidosis. In patients with PH, these should, if possible, be minimized.

Introduction

Pulmonary hypertension (PH) occurs frequently in critically-ill patients as part of several ICU syndromes, and, less commonly, as a primary cause for ICU admission. The presence of PH, especially when associated with right ventricular (RV) failure, is associated with high mortality. PH in the intensive care unit (ICU) may be due to acute or acute-on-chronic causes. RV failure is the mode of death in patients with pre-existing 'chronic' pulmonary arterial hypertension (PAH). This chapter outlines the definitions, epidemiology and pathophysiology of acute and acute-on-chronic PH, and resulting RV failure, in the critically ill.

Definitions

Pulmonary hypertension is defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg when measured at right-heart catheterization. Precapillary or PAH is defined when the pulmonary capillary or artery wedge pressure (PAWP), is ≤15 mmHg [1]. This is normally, though not always, associated with a low cardiac output and hence a high pulmonary vascular resistance (PVR), calculated according to the equation (mPAP – PAWP)/cardiac output. When PAWP exceeds 15 mmHg, pulmonary venous hypertension is present, although this is usually due to left heart disease. Importantly, however, these definitions were created for patients with chronic PH and may not be representative of patients with acute rises in PVR or acute RV dysfunction.

Acute right ventricular failure

The healthy pulmonary circulation is a 'high-flow–low-pressure system' able to tolerate large increases in blood flow without increasing pulmonary artery pressures. This occurs by recruitment and dilatation of pulmonary vessels through the actions of chemical stimuli (e.g. hypoxaemia), humoral, or neuronal transmitters (e.g. catecholamines, nitric oxide and prostaglandins) on muscular pulmonary vessels. In health, PVR thereby falls as blood flow rises.

In the setting of a pathologically raised PVR, increased RV wall tension increases end-diastolic volume and may overwhelm the RV, leading to ventricular dysfunction and failure. In acute PH, for example, in acute pulmonary embolism, where the thin-walled RV is 'naïve' to a high afterload, this may occur at relatively modest elevations in PVR [2]. Conversely, with an RV exposed to long-standing PH, the more gradual elevation in afterload allows the ventricle to adapt through hypertrophy, allowing stroke volume to be maintained. In either setting, a rapid decline in biventricular function may occur due to right-left ventricular interactions and the phenomenon of ventricular interdependence [3], reducing cardiac output and oxygen delivery. Mechanisms include:

- RV dysfunction reducing pulmonary blood flow and thus LV preload.
- Displacement of the intraventricular septum by the dilated RV impinging on LV filling.
- As LV filling may depend on atrial contraction, atrial fibrillation (if present) and vasodilating therapies will be tolerated very poorly.

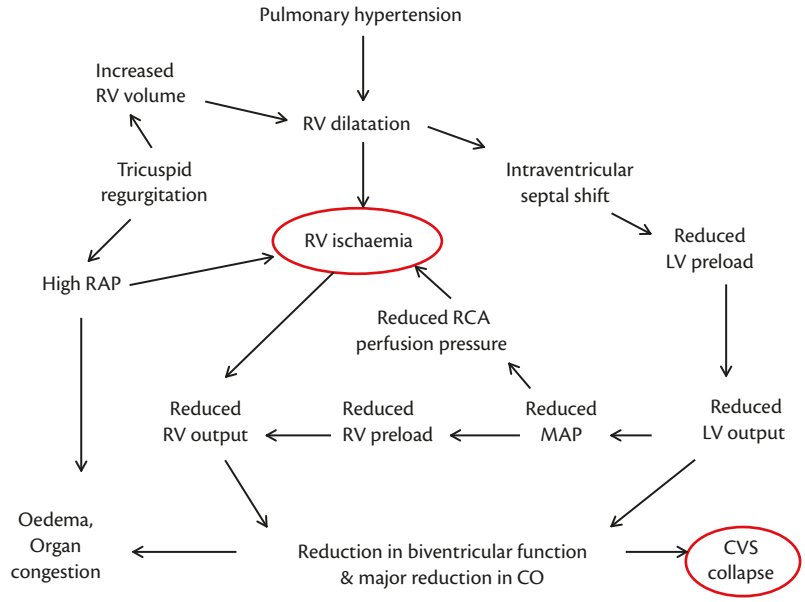


Fig. 168.1 Factors contributing to the onset of right ventricular failure in the setting of pulmonary hypertension.
PVR, pulmonary vascular resistance; CO, cardiac output; RAP, right atrial pressure; MAP, mean arterial pressure; RV, right ventricle; LV, left ventricle; RCA, right coronary artery; CVS, cardiovascular system.

The resulting systemic hypotension reduces the pressure gradient between the aorta and RV required for right coronary artery perfusion, thus precipitating RV ischaemia. In the setting of high PVR, right coronary perfusion is restricted to systole (rather than during the whole cardiac cycle) [4], maintaining aortic root pressure above RV pressure is paramount to avoid a downward spiral of RV failure (Fig. 168.1).

Clinically, acute or acute-on-chronic RV failure is characterized by a reduction in cardiac output and an elevation in RV filling pressure. However, no universal definition exists for this syndrome. In patients with (usually pre-existing) severe PH, 'PH crises' may occur, as defined by acute rises in PVR, such that systemic and pulmonary pressures equalize, with the risk of RV ischaemia and rapid cardiovascular collapse. RV failure may also present with elevated venous filling pressures with signs including raised jugular venous pressure (with 'CV waves' due to tricuspid regurgitation), limb oedema, pulsatile hepatomegaly, renal, and gut dysfunction.

RV failure causes morbidity and mortality with PH due to any cause. Although more commonly occurring in response to an elevated PVR, RV failure can also occur in conditions associated with decreased contractility, such as sepsis, myocarditis, or RV infarction.

Causes and epidemiology of PH in ICU

The most recent classification of PH (Box 168.1) is useful when considering patients with PH in the ICU due to pre-existing causes. It does not specifically encompass causes of PH relating to critical illness, nor contributions reflecting changes in acute physiology. As such, an ICU patient presenting with PH may broadly be classified into acute, pre-existing 'chronic' causes (or both), as well as ICU-related and iatrogenic causes (Box 168.1).

The relative prevalence of PH subtypes in the ICU setting is unknown. In general, pulmonary hypertension in ICU patients is most probably that related to group 2 (associated with left ventricular failure due to an increase in left atrial pressure) and group 3 (chronic hypoxaemic/hypercapnic lung disease such as chronic obstructive pulmonary disease) causes. Group 1 patients are less common, but still important causes of acute-on-chronic PH, where RV dysfunction is likely to be severe at presentation. Important acute causes of PH in the ICU setting include massive pulmonary embolism, acute lung injury, and following cardiothoracic surgery, which do not fit neatly into any of the classifications shown in Box 168.1.

Acute pulmonary hypertension in ICU

PH is a feature of several acute illnesses. As described in Chapter 169, 'Diagnosis of Management of Pulmonary Hypertension', the clinical signs of PH and RV dysfunction/failure are often non-specific, and the effects of ICU syndromes, and their treatment on the pulmonary circulation and the RV should be remembered. The most common important syndromes and factors contributing to PH are outlined.

Pulmonary embolism

Although unusual primary causes of ICU admission, massive and sub-massive PE are important causes of acute RV failure. Further to mechanical obstruction of the pulmonary circulation, hypoxaemia, and local vasoconstrictor release (e.g. serotonin) contribute to acute PH and acute RV dysfunction. In previously healthy patients, the degree of pulmonary obstruction correlates with haemodynamic severity:

- 5–15% angiographic obstruction causes systemic arterial hypoxaemia.
- 25% obstruction causes PH.
- 35% obstruction or mPAP >30 mmHg elevates right atrial pressure.
- A measurable haemodynamic disturbance occurs with 50% obstruction (the latter two also causing an increased central venous pressure) [2].

Registry data demonstrate a clear mortality increase in patients with haemodynamic instability due to acute PE [5].

Acute lung injury

RV dysfunction related to PH is seen in 12.5 (7–25)% of patients with acute lung injury (ALI) [6], although it was previously more common [7]. PH may also be present in non-pulmonary sepsis. One reason for the reduced frequency of PH is the introduction of lung-protective ventilation strategies [8]. However, even in the 'modern era', the presence of PH remains clinically important, with increased indexed PVR and transpulmonary gradient (mPAP – pulmonary arterial wedge pressure (PAWP), risk factors for mortality [9].

There are multiple contributing causes for PH (Fig. 168.1), which vary both anatomically and longitudinally throughout the illness. Early on, endothelial dysfunction causes release of inflammatory mediators and an imbalanced production of vasoconstrictors (e.g. endothelin-1) over vasodilator substances (e.g. nitric oxide), levels of which relate to PH severity [10]. Early studies demonstrate obstruction of the pulmonary microcirculation (Fig. 168.3), which has more recently been associated clinically with increased ventilation-perfusion mismatch, and strongly associated with increased early mortality [11].

Following activation of the pulmonary microvascular endothelium, which initiates inflammation and intravascular coagulation, intravascular microthrombi, fibrin, and intravascular sequestration of cells contribute to the observed pulmonary capillary occlusion. Clots can also form in larger vessels. Vascular tone is increased in muscular pulmonary arterioles and veins due to hypoxic pulmonary vasoconstriction (HPV) in an attempt to maintain ventilation/perfusion matching. An imbalance of vasoactive mediators also contributes, as does reduced lung volume, oedema, positive end-expiratory pressure (PEEP), and atelectasis by causing extrinsic vessel compression. From 14 days onwards, pulmonary vascular remodelling occurs, with neomuscularization of previously non-muscularized arterioles. Post-capillary PH may result from any cause of raised left atrial pressure. Some or all of these factors may contribute to the increase in PVR seen in acute respiratory distress syndrome (ARDS; see Fig. 168.2).

Pulmonary hypertension following cardiothoracic surgery

Post-operative PH may occur following certain cardiothoracic procedures and is associated with a high mortality. It is well recognized to follow corrective congenital cardiac surgery, valve replacement

Box 168.1 Updated clinical classification of pulmonary hypertension

Pulmonary arterial hypertension

- Idiopathic PAH.
- **Heritable PAH**:
  - BMPR2.
  - ALK-1, ENG, SMAD9, CAV1, KCNK3.
  - Unknown.
- Drug and toxin induced.
- **Associated with**:
  - Connective tissue disease.
  - HIV infection.
  - Portal hypertension.
  - Congenital heart diseases.
  - Schistosomiasis.

Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

Persistent pulmonary hypertension of the newborn

Pulmonary hypertension due to left heart disease

- Left ventricular systolic dysfunction.
- Left ventricular diastolic dysfunction.
- Valvular disease.
- Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies.

Pulmonary hypertension due to lung diseases and/or hypoxia

- Chronic obstructive pulmonary disease.
- Interstitial lung disease.
- Other pulmonary diseases with mixed restrictive and obstructive pattern.
- Sleep-disordered breathing.
- Alveolar hypoventilation disorders.
- Chronic exposure to high altitude.
- Developmental lung diseases.

Chronic thromboembolic pulmonary hypertension

Pulmonary hypertension with unclear multifactorial mechanisms

- **Haematological disorders**: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy.
- **Systemic disorders**: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis.
- **Metabolic disorders**: glycogen storage disease, Gaucher disease, thyroid disorders.
- **Others**: tumoural obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Adapted from *Journal of the American College of Cardiology*, Simonneau G et al., 'Updated clinical classification of pulmonary hypertension, 62, 25S, pp. D34–D41, copyright 2013, with permission from Elsevier and the American College of Cardiology.

BMPR, bone morphogenic protein receptor type II; CAV1, caveolin-1; ENG, endoglin; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension.

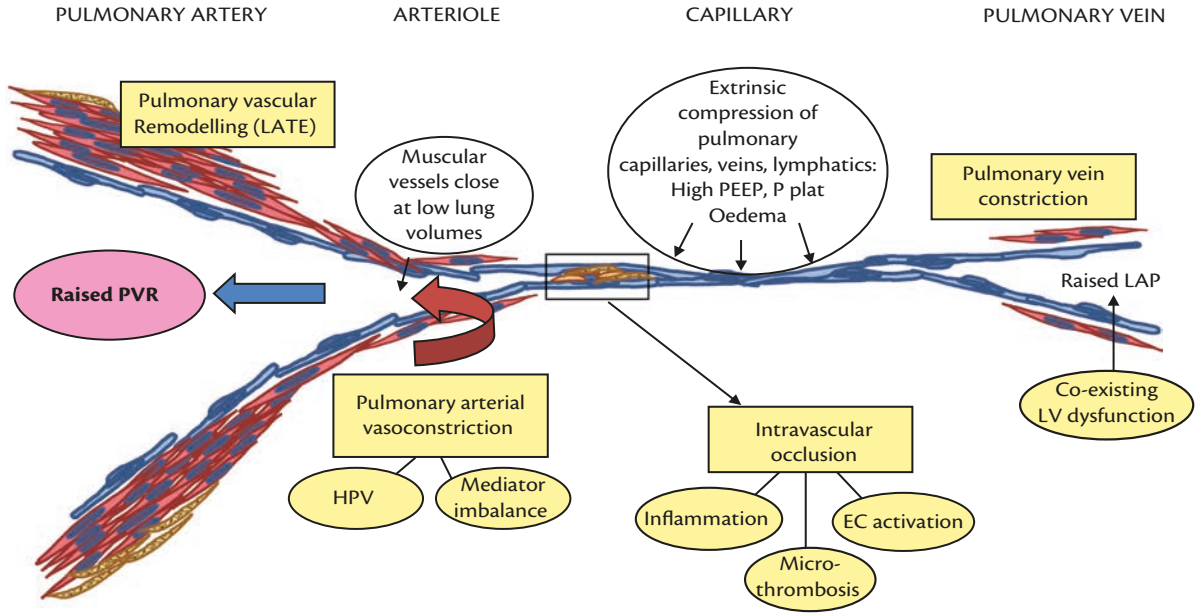


Fig. 168.2 Factors contributing to pulmonary hypertension in ARDS.
PVR, pulmonary vascular resistance; LAP, left atrial pressure; LV, left ventricle; HPV, hypoxic vasoconstriction; PEEP, positive end-expiratory pressure; Pplat, plateau pressure; EC, extracellular.
Reproduced from Price LC et al., 'Pathophysiology of pulmonary hypertension in acute lung injury', *American Journal of Physiology: Lung Cellular and Molecular Physiology*, **302**(9), pp. L803–15, copyright 2012, with permission from the American Physiological Society.

surgery (mitral more than aortic), cardiac transplantation surgery, and left ventricular assist device insertion. Predisposing factors include pre-existing PH, endothelial dysfunction related to cardiopulmonary bypass, positive-pressure, and single-lung ventilation, and the effects of certain drugs that increase PVR or depress myocardial function.

Effects of ventilatory strategies on the pulmonary circulation

Of several ICU factors recognized to increase PVR in ventilated patients, those potentially increasing PVR and reducing pulmonary blood flow include hypoxaemia, hypercapnia, and compression of the pulmonary circulation at extremes of lung volumes [12]. This latter phenomenon is for example seen after Fontan procedures where institution of positive pressure ventilation markedly increases intrathoracic pressure, impedes passive lung perfusion, and reduces cardiac output [13]. In ALI, high plateau pressures and high levels of PEEP increase PVR, and worsen cardiac output. While reduced with lower tidal volume ventilation, this must be balanced against the effects of resulting hypercapnia, which itself also increases PVR [14].

Chronic pulmonary hypertension

Chronic, or 'group 1', PAH is a rare, but devastating condition (Table 168.1) comprising idiopathic PAH (previously called primary PH

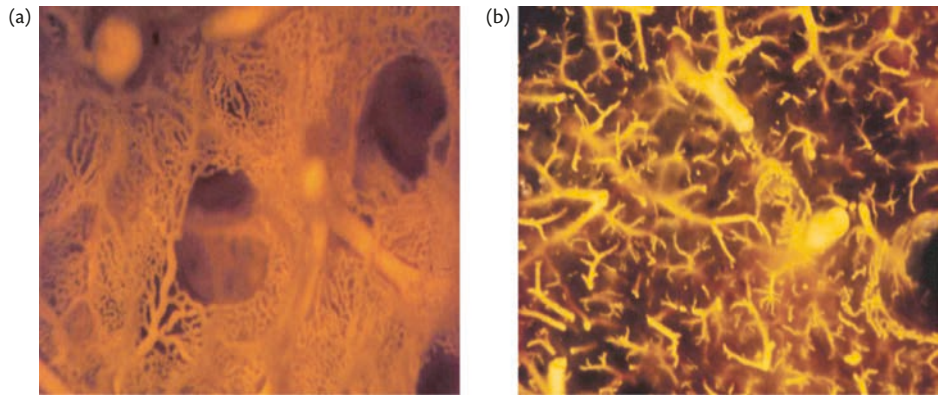


Fig. 168.3 Decreased vascular density in acute respiratory distress syndrome. Stereoscopic perfusion of pulmonary circulation with silicon polymers in post-mortem lung specimens from a patient who died 14 days following the onset of ARDS. (a) Normal human lung capillaries. (b) Lung capillaries day 14 ARDS.
Reproduced from Price LC et al., 'Pathophysiology of pulmonary hypertension in acute lung injury', *American Journal of Physiology: Lung Cellular and Molecular Physiology*, **302**(9), pp. L803–15, copyright 2012, with permission from the American Physiological Society.

Table 168.1 Causes of pulmonary hypertension in ICU patients

Acute *de novo* PH in ICU	Acute-on-chronic PH in ICU	ICU-related/iatrogenic
Acute pulmonary embolism Acute lung injury, sepsis **Acute post-capillary (group 2) PH**: ◆ Pulmonary venous hypertension due to LV dysfunction/failure with left atrial hypertension. ◆ Acute MI, congestive cardiac failure, diastolic dysfunction, severe valvular heart disease (MR, MS). Acute exacerbation of hypoxic +/– hypercapnic lung disease (with acute group 3 PH; e.g. asthma, COPD, IPF)	**Pulmonary arterial hypertension (group 1)**: ◆ Acute PAH exacerbation (due to hypoxia, sepsis/ALI, PE, peri-operative, pregnancy-related, etc.). ◆ Disease progression (no obvious precipitant). **Post-capillary (group 2) PH**: any acute-on-chronic cause PH due to other causes of pre-existing PH (groups 3–5) with an acute exacerbation	**Acute increase in PVR**: ◆ Hypoxaemia, acidosis, hypercapnia, pain (sympathetic stimulation), laryngoscopy. ◆ Drug-related increases in PVR (e.g. high-dose vasopressors; protamine). ◆ High Pplat or PEEP during IPPV causing small pulmonary vessel compression in high 'West zones' (also follows oedema). ◆ Endothelial dysfunction related to cardiopulmonary bypass

PAH pulmonary arterial hypertension; PH pulmonary hypertension; PVR pulmonary vascular resistance; Pplat plateau pressure; PEEP positive end-expiratory pressure; IPPV intermittent positive-pressure ventilation; COPD chronic obstructive pulmonary disease; IPF interstitial pulmonary fibrosis; MI myocardial infarction; MR mitral regurgitation; MS mitral stenosis; PE pulmonary embolism; LV left ventricular; ALI, acute lung injury.

(PPH)) or PAH due to several associated conditions, e.g. heritable PAH, PAH associated with HIV infection, congenital heart disease, connective tissue diseases and exposure to notable drugs and toxins [15]. Pulmonary veno-occlusive disease is a subgroup with occlusive lesions in small post-capillary pulmonary veins, where lung transplant is the only realistic treatment option. Before the modern treatment era, PAH therapy was usually symptomatic and life expectancy was short. Recent treatment advances have occurred in the last decade however the outlook remains poor with 3-year survival under 60% [16].

'Non-PAH' causes include PH secondary to left-sided heart disease ('group 2') and chronic respiratory disease ('group 3'). Chronic thromboembolic PH ('group 4' PH), is important to diagnose as treatment options differ significantly from other causes of PH, with pulmonary endarterectomy being a realistic cure for patients with surgically accessible disease.

Of all types of chronic PH, PAH is the best characterized. PAH pathophysiology and common acute syndromes will be briefly described.

Pathophysiology of PAH

Pulmonary vascular remodelling defines the characteristic proliferative lesions that occur in PAH in small- and medium-sized muscular pulmonary arteries. This is a maladaptive response where vessel walls thicken in response to a sustained rise in intravascular pressure. The findings originally described in patients with congenital heart diseases including early 'reversible' lesions, were medial hypertrophy, arteriolar neomuscularization, intimal proliferation and fibrosis. 'Irreversible' later lesions included fibrinoid necrosis and, in some cases, plexiform lesions (Fig. 168.4) [17]. These lesions occlude and obliterate the pulmonary circulation, reducing the capacity and thus compliance of the pulmonary vascular bed. Pulmonary endothelial dysfunction is an important initiating feature that increases vasoconstricting, pro-proliferative mediators (e.g. endothelin-1 (ET-1), serotonin and thromboxane A_2), and reduces levels of vasodilating, anti-proliferative mediators (e.g. nitric oxide (NO), prostaglandin I_2, (PGI2, prostacyclin)). Further to the resulting vasoconstriction, the prominent effect of treatments targeting endothelial dysfunction is that of

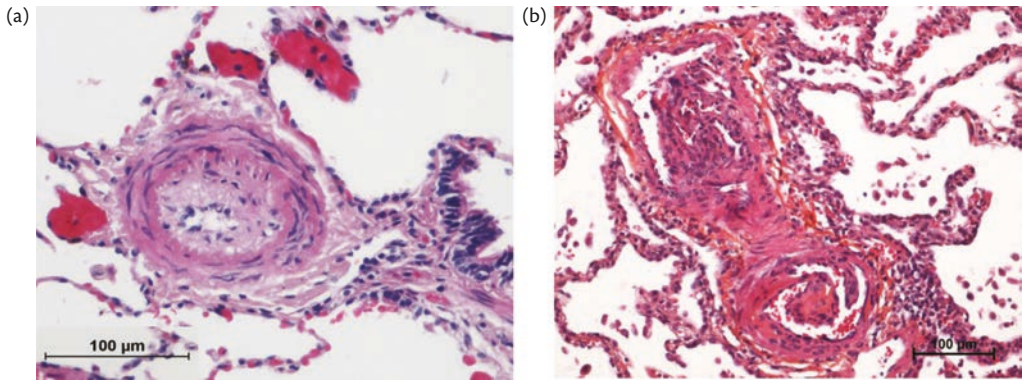


Fig. 168.4 Pulmonary vascular remodelling in PAH. Haematoxylin-eosin stained paraffin-embedded lung sections from a patient with idiopathic PAH following lung transplantation showing a patent remodelled pulmonary artery (a) and an obliterative plexiform lesion (b).
Courtesy of Dr Peter Dorfmuller, Hôpital Marie Lannelongue, University of South Paris, France.

structural vessel changes. The resulting excessive vascular cell growth has even been likened to a cancer-like phenotype, and the influence of growth factors and inflammation is important. A positive family history is found in up to 10% of patients with idiopathic PAH, with mutations seen in the 'pulmonary hypertension gene', bone morphogenetic protein receptor (BMPR) type II, which controls transforming growth factor (TGF) beta signaling. Reduced BMPR-II signalling is also a feature of diverse forms of PAH without mutations, resulting in the inability to dampen the growth of vascular cells.

Acute PAH exacerbations

Fortunately, ICU admission of patients with previously undiagnosed PAH in severe RV failure is increasingly rare. Patients with known PAH may present with a 'PH exacerbation' in severe RV failure due to either a known cause (e.g. infection, atrial dysrhythmias), or in the final stages of their disease with no further medical treatment options. Deterioration can be very rapid. ICU mortality relating to RV failure is up to 50% and almost invariably fatal if the patient is intubated. Predictors of ICU mortality include low systemic blood pressure on ICU admission, elevated serum brain natriuretric peptide and C-reactive protein, low serum sodium, and renal dysfunction [18]. An important multicentre study of cardiopulmonary resuscitation in these patients showed that, although attempts were mostly unsuccessful, resuscitation was most likely if the precipitant for deterioration was known [19].

Particularly high-risk scenarios for these patients include pregnancy and the perioperative setting. Maternal mortality exceeds 25%, even in recent series [20], which relates to the inability of the 'fixed' pulmonary circulation to cope with the cardiovascular demands related to pregnancy. The risk of RV failure increases as blood volume increases from 20 to 24 weeks, and during the peripartum period. Anaesthesia and surgery precipitate PH crises, RV failure, and high mortality in patients with severe PH, especially in those undergoing emergency surgery. Furthermore, bronchoscopy is a high-risk procedure with an increased risk of biopsy-related bleeding.

Conclusion

PH in ICU patients may reflect worsening of pre-existing PH and/or an acute *de novo* cause. PH is probably under-diagnosed in ICU patients. Multiple factors relating to acute derangements in physiology during critical illness contribute, including iatrogenic factors such as the effects of positive pressure ventilation. The adverse effect of increased afterload on RV function is associated with worse outcomes. The resulting acute RV failure may be difficult to monitor and very challenging to manage.

References

1. Galiè N, Humbert M, Vachiery JL, et al. (2015). ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *European Respiratory Journal*, **46**(4), 903–75.
2. McIntyre KM and Sasahara AA. (1974). Determinants of right ventricular function and hemodynamics after pulmonary embolism. *Chest*, **65**, 534–43.
3. Jardin F, Dubourg O, Gueret P, Delorme G, and Bourdarias JP. (1987). Quantitative two-dimensional echocardiography in massive pulmonary embolism: emphasis on ventricular interdependence and leftward septal displacement. *Journal of the American College of Cardiology*, **10**, 1201–6.
4. Gibbons Kroeker CA, Adeeb S, Shrive NG, and Tyberg JV. (2006). Compression induced by RV pressure overload decreases regional coronary blood flow in anesthetized dogs. *American Journal of Physiology—Heart and Circulatory Physiology*, **290**, H2432–8.
5. Kasper W, Konstantinides S, Geibel A et al. (1997). Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. *Journal of the American College of Cardiology*, **30**, 1165–71.
6. Price LC, McAuley DF, Marino PS, Finney SJ, Griffiths MJ, and Wort SJ. (2012). Pathophysiology of Pulmonary Hypertension in Acute Lung Injury. *American Journal of Physiology—Lung Cellular and Molecular Physiology*, **302**(9), L803–15.
7. Zapol WM and Snider MT. (1977). Pulmonary hypertension in severe acute respiratory failure. *New England Journal of Medicine*, **296**, 476–80.
8. Vieillard-Baron A, Schmitt JM, Augarde R, et al. (2001). Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. *Critical Care Medicine*, **29**, 1551–5.
9. Bull TM, Clark B, McFann K, and Moss M. (2010). Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. *American Journal of Respiratory and Critical Care Medicine*, **182**, 1123–8.
10. Langleben D, DeMarchie M, Laporta D, Spanier AH, Schlesinger RD, and Stewart DJ. (1993). Endothelin-1 in acute lung injury and the adult respiratory distress syndrome. *American Review of Respiratory Disease*, **148**, 1646–50.
11. Nuckton TJ, Alonso JA, Kallet RH, et al. (2002). Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *New England Journal of Medicine*, **346**, 1281–6.
12. West J (ed.) (2011). *Respiratory Physiology*. Baltimore, MD: Lippincott and Williams.
13. Shekerdemian LS, Shore DF, Lincoln C, Bush A, and Redington AN. (1996). Negative-pressure ventilation improves cardiac output after right heart surgery. *Circulation*, **94**, II49–55.
14. Mekontso Dessap A, Charron C, Devaquet J, et al. (2009). Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. *Intensive Care Medicine*, **35**, 1850–8.
15. Simonneau G, Gatzoulis MA, Adatia I, et al. (2013). Updated clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology*, **62**(25S), D34–41.
16. Humbert M, Sitbon O, Chaouat A, et al. (2010). Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation*, **122**, 156–63.
17. Wagenvoort CA. (1989). *Biopsy Pathology of the Pulmonary Vasculature*. Cambridge: Cambridge University Press.
18. Sztrymf B, Souza R, Bertoletti L, et al. (2010). Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. *European Respiratory Journal*, **35**, 1286–93.
19. Hoeper MM, Galie N, Murali S, et al. (2002). Outcome after cardiopulmonary resuscitation in patients with pulmonary arterial hypertension. *American Journal of Respiratory and Critical Care Medicine*, **165**, 341–4.
20. Bedard E, Dimopoulos K, and Gatzoulis MA. (2009). Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? *European Heart Journal*, **30**, 256–65.

CHAPTER 169

Diagnosis and management of pulmonary hypertension

Philip Marino and Laura Price

Key points

- The diagnosis of PH is suggested by echocardiography, ideally with invasive haemodynamic assessment to confirm the anatomical level (pre-/post-capillary), which determines accurate diagnosis of PH and thus influences management.
- The principles of managing right ventricular (RV) failure in a patient with PH include augmentation of RV function and maintenance of aortic root pressure (avoiding RV ischaemia), avoidance of arrhythmias, and reduction in pulmonary afterload.
- Systemic vasoactive agents and pulmonary vasodilators play an important role. The characteristics of individual agents must be considered and monitored carefully.
- Patients with pulmonary arterial hypertension, pulmonary embolism, or chronic thromboembolic PH should be anticoagulated. Those with haemodynamically unstable PE may require thrombolysis.
- Surgical options exist for patients with PH and RV failure including the use of atrial septostomy, pulmonary embolectomy, and pulmonary endartectomy for those with proximal chronic thromboembolic PH. Support of RV function is advancing through the use of extracorporeal circulatory circulations, increasingly used as a bridge to transplantation in patients with PH.

Introduction

Pulmonary hypertension (PH) is most likely to be detected when severe and associated with right ventricular (RV) dysfunction, and is probably under-diagnosed in the ICU setting. Although several advances have been made in outpatient management, no randomized, controlled trials have included ICU patients. Treatments are based on experimental studies or case reports/series and management can be challenging.

Diagnosis

The presence of PH and/or RV dysfunction may be suggested by clinical examination, although many of the signs will often be non-specific in ICU patients. An electrocardiogram may show enlargement of proximal pulmonary arteries (with peripheral pruning in most patients), and new-onset right heart strain. Chest radiography is often normal but may show right heart chamber enlargement. On computed tomography (CT), an enlarged central pulmonary artery diameter (exceeding that of the thoracic aorta) is usually seen (Fig. 169.1), although this sign is less reliable in lung disease. In ARDS, the presence of microvascular occlusion may be suggested by an elevation in pulmonary dead space fraction, if this is measured at the bedside. Detection of PH and RV dysfunction however rely mainly on a high index of suspicion and a combination of biomarkers,

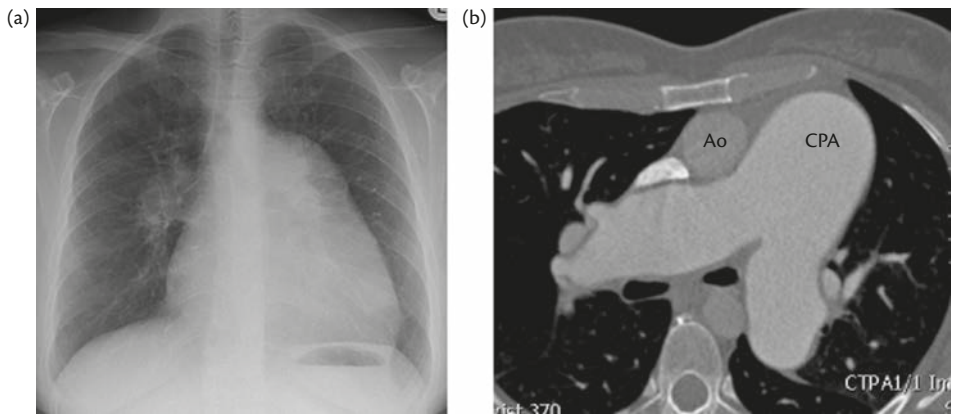


Fig. 169.1 Chest radiograph and computed tomography scan (CT) in a patient with idiopathic PAH. (a) Plain chest radiograph in a patient with idiopathic PAH showing cardiomegaly and enlargement of the proximal pulmonary arteries. (b) Marked enlargement of the central pulmonary artery (CPA) diameter in relation to the adjacent aorta (Ao) in a CT pulmonary angiogram.
Courtesy of Dr Michael Rubens, Royal Brompton Hospital, London, UK.

Table 169.1 Diagnosis of PH + RV dysfunction

Formal definition of PH at right heart catheterization*	Indicators of PH on echocardiography	Indicators of RV failure
mPAP ≥25 mmHg PAWP ≤15 mmHg (i.e. group 1, 3, 4 and 5 PH)	TR velocity >3.4 ms. Short PAT (<80 ms). Right heart dilatation and/or dysfunction RV/LV basal diameter ratio > 1 Flattening of interventricular septum Right atrial area (end-systole) >18cm^2	Low cardiac output (cardiac index <2.5 L/min/m^2). Rising RV filling pressure (RAP >8 mmHg)

*PH is defined at right-heart catheterization, where resting mPAP >25 mmHg. Echocardiographically, PH is suggested by an estimated RV systolic pressure (RVSP) >40 mmHg (severe if >50 mmHg), (note systolic PAP is age dependent, rising with 1mmHg per decade), and a shortened acceleration time across the pulmonary valve (PAT) due to the presence of high pulmonary vascular resistance (PVR). PH severity may depend on chronicity: the magnitude of the PAP generated increases with time because the RV hypertrophies and can generate high pressures. Conversely, in severe end-stage PH, the failing RV may be unable to develop an incremental increase in PA pressure.

PH, pulmonary hypertension; RHC, right-heart catheterization; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation; RV, right ventricular; RAP, right atrial pressure.

imaging techniques, and haemodynamic assessment, including early bedside echocardiography.

Biomarkers

B-type natriuretic peptide and troponins suggest ventricular strain with or without ischaemia in the setting of PH, although these markers are non-specific. Tests reflecting global oxygen delivery (e.g. mixed venous oxygen saturation, lactate) are useful in unstable patients. Of note, hyponatremia (due to renin-angiotensin axis activation and vasopressin release) is strongly associated with RV failure and poor survival in pulmonary arterial hypertension (PAH) [1].

Invasive haemodynamic assessment and monitoring

PH is classically diagnosed by right-heart catheterization (Table 169.1). This differentiates patients with PAH, i.e. with normal (non-elevated) ventricular end-diastolic pressures, from those with pulmonary venous hypertension (pulmonary artery wedge pressure (PAWP) >15 mmHg) due to left atrial hypertension. The distinction is important as those with PAWP exceeding 15mmHg are by definition group 2 patients, where pulmonary vasodilator therapies may precipitate pulmonary oedema as these agents increase pulmonary blood flow against a relatively fixed outlet. Measurements are classically taken at end-expiration and depend on the patient being euvolaemic, although the mean PAWP value is also used. In the stable setting, a fluid challenge can be used to unmask occult left-sided heart disease (usually heart failure with preserved ejection fraction (HFpEF), i.e. LV diastolic dysfunction), where rises in PAWP >15 mmHg are precipitated by a bolus of 250–500ml normal saline.

No formal guidelines exist regarding haemodynamic monitoring of PH patients with RV failure in the ICU setting. Although recent studies have cast doubt on the use of the pulmonary artery catheter (PAC) in other types of shock, it can provide crucial pulmonary haemodynamic measurements in PH and RV failure. The onset of RV failure is suggested by a rising right atrial pressure and falling systemic mean arterial pressure. With PAC data, a rise in pulmonary vascular resistance (PVR; a composite of pulmonary pressure and cardiac output) would pre-empt this late sign. However, there are potential limitations and complications associated with PAC, including difficulties with severe tricuspid regurgitation affecting thermodilution measurements; and complications including infection, clots, arrhythmias and pulmonary artery rupture. PAC should not be used in patients with significant intra-cardiac shunts or recent tricuspid valve surgery. Other cardiac output (CO) monitors may be useful, although have not been validated against invasive haemodynamic indices in these patients and have the same issues regarding inaccuracy with tricuspid regurgitation.

Echocardiography

Echocardiography is an important diagnostic modality in the assessment of PH in the ICU patient. Transthoracic echo (TTE) estimates pulmonary artery systolic pressure (sPAP) and provides information about aetiology (e.g. LV dysfunction, shunts, pulmonary embolus and right atrial thrombi). Estimation of sPAP is based on calculating the peak velocity of the tricuspid regurgitant jet by the simplified Bernoulli equation (peak pressure gradient of tricuspid regurgitation = 4× tricuspid regurgitation velocity). This value is added to the estimated right atrial pressure (RAP) to calculate right ventricular systolic pressure (RVSP), remembering that normal values for sPAP increase with age, sex, and body mass index [2]. RV function is assessed by several methods including descent of the RV base toward the apex (tricuspid annular plane systolic excursion, TAPSE) or RV fractional shortening. Echocardiographic signs of RV failure include RV dilatation with interventricular septal flattening, with resulting paradoxical septal movement causing LV compression due to ventricular interdependence (Fig. 169.2), RV hypokinesia, a dilated inferior vena cava (IVC) and pericardial effusion. TTE images may be suboptimal in ICU patients due to difficult positioning, other monitoring devices and/or ventilatory support. An alternative is transoesophageal echocardiography (TEE). Although often more accurate, current TEE techniques remain relatively invasive, and have limited repeatability.

Computed tomography

Pulmonary emboli should be excluded in any patient with acute PH and RV failure. Large proximal emboli may be identified using CT in the segmental and subsegmental arteries (up to the 4th division), with positive and negative predictive values >90% compared with conventional pulmonary angiography.

Management of ph in the icu patient

Compared with outpatient management, relatively few studies guide PH management in the ICU setting. Management principles include the prevention of RV failure through the use of optimum ventilatory and fluid balance strategies, prompt treatment of

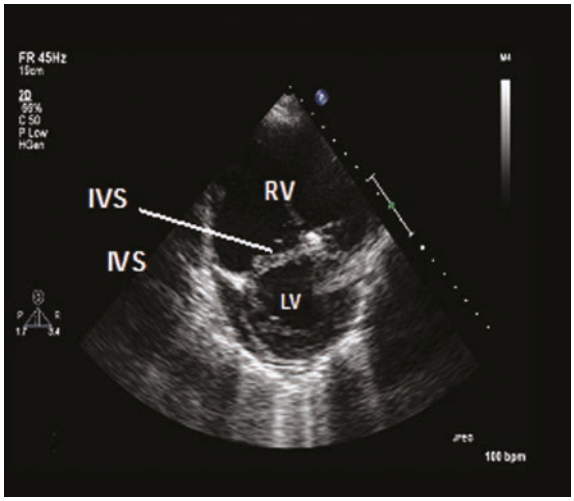


Fig. 169.2 Short-axis view of a transthoracic echocardiogram in a patient with acute pulmonary hypertension having acute dilatation of the right ventricle (RV) compressing the interventricular septum (IVS) and left ventricle (LV).
Courtesy of Dr Susanna Price, Royal Brompton Hospital, London, UK.

arrhythmias, reduced RV afterload and maintenance of an adequate systemic blood pressure (Fig. 169.3). It is important to note that many of these ICU interventions may adversely affect RV function.

Non-pharmacological therapies

Oxygen

In chronic PAH, maintaining arterial saturations >90% is advocated [3]. However, effects of oxygenation on pulmonary haemodynamics have not been formally assessed in ICU patients, where oxygenation is influenced both by the pre-existing baseline and the clinical situation (e.g. ARDS). It should be noted that in acute settings, hypoxia increases pulmonary pressures up to 30%—due to hypoxic pulmonary vasoconstriction—in those with and without underlying PH. This is reversible with resolution of, for example, an acute exacerbation of COPD.

Mechanical ventilation

Through inducing an increase in airway plateau pressure (Pplat), positive pressure ventilation can impair RV function. Positive end-expiratory pressure (PEEP) can also increase RV afterload, while diminishing venous return and preload. In the setting of ARDS with PH and RV failure, the most appropriate ventilation strategy is to keep Pplat and PEEP as low as possible to minimize any adverse effects, while achieving adequate oxygenation and avoiding excessive hypercapnia.

Fluid balance management

Diuretics

Patients with acute or acute-on-chronic RV dysfunction should not be given excessive fluid challenges in the face of hypotension. Decompensated RV failure in severe PAH is characterized by marked fluid retention; diuretics can reduce RV preload and restore ventricular length onto the optimal part of the Starling curve. Reduced RV dilatation in turn prevents LV compression, allowing increased diastolic and coronary artery filling, leading to improved myocardial perfusion, LV–RV synchrony and cardiac output. Although no studies have demonstrated that a strategy of preventing RV over-distension reduces mortality, its use remains a cornerstone of management. If diuretics are unsuccessful, haemofiltration may be needed.

Renal replacement therapy

Acute kidney injury (AKI) can arise in up to 20% of ICU patients. Renal replacement therapy (RRT) augments RV function through rapid fluid removal, as well as correcting acidaemia. However, little evidence is available to support this in terms of restoration of inotropic responsiveness.

Pulmonary vasodilators

Most pulmonary vasodilating agents when administered orally or intravenously, may cause systemic hypotension. This may be avoided with inhaled administration. It is of utmost importance in a patient with known PAH on oral PH therapies not to stop PH therapies in the face of systemic hypotension, as sudden withdrawal of these agents may precipitate sudden worsening of PH. An overview of pulmonary vasodilators is given, with suggestions for use in the ICU setting, as well as chronic use.

Inhaled nitric oxide (iNO)

Nitric oxide (NO) stimulates cyclic guanosine-3',5'-monophosphate (cGMP), which relaxes pulmonary vascular smooth muscle. When delivered to accessible lung units, inhaled NO (iNO) improves ventilation–perfusion mismatch, while lowering PH and RV afterload, with minimal effects on the systemic circulation. This has been demonstrated in patients with ARDS [4], as well as in pulmonary hypertension. iNO is administered to mechanically-ventilated patients via a specifically designed system to ensure adequate delivery and monitoring of concentrations. The gas may also be given by facemask, but drug delivery and monitoring can be difficult. NO is initially administered at 1 part per million (ppm) and increased gradually up to 20 ppm according to clinical response and tolerability. Prolonged administration may be associated with adverse effects, including nitrogen dioxide (NO_2) production, methaemoglobinaemia, and rebound PH following withdrawal [5]. iNO has also been used to treat PH and RV dysfunction following cardiac surgery and in association with acute massive PE. Overall, studies have failed to demonstrate a significant mortality benefit [6], although these have not focused on cases of life-threatening PH/RV failure.

Prostacyclin and prostacyclin analogues

These potent vasodilators also inhibit platelet activation and cell proliferation. The synthetic prostacyclin, epoprostenol, was the first disease-specific therapy approved for treatment of PAH. A landmark study in patients with NYHA III–IV heart failure due to PAH demonstrated an improvement in survival, symptoms, exercise capacity and pulmonary haemodynamics [7], and transformed the treatment of PAH—and indeed these agents remain the best drug treatment for severe PAH. Clinical effects of epoprostenol are similar to iNO, but it is usually only given intravenously, and has a short plasma half-life (3–6 minutes). Epoprostenol can cause systemic hypotension, as well as non-selective pulmonary vasodilatation, thus abolishing hypoxic pulmonary vasoconstriction and worsening oxygenation in patients with lung disease [8].

Iloprost (synthetic prostaglandin I_2) is licensed for the treatment of PAH in patients with NYHA class III symptoms. Administered by nebulization, it requires administration six to nine times per day due to its short duration of action (60–120 min). Clinical studies

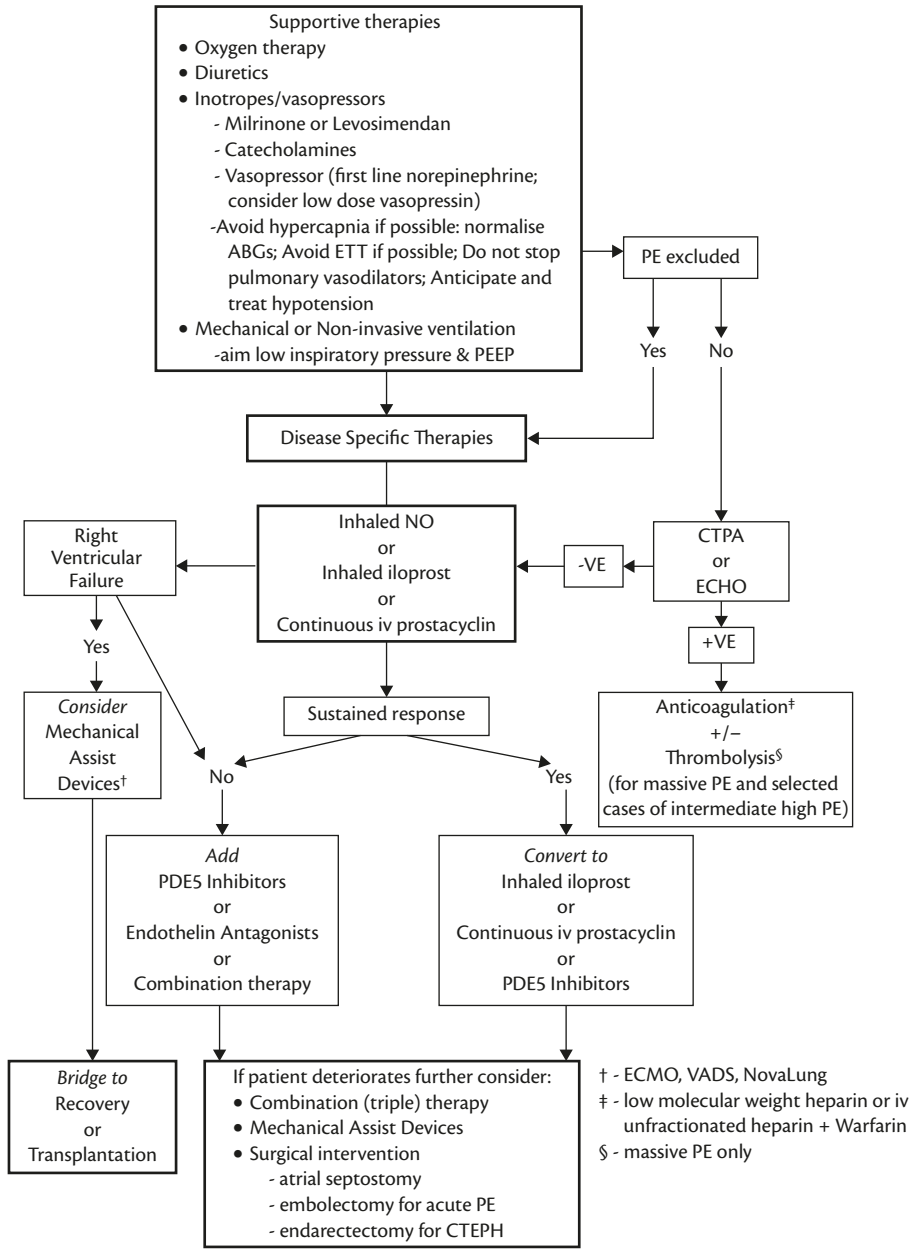


Fig. 169.3 Algorithm for ICU Management of PH and RV failure.

ABGs, arterial blood gases; –VE, negative; +VE, positive; CTEPH, chronic thrombembolic pulmonary hypertension; ETT endotracheal tube, PPV positive-pressure ventilation, PDE phosphodiesterase, PEA pulmonary endarterectomy, PE pulmonary embolism, NO nitric oxide, IV intravenous, ECMO Extracorporeal Membrane Oxygenation, VADs Ventricular Assist Devices, PEEP, positive end-expiratory pressure; CTPA, Computed tomography pulmonary angiogram; ECHO, echocardiography.

demonstrate significant improvement in pulmonary haemodynamics (20% reduction in PVR) without any detrimental effect on gas exchange or systemic blood pressure. The clinical response is at least comparable with that observed with iNO therapy, although iloprost can be used more easily in both ventilated and non-ventilated patients [9]. Despite these potential advantages, the frequency of administration and limited availability has restricted its use.

Phosphodiesterase (PDE) type V inhibitors

PDE5 inhibitors include sildenafil and tadalafil. These agents augment the NO pathway by increasing cGMP levels that are normally rapidly degraded by PDEs, and are common treatments for PAH. Further to promoting pulmonary vasodilation, sildenafil augments biventricular function and attenuates vascular remodelling. A growing literature supports its effectiveness in treating PH in the critically ill. Case series report improved cardiopulmonary haemodynamics, thereby allowing mechanical ventilation and inhaled NO to be withdrawn successfully [10]. Sildenafil is orally active and widely available, allowing it to be used in both general and specialized units. An intravenous preparation is also available for continuous infusion. Sildenafil should be introduced gradually, using low doses (20–25mg orally or 10mg IV (equivalent), 8-hourly), titrated to clinical response and side effects (e.g. systemic hypotension,

gastrointestinal disturbance). It should be used with caution in patients with ischaemic heart disease due to an increased risk of myocardial infarction and ventricular arrhythmias.

Endothelin receptor antagonists

Endothelin-1 (ET-1) is a potent vasoconstrictor and mitogen that stimulates smooth muscle cell proliferation via ET_A and ET_B receptors. Bosentan is an orally active dual ET_A and ET_B antagonist licensed for use in patients with idiopathic PAH, as well as for PAH associated with connective tissue diseases or congenital heart disease [11]. However, no clinical evidence supports its use in treating acute PAH in the critically ill. In addition, it can only be administered enterally, and there are potential concerns over drug-induced hepatic dysfunction (a class effect). Ambrisentan and macitentan are newer endothelin receptor antagonists in use.

Inotropes and vasopressors

These agents can profoundly affect pulmonary haemodynamics. They can improve, but also potentially worsen PH and RV function, depending on the agent and dose administered. Choice should depend upon maintaining a balance between the cardiopulmonary properties of the drug and treating the manifestations of underlying precipitating pathologies, such as severe sepsis.

Catecholamines

The effects of catecholamines on the pulmonary circulation and RV function are variable. Noradrenaline and adrenaline both act on α and β adrenoceptors causing potent systemic vasoconstriction and increased cardiac output, with α effects potentially causing pulmonary arterial vasoconstriction at higher doses. Dopamine induces a similar response, although vasopressor effects are less pronounced, and tachycardia more marked. Dobutamine increases cardiac output through inotropy and chronotropy (β_1 effects), while lowering systemic and pulmonary vascular resistances through vasodilatation (β_2 effect), thus reducing RV afterload. Inotropy must be balanced against increases in heart rate, which may compromise RV filling and RV coronary perfusion, and thereby impairing RV function [12]. In a canine model of acute RV failure, noradrenaline was an effective vasopressor while dobutamine had additional beneficial effects on right ventricular (RV)-pulmonary artery (PA) coupling [13]. Of note, studies in acute PH models show that catecholamines (up to 0.5mcg/kg/min noradrenaline; dopamine or dobutamine up to 10mcg/kg/min) do not increase pulmonary vascular resistance (a theoretical risk due to α effects). In the setting of RV failure in PH patients, dobutamine and then if hypotension persists, a vasopressor (noradrenaline or low dose vasopressin) are often used in combination.

Phosphodiesterase (PDE) type III inhibitors

Milrinone and enoximone are inodilators, acting as competitive inhibitors of PDE isoenzyme 3, raising cyclic adenosine-3,5-monophosphate (cAMP) within cardiomyocytes. This improves myocardial contractility and promotes calcium re-sequestration by the sarcoplasmic reticulum, aiding diastolic relaxation, and thereby improving ventricular compliance and diastolic filling. Milrinone is a potent pulmonary vasodilator, reducing pre- and afterload to both ventricles and, importantly, lowering both PVR and PAP [11]. As a consequence, milrinone is often used in patients with PH and RV failure, including in a nebulised form. It can induce ventricular and atrial arrhythmias, so should be used with caution in patients with prior tachyarrhythmias. It may also cause significant systemic vasodilatation and hypotension requiring pre-emptive vasopressor use.

Calcium channel sensitizers

Levosimendan increases the sensitivity of cardiac myofilaments to calcium ions, thereby improving contractility without increasing myocardial oxygen demand. Levosimendan also causes systemic and pulmonary vasodilatation due to stimulation of ATP-sensitive potassium channels, and PDE III inhibition. These effects may be beneficial in patients with PH and RV failure. A single, randomized control study demonstrated a significant improvement in cardiac output and pulmonary haemodynamics in patients who develop PH and RV failure following ARDS due to severe sepsis [14]. Like milrinone, levosimendan can be associated with atrial arrhythmias (up to 20% of cases) and systemic hypotension so should be used with caution.

Vasopressin analogues

Low-dose vasopressin (0.04 μ/min) and its analogues (e.g. terlipressin) may provide an alternative to catecholamines, causing systemic vasoconstriction (V1 receptor effect) but, paradoxically, promoting vasodilatation, via nitric oxide release, in the pulmonary circulation [15]. This latter effect may be particularly advantageous when patients with PH develop systemic hypotension with certain inotropes (e.g. milrinone, levosimendan) and require a systemic vasopressor. Of note, however, RV-PA coupling experiments are missing for vasopressin and its analogues in models of PH. In addition, vasopressin at higher doses may cause coronary vasoconstriction.

Anticoagulation and thrombolysis

Anticoagulation therapy

Formal anticoagulation is advised in patients with PAH and chronic thromboembolic PH (CTEPH). By contrast, the potential benefit in critically- ill patients with PH has yet to be determined, though routine thromboembolic prophylaxis is advocated in all patients [3].

Thrombolytic agents

Acute PE is the commonest cause of acute PAH in the critically-ill patient with an associated mortality of 6–8%, rising to 30% in massive PE, i.e. in the presence of systemic hypotension, metabolic acidosis or cardiac arrest [16]. Thrombolysis is recommended for treating massive PE with haemodynamic compromise or cardiac arrest [17].

Surgical interventions

Surgery may be considered in patients with severe PH and RV failure despite receiving maximal medical therapy. Such procedures are complex and undertaken only at specialist cardiothoracic centres.

Atrial septostomy

An artificial shunt is created between the atria, with the resulting right-to-left shunt decompressing the right heart and aiding left atrial filling, thereby improving biventricular function and cardiac output, despite the fall in systemic arterial oxygen saturation [18]. This was first used as a palliative measure in 1983 in patients with refractory PH and RV failure. It was subsequent shown to offer significant clinical and haemodynamic improvement in patients with advanced PH. This has not yet been examined in ICU patients who develop acute severe PH and RV failure. Indeed, indicators of very severe RV failure including RAP >20 mmHg are indicative

of procedure-related mortality [18]. In practice it is rarely used in most centres and only as a bridging measure to definitive ongoing treatment (i.e. transplantation).

Pulmonary embolectomy and pulmonary endarterectomy surgery

Surgical pulmonary embolectomy may be considered in patients with massive PE and haemodynamic compromise, where thrombolysis is absolutely contraindicated or in whom thrombolysis has failed. The procedure has been associated with significant perioperative mortality (25–50%), although more recent studies report 15% mortality and an 80% 1-year survival [19]. Pulmonary endarterectomy surgery involves dissection of the organised fibrous tissue from the vessel wall under cardiopulmonary bypass and deep hypothermic arrest, and is highly effective in treating patients with PAH due to proximal CTEPH with low mortality in experiences centres (Papworth data suggests less than 3% mortality). Notable postoperative ICU complications include persistent PH and RV failure, reperfusion pulmonary oedema and pulmonary haemorrhage.

Extracorporeal devices

Extracorporeal membrane oxygenation (ECMO), ventricular assist devices (VADs) and interventional lung assists (iLAs, e.g NovaLung) are being increasingly used to support the RV and reduce afterload in patients with end-stage PAH and RV failure requiring lung transplantation [20]. In most cases, these interventions are used as a bridge to transplantation, but successful recovery of RV function has been described in some case reports. Further evaluation of these techniques is required in the critically ill.

Conclusion

PH with or without RV dysfunction is a poor prognostic indicator when complicating diseases that afflict the critically ill. This suggests that early diagnosis and treatment is important, however there is a paucity of trial data concerning the application of interventions in the critically ill. Indeed, the acute changes in physiology faced by these patients in the ICU setting make large trials difficult to perform. Therefore, understanding of the pathophysiology of PAH and the ICU context (including the effects of mechanical ventilation, high/low pO_2, systemic and pulmonary vasoactive agents, RV and LV physiology) are essential in understanding how to manage these patients. The development of new, disease-specific pulmonary vasodilators, inotropes, and extracorporeal support systems should in theory improve outcomes, but further studies, however difficult to implement, are needed. The impact of advancing and awake extracorporeal life support techniques although exciting bring new challenges to patients and caregivers, where all members of the ICU team including clinical psychologists play an important role.

References

1. Forfia PR, Mathai SC, Fisher MR, et al. (2008). Hyponatremia predicts right heart failure and poor survival in pulmonary arterial hypertension. *American Journal of Respiratory and Critical Care Medicine*, **177**, 1364–9.
2. McQuillan BM, Picard MH, Leavitt M, and Weyman AE. (2001). Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation*, **104**, 2797–802.
3. Gibbs S, Corris P, Coghlan J, et al. (2008). Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. National Pulmonary Hypertension Centres of the UK and Ireland. *Thorax*, **63**(Suppl. II), ii1–41.
4. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, and Zapol WM. (1993). Inhaled nitric oxide for the adult respiratory distress syndrome. *New England Journal of Medicine*, **328**, 399–405.
5. Griffiths MJ and Evans TW. (2005). Inhaled nitric oxide therapy in adults. *New England Journal of Medicine*, **353**, 2683–95.
6. Adhikari NK, Burns KE, Friedrich JO, Granton JT, Cook DJ, and Meade MO. (2007). Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *British Medical Journal*, **334**, 779.
7. Barst RJ, Rubin LJ, Long WA, et al. (1996). A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *New England Journal of Medicine*, **334**, 296–302.
8. Ghofrani HA, Wiedemann R, Rose F, et al. (2002). Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet*, **360**, 895–900.
9. Hoeper MM, Olschewski H, Ghofrani HA, et al. (2000). A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. German PPH study group. *Journal of the American College of Cardiology*, **35**, 176–82.
10. Ng J, Finney SJ, Shulman R, Bellingan GJ, Singer M, and Glynne PA. (2005). Treatment of pulmonary hypertension in the general adult intensive care unit: a role for oral sildenafil? *British Journal of Anaesthesia*, **94**, 774–7.
11. Seino Y, Momomura S, Takano T, Hayakawa H, and Katoh K. (1996). Multicenter, double-blind study of intravenous milrinone for patients with acute heart failure in Japan. Japan Intravenous Milrinone Investigators. *Critical Care Medicine*, **24**, 1490–7.
12. Price LC, Wort SJ, Finney SJ, Marino PS, and Brett SJ. (2010). Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. *Critical Care*, **14**, R169.
13. Kerbaul F, Rondelet B, Motte S, et al. (2004). Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure. *Critical Care Medicine*, **32**, 1035–40.
14. Morelli A, Teboul JL, Maggiore SM, et al. (2006). Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. *Critical Care Medicine*, **34**, 2287–93.
15. Tayama E, Ueda T, Shojima T, et al. (2007). Arginine vasopressin is an ideal drug after cardiac surgery for the management of low systemic vascular resistant hypotension concomitant with pulmonary hypertension. *Interactive Cardiovascular and Thoracic Surgery*, **6**, 715–19.
16. Kasper W, Konstantinides S, Geibel A, et al. (1997). Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. *Journal of the American College of Cardiology*, **30**, 1165–71.
17. Torbicki A, Perrier A, Konstantinides S, et al. (2008). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *European Heart Journal*, **29**, 2276–315.
18. Rich S, Dodin E, and McLaughlin VV. (1997).Usefulness of atrial septostomy as a treatment for primary pulmonary hypertension and guidelines for its application. *American Journal of Cardiology*, **80**, 369–71.
19. Leacche M, Unic D, Goldhaber SZ, et al. (2005). Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. *Journal of Thoracic and Cardiovascular Surgery*, **129**, 1018–23.
20. Strueber M, Hoeper MM, Fischer S, et al. (2009). Bridge to thoracic organ transplantation in patients with pulmonary arterial hypertension using a pumpless lung assist device. *American Journal of Transplantation*, **9**(4), 853–7.

PART 5.15

Pulmonary embolus

CHAPTER 170

Pathophysiology and causes of pulmonary embolism

Mervyn Singer

Key points

- Pulmonary emboli are predominantly related to thrombi arising from heart or deep veins.
- Non-thrombotic causes include air, fat, foreign body, septic, tumour and amniotic fluid (although the latter does not cause flow obstruction).
- Outcome largely depends on the degree of right ventricular dysfunction.
- There are multiple risk factors including surgery, arrhythmias, prolonged immobility, venous stasis, pregnancy, and an underlying pro-thrombotic tendency, either congenital or acquired, e.g. during pro-inflammatory states such as sepsis.
- Numerous risk stratification scores have been developed derived from clinical features, imaging findings, and biochemical markers of right ventricular strain and myocardial damage.

Causes

Thrombus predominantly form within deep leg veins, pelvic or abdominal veins, within the right atrium or ventricle (especially in patients with long-standing arrhythmias) or, occasionally, within the pulmonary artery itself. The thrombi break off and lodge within the pulmonary vasculature, either as single or multiple emboli.

A small number of cases may be related to non-thrombotic causes, including air, fat or gas, foreign body, septic or tumour emboli, and amniotic fluid embolus. Air embolism occurs following vascular instrumentation or surgical mishaps, or lung trauma with air sucked into disrupted blood vessels. It may also occur following diving accidents or rapid decompression. Fat emboli follows physical trauma (accidental or orthopaedic), usually to long bones or the pelvis. Foreign body emboli are usually related to iatrogenic complications during a vascular procedure, while septic emboli follow infections of veins (usually from in-dwelling cannulae), heart valves, or infected mural thrombi. Features relating to amniotic fluid embolism are related to an acute inflammatory/anaphylactoid reaction following entry of amniotic fluid, fetal cells and other debris into the mother's blood stream via the placental bed, than to physical blockage of the pulmonary vasculature.

The remainder of this chapter focuses on risk factors, risk stratification, and cardiopulmonary consequences of thrombotic pulmonary emboli. Many of the cardiopulmonary consequences are, however, also common to non-thrombotic emboli.

Risk factors

The annual incidence of acute pulmonary embolism (APE) of a thrombotic aetiology ranges between 23 and 69 cases per 100,000 population with a 2-week fatality rate estimated at 11% [1]. From US hospital discharge data, the reported incidence of PE is 0.4% of hospitalized admissions [2]. Risk factors include surgery, arrhythmias, prolonged immobility, venous stasis, pregnancy, and an underlying thrombotic tendency [3]. This heightened procoagulant status may either be congenital, e.g. Factor V Leiden deficiency, related to a pathology such as antiphospholipid syndrome, or in severe pro-inflammatory conditions such as sepsis or major surgery (Table 170.1). Cook et al. [4] identified four independent risk factors for intensive care unit-acquired deep venous thrombosis, namely a personal or family history of venous thromboembolism (hazard ratio 4.0, 95% confidence interval 1.5–10.3), end-stage renal failure (HR 3.7, 95% CI 1.2–11.1), platelet transfusion (HR 3.2, 95% CI 1.2–8.4), and vasopressor use (HR 2.8, 95% CI 1.1–7.2).

However, notwithstanding all these risk factors, the incidence of clinically relevant APE is low in critical care patients treated with a prophylactic heparin. A recent multicentre study of 3764 patients in which two heparin regimens were compared reported an approximate 2% incidence of pulmonary embolism, and a 5.5% incidence of proximal leg deep vein thrombosis diagnosed by compression ultrasonography [5]. Notably, the prevalence of proximal deep vein thrombosis on initial baseline screening was 3.5%.

Classification

Different nomenclatures have been developed due to a profusion of guidelines developed independently by North American and European cardiology and respiratory bodies [3,6–8]. These classifications are based on an assessment of the individual risk of early mortality, and are essentially similar as the presence or absence of right ventricular dysfunction is the critical factor determining outcome following APE. In essence, they can be divided into massive/high-risk (symptomatic RV dysfunction), submassive/intermediate risk (asymptomatic dysfunction and/or RV overload), and small/low-risk (normal RV function)

Risk stratification

A similar problem has arisen with risk stratification with multiple scores reported in the literature, e.g. GRACE, Geneva, Wells,

Table 170.1 Risk factors for thromboembolism

Major risk factors (relative risk 5–20)	Minor risk factors (relative risk 2–4)
Surgery: major abdominal/pelvic surgery, hip/knee joint replacement, post-operative intensive care	**Cardiovascular:** congenital heart disease, heart failure, hypertension, superficial venous thrombosis, central venous catheterization
Obstetrics: late pregnancy, Caesarean section, puerperium	**Oestrogens:** oral contraception, hormone replacement therapy
Lower limb problems: fractures	**Miscellaneous:** obesity, chronic obstructive lung disease, neurological disability, occult malignancy, pro-thrombotic tendency (e.g. Factor V Leiden or protein C deficiency), long-distance sedentary travel
Malignancy: abdominal/pelvic, advanced/metastatic stage	
Reduced mobility: hospitalization, institutional care	
Other: history of previous venous thromboembolism	

Arrhythmias are not noted in these guidelines as a risk factor, although these are clearly recognized as such. Likewise, inflammatory conditions such as sepsis will predispose to a prothrombotic state and an increased risk of embolus.

Simplified Pulmonary Embolism Severity Index, Shock Index, and European Society of Cardiology risk scores [9,10]. These are used both to prognosticate and to define what imaging work-up, and subsequent clinical management should be offered, although none approach very high levels (>90%) of sensitivity and specificity. The scoring systems generally utilize clinical features (e.g. blood pressure (BP), acidosis) with or without markers of myocardial injury or dysfunction (e.g. troponin). In the International Cooperative Pulmonary Embolism Registry [11], haemodynamically unstable patients (based on shock, systolic BP <90 mmHg or a fall in systolic BP >40 mmHg for >15 minutes) had a mortality rate above 50% compared with 15% in haemodynamically stable patients. The Pulmonary Embolism Severity Index is a clinical assessment score derived and validated in >16,000 patients with pulmonary embolism [12].

Table 170.2 lists risk stratification markers proposed by the European Society of Cardiology [6]. Prognostication can also be made in haemodynamically stable patients on the basis of right ventricular dysfunction assessed echocardiographically [13], troponin [14], and plasma B-type natriuretic peptide [15]. A normal B-type natriuretic peptide level had a near 100% negative predictive value for adverse outcomes. While the combination of an increased troponin level and right ventricular dysfunction identified a subgroup at particularly high risk [16], viewed individually the positive predictive value for an adverse outcome ranged from 10 to 20%. Table 170.3 summarizes data on the mortality rates of acute pulmonary embolism.

Table 170.2 Markers used for risk stratification

Clinical markers	Shock Hypotension*
Markers of right ventricular dysfunction	Right ventricular dilatation, hypokinesis, or pressure overload on echocardiography
	Right ventricular dilatation on CT-PA
	Increase in plasma BNP or NT-proBNP levels
	Increase in right heart pressures
Markers of myocardial injury	Raised plasma troponin levels

*Systolic BP <90 mmHg of by >40 mmHg for 15 min.

BNP, Brain natriuretic peptide; NT-proBNP, N-terminal proBNP; CT-PA, computed tomographic—pulmonary angiography.

Cardiovascular consequences

Even though breathlessness or chest pain are the commonest presenting features, the clinical severity of APE is predicated by its impact on the circulatory system, in particular the degree of sudden pulmonary obstruction causing right ventricular overload and failure, and the reduction in cardiac output [17]. An individual patient's baseline cardiovascular reserve is crucial in determining how they cope with the acute obstruction. Various pulmonary and neurohormonal adaptations also aid in providing compensatory responses. Thus, a large embolus in a previously fit and healthy individual may be relatively symptom-free, while patients with long-standing heart or lung problems may decompensate with much smaller emboli.

The acute onset of pulmonary hypertension following APE leads to an increase in right ventricular afterload and strain that may evolve into right ventricular dilation and failure. When severe, the fall in right heart output will reduce cardiac output, even to the point of shock (hypotension and/or organ hypoperfusion), syncope (if brain blood flow is compromised), or an acute cardiovascular collapse with pulseless electrical activity or asystole. APE accounts for 10% of patients admitted with non-traumatic sudden death and 50% of those arriving with electromechanical dissociation or asystole on ECG [18]. In such shock/collapse situations, the right ventricle may not have had sufficient time to dilate so its size on imaging (e.g. computerized tomography, echocardiography) may appear relatively normal, although its functionality may be severely impaired. The reduction in coronary flow secondary to high pressures within the right ventricle may cause subendocardial ischaemia or even infarction of that ventricle. This may further contribute to the degree of right heart failure. Of note, the prognostic value of

Table 170.3 Mortality rates of acute pulmonary embolism

Clinical presentation	Mortality rate
Unselected population	7% at 1 week 13% at 1 month 18% at 3 months
Massive pulmonary embolism	Overall 18–65% (lower with treatment) With cardiogenic shock 25–30% Needing resuscitation 65%
Submassive pulmonary embolism	5–25%
Small pulmonary embolism	Up to 1%

Data from: 'British Thoracic Society guidelines for the management of suspected acute pulmonary embolism', *Thorax*, 2003, **58**, pp. 470–83; PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group, et al., 'Dalteparin versus unfractionated heparin in critically ill patients', *New England Journal of Medicine*, 2011, **364**, pp. 1305–14; Torbicki A et al., 'ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology', *European Heart Journal*, 2008, **29**, pp. 2276–15; Jaff MR et al., 'Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association', *Circulation*, 2011, **123**, pp. 1788–830; Lucassen W et al., 'Clinical decision rules for excluding pulmonary embolism: a meta-analysis', *Annals of Internal Medicine*, 2011, **155**, 448; Goldhaber SZ et al., 'Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER)', *Lancet*, 1999, **353**, pp. 1386–9; Aujesky D et al., 'Derivation and validation of a prognostic model for pulmonary embolism', *American Journal of Respiratory Critical Care Medicine*, 2005, **172**, pp. 1041–6.

syncope as a sign of massive APE has yet to be conclusively demonstrated, particularly where it is not followed by prolonged haemodynamic instability.

When not severe enough to cause shock or collapse, there may still be a fall in cardiac output due to the decrease in left ventricular filling from the obstruction to flow, as well as left ventricular diastolic dysfunction due to right ventricular dilation and bulging of the interventricular septum to the left. This fall in output may be progressive, over hours, days, or even weeks, related to the degree of evolving right heart failure induced by the pulmonary hypertension.

The failing right heart in the post-acute period may thus be a result of maladaptation of compensatory mechanisms. Activation of the sympathetic nervous system with both inotropic and chronotropic stimulation, and the generation of high right ventricular pressures to drive blood through the obstructed pulmonary vasculature are appropriate mechanisms to preserve blood pressure and flow, and thus life, in the short term. However, chronic thromboembolic pulmonary hypertension (CTEPH) may prove harmful later on [19]. There is a reported incidence of 4% of CTEPH after APE. There is still considerable debate in the literature about the long-term risk of right heart failure due to intermediate pulmonary embolism causing ongoing pulmonary hypertension but without initial shock.

Respiratory consequences

Respiratory failure occurs in approximately 10% of APE patients due to several mechanisms. The low cardiac output from a significant APE results in desaturation of mixed venous blood related to increased oxygen extraction by peripheral tissues, which then fails to become fully re-oxygenated on passage through the lungs with resulting arterial hypoxaemia. This will be exacerbated by ventilation-perfusion mismatching due to:

- Atelectasis related to both hypoventilation induced by pain and/or reduced respiratory muscle perfusion.
- Possible areas of pulmonary infarction.
- Development of a right to left shunt (due to inversion of pressures between the right and left atria) through a patent foramen ovale that is anatomically present in varying sizes in 30% of people.
- An excessive systemic inflammatory response related to the acute insult with development of increasing capillary leak and an ARDS-type picture replacing the initial radiographic appearance of clear lung fields.

Pulmonary infarction is caused by small, distally embolizing thrombi usually with no haemodynamic consequences. Alveolar haemorrhage with possible haemoptysis, pleurisy and pleural exudate that often haemorrhagic, are all associated features. Peripheral, often wedge-shaped, infarcts may be seen on X-ray or CT scan.

References

1. Konstantinides S. (2008).Acute pulmonary embolism. *New England Journal of Medicine*, **359**, 2804–13.
2. Stein PD, Beemath A, and Olson RE. (2005). Trends in the incidence of pulmonary embolism and deep venous thrombosis in hospitalized patients. *American Journal of Cardiology*, **95**, 1525–6.
3. British Thoracic Society. (2003). Guidelines for the management of suspected acute pulmonary embolism. *Thorax*, **58**, 470–83.
4. Cook D, Crowther M, Meade M, et al. (2005). Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. *Critical Care Medicine*, **33**, 1565–71.
5. PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Cook D, et al. (2011). Dalteparin versus unfractionated heparin in critically ill patients. *New England Journal of Medicine*, **364**, 1305–14.
6. Torbicki A, Perrier A, Konstantinides S, et al. (2008). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. *European Heart Journal*, **29**, 2276–315.
7. Jaff MR, McMurtry MS, Archer SL, et al. (2011). Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation*, **123**, 1788–830.
8. Kearon C, Akl EA, Comerota AJ, et al. (2012). Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th edn: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, **141**, e419S–94S.
9. Lucassen W, Geersing GJ, Erkens PM, et al. (2011). Clinical decision rules for excluding pulmonary embolism: a meta-analysis. *Annals of Internal Medicine*, **155**, 448.
10. Paiva LV, Providencia RC, Barra SN, Faustino AC, Botelho AM, and Marques AL. (2013). Cardiovascular risk assessment of pulmonary embolism with the GRACE risk score. *American Journal of Cardiology*, **111**, 425–31.
11. Goldhaber SZ, Visani L, and De Rosa M. (1999). Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*, **353**, 1386–9.
12. Aujesky D, Obrosky DS, Stone RA, et al. (2005). Derivation and validation of a prognostic model for pulmonary embolism. *American Journal of Respiratory and Critical Care Medicine*, **172**, 1041–6.

13. Sanchez O, Trinquart L, Colombet I, et al. (2008). Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. *European Heart Journal*, **29**, 1569–77.
14. Becattini C, Vedovati MC, and Agnelli G. (2007). Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation*, **116**, 427–33.
15. Klok FA, Mos ICM, and Huisman MV. (2008).Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. *American Journal of Respiratory and Critical Care Medicine*, **178**, 425–30.
16. Binder L, Pieske B, Olschewski M, et al. (2005). N-terminal pro-brain natriuretic peptide or troponin testing followed by echocardiography for risk stratification of acute pulmonary embolism. *Circulation*, **112**, 1573–9.
17. Agnelli G and Becattini C. (2010). Acute pulmonary embolism. *New England Journal of Medicine*, **363**, 266–74.
18. Courtney DM, Sasser HC, Pincus CL, et al. (2001). Pulseless electrical activity with witnessed arrest as a predictor of sudden death from massive pulmonary embolism in outpatients. *Resuscitation*, **49**, 265–72.
19. Pengo V, Lensing AWA, Prins MH, et al. (2004). Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *New England Journal of Medicine*, **350**, 2257–64.

CHAPTER 171

Diagnosis and management of pulmonary embolism

Mervyn Singer

Key points

- Computed tomographic pulmonary angiography is the current gold standard tool for the diagnosis of pulmonary embolism.
- Mortality risk stratification based on clinical, imaging and biochemical indices dictates the treatment strategy employed in an individual patient, from outpatient anticoagulation to surgical or percutaneous embolectomy for severe, life-threatening cases.
- Anticoagulation is the mainstay of treatment. Fixed dose, subcutaneous heparin is initially commenced (unless contraindicated), with early introduction of oral therapy such as coumadin (warfarin) generally continued for 3–6 months (but may be lifelong).
- Thrombolytic agents should be used in patients with haemodynamic compromise.
- In intermediate-risk, normotensive patients, thrombolysis reduces early mortality or haemodynamic collapse, but this is counterbalanced by an increase in major haemorrhage (including stroke), especially in the elderly.

Diagnosis

Acute pulmonary embolism (APE) should be suspected in patients with new-onset or worsening breathlessness, sharp pleuritic or substernal chest pain, cough, haemoptysis, syncope, hypotension, shock or cardiac arrest with pulseless electrical activity or asystole [1]. Patients may be asymptomatic with the diagnosis made serendipitously during diagnostic imaging for another indication, e.g. cancer staging. Signs include tachypnoea, tachycardia, evidence of deep venous thrombosis (DVT) in 15%, cyanosis in 11%, and pyrexia. Table 171.1 reports clinical presentations in 209 patients with documented APE [2].

Diagnosis is usually made by initial clinical suspicion that prompts more specialized imaging and investigation. Electrocardiographic evidence of right heart strain includes T wave inversion in leads V1–V4, the classic $S_1Q_3T_3$ pattern in leads I–III, peaked P waves, and incomplete or complete right bundle branch block. There may be atrial arrhythmias and evidence of right ventricular (RV) ischaemia or infarction with ST elevation in chest lead V1 plus ST depression in lead V2 being highly specific for RV infarction. Diagnosis is more easily made if a right-sided electrocardiogram (ECG) shows ST elevation in leads V3R–V6R.

The ECG may be normal with smaller pulmonary emboli not causing RV strain/damage, as may the initial chest X-ray, despite concurrent hypoxaemia. X-ray abnormalities include bands of atelectasis, pleural effusions, or hemidiaphragm elevation. Focal, peripheral consolidation may be due to infarction or haemorrhage. Wedge-shaped peripheral infarcts are relatively unusual. Westermark's sign describes focal oligaemia distal to the occluded pulmonary artery that is often enlarged proximal to the clot.

The utility of plasma D-dimer levels, a degradation product of cross-linked fibrin, has been heavily studied [3]. D-dimer levels rise with excessive degrees of coagulation and fibrinolysis, although this can occur due to multiple other reasons, including sepsis, cancer, and trauma. It has reduced specificity in pregnancy, cancer, the elderly, and hospitalized patients [4]. Due to its poor positive predictive value but high negative predictive value, D-dimer testing is frequently used as a 'rule-out' test with a negative value suggesting a low likelihood of pulmonary embolus.

Computed tomographic pulmonary angiography (CT-PA) is the current gold standard diagnostic tool, particularly with the newer high resolution multidetector devices that can even image 5th and 6th order subsegmental vessels [5]. A 97% sensitivity for detecting emboli in the main pulmonary arteries is reported in haemodynamically unstable patients [6]. The PIOPED II study reported 83% sensitivity and 96% specificity for detecting pulmonary emboli by CT-PA [7]. With newer-generation scanners, the yield is likely to be higher still, although the clinical significance of small isolated subsegmental emboli, reported at an incidence of 3–36%, remains open to question [5]. Lower limb CT venography can be performed in tandem to identify DVT, but this increases radiation exposure so is not generally performed.

Isotopic ventilation–perfusion scintigraphy is still used occasionally. This utilizes intravenous injection of technetium (Tc)-99m labelled albumin particles to demonstrate 'cold' abnormalities in lung perfusion due to occlusion of pulmonary arterial branches, but concurrent normal ventilation using tracers such as Tc-99m labelled aerosols or microparticles. The proportion of 'high probability' scans is relatively low as this technique is heavily dependent upon normal lung ventilation, which is frequently not the case, either due to the PE itself or to pre-existing lung morbidity. It has more utility in excluding APE if the perfusion scan is normal [8].

Echocardiography, especially transoesophageal echocardiography, is useful as a bedside tool to assess right ventricular (RV) strain and dysfunction, especially in the emergency department and in patients too haemodynamically unstable to be transferred

Table 171.1 Incidence of individual clinical manifestations of acute pulmonary embolism

Clinical status	Incidence (%)
Cardiac arrest or shock	13
Hypotension without signs of shock	9
Haemodynamic stability, but echocardiographic signs of right ventricular dysfunction	31
Haemodynamic stability, without echocardiographic signs of right ventricular dysfunction	47

Data from Grifoni S et al., 'Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction', *Circulation*, 2000, **101**, pp. 2817–22.

for CT-PA [4]. Occasionally, large emboli can be imaged in the main pulmonary arteries. In patients with shock or hypotension, the absence of echocardiographic signs of RV overload or dysfunction strongly excludes APE as the cause of the haemodynamic compromise [9]. This technique is, however, heavily operator-dependent and the more subtle signs of RV dysfunction may be easily missed.

Conventional pulmonary angiography can also be performed to confirm the diagnosis of APE, but this is usually as a prelude to embolectomy that, at the present time, is rarely performed. The PIOPED III trial found that magnetic resonance angiography had insufficient sensitivity and a high rate of technically inadequate images when used to diagnose pulmonary embolism [10].

Biochemical markers of RV dysfunction (e.g. B-type natriuretic peptide) and injury (e.g. troponin) are also measured as markers of prognostication, either alone or in combination with other markers [11,12].

Treatment

The treatment stratagem for acute pulmonary thromboembolism in an individual patient is generally based on the perceived mortality risk for which numerous scoring systems have been developed. Table 171.2 provides one such example with the potential treatment implications listed [1].

The mainstay of treatment is anticoagulation with a rapid-onset agent, such as a subcutaneous low molecular weight heparin (e.g. dalteparin, enoxaparin) or fondaparinux given as a fixed dose regimen (Table 171.3). Unfractionated heparin given by continuous infusion is advised in patients with renal failure (creatinine clearance <30 mL/min) with dosing titrated to achieve a partial thromboplastin time of 1.5–2.5 times above the normal range. The efficacy and safety profile are similar with an in-hospital bleeding risk of 3% [13,14].

Within a day, oral anticoagulation with a vitamin K antagonist (e.g. coumadin (warfarin)) should be commenced in most patients. The two agents should be given in tandem for at least 24 hours after the patient has been fully anticoagulated as adjudged by an international normalized ratio (INR) of 2.0–3.0 (Table 171.3). Vitamin K antagonists are usually given for 3–6 months, although treatment may need to be lifelong in high-risk patients, e.g. those with chronic arrhythmia, active cancer, or recurrent venous thromboembolism [1]. A careful risk-benefit analysis needs to be undertaken in those individuals at risk of bleeding, e.g. those with peptic ulceration or angiodysplasia. Pregnant patients are usually managed on heparin alone, due to the risk of teratogenicity from vitamin K antagonists. Symptomatic patients at low risk (pulmonary embolism severity index risk Classes I and II) could be safely discharged home within 24 hours and managed as an outpatient [14]. Ninety day mortality was 0.6% in both out- and inpatient groups. In recent years new oral Factor Xa inhibitors, such as rivaroxaban, have had equal efficacy and superior safety demonstrated over warfarin [16,17]. Their advantage is administration at fixed doses without the need for routine monitoring of coagulation.

For haemodynamically unstable patients, thrombolysis is advocated on the grounds that clot dispersal is more rapid, right ventricular dysfunction is more actively and effectively treated, short-term mortality is improved, and the risk of long-term pulmonary hypertension and right heart failure reduced. After the thrombolytic has been infused, an infusion of intravenous unfractionated heparin is commenced with a vitamin K antagonist added subsequently (as above).

Mortality can be halved with prompt thrombolysis from the approximate 60% rate reported in patients with massive APE and haemodynamic compromise not treated with thrombolytics [18]. The risk of major bleeding is much higher with thrombolysis compared with anticoagulant therapy alone. Major contraindications

Table 171.2 Mortality risk stratification of acute pulmonary embolism

PE-related early mortality risk	Risk markers			Potential treatment implications
	Clinical (shock or low BP)	RV dysfunction	Myocardial injury	
High (>15%)	+	+	+	Thrombolysis or embolectomy
Intermediate (3–15%)	–	+/–	+/–	Hospital admission
Low <1%	–	–	–	Early discharge or home-based management

Reproduced from Torbicki A et al., 'ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology', *European Heart Journal*, 2008, **29**, pp. 2276–315, by permission of Oxford University Press © European Society of Cardiology, www.escardio.org/guidelines.

Table 171.3 Parenteral anticoagulant agents

Anticoagulant agent	Dose	Monitoring
Unfractionated heparin	80 IU/kg iv bolus, then infusion at 18 IU/kg/hour	Adjust infusion rate to maintain APTT between 1.5–2.5× control Monitor platelet count for heparin-induced thrombocytopenia
Low molecular weight heparins		No monitoring routinely needed. Anti-factor Xa levels may be helpful if at increased risk for bleeding. Avoid (or monitor) if creatinine clearance <30 mL/min
◆ Enoxaparin	1 mg/kg sc every 12 hours or 1.5 mg/kg od	
◆ Tinzaparin	175 U/kg sc od	
◆ Dalteparin	200 U/kg (maximum dose of 18,000 units) od	
Factor Xa inhibitor		
Fondaparinux	od sc injection of: ◆ 5 mg if body weight <50 kg ◆ 7.5 mg if weight 50–100 kg ◆ 10 mg if weight >100 kg	No monitoring routinely needed. Anti-factor Xa levels may be helpful if at increased risk for bleeding. Avoid (or monitor) if creatinine clearance <30 mL/min

include intracranial disease, uncontrolled hypertension and major surgery or trauma within the past 3 weeks. Table 171.4 shows some common thrombolytic regimens. No studies have directly compared thrombolytic regimens, although more rapid infusion (within 2 hours) is generally recommended to achieve faster clot breakdown.

Conclusion

To address the question of thrombolytic use in normotensive intermediate-risk patients, the recently completed PEITHO trial compared anticoagulation with or without tenecteplase in 1006 haemodynamically stable patients with evidence of RV dysfunction and an elevated troponin. While thrombolysis substantially reduced the combined endpoint of early mortality or haemodynamic collapse, this was at the expense of a significant increase in major haemorrhage (including stroke), especially in patients >75 years [19].

No study has clearly demonstrated an advantage of catheter-directed over intravenous thrombolysis. In a recent meta-analysis, catheter-directed therapy had a clinical success rate of 86% and a rate of major complication rate of only 2.4% [19].

Percutaneous mechanical thrombectomy (fragmentation and aspiration of the thrombus under radiographic imaging) or surgical embolectomy under cardiopulmonary bypass is restricted to those high-risk patients in whom thrombolysis is either contraindicated or in those where it has failed to improve a parlous circulatory state.

Inferior vena cava filters can be used in patients in whom anticoagulation is contraindicated and there is a high risk of recurrence of emboli. Retrievable filters can be placed in patients in whom a contraindication to anticoagulation is temporary, or in those where a major surgical procedure is being contemplated. There are no data to support routine use in patients with free-floating proximal DVT. As they carry a significant complication rate including DVT recurrence and post-thrombotic syndrome, their systematic use is not recommended [1].

Table 171.4 Thrombolytic regimens

Thrombolytic agent	Dose
Streptokinase	250 000 U iv bolus followed by 100,000 U/hour infusion for 12–24 hours
Urokinase	4400 U/kg bolus, followed by 4400 U/kg/hour for 12–24 hours
Alteplase	100 mg iv infusion over 2 hours
Reteplase	Two boluses of 10 U given iv 30 minutes apart
Tenecteplase	Weight-adjusted iv bolus given over 5 seconds, ranging from 30 mg (if weight below 60 kg), increasing in 5 mg increments for every 10 kg, to a fixed dose of 50 mg if ≥90 kg

References

1. Torbicki A, Perrier A, Konstantinides S, et al. (2008). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. *European Heart Journal*, **29**, 2276–315.
2. Grifoni S, Olivotto I, Cecchini P, et al. (2000). Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. *Circulation*, **101**, 2817–22.
3. Di Nisio M, Squizzato A, Rutjes AW et al. (2007). Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. *Journal of Thrombosis and Haemostasis*, **5**, 296–304.
4. Agnelli G and Becattini C. (2010). Acute pulmonary embolism. *New England Journal of Medicine*, **363**, 266–74.
5. Kuriakose J and Patel S. (2010). Acute pulmonary embolism. *Radiology Clinics of North America*, **48**, 31–50.
6. van Belle A, Büller HR, Huisman MV, et al. (2006). Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *Journal of the American Medical Association*, **295**, 172–9.
7. Stein PD, Fowler SE, Goodman LR, et al. (2006). Multidetector computed tomography for acute pulmonary embolism. *New England Journal of Medicine*, **354**, 2317–27.
8. Anderson DR, Kahn SR, Rodger MA, et al. (2007). Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. *Journal of the American Medical Association*, **298**, 2743–53.
9. Kurzyna M, Torbicki A, Pruszczyk P, et al. (2002). Disturbed right ventricular ejection pattern as a new Doppler echocardiographic sign of acute pulmonary embolism. *American Journal of Cardiology*, **90**, 507–11.
10. Stein PD, Chenevert TL, Fowler SE, et al. (2010). Gadolinium-enhanced magnetic resonance angiography for pulmonary embolism: a multicenter prospective study (PIOPED III). *Annals of Internal Medicine*, **152**, 434–43.
11. Klok FA, Mos ICM, and Huisman MV. (2008). Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with

pulmonary embolism: a systematic review and meta-analysis. *American Journal of Respiratory and Critical Care Medicine*, **178**, 425–30.
12. Becattini C, Vedovati MC, and Agnelli G. (2007). Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation*, **116**, 427–33.
13. Quinlan DJ, McQuillan A, and Eikelboom JW. (2004). Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. *Annals of Internal Medicine*, **140**, 175–83.
14. The Matisse Investigators. (2003). Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *New England Journal of Medicine*, **349**, 1695–702.
15. Aujesky D, Roy P-M, Verschuren F, et al. (2011). Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet*, **378**, 41–8.
16. Vanassche T and Verhamme P. (2013). Rivaroxaban for the treatment of pulmonary embolism. *Advances in Therapy*, **30**, 589–606.
17. Hokusai-VTE Investigators, Büller HR, Décousus H, et al. (2013). Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *New England Journal of Medicine*, **369**, 1406–15.
18. Wan S, Quinlan DJ, Agnelli G, and Eikelboom JW. (2004). Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation*, **110**, 744–9.
19. Jaff MR and Weinberg I. (2013). Accelerated thrombolysis for pulmonary embolism: will clinical benefit be ULTIMAtely realized? *Circulation*, **129**(4), 420–1.
20. Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, and Hofmann LV. (2009). Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. *Journal of Vascular and Interventional Radiology*, **20**, 1431–40.

SECTION 6

The gastrointestinal system

PART 6.1

Physiology

CHAPTER 172

Normal physiology of the gastrointestinal system

Annika Reintam Blaser and Adam M. Deane

Key points

- The gastrointestinal (GI) system carries out digestive, endocrine, immune, and barrier functions.
- The GI system protects against antigens using physical, non-immune, and immune-mediated mechanisms.
- GI motor patterns differ according to fasting or post-prandial phases, and assist with storage, mixing, absorption, and eventual evacuation of luminal contents.
- Intestinal blood flow is increased several-fold in the post-prandial phase.
- Although not well clarified, critical illness appears to have profound effects on GI function.

Introduction

Digestion and absorption are the most obvious functions of the gastrointestinal (GI) system, but this region also carries out important endocrine, immune, and barrier activities that are often tightly integrated with other organs. Additionally, the GI system plays an important role in fluid, electrolyte, and acid-base balance [1]. Adequate blood flow to the GI tract is essential for adequate functioning. In this chapter, information relating to the accessory GI organs is limited to endocrine and exocrine secretions.

Structure and organization of the GI tract

The GI system consists of a series of hollow organs (GI tract) into which accessory organs add their secretions. The basic anatomic structure of the GI tract wall includes mucosa, submucosa, muscle, and serosa (or adventitia, if retroperitoneal) [1]. The mucosal layer consists of epithelium (with glands, microvilli, villi, and crypts depending on location) and lamina propria (with capillaries, neurons, immune cells, and a thin layer of smooth muscle—lamina muscularis mucosae) [1]. The submucosal layer contains connective tissue, glands, and larger blood vessels, while the muscle layer consists of inner circular and outer longitudinal layers, with neurones in between.

The enteric nervous system (ENS) consists of the submucosal (Meissner's) plexus located in both small and large bowel, and the myenteric (Auerbach's) plexus located between the circular and longitudinal muscle layers running from oesophagus to rectum [1]. The ENS can operate independently, but extrinsic pathways (usually parasympathetic) regulated by the brainstem are also integrated.

The mouth and oropharynx are essential for chewing and lubrication of food, but also initiate carbohydrate and fat digestion. The oesophagus is a conduit for ingesta to enter the stomach, and limit or clear reflux. The stomach stores ingesta and has substantive motor, secretory, humoral, and digestive functions. The small bowel absorbs nutrient, fluid, and electrolytes, and secretes peptides. Pancreatic secretions and bile enter the duodenal lumen, the former are pivotal for digestion, as well as neutralization of gastric acid entering the small bowel, while the latter assists with excretion of waste products and digestion of lipids. The large bowel absorbs water and electrolytes, as well as carbohydrate that reaches the large bowel unabsorbed, stores luminal contents until evacuation, and secretes fluid and electrolytes.

GI functions

Energy intake

Ingestion requires integration of oro-pharyngeal and oesophageal motility but, in the critically ill, ingestion is commonly bypassed with insertion of nasogastric tubes.

Digestion and absorption are the components of nutrient assimilation [1]. Many dietary foods require digestion before absorption can occur as nutrient needs to be in a component form for transluminal transportation. While enzymes secreted from the pancreas are primarily responsible for luminal digestion, enzymes from the brush border membrane of the small intestinal epithelium are essential for the final part of carbohydrate and protein digestion (membrane digestion) [1]. Absorption mostly takes place at the apical membrane of the small intestine, with active transportation, passive diffusion, facilitated diffusion (requires a carrier, but no energy), or phagocytosis.

Carbohydrates must be broken down into their constituent monosaccharides prior to absorption [1]. Amylase hydrolyses starch into oligo- and disaccharides that are non-absorbable. Enzymes from the brush border membrane, carbohydrases, are necessary to complete digestion to monosaccharides, which are absorbed via the sodium-dependent glucose co-transporter (SGLT1) located in the brush border membrane.

Lipids are disrupted mechanically in the mouth and stomach, with the particles stabilized as an emulsion [1]. Emulsification of fat is assisted by gastric motility. However, lecithin and bile salts are pivotal to this process, facilitating digestion of triglycerides into free fatty acids and monoglycerides by pancreatic lipase. Bile salts also play an important role in forming fatty acids and monoglycerides

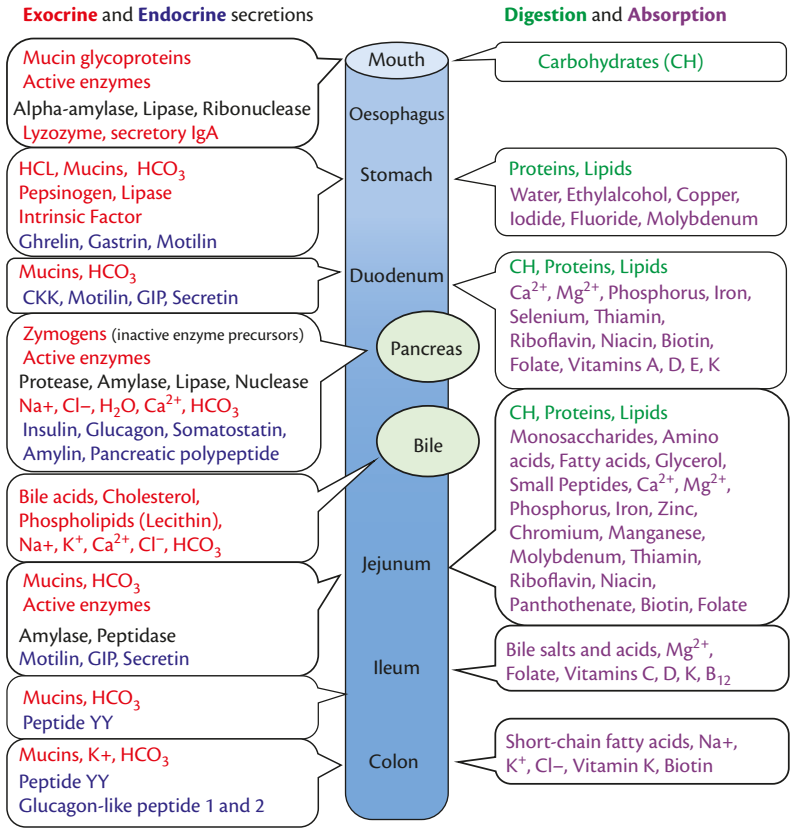


Fig. 172.1 Absorption and digestion of nutrients presented together with secretions of the GI tract.

into micelles that are passively absorbed across the brush border epithelium into the bloodstream.

Protein is partially degraded in the stomach by pepsin. Pancreatic proteolytic enzymes secreted into the proximal small intestine are capable of digesting proteins to oligo-peptides (branches of 2–6 amino acids). Brush border enzymes then digest oligo-, tri-, and di-peptides to amino acids, and the latter are absorbed via several specific co-transporters.

Locations for digestion and absorption of nutrients are presented in Fig. 172.1.

Immunological and barrier functions

The protective mechanisms of the GI system consist of physical, non-immune, and immune elements. Intact gut mucosa provides a physical barrier while gastric acid, intestinal mucin, bile, and peristalsis are part of the non-immunological protective response. The immune-mediated response relies upon gut-associated lymphoid tissue (GALT). GALT consists of aggregates of lymphoid tissue (e.g. Peyer's patches), and diffuse populations of immune cells (lymphocytes and mast cells) mostly located in the small intestine [1,2]. Orally ingested antigens are taken up by GALT where immunocytes are activated [2]. Activated T-lymphocytes secrete IgA in response to prolonged antigen exposure. Transported into the lumen via B-lymphocytes, IgA neutralizes intraluminal antigen/s. The digestive microflora is the major antigenic stimulant for the maturation and migration of precursor lymphoid cells [2]. 'Oral tolerance' describes the immune response to the GI system that allows systemic unresponsiveness to a previously ingested antigen, which is crucial for life [2].

Endocrine function

Peptides released from the stomach, pancreas, and/or intestine modulate motility, secretion, absorption, mucosal growth, and immune function. Many peptides have paracrine and neurotransmitter actions, but only peptides with substantial endocrine action are discussed here.

Hormones secreted from the GI tract

- Ghrelin is secreted primarily by the stomach during fasting, with secretion suppressed by meal ingestion. Ghrelin, the natural secretagogue for growth hormone, is a potent appetite stimulant and accelerates gastric emptying [3].
- Motilin is secreted during fasting and suppressed by nutrient. Exogenous motilin accelerates gastric emptying. In the critically ill the motilin agonist, erythromycin, has a similar effect.
- Gastrin is secreted principally from the gastric antrum in response to nutrients, in particular protein, and is suppressed by acid. Gastrin is the major hormonal regulator of gastric acid secretion.
- Cholecystokinin (CCK) is secreted in response to the presence of nutrient in the duodenum and jejunum. CCK is the major hormonal stimulant of gallbladder emptying, and also suppresses appetite and energy intake. CCK stimulates pancreatic secretion and slows gastric emptying.
- Secretin is principally released in response to acid within the duodenum, but partially digested products of fat and protein as well as bile acid also stimulate its release. Secretin is a potent

stimulant of pancreatic exocrine secretion, but also reduces gastric acid secretion and slows gastric emptying.

- Peptide YY (PYY) is secreted predominantly from the colon and rectum in response to nutrient, with fat as the principal stimulant. PYY slows both gastric emptying and small intestinal transit, and inhibits appetite.
- Glucose-dependent insulinotropic peptide (GIP) is secreted in response to duodenal nutrient and is a potent insulinotropic hormone.
- Glucagon-like peptide-1 (GLP-1) is secreted from the small and large intestine in response to unabsorbed nutrient or bile acids. Together, GLP-1 and GIP are termed the 'incretin' hormones, being pivotal for glycaemic regulation following a meal. In health, GLP-1 stimulates insulin and suppresses glucagon secretion, as well as slows down gastric emptying.
- Glucagon-like peptide-2 (GLP-2) is co-secreted with GLP-1 and has a profound intestinotropic response.

Hormones secreted from the pancreas

- Somatostatin is an inhibitory hormone secreted in response to mechanical and nutrient stimulation. Somatostatin reduces gastric acid, pepsinogen, pancreatic exocrine secretion, and bile flow [4]. Somatostatin analogues (e.g. octreotide) markedly reduce splanchnic blood flow.
- Insulin is secreted from pancreatic β cells, with plasma glucose being the principal stimulant [4]. Insulin lowers blood glucose and promotes storage of carbohydrate and fat.
- Amylin is co-secreted with insulin from pancreatic β cells and slows gastric emptying, insulin and amylin probably act synergistically to attenuate post-prandial glycaemic excursions [4].
- Glucagon is a pivotal counter-regulatory hormone. Glucagon stimulates glycogenolysis and gluconeogenesis in the liver and the kidney [4].
- Pancreatic polypeptide inhibits pancreatic exocrine function and gallbladder contraction.

Requisites to perform GI functions

Motility

The motor activity of the GI tract assists with mixing (non-propulsive movements), propulsion (progressive wave of relaxation, followed by contraction), retropulsion (reflux), and storage. The motor activity of the GI system differs between fasting and fed states, but both appear to be profoundly disturbed during critical illness.

Oro-pharynx and oesophagus

Chewing and swallowing are the main motor functions of the oro-pharynx, with the latter integrated with the oesophagus. Swallowing is a complex process mainly controlled by the swallowing centre in the medulla. The upper oesophageal sphincter opens with swallowing and closes with inspiration. Peristalsis in the oesophageal body is primary when initiated by swallowing, or secondary when initiated by residual bolus or refluxate in the oesophagus. The lower oesophageal sphincter allows coordinated passage of the bolus into the stomach, appropriate venting of gas or liquid from the stomach while limiting noxious gastric content refluxate [5]. Lower oesophageal sphincter relaxation occurs not only because of primary or secondary peristalsis, but also independent of these peristaltic reflexes, which are termed transient lower oesophageal relaxations. In the critically ill, basal lower oesophageal sphincter pressure is profoundly reduced, primary peristalsis appears absent and secondary peristalsis is probably impaired [5]. Accordingly, reflux events are common and poorly cleared.

Stomach

The motor function of the stomach prepares solid digestible nutrient by mixing and grinding chyme, regulates nutrient supply (i.e. gastric emptying), and expels non-nutrient material during fasting.

- Fasting stomach motility is arbitrarily divided into three phases, the so-called 'migrating motor complex' (MMC). MMC phase I is characterized by motor quiescence, phase II by irregular contractile activity, and phase III by periods of regular contractions sometimes referred to as 'activity fronts'. Propulsion of luminal contents occurs mainly during late phase II or phase III.
- Post-prandial stomach motility is initiated by nutrient intake and ends with the recurrence of fasting motility patterns. In contrast to solids, liquid nutrient is initially emptied from the stomach at a more rapid rate and, thereafter, follows an overall linear rate of emptying. Mechanisms underlying this transition likely involve interactions with nutrient receptors in the small intestine (enterogastric feedback). The stomach is separated into two functional regions; proximal (fundal) and distal (antral and pyloric). In the critically ill, delayed gastric emptying occurs commonly. It is usually associated with disordered motility throughout the entire stomach and impaired integration of motor function [5].

Following ingestion of a meal the proximal stomach acts as a reservoir, with inhibition of tonic contraction of the smooth muscle. The resulting 'receptive' relaxation of the proximal stomach allows filling with ingesta, with only minor increases in pressure. This is followed by gastric 'accommodation', which may be prolonged (up to 3 hours) and persists until emptying is almost complete. Fundal contractions then assist with aboral movement of the ingesta.

Post-prandial activity in the distal stomach is characterized by irregular contractions that aid mixing and propagation of nutrient along the gastrointestinal tract. Antral pressure activity assists with mixing and is also a substantial regulator of gastric emptying. However, to retard gastric emptying, limit duodenogastric reflux, and facilitate the mixing of chyme, intermittent pyloric pressure waves (IPPWs) enable prolonged periods of pyloric closure to occur [5].

Small intestine

Fasting MMC patterns propagate from the gastro-duodenal region through the small intestine. In the duodenum the post-prandial motor pattern is characterized by irregular contractions with both antegrade and retrograde pressure wave sequences which usually propagate over short distances only [6]. This pattern causes intermittent and bidirectional flow of chyme to facilitate mixing and grinding. In the critically ill a fasting 'MMC type' of pattern continues during nutrient stimulation, which means that the conversion from a fasting to an inter-digestive motor pattern fails.

Large intestine

The irregular motor activity of the colon includes tonic and phasic contractions. Short duration contractions cause both antegrade and retrograde movement, and assist with mixing and absorption of luminal contents. High-amplitude propagated contractions cause contraction over several segments. They occur more commonly after waking, meals, and may be associated with the urge to defecate [6].

Integrative steering

The GI system is modulated by complex myogenic, neural, and humoral mechanisms. The interstitial cells of Cajal initiate and conduct myogenic activity throughout the gut independent of neural and humoral control. Whether or not the electrical stimulus initiates mechanical contraction is then determined by a number of intraluminal and systemic factors, mediated via neural and/or hormonal pathways.

Neuronal

Neural regulation of the GI system is mediated via extrinsic (**vagus** nerve with both afferent and efferent components) and intrinsic (**enteric** nerves) pathways. The efferent **vagus** nerve provides parasympathetic motor supply to the gut, controlled by a cholinergic excitatory pathway and a non-adrenergic non-cholinergic inhibitory pathway. **Enteric** nerves can convey information in ascending and descending directions via excitatory (acetylcholine and serotonin) and inhibitory (nitric oxide) neurotransmitters.

Hormonal

Hormonal regulation is described in 'Endocrine Function'.

Exocrine secretions

Gastric secretions

The stomach secretes fluid comprising hydrochloric acid, pepsinogen, intrinsic factor, mucous, and bicarbonate, as well as peptides that have paracrine effects. The rate of secretion during the post-prandial phase differs according to whether an individual is aware of food (anticipation), and when nutrient is within the stomach or the duodenum (cephalic, gastric and intestinal phases, respectively). Secretions from the stomach aid sterilization of ingesta (hydrochloric acid), commence digestion (pepsinogen), protect the stomach and duodenum (mucous and bicarbonate), and are essential for the subsequent absorption of vitamin B_{12} (intrinsic factor) [6].

Pancreatic and salivary secretions

The exocrine pancreas secretes >20 proteins, as well as calcium and bicarbonate, and is essential for digestion [1]. Salivary secretions include alpha-amylase and mucins [1].

Intestinal secretions

To facilitate motor and absorptive functions a substantial amount of intestinal fluid is secreted. While nearly all is resorbed in the absence of intestinal disease, net bicarbonate, chloride, and potassium secretion are important.

Perfusion

The coeliac artery is responsible for the main blood flow to stomach, pancreas, and spleen [1]. Small and large intestinal blood supply is from superior and inferior mesenteric arteries, with interconnections between the arcading branches providing multiple collateral pathways [1]. Venous flow from stomach, intestines, pancreas, and spleen is via the portal vein. In health, intestinal blood flow is increased several-fold in the post-prandial phase, but this response may be attenuated in the critically ill. [7]

Fenestrated capillaries in the villi absorb nutrients from the intestinal lumen [1]. The fountain-like arrangement of villi microvessels facilitates counter-current exchange, enabling solutes to move from arteriole to venule without traversing the entire length of the villus [1]. However, this arrangement makes the villus tip susceptible to damage from hypoxia and/or hypotension.

Sympathetic activity directly constricts splanchnic vessels. Parasympathetic activity stimulates intestinal motility and secretion and increases metabolism, thereby indirectly increasing perfusion. The splanchnic circulation serves as a major reservoir of blood; about half the splanchnic blood volume can be rapidly mobilized [1]. A reduction in blood flow leads to production of vasodilatory metabolites. At rest only 20% of O_2 is extracted [1]. This extraction rate can be increased remarkably so temporary reductions in blood flow can be tolerated. Longer durations of such periods may result in irreversible damage as the ischaemic mucosal epithelium at the villi tips sloughs off [1]. This sloughing results in disruption of the barrier allowing entrance of toxic substances and bacteria into the circulation; this is a putative mechanism underlying the development of multi-organ dysfunction.

Conclusion

The GI system plays a crucial role in health. While effects of critical illness on the GI system are incompletely understood, critical illness does appear to have profound effects on this system.

References

1. Boron WF and Boulpaep EL. (2012). *Medical Physiology*, 2nd edn. Philadelphia, PA: Saunders 2012.
2. Speckmann EJ, Hescheler J, and Köhling R. (2008). *Physiologie*, 5th edn. Munich: Elsevier.
3. Deane A, Chapman MJ, Fraser RJL, and Horowitz M. (2010). Bench-to-bedside review: The gut as an endocrine organ in the critically ill. *Critical Care*, **14**, 228.
4. Yamada T. (ed). (2009). *Textbook of Gastroenterology*, 5th edn. Oxford: Blackwell.
5. Chapman MJ, Nguyen NQ, and Deane AM. (2011). Gastrointestinal dysmotility: clinical consequences and management of the critically ill patient. *Gastroenterology Clinic in North America*, **40**, 725–39.
6. Barrett KE. (2006). *Gastrointestinal Physiology*. New York, NY: Lange Medical.
7. Sim JA, Horowitz M, Summers MJ, et al. (2013). Mesenteric blood flow, glucose absorption and blood pressure responses to small intestinal glucose in critically ill patients older than 65 years. *Intensive Care Medicine*, **39**, 258–66.

CHAPTER 173

Normal physiology of the hepatic system

William Bernal and Alberto Quaglia

Key points

- Hepatic blood inflow is from two sources; high-pressure, well-oxygenated blood from the hepatic artery and low-pressure, partly deoxygenated blood from the portal vein. Hepatic inflow is maintained by variation in flows in these two systems.
- Although less than a third of total blood flow is delivered via the hepatic artery, it is responsible for the majority of hepatic oxygen supply.
- The liver can be subdivided into eight functionally-independent segments, each with its own vascular inflow, outflow, and biliary drainage.
- The tri-dimensional hepatic microstructure is complex with geographic heterogeneity of hepatocellular function, and resistance to toxic, ischaemic, and metabolic damage.
- The liver is central to a wide variety of synthetic, metabolic, and detoxification functions. The overall balance of activity may be altered rapidly in response to systemic inflammatory stimuli.

The hepatic system

The liver is the largest internal organ, weighing between 1.4 and 1.7 kg in adults. Situated in the right upper quadrant of the abdominal cavity, it is partially subcostal and immediately inferior to the right hemi-diaphragm. It is subdivided into right and left lobes, with the former further divided into caudate and quadrate lobes. The right lobe usually represents three-quarters of the overall liver mass. The liver serves a huge variety of functions and its presence is vital for life. Survival in the anhepatic state is possible only for a few days.

Liver cells may be grossly categorized as parenchymal and non-parenchymal, with the former occupying 80% of liver volume and with the hepatocyte being the predominant cell type. Non-parenchymal cell types include sinusoidal endothelial, hepatic stellate cells and a lymphoid population which represent less than 10% of liver volume, but 40% of cell numbers. The complex macro- and micro-structural arrangement of these cells, and their nutritive blood supply have important functional and pathophysiological consequences.

Hepatic blood supply

The liver receives about 75% of its blood supply through the portal vein (PV) that carries partly deoxygenated blood from the major part of the digestive tract, including spleen, pancreas, and gallbladder. The remaining 25%, yet accounting for 50% of the liver's oxygen supply—arises from the hepatic artery (HA), the second major branch of the celiac axis. The liver may be subdivided into eight functional segments based upon the distribution of vascular supply (Fig. 173.1) [1].

Total hepatic blood flow is equivalent to approximately 100 mL/min per 100 g liver wet weight. Though liver mass constitutes only 2.5% of total body weight, it receives nearly 25% of cardiac output. The liver also accounts for 12% of total blood volume, half may be expelled from the liver through active or passive mechanisms with a potential role as a blood volume reservoir.

Though neural and humoral control mechanisms may play a role, hepatic perfusion is primarily maintained by variation in flows of the hepatic arterial and portal venous systems. While the liver cannot directly control total PV blood flow, the HA can produce reciprocal compensatory flow changes in response to changes in PV flow. This 'hepatic arterial buffer response' (HABR) maintains constancy of total hepatic blood flow. When portal venous flow decreases, hepatic arterial resistance decreases and arterial flow increases, and vice versa through mediators including locally produced adenosine [2].

Increases or decreases in hepatic venous pressure may further influence hepatic blood flow and volume, for example, clinically important effects may be seen in patients when elevated right-sided cardiac pressures result in marked hepatic venous congestion.

Microscopic structure

The tri-dimensional hepatic microstructure is complex and remains to be fully characterized. On conventional bi-dimensional histology preparations, the basic morphological elements are the portal tracts, hepatic sinusoids, hepatocellular plates, and centrilobular venules (Fig. 173.2).

The portal tracts consist of a connective tissue framework incorporating branches of the PV and the HA, bile duct tributaries, nerve twigs and lymphatics (Fig. 173.2) [3].

Portal venous and arterial blood converges into the hepatic sinusoidal vascular network. These sinusoids are delineated by a layer of endothelial cells, with fenestrations allowing the underlying hepatocytes to come into contact with sinusoidal blood. In contact with the internal sinusoidal surface are macrophages (Kupffer cells) and lymphocytes. Blood flows uni-directionally along the sinusoid toward the hepatic venule, with canalicular bile flow in the opposite direction.

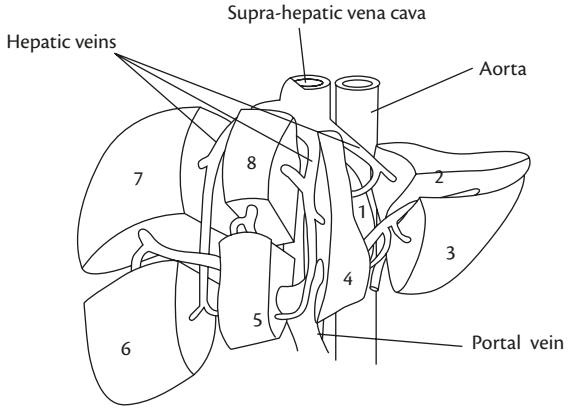


Fig. 173.1 Liver gross and segmental anatomy. Note: Antero-superior view is shown, excluding bile ducts. The Couinaud classification of liver anatomy divides the liver into eight functionally independent segments. Each segment has its own vascular inflow, outflow, and biliary drainage. In the centre of each segment there is a branch of the portal vein, hepatic artery, and bile duct. In the periphery of each segment there is vascular outflow through the hepatic veins.
Segment 1: caudate lobe; 2,3 and 4 left lobe; 5,6,7 and 8 right lobe.

Hepatocytes are separated from the sinusoidal endothelial cells by the space of Disse that is made up of extracellular matrix and contains hepatic stellate cells. Hepatocytes are organized in interlacing 'plates' with their basolateral aspects facing the space of Disse and sinusoidal lumen, and apical aspects coming into reciprocal contact to form canaliculi. Bile constituents are secreted into the canaliculi and eventually drained by the portal bile ducts. The centrilobular venules drain sinusoidal blood into the tributaries of the hepatic veins.

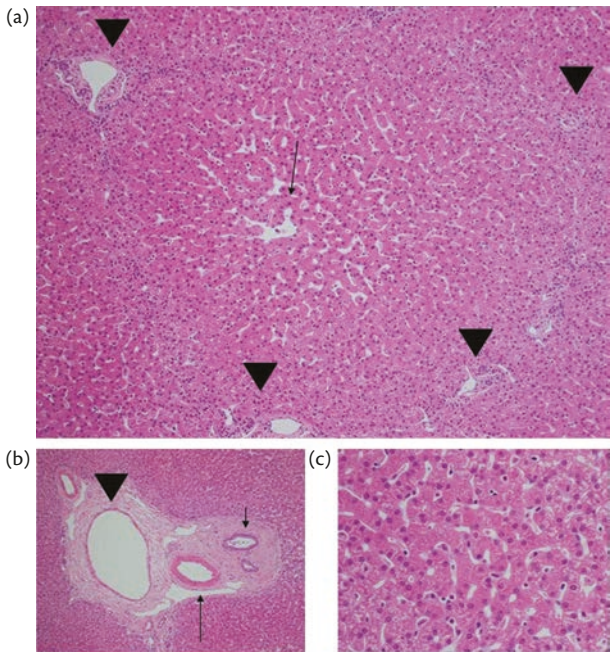


Fig. 173.2 Microscopic anatomy. (a) Arrowheads show portal tracts arranged around a hepatic venules (arrow). (b) A large portal tract include an artery (long arrow), a bile duct (short arrow), and a portal vein branch (arrowhead). (c) Hepatocyte plates and intervening sinusoids.

The orderly histological disposition of portal tracts sinusoids, hepatocellular plates, and centrilobular venules has provided the basis for microscopic structural models such as the Kiernan lobule, Rappaport acinus, and more recently, the Matsumoto primary lobule, the latter based on complex tri-dimensional reconstruction studies. These models have contributed to our interpretation of the various histological patterns of liver injury, inflammation, scarring, and regeneration [4,5].

Anatomic and physiological relationships

Main considerations on the relationship between microscopic anatomy, function, and pathological states include:

- Hepatocellular plates receive a dual arterial and blood supply. In contrast, the biliary tree is largely dependent on the arterial supply, and thus has a poor resistance to ischaemic injury [6].
- Hepatic arterioles and portal branches are regulated by sphincters that can modulate vascular inflow. Hepatic venules are also contractile as are hepatic stellate cells, providing further modulation of vascular in- and outflows. Periportal connections between arterioles and sinusoids and the action of sphincters may provide the basis for functional arterioportal shunts.
- There is a gradient of oxygen tension and distribution of blood constituents between different zones, in particular the periportal and perivenular regions. Blood becomes progressively poorer in oxygen and nutrients from the periportal zone 1 to perivenular zone 3. This is reflected in a geographic heterogeneity of hepatocellular function, and resistance to toxic, ischaemic, and metabolic damage (Figs 173.3, and 173.4) [7].
- Bile secreted into the canaliculi drains into portal bile ducts. The point of contact between the canalicular system and the interlobular bile duct is thought to be the canal of Hering. This is also likely to be the location of progenitor cells that may activate in response to liver injury and contribute to regeneration [8].
- Bile synthesis is heterogeneous with a portal-perivenular gradient. Bile constituents are reabsorbed by biliary epithelial cells

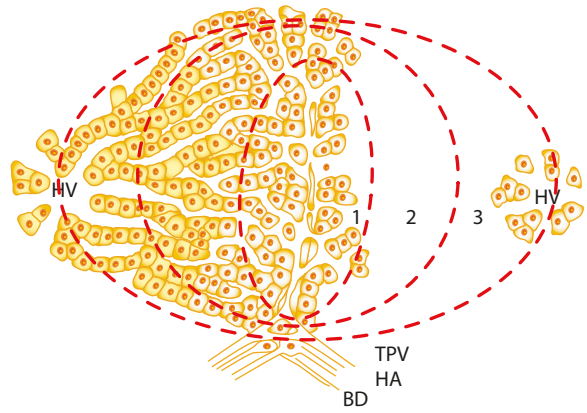


Fig. 173.3 Hepatic acinus. The acinar axis is formed by terminal branches of the portal venule (TPV), hepatic arteriole (HA), and bile ductule (BD). Blood enters the acinar sinusoids and flows sequentially through zone 2 and into zone 3, where it exits via the terminal hepatic venules (HV).

and secreted through their basolateral aspect, followed by reabsorption by the peribiliary vascular plexus in a countercurrent fashion.

- Sinusoidal lymphocytes and Kupffer cells are part of the immunologic defence mechanisms, activating following liver injury and mediating regeneration and fibrosis. Mediator release from Kupffer cells and circulating macrophages homing to an acutely injured liver may modulate the systemic inflammatory response.
- Liver injury induces activation of hepatic stellate cells from a vitamin A storing mode to myofibroblast-like cells, and activation of portal fibroblasts to induce fibrogenesis. The subsequent alteration of the orderly microscopic architecture by fibrous scarring is the basis for the pathophysiology of advanced stage liver disease and its complications.
- The regenerative ability of the liver parenchyma is based on hepatocyte and cholangiocyte re-entry into the cell cycle, and replication. This is observed, for example, after partial hepatectomy. Progenitor cells contribute to regeneration when hepatocyte loss reaches a certain trigger point or when hepatocyte proliferation is impaired. Activation and proliferation of these progenitor cells is followed by their differentiation into hepatocytes or cholangiocytes; the contribution of circulating extra-hepatic stem cells to liver regeneration remains controversial.

Synthetic, metabolic, and detoxification functions

The liver is central to a wide variety of synthetic, metabolic, and detoxification functions [9]. It is the main site of protein synthesis, e.g. exporting up to 12 g albumin daily. Protein synthesis is regulated by various factors, in the case of albumin by changes in osmotic pressure, nutritional state, systemic inflammation, and drugs, particularly corticosteroids.

As the liver serves as the source of most blood coagulation factors, changes in synthetic capacity may also be reflected in altered coagulation status on laboratory testing. However, the functional consequences are complex as a balanced loss of pro- and anti-coagulant proteins may occur [10,11].

Synthesis of coagulation factors II, VII, IX and X is dependent on lipid-soluble Vitamin K. Prolongation of the prothrombin time (PT) may reflect failure of gastrointestinal lipid absorption rather than hepatocellular failure. When the PT is prolonged, intact hepatic function may be inferred by an improvement >30% within 24 hours of parenteral vitamin K administration.

The liver is the primary site of the body's stores of a number of substances including vitamins A, B_{12} and D, and minerals including iron and copper. It also stores most of the body's carbohydrate energy reserves as glycogen, which may represent up to 10% of hepatocyte mass. Synthesis is increased when blood glucose concentrations are high. When blood glucose is low, glycogenolysis is stimulated along with gluconeogenesis from amino acids. The loss of hepatic carbohydrate homeostasis and consequent hypoglycaemia may be an ominous reflection of critically impaired hepatic function. The liver is also key to lipid handling, transport, and metabolism, and is responsible for the synthesis of cholesterol and lipoproteins including high-density lipoprotein. It is also the site of synthesis of hormones and mediators including thrombopoetin, insulin-like growth factor 1, and angiotensinogen, and of the degradation of hormones, e.g. insulin.

The overall balance of hepatic metabolic activity may be shifted rapidly in response to systemic inflammation with an 'acute phase reaction' (APR). Triggered by circulating inflammatory mediators, this results in a series of acute phase phenomena including complex

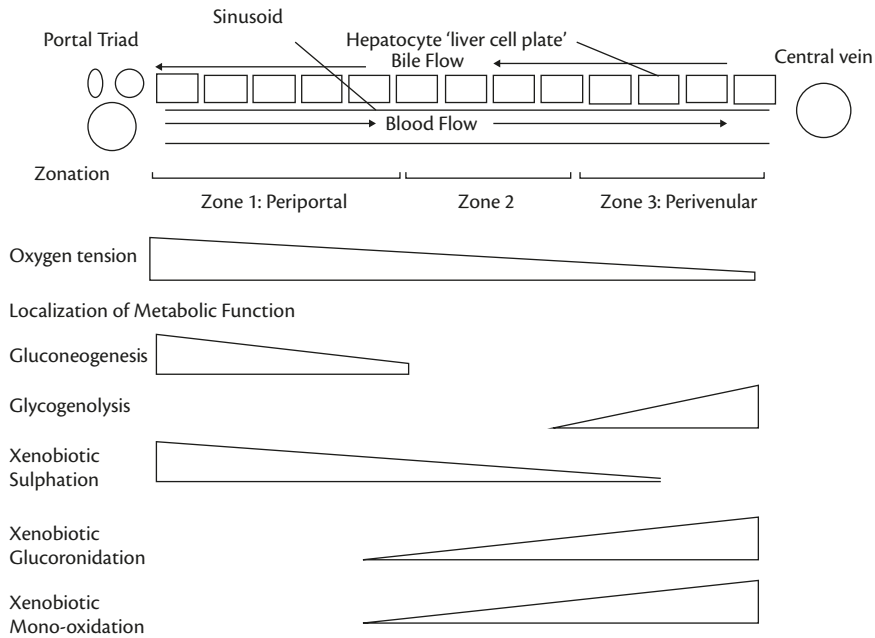


Fig. 173.4 Hepatocyte zonation.
Hepatocytes exhibit marked metabolic heterogeneity or 'zonation' along the liver cell plate, in part reflecting unidirectional perfusion of oxygen and metabolic substrates. Zone I hepatocytes are specialized for oxidative liver functions, while glycolysis, liopgenesis and xenobiotic oxidation is concentrated in perivenular or 'zone 3' hepatocytes. This area is predisposed to toxicity from reactive oxygen intermediates.
Data from Luxon B, 'Functions of the Liver'. In: Bacon B et al. (Eds), *Comprehensive Clinical Hepatology*, 2nd Edition, Elsevier, 2006, pp. 43–61.

Table 173.1 Examples of hepatic acute phase reactants

Name	Function
Positive: increased synthesis	
C-reactive protein	Opsonization, complement activation
Serum amyloid A protein	Immune cell recruitment
Complement proteins	Opsonization, chemotaxis, cell lysis
Mannose binding protein	Complement activation
Alpha-2-macroglobulin	Protease inhibitor: fibrinolysis, coagulation
Hepcidin	Regulation of plasma iron levels
Ferritin	Iron binding
Haptoglobin	Haem-binding
Ceruloplasmin	Copper and iron binding
Alpha-1-antitrypsin	Inflammatory protease inhibitor
Negative: reduced synthesis	
Albumin	Amino acid preservation
Transferrin	Amino acid preservation
Antithrombin	Protease inhibitor; coagulation

changes in circulating and functional levels of immunologic, transport, and coagulation proteins (Table 173.1). APR proteins include anti-infectious agents (such as complement components, C-reactive protein (CRP) and serum amyloid P (SAP)), as well as proteins that promote increased breakdown of lipids and glycogen, fatty acid synthesis, and gluconeogenesis, and coagulation-modulating factors [5,6].

The detoxification functions of the liver are of great clinical relevance in relation to the processing and disposal of endogenous metabolites and toxic compounds of both endogenous and exogenous origin. Intact hepatic urea synthesis is required for the disposal of ammonia, the toxic end-product of nitrogen metabolism. Hyperammonaemia may result in encephalopathy, and is indicative of critically impaired hepatocellular function and/or abnormal portosystemic shunting.

The liver serves as the major site of drug metabolism and excretion; consequently, it is a frequent site of both idiosyncratic and dose-related adverse drug reactions. Alteration in hepatic metabolic function as a consequence of age, gender and hepatic disease may dramatically affect drug clearances with unpredictable therapeutic consequences.

Drug uptake into hepatocytes is followed by metabolism by several families of enzymes. 'Phase 1' reactions of oxidation or reduction may be followed by 'Phase 2' reactions conjugating often reactive intermediates to glucuronic acid, glutathione, sulphate, or acetate. Hepatically bio-transformed drugs may either be transported to sinusoidal blood for eventual urinary excretion, or into bile. Conjugate excretion may be through active molecular transport. Genetic variation in bio-transforming and transporter proteins contributes to the highly complex inter-individual differences in responses to drugs and other xenobiotics.

Bile formation is a highly complex process, resulting in the production of 500 mL of bile each day in adults. Bile serves both excretory and digestive functions. Its constituents reflect the complex transport mechanisms associated with the sinusoidal plasma membranes. It is composed of water, inorganic electrolytes, and organic solutes including bile acids, cholesterol, and phospholipids and bile pigments. Biochemical evidence of cholestasis is a frequent finding in critical illness, and results most commonly from functional changes relating to sepsis and medication including parenteral nutrition rather than overt mechanical biliary obstruction.

References

1. Traber PG, Chianale J, and Gumucio JJ. (1988). Physiologic significance and regulation of hepatocellular heterogeneity. *Gastroenterology*, **95**, 1130–43.
2. Lautt WW. (2007). Regulatory processes interacting to maintain hepatic blood flow constancy: Vascular compliance, hepatic arterial buffer response, hepatorenal reflex, liver regeneration, escape from vasoconstriction. *Hepatology Research*, **37**, 891–903.
3. Crawford AR, Lin XZ, and Crawford JM. (1998). The normal adult human liver biopsy: a quantitative reference standard. *Hepatology*, **28**, 323–31.
4. Burt A, Portman B, and Ferrell L (eds) (2011). *MacSween's Pathology of the Liver*, 6th edn. London: Churchill Livingstone.
5. Reuben A. (2003). Now you see it, now you don't. *Hepatology*, **38**, 781–84.
6. Ekataksin W. (2000). The isolated artery: an intrahepatic arterial pathway that can bypass the lobular parenchyma in mammalian livers. *Hepatology*, **31**, 269–79
7. Colnot S and Perret C. (2011). Liver zonation. In: Monga S (ed.) *Molecular Pathology of Liver Diseases*, pp. 7–16. London: Springer.
8. Saxena R, Theise ND, and Crawford JM. (1999). Microanatomy of the human liver -exploring the hidden interfaces. *Hepatology*, **30**, 1339–46.
9. Luxon B. (2006). Functions of the liver. In: Bacon B, O'Grady J, Bisceglie AD, and Lake J (eds) *Comprehensive Clinical Hepatology*, 2nd edn, pp. 43–61. Amsterdam: Elsevier.
10. Lisman T and Porte RJ. (2010). Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood*, **116**, 878–85.
11. van der Werf J, Porte RJ, and Lisman T. (2009). Hemostasis in patients with liver disease. *Acta Gastroenterologica Belgica*, **72**, 433–40.

PART 6.2

Gastrointestinal monitoring

CHAPTER 174

Imaging the abdomen in the critically ill

Imran Khalid Niazi and Navin Ramachandran

Key points

- Haemodynamic stability remains the single most important deciding factor in the choice for imaging modality used. Initial resuscitation is the priority and should never be delayed for any radiological investigation.
- Each individual scan should be tailored to the patient's clinical history and examination findings.
- Plain film and ultrasound scans are the first-line investigations in most unstable patients.
- CT remains the ideal investigation in haemodynamically stable patients.
- Magnetic resonance imaging has a limited role at present, but may be of value, particularly in children and pregnant patient.

Introduction

Abdominal evaluation of the critically-ill patient is challenging. The patient may have a vague presentation, sometimes with a poor clinical history, few localizing signs, multiple co-morbidities and multi-organ involvement. Often the patient will require resuscitation prior to diagnostic workup, and support devices such as mechanical ventilators and haemofilters may hamper assessment. Indeed in one study, physical examination had a diagnostic specificity of only 45% in blunt abdominal trauma, while clinical signs were helpful in only 43–69% of cases of abdominal abscesses [1].

Such unreliability of clinical indicators and the myriad of abdominal pathologies in a critically-ill patient may lead to diagnostic uncertainty with consequent delays in treatment. These challenges make imaging one of the most critical steps in the management of such patients.

The optimal imaging pathway should be sensitive, specific, and minimize delay in therapy, but should also account for the patient's clinical state and overall radiation dose. The following modalities have a role in abdominal evaluation of the critically ill.

Plain radiographs

Abdominal radiographs have a limited role in evaluation of the critically-ill patient. Supine and erect abdominal films may be useful to look for dilated bowel in intestinal obstruction. However, if the dilated loops contain fluid rather than air they may be missed on plain film. Furthermore, the exact site of obstruction is not usually obvious on plain film. Therefore, most patients will be further assessed with computed tomography (CT) if there is ongoing concern regarding obstruction.

Free intraperitoneal gas may also be evaluated. Erect chest X-rays are still the mainstay of initial investigation for suspected hollow viscus perforation, as small quantities of extra-luminal free gas may be seen beneath the diaphragm (Figs 174.1 and 174.2). To maximize sensitivity, the patient is sat upright for 10 minutes to allow free air to rise to the diaphragm. If the patient is not fit enough to be placed upright, decubitus abdominal films may be of value.

However, a negative plain film does not rule out perforation. Indeed, many surgeons prefer CT for its increased sensitivity, its ability to identify the site of perforation and to rule out occult sealed perforation. The higher radiation burden of CT should be, however, remembered.

In most other scenarios (e.g. abdominal sepsis) plain X-ray findings are non-specific and other modalities are suggested.

Ultrasound

Abdominal ultrasound is particularly useful as it is portable, cheap, and safe. Therefore, it may be used when:

- The patient cannot easily be transferred to the radiology department for more definitive tests such as CT or magnetic resonance imaging (MRI).

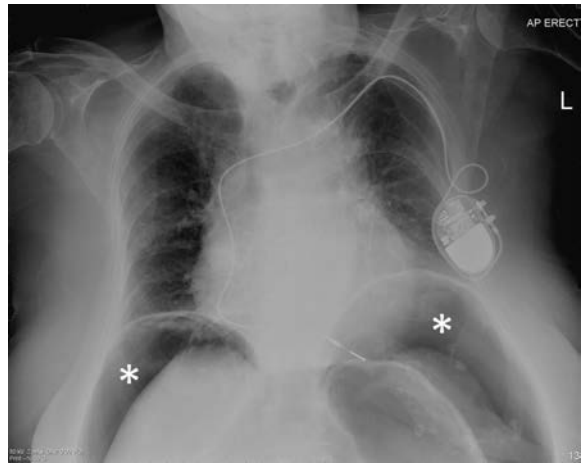


Fig. 174.1 Erect chest X-ray shows extensive free gas beneath the diaphragm (*) in a patient with large bowel perforation.

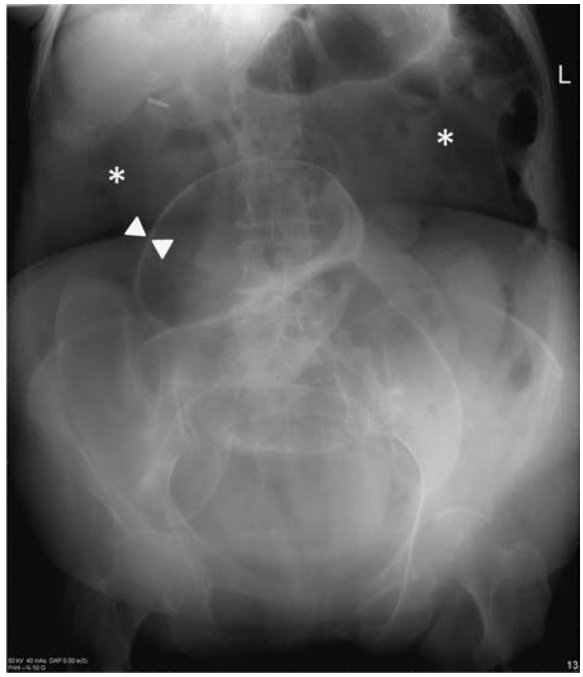


Fig. 174.2 Abdominal X-ray. Extensive pneumoperitoneum with free gas in the upper abdomen (*) and Rigler's sign (arrowheads, pointing out air on both sides of the bowel wall).

- The patient has already had multiple CTs, and ultrasound follow-up (if suitable) effectively reduces overall radiation dose to the patient. This may be particularly important in the younger patient.

Focused Assessment with Sonography for Trauma (FAST) has now become a standard investigation in the trauma patient. FAST is a bedside ultrasound examination focused on evaluation of free fluid in four areas—the 4P's—perihepatic, perisplenic, pelvis, and the pericardium. It is indicated in the unstable critical trauma patient group where detection of any free abdominal fluid will require an urgent laparotomy—any free fluid detected on FAST scan is considered haemorrhage until proven otherwise. Further evaluation with a CT in such a scenario may not be appropriate as it may delay urgently required treatment, unless the patient can be stabilized quickly. In one prospective study, FAST changed trauma patient management in 32.8% of cases, reducing the need for diagnostic peritoneal lavage (DPL) from 9–1 % [2].

Ultrasound is very useful in examining the liver and biliary tract. The commonest scenario is that of the patient with deranged liver function—ultrasound may be used to look for:

- Cholecystitis and its complications. Gall bladder wall thickening with or without adjacent fluid are seen most commonly. Conversely, suspected gall bladder inflammation on CT often requires confirmation with a subsequent ultrasound.
- Biliary tract obstruction with dilatation of the ducts. However, this often requires further evaluation with either CT or MRI to look for the site/cause of obstruction (often obscured by bowel gas on ultrasound) (Fig. 174.3).
- Generalized abnormalities of liver parenchyma such as cirrhosis, or focal lesions such as abscess.
- Occlusion of the portal or hepatic veins. This is not uncommon in the critically ill with abdominal sepsis.

Ultrasound is also used for guidance in abdominal drainage procedures, and for follow-up of fluid collections, e.g. abdominal abscesses, post-surgical collections, and even simple ascites.

Potential pitfalls of ultrasound are:

- **Operator dependence**: the operator should be adequately trained and accredited.
- Inadequate evaluation in the obese.
- **Inappropriate timing of the scan**: e.g. if performed too early in the post-trauma phase, the patient may have minimal intraperitoneal fluid despite widespread injury. Serial exams may help in this situation.
- **Poor localization of the site of injury**: this is the role of CT in the more stable patient where transfer to the scanner is possible.

Fluoroscopy

Fluoroscopy is not commonly used in assessment of critically-ill patients. Its predominant diagnostic role is in upper GI contrast studies to rule out post-operative anastomotic leakages (Fig. 174.4), evaluate bowel stent patency and evaluation of enteral feeding tubes. In many cases, it has now been replaced by CT.

Fluoroscopy is routinely used for guidance in various interventional procedures. Fluoroscopic-guided naso-enteral feeding tube

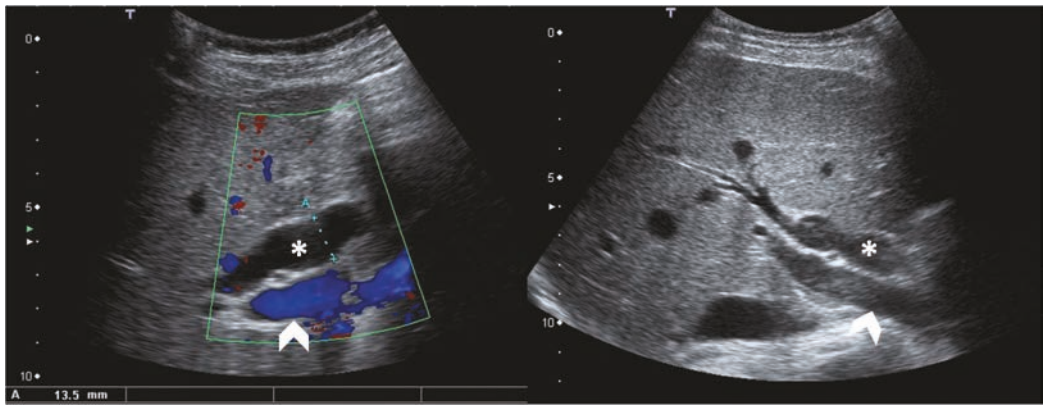


Fig. 174.3 Ultrasound of the biliary system shows common bile duct dilatation (*) with the normal adjacent portal vein (arrowhead).

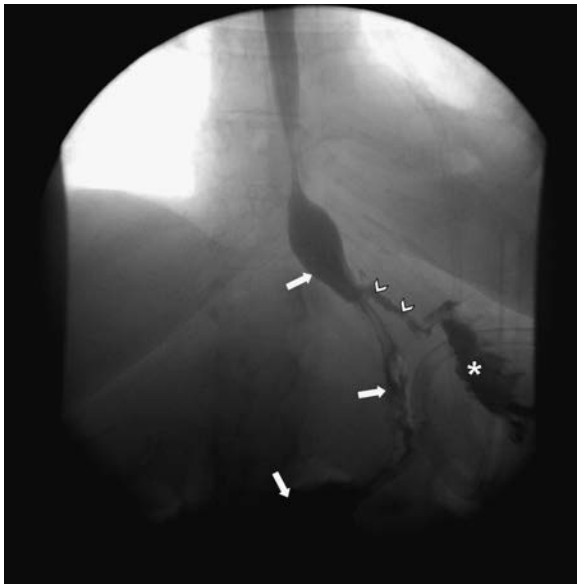


Fig. 174.4 Spot fluoroscopy image of an upper GI contrast study in a patient post-bariatric gastric sleeve surgery. Contrast flows unimpeded down the oesophagus, through the reconstructed gastric tube and into the duodenal loop (arrows). Note leakage of contrast from the lateral border of the newly constructed gastric tube (arrowheads). Extraluminal contrast pools in the peritoneal cavity (*).

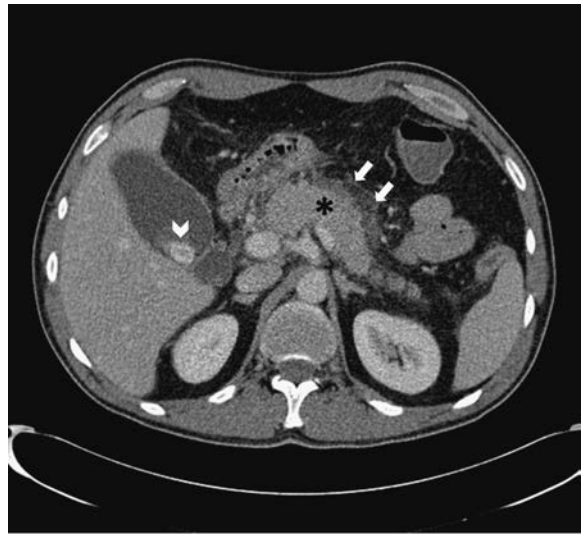


Fig. 174.5 Axial section of a CT scan at the level of the pancreatic body, which appears swollen (*) with retroperitoneal fat stranding (arrows). Note the calculus within the gall bladder body (arrowhead).

insertion has been proven to be safe, feasible, and accurate with reduced morbidity and higher caloric delivery for the patient [3]. Fluoroscopy also provides guidance in ERCP and other percutaneous biliary procedures, angiography and vascular embolization, and various urological interventions (percutaneous nephrostomies, ureteric stenting).

Computed tomography

CT remains the investigation of choice for most haemodynamically stable patients with suspected abdominal pathology. In the unstable patient it can be a viable option if deemed clinically important. Abdominopelvic CT can be performed under many different scan protocols, each tailored to the clinical question. Use of iodinated IV contrast is recommended in most circumstances and helps to optimize assessment of almost all abdominal pathologies. CT can be performed without IV contrast in patients with renal impairment or a definite history of contrast allergy. This however, significantly reduces the sensitivity and accuracy of disease assessment, often requiring augmentation with other imaging, usually ultrasound.

Scans can be performed at various phases of IV contrast enhancement:

- **Pre-contrast**: ideal for renal calculi or as a 'control' prior to administration of contrast, e.g. to look for subsequent enhancement or leak.
- **Arterial phase**: for arterial assessment in suspected ischaemic bowel or abdominal haemorrhage.
- **Venous phase**: this is the standard phase for CT scanning used in almost all abdominopelvic CTs and is ideal for visualization of solid viscera and most inflammatory conditions. Mesenteric and portal vein assessment is optimal in this phase.
- **Delayed phase**: used for urinary tract evaluation in suspected cases of urinary leakages/trauma, or for assessment of some liver and adrenal lesions.

Bowel-related inflammation such as appendicitis, diverticulitis, and inflammatory disease are usually well-identified on CT, most often with wall-thickening, adjacent fat-stranding and fluid.

Pancreatitis may be identified as thickening and adjacent fat-stranding (Fig. 174.5), as well as its associated complications such as necrosis, fluid collections, and vascular thrombosis/aneurysm formation. In cases of severe pancreatitis, patients may undergo several CTs over a few weeks. The overall radiation burden is thus potentially very high and other modalities such as US or MRI should therefore be considered.

As previously discussed, CT has a high sensitivity for hollow viscus perforation and bowel obstruction. CT is extremely sensitive at delineating intra-abdominal free or contained air (Figs 174.6 and Fig. 174.7)—as low as 0.3 mL of free air can be visible [4]. Furthermore, even smaller amounts of air (invisible on plain film) within the biliary tract, portal vein, or within the bowel wall (*pneumatosis intestinalis*) may be detected.

CT is invaluable in diagnosing abdominal sepsis/abscess. Abscesses are seen as low-density fluid collections with thick enhancing walls. IV contrast demonstrates this enhancement, helping to differentiate collections from free intra-abdominal fluid (Fig. 174.8). Oral contrast administration helps in differentiating these fluid collections from adjacent bowel loops and can also sometimes accurately localize a bowel leak or fistula. Post-operative bowel anastomotic leakages usually present as peri-anastomotic loculated fluid collections with air pockets [5].

CT angiogram has supplanted catheter angiography for assessment of mesenteric ischaemia and GI bleeding. This allows visualization of the mesenteric arteries and veins, and also assessment of bowel enhancement, pneumatosis, and portal venous air (poor prognostic indicators in ischaemia). For intestinal haemorrhage, it should only be used as an adjunct to upper and lower GI endoscopy, which remain the primary investigative tools. Such CTs should only

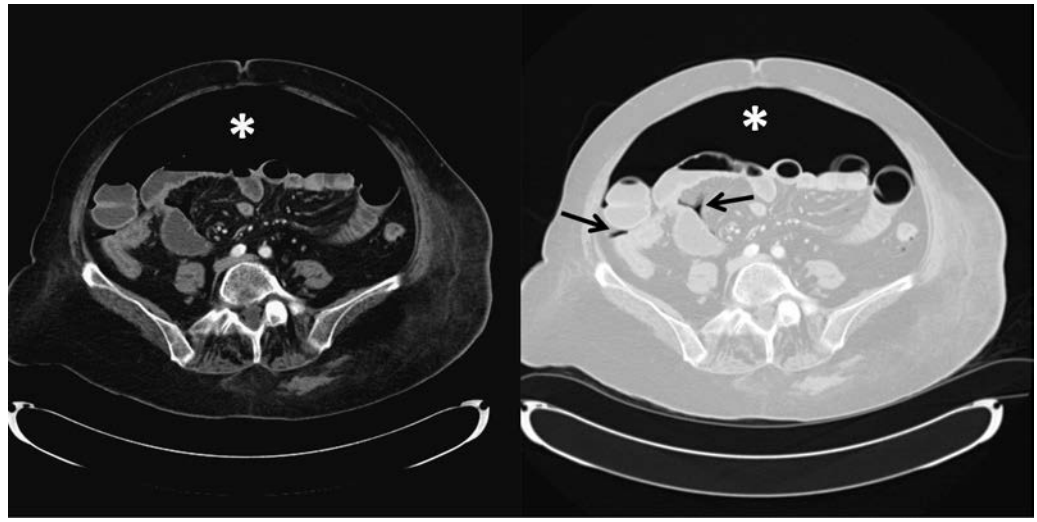


Fig. 174.6 Axial section of CT scan at level of aortic bifurcation in a patient with iatrogenic gastric perforation. Massive pneumoperitoneum with free intraperitoneal air (*) seen between the anterior abdominal wall anteriorly and the bowel loops posteriorly. The free gas is better seen on lung windows (image on the right, *) with locules of inter-bowel loop gas (arrows).

be performed in a clinically stable patient once initial resuscitation has been instituted. A CT angiogram will not be helpful in pinpointing very slow flow bleeding points—these do not usually show up. CT enterographic techniques described by Huprich et al. [6] in 2008 have a 45% active bleeding source detection rate for obscure gastrointestinal bleeding.

Overall, the effectiveness of CT in the management of the critically ill is well documented. Abdominal CT detected an abnormality in 58% of patients, while 69% of critically-injured patients admitted to the ICU with sepsis benefitted from a change in management after an abdominal CT scan [7]. In another prospective study [8], CT changed the management of 81% of critically-ill patients, with management being dependent solely on CT in 37.5% of the patients.

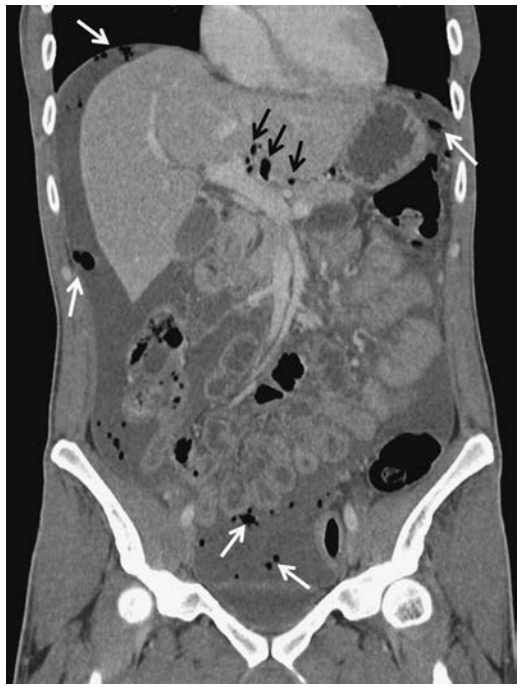


Fig. 174.7 Coronal section of a CT performed a patient with faecal peritonitis. Large amount of free fluid with numerous small air locules (white arrows). Note small air pockets along the inferior edge of the left hepatic lobe (black arrows).

Factors limiting the accuracy of CT include:

- **Patient body habitus**: unlike ultrasound, thinner patients often prove more challenging on CT as adjacent organs are not separated by the usual fat planes.
- **Breathing artefact**: most marked close to the diaphragms, though reduced in the newer, faster generation of CT scanners.
- **Artefact**: from metallic implants/foreign bodies or previous contrast investigations.

Radiation dose incurred by the patient should always be borne in mind when considering a CT scan. For example, multiphase scans should only be performed when needed (e.g. urograms in case of renal tract injuries and CT angiography for haemorrhage and vascular trauma). This is particularly important in paediatric or pregnant patients, where ultrasound is the front-line imaging modality.

Magnetic resonance imaging

MRI has a limited role in evaluation of the abdomen in critically-ill patients. It is often a second-line study when the initial test is inconclusive, e.g. MR cholangiopancreatography (MRCP; Fig. 174.9) or MR small bowel following USS and/or CT. MRI is also used commonly as a second-line investigation in pregnant patients and children after initial ultrasound assessment.

Factors limiting MRI use include:

- Long scan times, which can be a limiting factor in critically-ill patients.
- Increased breathing and movement artefacts compared to CT.
- Limited out-of-hours availability.
- Contraindicated with metallic implants (e.g. pacemakers, foreign bodies, prosthesis), especially if surgery was recent.

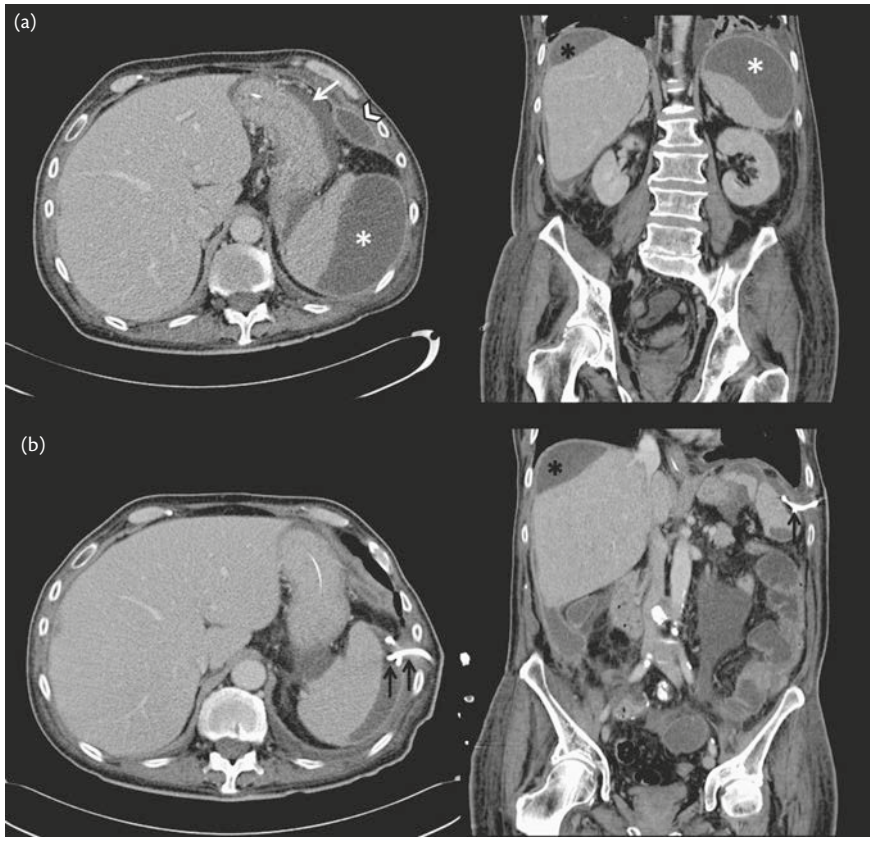


Fig. 174.8 (a) Axial and coronal CT sections of an ICU patient with anastomotic leak after right hemicolectomy. Note the walled-off left subphrenic abscess (*) adjacent to the spleen. Another smaller right subphrenic collection also seen (black *). A small rim of free ascites is seen around the greater curve of the stomach (white arrow). (b) Post-catheter drainage of the left subphrenic abscess—the collection has reduced significantly with a drain *in situ* (black arrows). Note the right subphrenic collection (black *) has slightly increased and subsequently drained.

- Contraindicated in the first trimester of pregnancy (unknown magnetic effect on fetal development), and gadolinium MRI contrast should be avoided if possible throughout pregnancy (again unknown effect on fetus).
- Gadolinium MRI contrast is contraindicated in renal failure (risk of nephrogenic systemic fibrosis).

As scan times are reduced with newer scanners and out-of-hours availability improves, MRI promises to play an increasing role in imaging.

Conclusion

The choice of abdominal imaging in the critically-ill patient is most dependent on the stability of the patient. In unstable patients, initial resuscitation is the priority and only portable radiographs or perhaps portable ultrasound may be possible. As transfer may be extremely hazardous CT scanning is only performed once haemodynamic stability is achieved, or unless management cannot further progress without it [9]. Stable patients may be mobilized for

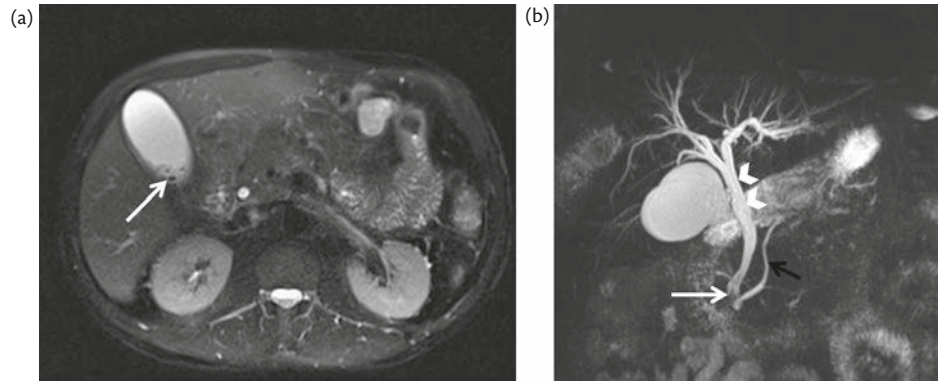


Fig. 174.9 (a) Axial T2 MRI through the gall bladder. Multiple tiny rounded areas of signal loss represent gall bladder calculi (white arrow). (b) MIP Slab MRCP shows the whole biliary tree with mildly dilated common bile duct (arrowheads) and intrahepatic channels, with a calculus in the distal common bile duct (white arrow). Pancreatic duct appears normal (black arrow).

more definitive scans. Apart from biliary pathologies for which ultrasound remains the first choice, CT is the mainstay for imaging in a stable patient. CT allows adequate evaluation for abdominal sepsis, trauma, perforation, inflammatory conditions such as pancreatitis and intestinal haemorrhage.

References

1. Crandall M and West MA. (2006). Evaluation of the abdomen in the critically ill patient: opening the black box. *Current Opinion in Critical Care*, **12**, 333–9.
2. Ollerton JE, Sugrue M, Balogh Z, D'Amours SK, Giles A, and Wyllie P. (2006). Prospective Study to Evaluate the Influence of FAST on Trauma Patient Management. *Journal of Trauma*, **60**, 785–91.
3. Huerta G and Puri VK. (2000). Nasoenteric feeding tubes in critically ill patients (fluoroscopy versus blind). *Nutrition*, **16**, 264–7.
4. Earls JP, Dachman AH, and Colon E. (1993). Prevalence and duration of postoperative pneumoperitoneum: sensitivity of CT vs left lateral decubitus radiography. *American Journal of Research*, **161**, 781–5.
5. Power N, Atri M, Ryan S, Haddad R, and Smith A. (2007). CT assessment of anastomotic bowel leak. *Clinical Radiology*, **62**, 37–42.
6. Huprich JE, Fletcher JG, Alexamder JA, Fidler JA, Burton SS, and McCullough CH. (2008). Obscure gastrointestinal bleeding: evaluation with 64-section CT multiphase CT enterography—initial experience. *Radiology*, **246**, 562–71.
7. Velmanos GC, Kamel E, Berne TV, et al. (1999). Abdominal computed tomography for the diagnosis of intra-abdominal sepsis in the critically ill patients. *Archives of Surgery*, **134**, 831–6.
8. Kumta ND, Park G, Toms A, Housden B, and Dixon AK. (2002). Body computed tomography in critically ill patients. *Anesthesia*, **57**, 544–8.
9. Szem JW, Hydo LJ, Fischer E, Kapur S, Klemperer J, and Barie PS. (1995). High-risk intra-hospital transport of critically ill patients: safety and outcome of the necessary road trip. *Critical Care in Medicine*, **23**, 1660–6.

CHAPTER 175

Hepatic function in the critically ill

Andreas Kortgen and Michael Bauer

Key points

- Hepatic dysfunction is a common problem in the critically ill.
- Inflammatory processes such as sepsis or pancreatitis, ischaemia/reperfusion phenomena, or tissue damage in trauma or surgery may lead to a hepatic stress response.
- Due to the multiple complex functions of the liver, no single test can determine hepatic function as a whole.
- Conventional laboratory measurements, such as enzyme levels, can be useful tools for diagnosis and differential diagnosis of hepatic diseases.
- While conventional markers appear to have advantages in predicting the course of dysfunction in chronic liver disease, especially combined with scoring systems, 'dynamic' quantitative liver function tests are especially useful in assessing hepatic function in the critical care setting.

Introduction

Parenchymal as well as non-parenchymal cells contribute to the manifold hepatic functions of metabolism, synthesis, detoxification, excretion, and the host response, making the liver a crucial organ in the critically ill. The liver is not only a target in multi-organ dysfunction. Liver dysfunction can also lead to further remote organ failure as can be best seen in patients with acute or chronic liver failure, where hepatic encephalopathy, hepatorenal syndrome, and cardiomyopathy are common events. In critical care patients liver dysfunction is an often-underestimated problem in frequency and severity as scoring systems, e.g. the Sequential Organ Failure Assessment (SOFA) score focus on single conventional laboratory parameters, in this case, bilirubin [1]. Using quantitative liver function tests, an incidence of hepatic dysfunction in critical care patients of over 50% is described.

Physiology and pathophysiology of liver blood flow

A quarter of cardiac output is delivered to the liver, making it one of the best-perfused organs. About 70% of liver blood flow is contributed by the portal vein, thus exceeding blood flow via the hepatic artery. Nevertheless, due to partial deoxygenation of portal blood during passage through the splanchnic bed, the contribution of both vessels to hepatic oxygen delivery is almost equal. However, proportions of blood flow via hepatic artery and portal vein may differ substantially, e.g. depending on food intake.

Terminal portal venules and hepatic arterioles are controlled by the autonomic nervous system. In addition, intrinsic factors regulate liver blood flow, changes in portal vein flow lead to contrary changes in hepatic artery flow (hepatic arterial buffer response) while an increase in portal vein pressure leads to an increased vascular resistance of splanchnic vessels (veno-arterial response). All these regulatory mechanisms may be impaired under pathophysiologic conditions. Furthermore, sinusoidal perfusion can be regulated by gradual contraction of sinusoids through perisinusoidal cells. Altogether, failure of these mechanisms may lead to (functional) shunting with impaired regional perfusion and oxygen delivery. This may sometimes occur even when global oxygen delivery to the liver is sufficient. Hepatocellular damage then occurs, most frequently in the pericentral region where oxygen supply is already reduced under physiologic conditions.

Acute phase response and altered gene expression

Inflammatory processes such as sepsis or pancreatitis, ischaemia/reperfusion phenomena, or tissue damage in trauma or surgery may lead to a hepatic stress response. Many key enzymes of metabolic pathways reveal an altered gene expression pattern in such situations. This 'acute phase' response leads to either increased synthesis of, for example, C-reactive protein and fibrinogen (positive acute phase proteins) or, on the other hand, to suppressed protein synthesis, e.g. albumin (negative acute phase protein). Modulation of hepatocellular gene expression and metabolism are influenced by inflammatory mediators released in part by macrophages (Kupffer cells) located within the liver.

Excretory dysfunction

Sepsis-associated cholestasis is a common problem in intensive care unit (ICU) patients, and one of the leading causes of jaundice in hospitalized patients. Hepatocellular excretory dysfunction may be due to altered blood flow and, in particular, to altered transmembrane transport. Many basolateral and canalicular transport proteins are down regulated in the critically ill. In combination with altered gene expression of enzymes of phase I and II metabolism, this may lead to profound changes of endo- and xenobiotic detoxification. In addition to these hepatocellular alterations, ductular

cholestasis may also appear. While hepatocellular impairment is, in principle, fully reversible, ductular damage of epithelium may lead to persistent alterations, up to secondary sclerosing cholangitis [1].

Diagnostic assessment

Due to the multitude of hepatic functions, no single test can provide a sufficient overview of the liver as a whole. If anything, liver assessment comprises a portfolio of different tests. Conventional 'static' laboratory measures include, for example, more or less specific liver enzymes, coagulation factors, albumin, and bilirubin [2,3]. By contrast, quantitative liver function tests assess specific partial liver functions at the time of testing. Such 'dynamic' tests can estimate clearance capacities and metabolic functions of the liver [1].

Conventional laboratory measures

Several laboratory measures are routinely used to evaluate hepatic function and impairment, e.g. plasma concentrations of liver enzymes [3]. These enzymes can be divided into two main groups:

- Those indicating hepatocellular damage such as transaminases.
- Those reflecting cholestasis and damage of bile epithelia, such as alkaline phosphatase or γ-glutamyltransferase (GGT).

They have discrete distributions in different tissues, are measurable in blood under normal physiological conditions, and do not represent measures of liver function.

Aspartate aminotransferase (ASAT) is produced in many different organs including liver, heart, brain, pancreas, kidney, and lung, and in white and red blood cells. Its intracellular location is both cytosolic and mitochondrial. By contrast, alanine aminotransferase (ALAT) is a liver-specific enzyme located almost exclusively within the cytosol. Glutamate dehydrogenase is located within mitochondria, predominately in the pericentral region of the liver lobuli, i.e. the boundary zones of the liver. Although it is a ubiquitous enzyme, measurable increases are solely due to hepatocellular necrosis. GGT is located at the cytosolic membrane. Measurable elevations are usually due to liver or biliary tract injury, e.g. different cholestatic diseases or in alcohol- or drug-induced injury. Elevated values of alkaline phosphatase can be found in hepatobiliary diseases, bone diseases, and malignant tumours.

Measures of synthetic liver function include albumin, cholinesterase, standard coagulation tests, e.g. prothrombin time, international normalized ratio (INR), or individual coagulation factors. While plasma or serum concentrations of these biochemical measures can reflect loss of functional hepatocytes in chronic liver disease, they have major limitations in acute care. This may be related to a long half-life, e.g. for cholinesterase. In addition, the mentioned acute phase response is accompanied by a profound reprogramming of gene expression and thus liver synthesis, leading to hypoalbuminaemia and other protein deficiencies. Blood loss and activation of the coagulation system may impair the corresponding tests. Furthermore, many critical care interventions, such as transfusion of albumin and plasma preparations, or anticoagulation therapy (e.g. with argatroban), can lead to iatrogenic changes in the previously mentioned measures.

Bilirubin is formed during degradation of haem derived predominantly from the haemoglobin within erythrocytes. Bilirubin is transported to the liver bound to albumin, where it is taken up into hepatocytes by membrane transporters and then conjugated with glucuronic acid. Water-soluble glucuronized bilirubin is then excreted into bile in an ATP-dependent process (Fig. 175.1). Elevated serum/plasma bilirubin levels can be due to prehepatic causes such as haemolysis with predominantly unconjugated bilirubin, or intra- and post-hepatic causes with a predominantly conjugated hyperbilirubinaemia. Typically, critically-ill patients with jaundice have a conjugated hyperbilirubinaemia. In an Austrian survey, about 11% had elevated bilirubin levels (>2 mg/dL [34 μmol/L], SOFA liver subscore ≥2) within 48 hours of ICU admission [2]. This was an independent risk factor of mortality. Nevertheless, bilirubin as a marker for liver dysfunction in ICU patients has limitations, for example, turnover of haem and liver function may be altered concurrently.

In summary, conventional ´static´ liver measures can yield valuable diagnostic data. In critically-ill patients, however, these have limitations, especially when rapid changes of liver function and perfusion occur. On the other hand, they are advantageous in assessing the prognosis of chronic liver diseases, especially when used in combination with scoring systems such as the model for end-stage liver disease (MELD) Score or the Child–Turcotte–Pugh (CTP) Score (Table 175.1 and Box 175.1) [4]. However, there is still an ongoing search to improve these scores, e.g. incorporating sodium values in the MELD-Score to generate a MELDNa Score which led to an improved prediction of outcome [1].

Liver function tests

Dynamic quantitative liver function tests assess current liver function with respect to the ability of the liver to eliminate and/or metabolize a specific substance. Values of these tests generally depend upon the specific hepatic function being measured and on functional liver blood flow. Many of these tests have profound limitations in the ICU patient with respect to practicability, i.e. logistic effort, staff expenditure, and duration. Suitable tests for daily clinical practice are the MEGX (monoethylglycinexylidide) test, assessment of indocyanine green elimination and, probably, a recently introduced methacetin breath test [1].

For the MEGX-Test lidocaine 1 mg/kg is administered intravenously. Lidocaine is metabolized in hepatocytes by the cytochrome P450 enzyme CYP3A4 to MEGX (Fig. 175.1). At 15 and/or 30 minutes after injection blood samples are drawn to measure MEGX concentrations by HPLC or GLC. When evaluating the MEGX test result, any confounding influence of drugs that inhibit or induce CYP3A4, or that are simply metabolized by CYP3A4, must be taken into account. Healthy volunteers have gender-specific differences of MEGX production. In addition, lidocaine may cause major side-effects. Nevertheless, the MEGX test result does prognosticate in critical care patients.

Indocyanine green (ICG) is an anionic, infrared absorbing dye. After intravenous application ICG is bound to plasma proteins, most notably albumin and α_1-lipoprotein, and is taken up nearly exclusively into hepatocytes by basolateral transport proteins. Without transformation it is excreted into bile by multidrug resistance protein (MDR)-3, an ATP-dependent transport protein (Fig. 175.1). There is no enterohepatic recirculation. The plasma disappearance rate of ICG (PDR_{ICG}) can be non-invasively assessed at the bedside with a transcutaneous finger probe. For pulse densitometry measurement, a bolus of 0.25–0.5 mg/kg body weight ICG

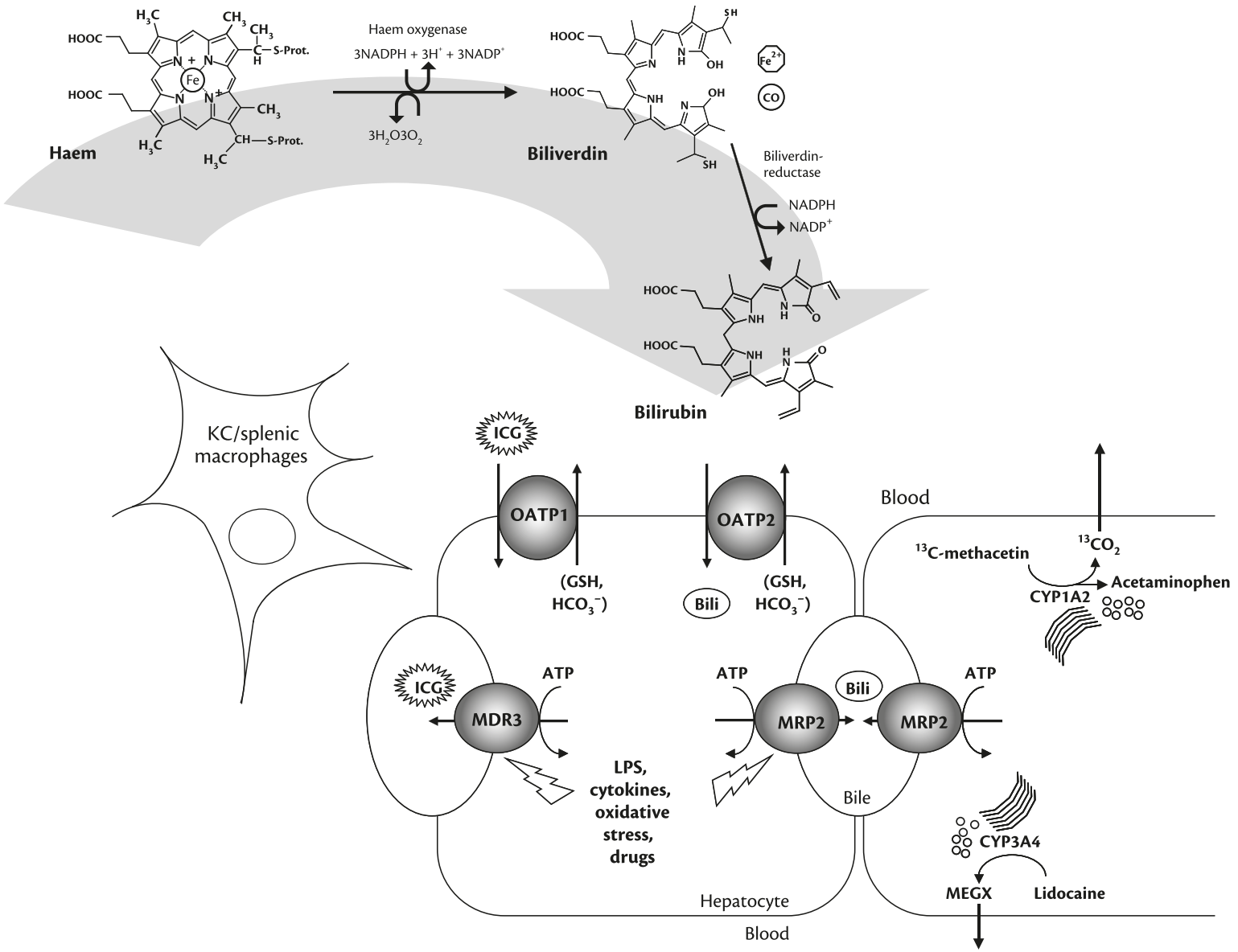


Fig. 175.1 Molecular mechanisms of some examples of hepatic function tests. Haem, for example, derived from breakdown of haemoglobin is degraded to biliverdin and further to bilirubin under the catalytic influence of haem-oxygenase and biliverdin reductase. This degradation primarily takes place in spleen and hepatic macrophages (Kupffer cells) for senescent erythrocytes, and in hepatocytes for free or haptoglobin-bound haem. Due to variable amounts of haem, multiple conversion steps and alterations in hepatocellular function, bilirubin displays an overall slower and less predictable kinetic than the xenobiotic ICG. The MEGX- and ^{13}C-methacetin breath tests measure the function of specific cytochromes involved in xenobiotic metabolism.

GSH, glutathione; ICG, indocyanine green; KC, Kupffer cell; LPS, lipopolysaccharide; MDR, multidrug resistance protein; MRP, multidrug resistance-associated protein; OATP, organic anion transporting polypeptide; CYP, cytochrome P450; MEGX, monoethylglycinexylidide.

Data from various sources (see references).

Table 175.1 Child–Turcotte–Pugh Score

Score	1	2	3
Bilirubin [mg/dL] ([μmol/L])	<2 (<34)	2–3 (34–51)	>3 (>51)
Albumin [g/dl]	>3.5	2.8–3.5	<2.8
INR (prothrombin time [s] prolonged)	<1.7 (<4)	1.7–2.3 (4–6)	>2.3 (>6)
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	Absent	I–II°	III–IV°

Single score values are summed up and grouped as:

Child class A: 5–6, compensated disease, 1-year survival rate about 100%.

Child class B: 7–9, significant functional impairment, 1-year survival rate about 80%.

Child class C: 10–15, decompensated disease, 1-year survival rate about 45%.

Reproduced from Pugh RNH et al., 'Transection of the oesophagus for bleeding oesophageal varices', *British Journal of Surgery*, **60**(8), pp. 646–9, with permission from John Wiley and Sons. Copyright © 1973 British Journal of Surgery Society Ltd.

Box 175.1 Model for Endstage Liver Disease (MELD) score

$$\text{MELD Score} = 10 \times (0.378 \times \log_e(\text{bilirubin in mg / dL}) + 1.12 \times \log_e(\text{INR}) + 0.957 \log_e(\text{creatinine in mg / dL}) + 0.643) \quad \text{[eqn B1.1]}$$

Calculated values are rounded to integers and range from 6 to 40. Higher calculated values are set to 40. Measured laboratory values <1 are set to 1. Maximum value of creatinine is 4. In patients with a need for intermittent dialysis on two occasions, or for continuous renal replacement therapy for >24 hours during the last week, creatinine values are set to 4. Patients must be at least 12 years old. For younger patients a paediatric score (PELD) is used.

Predicted 3-month-mortality rates:

- **MELD score 6:** 1.9%
- **MELD score 20:** 11%.
- **MELD score 30**: 49%.
- **MELD score 40**: 98%.

Reproduced from Kamath PS and Kim WR, 'The model for end-stage liver disease (MELD)', *Hepatology*, **45**(3), pp. 797–805, with permission from John Wiley and Sons. Copyright © 2007 American Association for the Study of Liver Diseases.

is given intravenously. Normal values of PDR_{ICG} range from 18 to 25%/min. The retention rate of ICG after 15 minutes (R15, normal range 0–10%) is another parameter of ICG elimination reflecting similar information [1].

PDR_{ICG}/R15 measurements have been evaluated in major hepatobiliary surgery including liver transplantation, as well as in non-hepatic surgery (e.g. cardiac surgery) and in the critical care setting [4]. In liver transplant recipients, perfusion disorders or episodes of rejection are reflected by an impaired PDR_{ICG}. In both liver resection and after cardiac surgery, a reduced ICG elimination was associated with higher morbidity and a prolonged length of ICU stay. Its prognostic value was also demonstrated in septic patients and a mixed cohort of ICU patients. PDR_{ICG} may be reversibly reduced in obstructive jaundice. While a reduced PDR_{ICG} still leaves uncertainties regarding sinusoidal hypoperfusion and true hepatocellular dysfunction, normal values make such disturbances unlikely. Rapid changes within a few hours are likely to reflect changes in perfusion. However, measured values may still underestimate the true impairment of canalicular excretory function.

Another recently introduced bedside test is the ^{13}C-methacetin breath test. ^{13}C-methacetin is metabolized in hepatocytes by the cytochrome P450 isoform 1A2 (CYP1A2) to paracetamol and ^{13}C-labeled carbon dioxide (Fig. 175.1) that can be measured in the exhaled breath. ^{13}C-methacetin 2 mg/kg is given intravenously and the $^{12}C/^{13}C$ ratio is measured by an isotope-selective monitor in expired air from 10 minutes pre-injection until 1 hour post-injection to assess the maximum values of exhaled $^{13}CO_2$. Carbon dioxide production is assumed to be 300 mmol/hour/m^2. Results represent the maximum capacity of methacetin metabolism if turnover is saturated. Normal values are >315 μg metabolized methacetin/hour/kg body weight. Results can be influenced by increased overall metabolism and food intake. Several drugs can also inhibit/induce production or are also metabolized by CYP1A2, potentially influencing test values. The test is being evaluated in patients after hepatic resection or liver transplantation as well as septic patients, and seems to reflect liver dysfunction in both the early post-operative course and in sepsis.

Conclusion

Hepatic dysfunction is an underestimated problem in critical care patients. Manifold partial functions require a portfolio of different liver tests to get an overview of hepatic function. Quantitative 'dynamic' liver functions test add substantial information and may help to guide therapy especially in the dynamic course of critically-ill patients [1].

References

1. Kortgen, A, Recknagel P, and Bauer M. (2010). How to assess liver function? *Current Opinions in Critical Care*, **16**, 136–41.
2. Kramer L, Jordan B, Druml, W, Bauer P, Metnitz PG, for the Austrian Epidemiologic Study on Intensive Care, ASDI Study Group (2007). Incidence and prognosis of early hepatic dysfunction in critically ill patients—a prospective multicenter study. *Critical Care Medicine*, **35**, 1099–104.
3. Reichling JJ, Kaplan MM. (1988). Clinical use of serum enzymes in liver disease. *Digestive Disease Science*, **33**, 1601–14.
4. Stauber RE, Wagner D, Stadlbauer V, et al. (2009). Evaluation of indocyanine green clearance and model for end-stage liver disease for estimation of short-term prognosis in decompensated cirrhosis. *Liver International*, **29**, 1516–20.

PART 6.3

Gastrointestinal haemorrhage

CHAPTER 176

Pathophysiology and causes of upper gastrointestinal haemorrhage

Tasneem Pirani and Tony Rahman

Key points

- Thorough history and examination is key for accurate diagnosis pre-endoscopy.
- Upper gastrointestinal haemorrhage may be oesophageal or gastroduodenal in origin.
- Peptic ulcer disease (PUD) is the most common cause of upper gastrointestinal haemorrhage.
- Gastric protection should be considered in high risk patients using non-steroidal anti-inflammatory agents.
- *Helicobacter pylori* testing and treatment is recommended for anyone with PUD.

Introduction

Causes of upper gastrointestinal haemorrhage (UGIH) can be described according to the underlying pathophysiology. Older studies reported an incidence of peptic ulcer disease (PUD) at endoscopy as high as 50%. More recent studies show that it remains the most common diagnosis, accounting for approximately a third of cases, with gastric ulcers being more common than duodenal ulcers [1].

Detailed history and clinical examination at the time of presentation with UGIH is invaluable in providing clues as to the cause of the bleeding and appropriate management. Table 176.1 summarizes some of the diagnoses that should be suspected on the basis of clinical history and examination.

Causes classified anatomically

Oesophageal

Inflammation and ulceration of the oesophagus is caused by exposure to gastric acid. This may be exacerbated by increased production of acid, stress, drugs, and Zollinger–Ellison syndrome. Incompetence of the lower oesophageal sphincter due to the presence of a hiatus hernia, medication that cause relaxation of the physiological sphincter, delayed gastric emptying and nasogastric tubes all lead to increased acid exposure. Bleeding from this region is usually diffuse. Oesophageal varices in patients with portal hypertension can cause massive haemorrhage. Portal hypertension leads to development of collateral vessels that divert blood to the systemic circulation. These collateral vessels form by opening and dilating existing vascular channels. Oesophageal varices are such portosystemic collaterals and should be suspected in patients with cirrhosis.

Oesophagitis from other causes such as candidiasis or herpes simplex infection may cause pain, dysphagia, and bleeding. These causes should be suspected in immunocompromised individuals and require appropriate antifungal, antiviral, and acid suppression therapies.

A history of protracted or violent retching and, subsequently, haematemesis suggests a possible Mallory–Weiss tear at the oesophagogastric junction. This linear tear is thought to arise from a rapidly occurring and transient transmural pressure gradient.

Gastro-intestinal malignancy may lead to haemorrhage from the ulcerating lesion itself, or following invasion of submucosal vessels causing either or both haematemesis and melena. These may halt spontaneously or require therapies such as argon plasma coagulation (APC), laser coagulation, or even surgery.

Gastroduodenal

A clinical history of abdominal pain, antacid use, weight loss, regular use of non-steroidal anti-inflammatory agents (NSAIDs) or aspirin may point towards gastric or PUD.

NSAID-induced injury results from both local effects and systemic prostaglandin inhibition. Symptomatic PUD caused by exposure to NSAIDs is mainly a consequence of systemic (post-absorptive) inhibition of gastrointestinal mucosal cyclo-oxygenase (COX) activity. Healthy gastric and duodenal mucosa use COX-1 to produce mucosal-protective prostaglandins [2]. These prostaglandins not only reduce acid secretion, but also stimulate bicarbonate secretion in addition to other cytoprotective mechanisms. Gastrointestinal toxicity from NSAIDs is higher in older patients, particularly if there is a prior history of ulcer disease, use of dual antiplatelet therapy, or when NSAIDs are used with concomitant anticoagulant therapy [3]. In such cases, gastroprotection with a proton pump inhibitor (PPI) is often used.

Selective serotonin reuptake inhibitor (SSRI) use also increases the risk of UGIH, whether used alone or in combination with NSAIDs [4]. This is likely related to inhibition of platelet aggregation.

Helicobacter pylori is implicated in duodenal ulceration and is a recognized carcinogen for gastric carcinoma [5]. The risk of

Table 176.1 Likely sources of bleeding based on history and examination findings

Clues from history and examination	Cause of bleeding
Stigmata of chronic liver disease: spider naevi, clubbing, palmar erythema, jaundice, encephalopathy, ascites, cachexia, cirrhosis alcoholism, chronic viral hepatitis, and all causes of non-cirrhotic portal hypertension	Portal hypertensive gastropathy, varices, and coagulopathy
Protracted retching, alcoholic binge, a period of emesis preceding haematemesis	Mallory–Weiss tear
Weight loss, anorexia, dysphagia, early satiety, and abdominal mass	Malignancy
Abdominal pain, regular use of NSAIDs or aspirin, heart burn, smoking, and *Helicobacter pylori*	Peptic ulcer disease
Prescribed immunosuppressant, diabetes, HIV, heartburn, regurgitation, and odynophagia	Oesophagitis, oesophageal candidiasis, oesophageal ulceration
Hereditary haemorrhagic telangiectasia, aortic valve replacement, and chronic renal failure	Angiodysplasia
Previous aortic aneurysm repair, infected aortic graft, palpable pulsatile abdominal mass, and fistulating disease (e.g. Crohn's Disease)	Aorto-enteric fistula
Known pancreatic or hepatic malignancy, and coagulopathy	Local invasion of duodenum, haemobilia
ICU admission, multi-organ failure and inotrope requirements	Stress ulceration

uncomplicated PUD is significantly higher among NSAID users who are also positive to *H. pylori* [6]. Diagnosis of duodenal ulceration should be followed by empirical *H. pylori* eradication with 'triple or quadruple therapy'. This consists of a PPI and 2 or 3 antibiotics given over 1–2 weeks. The choice of antibiotics should take into account local antibiotic resistance patterns and any history of antibiotic allergy. PPI therapy may lead to false negative results with Helicobacter stool antigen tests and rapid urease tests on gastric biopsy samples.

Stress ulceration commonly occurs in critically unwell patients and those in multi-organ failure. Transient ischaemic insults to the gastric mucosa lead to inflammation, erosions, and ulceration. Classically, this affects the antrum and may appear as gastritis with erosions or ulcers. Endoscopic treatment may be required if a specific source of bleeding has been identified. In the case of more generalized gastritis or duodenitis, acid suppression therapy is required. Nasogastric feeding is protective. These lesions resolve as the patient recovers.

Risk factors in intensive care patients include mechanical ventilation, renal replacement therapy, thrombocytopenia or other coagulopathy, and administration of aspirin, clopidogrel or other anticoagulant therapies [7]. Prophylaxis in the form of H_2 receptor antagonists, or PPIs are routinely used. Prophylaxis may however, increase the risk of ventilator-associated pneumonia and *Clostridium difficile* diarrhoea, and may even affect iron absorption.

Gastric and ectopic varices as a consequence of cirrhosis and portal hypertension, or as a result of splenic vein thrombosis following pancreatitis, can lead to life-threatening haemorrhage. Clinical suspicion should be high when faced with a patient with an appropriate history and clinical examination. Diffuse gastric ooze secondary to portal hypertensive gastropathy may also present with UGIH. Management is focused on correcting coagulopathy and blood transfusion.

Angiodysplasia is the acquired degenerative dilatation of normal blood vessels that can be found anywhere throughout the gastrointestinal tract. They are seen as isolated, tortuous, thin-walled vessels that either cause occult bleeding and present with anaemia, or cause overt UGIH. Gastric antral vascular ectasia (GAVE), also known as watermelon stomach, is a condition where prominent erythematous streaks traverse the antrum and converge on the pylorus. These usually present with recurrent anaemia. Conditions associated with GAVE include connective tissue disorders, particularly scleroderma, portal hypertension, chronic renal failure, and bone marrow transplantation.

Aorto-enteric fistulae may occur in the presence of previous aortic aneurysm repair, aortic stent insertion, the use of aortic balloon pumps, and other fistulating diseases such as Crohn's disease. This can cause catastrophic bleeding requiring surgical intervention. Zollinger Ellison syndrome (hypergastrinaemia) is another rare cause of UGIH, presenting with weight loss, abdominal pain, and diarrhoea. It should be suspected in cases where multiple ulcers are seen, or when ulcers fail to heal despite optimal therapy.

Dieulafoy lesions are dilated aberrant submucosal vessels that erode the overlying epithelium in the absence of an ulcer. They are approximately 10 times the normal calibre of mucosal capillaries, and are typically located within 5 cm of the oesophagogastric junction. Bleeding is often self-limiting, but can be significant. The bleeding site is often difficult to locate in the absence of active bleeding.

Knowledge of the possible causes of UGIH and the associated risk factors allows the clinician to manage their patients holistically to reduce further risk.

References

1. Enestvedt BK, Gralnek IM, Mattek N, Lieberman DA, and Eisen G. (2008). An evaluation of endoscopic indications and findings related to nonvariceal upper-GI hemorrhage in a large multicenter consortium. *Gastrointestinal Endoscopy*, **67**, 422–9.
2. Cryer B and Feldman M. (1998). Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *American Journal of Medicine*, **104**, 413–21.
3. Bhatt DL, Scheiman J, Abraham NS, et al. (2008). ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation*, **118**, 1894–909.
4. Loke YK, Trivedi AN, Singh S. (2008). Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. *Aliment Pharmacology Therapy*, **27**, 31–40.
5. Nomura A, Stemmermann GN, Chyou PH, Perez-Perez GI, and Blaser MJ. (1994). *Helicobacter pylori* infection and the risk for duodenal and gastric ulceration. *Annual of Internal Medicine*, **120**, 977–81.
6. Papatheodoridis GV, Sougioultzis S, and Archimandritis AJ. (2006). Effects of Helicobacter pylori and nonsteroidal anti-inflammatory drugs on peptic ulcer disease: a systematic review. *Clinical Gastroenterology and Hepatology*, **4**, 130–42.
7. Cook DJ, Fuller HD, Guyatt GH, et al. (1994). Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients. *New England Journal of Medicine*, **330**, 377–81.

CHAPTER 177

Diagnosis and management of upper gastrointestinal haemorrhage in the critically ill

Tasneem Pirani and Tony Rahman

Key points

- Detailed history and examination may indicate the cause of bleeding and direct management.
- The patient should be resuscitated and stabilized prior to endoscopy.
- Scoring systems can be used to guide the urgency for endoscopic therapy.
- Initiation of pre-endoscopy proton pump inhibitors (PPI) is not routinely recommended.
- Routine re-scoping at 24 hours is reserved for cases where initial endoscopy is considered suboptimal, or in cases where rebleeding is considered life-threatening.

Introduction

Upper gastrointestinal haemorrhage (UGIH) usually presents with melaena or haematemesis. Occasionally, a brisk UGIH presents with haematochezia.

Melaena is a 'tarry' black stool with a characteristic offensive odour resulting from digestion of blood within the small intestine. Brisk UGIH can also present with passage of bright red blood or haematochezia per rectum, for example in the case of an aorto-enteric fistula.

Haematemesis is vomiting of blood from the upper gastrointestinal (GI) tract and may occur after swallowing blood following a nasopharyngeal haemorrhage. Patients presenting with haematemesis have a higher mortality than those presenting with melaena alone [1]. 'Coffee ground vomiting', often taken as an indicator of UGIH, is a poor clinical sign.

Haematochezia is the passage of fresh blood per rectum. This is usually from a colonic source, but a brisk UGIH can occasionally be responsible.

Diagnosis

A thorough medical history focusing on past medical history, particularly of gastrointestinal bleed and co-morbidities such as clotting disorders, malignancy, or liver disease should be sought. Direct questions pertaining to risk factors for gastrointestinal bleeding should be asked, and a history of medication such as aspirin, clopidogrel, warfarin, non-steroidal anti-inflammatory drugs, selective serotonin re-uptake inhibitors, and other novel antiplatelet agents or anti-coagulants ascertained.

Symptom assessment followed by clinical examination to identify signs of hypovolemia, chronic illness, or cirrhosis is useful. It is important to identify the likely source of the bleed, and determine subsequent management. The information gathered also guides decisions regarding resuscitation, empirical medical therapy, and subsequent diagnostic tests required. Several factors associated with poor outcome in terms of the severity of the bleed and need for intervention have been recognized; these can be used to obtain a severity score.

Laboratory investigations such as full blood count (FBC), biochemistry, and coagulation studies should be performed urgently, and cross-matching of blood (+/– blood products) requested. The results may provide useful information about the chronicity of the haemorrhage (mean corpuscular volume, platelet count, renal dysfunction, and coagulopathy), or indicate factors that may be associated with increased risk of severity and/or mortality such as concomitant anti-coagulation therapy, liver, and renal dysfunction.

Initial management

Regardless of the exact cause of the haemorrhage, the priority is prompt initial assessment (Airway, Breathing, Circulation, and Disability) and resuscitation, avoiding complications of haemodynamic compromise. Resuscitation should take priority over endoscopic and radiological investigations. Admission to a GI bleed or Specialist Unit results in improved outcomes [2]. In the absence of such Units, patients should be managed in an environment where vital signs such as heart rate, blood pressure, respiratory rate, conscious level, and urine output are monitored at least hourly. Resuscitation should be guided by clinical and physiological variables, while taking into consideration the patient's age and co-morbidities. Definitive airway protection is recommended in patients with haematemesis and a reduced level of consciousness.

Traditional resuscitation techniques using large amounts of crystalloid and packed red blood cells without other blood products can exacerbate the dilutional and consumptive coagulopathy of a

large haemorrhage [3]. Over-resuscitation may also theoretically increase the risk of rebleeding as a result of increased venous and arterial flow. Recent published reports support conservative transfusion policies over generous policies (i.e. transfuse when haemoglobin <7 g/dL versus <9 g/dL) [4]. However, it should be stressed that individual patients require individualized transfusion regimens based on their clinical condition. Crystalloids and/or volume expanders should be used initially to restore tissue oxygenation and perfusion [5]. Placement of a central venous catheter may be useful in elderly patients and those with cardiac co-morbidities. Large bore peripheral venous cannulation is sufficient in most cases.

Initiation of a pre-endoscopy PPI does not alter important clinical outcomes of mortality, rebleeding or the need for surgery. Its routine use pre-endoscopy is thus not recommended and should not delay or replace endoscopic therapy. In patients awaiting endoscopy, pre-emptive high-dose intravenous PPI may be used [6].

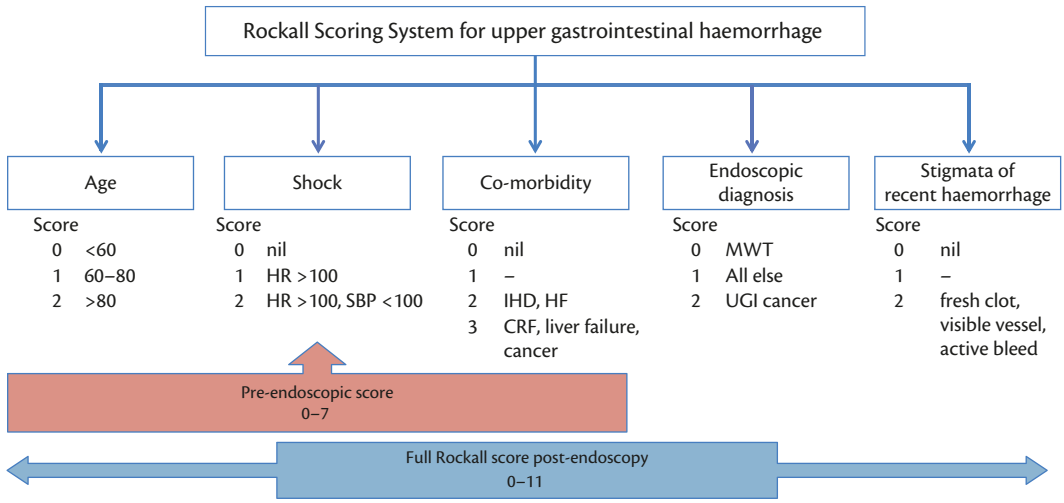
The risk of discontinuing antiplatelet and anti-coagulant agents needs to be assessed for individual patients by weighing up risks and benefits. Early discussion with relevant experts such as cardiologists and haematologists is advised. This ensures that the patient receives the correct composition and quantity of products in order to control the situation, and to permit diagnostic and therapeutic endoscopic assessment to take place safely. This is particularly suggested in complex clinical scenarios, e.g. mechanical heart valve replacement, post-coronary artery bypass surgery, disseminated coagulopathy, severe sepsis, recent coronary stent insertion, and massive haemorrhage.

Prothrombin concentrates should be considered in patients on warfarin who are actively bleeding. Platelet transfusions, fresh frozen plasma and cryoprecipitate should also be given as needed in situations of active bleeding when clotting parameters are impaired (i.e. INR >1.5, platelet count $<50 \times 10^9$/L, fibrinogen <1g/L). Platelet transfusion should be given to patients with life-threatening bleeds who have received antiplatelet drugs such as aspirin or clopidogrel [7]. Thromboelastography (TEG®) or thromboelastometry (TEM®) can provide a global assessment of haemostatic function from initial clot formation to clot dissolution [8]. These assessment techniques can be used in parallel with conventional coagulation screen to guide treatment. The anti-fibrinolytic agent, tranexamic acid has not yet been shown to have a beneficial effect in UGIH and is therefore not recommended for routine use.

Administration of intravenous erythromycin prior to endoscopy improves gastric motility and thereby mucosal views for the endoscopist. Prokinetics may be administered 30–90 minutes prior to endoscopy.

Scoring systems

Scoring systems have been developed and validated to risk stratify patients into low, medium, and high risk of rebleed and mortality. They can help to predict the need for hospital admission and endoscopic treatment. The Rockall score (Fig. 177.1) provides information on rebleed and mortality risk [9]. Its main disadvantage is that a complete score requires results of an upper GI endoscopy. The Glasgow Blatchford score (GBS) (Table 177.1) [10] is based on simple clinical and laboratory variables and is extremely useful in predicting the need for treatment. The lack of subjective variables or the need for endoscopy to complete the score makes



Rockall score	% Pre-OGD Mortality	% Post-OGD Mortality
0	0	0
1	2.4	0
2	5.6	0.2
3	11	2.9
4	24.6	5.3
5	39.6	10.8
6	48	17.3
7	50	27
8	>80	41.1

Fig. 177.1 Rockall numerical risk scoring system.

Table 177.1 Glasgow–Blatchford Score for assessing the severity of UGIH

Admission risk factor	Score
Blood urea (mmol/L)	
≥6.5–7.9	2
8–9.9	3
10–24.9	4
≥25	6
Haemoglobin g/L (male)	
≥12–13	1
10–11.9	3
<10	6
Haemoglobin g/L (female)	
≥10–12	1
<10	6
Systolic blood pressure (mmHg)	
100–109	1
90–99	2
<90	3
Other markers	
Pulse ≥100	1
Presentation with melaena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac failure	2

Reprinted from *The Lancet*, **356**, 9238, Blatchford O et al., 'A risk score to predict need for treatment for upper gastrointestinal haemorrhage', pp. 1318–21, Copyright 2000, with permission from Elsevier.

the GBS easier to use. A score of zero carries a minimal risk for requirement of interventions such as transfusion, endoscopy, or surgery. These patients can therefore be considered for early discharge and outpatient management. Scores ≥6 are associated with a >50% risk of needing an intervention. However, scoring systems are not designed to be used in isolation and do not replace clinical history and diagnostic skills in informing decisions about further care.

Endoscopy

Confirmation of the diagnosis of UGIH may be achieved by oesophagogastroduodenoscopy (OGD). This is the diagnostic modality of choice as it also provides the opportunity for therapeutic intervention. If unsuccessful, computed tomography (CT) angiography and/or mesenteric angiography may be required. Video capsule endoscopy also offers a diagnostic option, particularly in cases of bleeding from the small bowel, but it does not provide a therapeutic option.

Endoscopy should be offered to unstable patients with severe acute upper gastrointestinal bleeding immediately after resuscitation. All other patients should receive endoscopy within 24 hours of admission [11]. This should only be performed by trained staff, ideally in the surroundings of a dedicated and well-equipped endoscopy unit. Early endoscopy is associated with reduced transfusion requirements and reduced length of stay in hospital. However, in unstable patients it is also associated with a reduction in rebleeding rates and the need for surgery when compared with patients undergoing later endoscopy [12]. If the patient requires airway protection and ventilation, endoscopy should be performed in the operating room or the intensive care unit. Appropriate consent should be obtained from the patient or their next of kin/legal representative. Thorough documentation is mandatory.

Urgent OGD requires the patient to be kept nil by mouth for at least six hours prior to the procedure. Such preparation is not possible in emergency cases. Awake patients with a patent airway are likely to require either local anaesthetic to the oropharynx or low dose intravenous sedation for procedure tolerance. Sedated patients require blood pressure and pulse oximetry monitoring as a minimum.

Pharmacological and endoscopic therapies

Ulceration involving a visible or actively bleeding blood vessel or stigmata of recent bleed may require injection of 1:10,000 adrenaline in four quadrants around the vessel to provide local vasoconstriction and tamponade. It is recommended that epinephrine is not used as monotherapy and should be followed by a second intervention, e.g. thermo-coagulation involving application of compressive pressure to the vessel with the probe, while coagulation is being performed, or endoscopic clips applied to achieve haemostasis in a manner similar to surgical ligation. Endoscopic injection of fibrin or thrombin may also be used to achieve haemostasis. The oesophagus is thin-walled so caution must be exercised when injecting epinephrine or when applying thermo-coagulation as perforation may occur.

Haemospray is a nanopowder that has shown encouraging success in achieving acute haemostasis in pilot studies. It becomes cohesive and adhesive when in contact with moisture, forming a stable mechanical barrier at the site of bleeding. It is easy to apply and does not require direct tissue contact.

Endoscopic therapy should only be delivered to actively bleeding lesions, non-bleeding visible vessels, and to ulcers with an adherent blood clot [13]. A combination of endoscopic therapies is superior to a single modality alone [14].

Other therapies such as argon plasma coagulation (APC), where a jet of ionized argon gas is directed towards a bleeding lesion, and laser coagulation are frequently used to halt bleeding from angiodysplastic lesions and malignancies. Failure to control haemorrhage from these lesions may necessitate surgery.

Patients with active bleeding or other high-risk stigmata (such as a visible vessel or adherent clot) should receive a combination of endoscopic therapy and a PPI infusion to prevent recurrent bleeding [15], mortality and the need for surgical intervention. An intravenous bolus of PPI (e.g. omeprazole, pantoprazole) followed by continuous infusion is commenced. This helps to stabilize the clot by maintaining gastric pH >6, thus optimizing platelet aggregation and clot formation [16].

In bleeding from peptic ulcer disease (PUD) a biopsy should be taken for histological examination or for rapid urease testing (if not already on a PPI), to test for *Helicobacter pylori*. Eradication therapy should be instituted if confirmed positive. There is no evidence

to suggest that *H. pylori* eradication influences the rate of rebleeding in the acute phase of peptic ulcer bleeding [17].

Endoscopy should only be repeated within 24 hours if the initial procedure is considered sub-optimal, or in patients in whom rebleeding is likely to be life-threatening [18].

Detailed management of variceal bleeding is covered in a separate chapter. Endoscopic band ligation (EBL) is the treatment of choice for bleeding oesophageal varices. Sclerotherapy using agents such as ethanolamine oleate injection above and below the rupture point of the varix is another possibility. No differences are found in rebleed rates, complication or mortality when endoscopic sclerotherapy is compared with EBL. Injection of the tissue glue, cyanoacrylate is predominantly used for gastric or ectopic varices. The use of self-expandable metal stents (SEMs) in cases of refractory oesophageal variceal haemorrhage has been successful in small case series. More commonly, however, balloon tamponade using a Sengstaken–Blakemore tube is used in such cases with elective deflation at time of re-endoscopy within 24 hours. Occasionally, referral for transjugular intrahepatic portosystemic stent shunting (TIPSS) may become necessary.

Interventional radiology, video capsule endoscopy, and balloon enteroscopy

Occasionally, despite ongoing bleeding, the OGD is non-diagnostic. In other cases bleeding continues despite optimal attempts at endoscopic therapy. Computerized tomographic angiography (CTA) can be used to show extravasation of contrast at the site of the bleed. Arterial bleeding rates as low as 7.0 mL/min can potentially be detected [19]. Once the bleeding site is located, digital subtraction angiography and super-selective embolization of the arterial supply to the bleeding lesion is performed. Embolic agents such as coils, glue, or polyvinyl alcohol may be administered. This is a very successful method of controlling mesenteric bleeding. Bowel infarction and ischaemia account for the majority of complications. Super-selective catheter deployment may reduce this risk. Other potential complications include contrast allergy and contrast nephropathy, particularly in situations of concurrent dehydration, use of nephrotoxic drugs, chronic kidney disease, and prior use of intravenous contrast for CTA. Bleeding from the arterial puncture site and pseudo-aneurysm formation are other recognized complications. Clinical success and cessation of bleeding with embolization is quoted between 67–89%, however, rebleeding is evident in up to 30% of cases [20].

Radionuclide scanning with Technetium 99m-labelled red cells detects bleeding at rates as low as 0.1 ml/min. This can be useful to detect subtle bleeding not seen on endoscopy or CT angiography. It is most useful in slow bleeding and, as the labelled red cells circulate for 48 hours, it allows for repeat scanning. It is most commonly used in non-emergency situations, following which appropriate targeted therapy is chosen.

Video capsule endoscopy (VCE) is a frequently used modality for detecting bleeding beyond the reach of a standard endoscope. The advantages are relative non-invasiveness, a higher magnification than conventional endoscopes and, since the capsule moves passively, it does not inflate the bowel and thus images the mucosa in the collapsed state. This enables a more physiological examination of the small bowel. The obvious disadvantage is that once a bleeding point or pathology is identified, balloon enteroscopy, radiological embolization, or surgery is required to treat the area as VCE is only a diagnostic technology.

Enteroscopy

Visualization of the small bowel beyond the distal duodenum can be challenging. However, if bleeding is suspected from the small bowel, which averages 4–6 m in length in an adult, other diagnostic and therapeutic modalities may become necessary. Push enteroscopy, using longer paediatric colonoscopes or an enteroscope, requires the scope to be manoeuvred into the small bowel as far as possible, usually up to the jejunum. Though this procedure is readily available, it still carries the disadvantage of not being able to cover the entire length of the small bowel. Single or double balloon enteroscopy technique, advances the endoscope through the small bowel by alternately inflating and deflating balloons, and pleating the small bowel over an 'over' tube. In effect this shortens the length of the bowel and allows for more distal visualization of the small bowel as well as treatment to bleeding lesions. These procedures are usually lengthy, and require deep sedation or general anaesthesia. The other disadvantage of these techniques is the lack of universal expertise and availability in emergency situations.

If significant haemorrhage continues despite non-surgical therapeutic attempts, the patient should be reviewed for consideration of surgery to control the haemorrhage. A second attempt at endoscopic therapy is generally recommended in most cases.

References

1. Blatchford O, Davidson LA, Murray WR, and Blatchford M, Pell J. (1997). Acute upper gastrointestinal haemorrhage in west of Scotland: case ascertainment study. *British Medical Journal*, **315**, 510–14.
2. Sanders DS, Perry MJ, Jones SGW, et al. (2004). Effectiveness of an upper-gastrointestinal haemorrhage unit: A prospective analysis of 900 consecutive cases using the Rockall score as a method of risk standardisation. *European Journal of Gastroenterology and Hepatology*, **16**, 487–94.
3. Hardy JF, DeMoerloose P, and Samama CM. (2005). The coagulopathy of massive transfusion. *Vox Sanguinis*, **89**, 123–7.
4. Villanueva C, Colomo A, Bosch A, et al. (2013). Transfusion strategies for acute upper gastrointestinal bleeding. *New England Journal of Medicine*, **368**, 11–21.
5. British Committee for Standards in Haematology, Stainsby D, MacLennan S, et al. (2006). Guidelines on the management of massive blood loss. *British Journal of Haematology*, **135**, 634–41.
6. Lau JY, Leung WK, Wu JC, et al. (2007). Omeprazole before endoscopy in patients with gastrointestinal bleeding. *New England Journal of Medicine*, **356**, 1631–40.
7. ASGE Standards of Practice Committee, Anderson MA, Ben-Menachem T, et al. (2009). Management of antithrombotic agents for endoscopic procedures. *Gastrointestinal Endoscopy*, **70**, 1060–70.
8. Chau TN, Chan YW, Patch D, Tokunaga S, Greenslade L, and Burroughs AK. (1998). Thromboelastographic changes and early rebleeding in cirrhotic patients with variceal bleeding. *Gut*, **43**, 267–71.
9. Rockall TA, Logan RF, Devlin HB, Northfield TC. (1996). Selection of patients for early discharge or outpatient care after acute upper gastrointestinal haemorrhage. National Audit of Acute Upper Gastrointestinal Haemorrhage. *Lancet*, **347**, 1138–40.
10. Blatchford O, Murray WR, and Blatchford M. (2000). A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. *Lancet*, **356**, 1318–21.
11. Tsoi KK, Chiu PW, Chan FK, Ching JY, Lau JY, and Sung JJ. (2012). The risk of peptic ulcer bleeding mortality in relation to hospital admission

on holidays: a cohort study on 8,222 cases of peptic ulcer bleeding. *American Journal of Gastroenterology*, **107**, 405–10.
12. Spiegel BMR, Vakil NB, and Ofman JJ. (2001). Endoscopy for acute nonvariceal upper gastrointestinal tract hemorrhage: Is sooner better? A systematic review. *Archives of Internal Medicine*, **161**, 1393–404.
13. Barkun A, Bardou M, and Marshall JK. (2003). Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. *Annals of Internal Medicine*, **139**, 843–57.
14. Calvet X, Vergara M, Brullet E, Gisbert JP, and Campo R. (2004). Addition of a second endoscopic treatment following epinephrine injection improves outcome in high-risk bleeding ulcers. *Gastroenterology*, **126**, 441–50.
15. Lau JYW, Sung JJY, Lee KKC, et al. (2000). Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *New England Journal of Medicine*, **343**, 310–16.
16. Green FW, Jr, Kaplan MM, Curtis LE, and Levine PH. (1978). Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. *Gastroenterology*, **74**, 38–43.
17. Schilling D, Demel A, Nusse T, Weidmann E, and Riemann JF. (2003). *Helicobacter pylori* infection does not affect the early rebleeding rate in patients with peptic ulcer bleeding after successful endoscopic hemostasis: a prospective single-center trial. *Endoscopy*, **35**, 393–6.
18. Imperiale TF and Kong N. (2012). Second-look endoscopy for bleeding peptic ulcer disease: a decision-effectiveness and cost effectivess analysis. *Journal of Clinical Gastroenterology*, **46**, 71–5.
19. Ernst O, Bulois P, Saint-Drenant S, Leroy C, Paris JC and Sergent G. (2003). Helical CT in acute lower gastrointestinal bleeding. *European Radiology*, **13**, 114–17.
20. Mirsadraee S, Tirukonda P, Nicholson A, Everett SM, and McPherson SJ. (2011). Embolization for non-variceal upper gastrointestinal tract haemorrhage: a systematic review. *Clinical Radiology*, **66**, 500–9.

CHAPTER 178

Diagnosis and management of variceal bleeding in the critically ill

Deanna Blisard and Ali Al-Khafaji

Key points

- The normal hepatic venous pressure gradient (HVPG) is 3–5 mmHg, and an HVPG of at least 10–12 mmHg defines clinically significant portal hypertension and predicts the clinical course.
- Primary prophylaxis of variceal bleeding is primarily achieved with non-selective β-blockers.
- Secondary prophylaxis is best achieved by a combination of non-selective β-blockers and endoscopic band ligation.
- The combination of endoscopic intervention and pharmacological treatment (vasoactive drugs and antibiotics) is the best management of an acute variceal bleed.
- Early referral of high-risk patients for transjugular intrahepatic portosystemic shunt (TIPS) is important.

Introduction

Portal hypertension is the increase in portosystemic pressure gradient in any portion of the portal venous system. It can result from pre-hepatic abnormalities (e.g. portal vein (PV) thrombosis), intrahepatic non-cirrhotic causes (e.g. schistosomiasis), or post-hepatic abnormalities (e.g. Budd–Chiari syndrome). Cirrhosis is the most common cause. Portal pressure increases initially due to increased resistance to flow, mostly due to architectural distortion of the liver from fibrous tissue and regenerative nodules, as well as increased PV inflow. There is also active intra-hepatic vasoconstriction, mainly related to decreases in nitric oxide bioavailability [1].

Varices are collateral venous channels through which portal blood reaches the systemic venous system. The portal-mesenteric venous system drains the entire GI tract, from oesophagus to rectum, with the most clinically significant of these channels being around the cardia of the stomach. Varices also occur around the umbilicus ('caput medusae'), around the spleen, and in the rectum.

Evaluation

Measurement of portal pressure by the hepatic venous pressure gradient (HVPG) is the best method to stratify risk [1–3]. The HVPG in cirrhotics is best assessed by measuring the gradient between the wedged hepatic venous pressure (WHVP, a measure of sinusoidal hepatic pressure) and the free hepatic venous pressure (FHVP, systemic pressure) [1–3]. The WVHP is obtained by placing a catheter in the hepatic vein under fluoroscopy and wedging it into a small branch. It is corrected for increases in intra-abdominal pressure or ascites by subtracting the FHVP [1].

The normal HVPG range is 3–5 mmHg; values >5 mmHg define portal hypertension, while a HVPG of at least 10–12 mmHg defines clinically significant portal hypertension and predicts the clinical course in cirrhotics. Both the absolute value of HVPG and temporal changes have predictive value for the development of oesophagogastric varices [1], risk of variceal haemorrhage [3], development of non-variceal complications of portal hypertension (e.g. ascites, encephalopathy) [1], Hepatocellular carcinoma (HCC) [1], and death [1,3].

Natural history of varices

Varices and variceal haemorrhage are the complications that result most directly from portal hypertension. Gastroesophageal varices (GEV) are present in approximately 50% of cirrhotic patients [1]. The presence of varices correlates with the severity of liver disease, ranging from 40% in Child A patients to 85% in Child C patients [1,2].

Cirrhotic patients without varices develop them at a rate of 5–10% per year, higher in decompensated cirrhosis [1,4]. The strongest predictor for development of varices is a baseline HVPG >10 mmHg [1]. Variceal haemorrhage occurs at a yearly rate of 5–15%, with the most important predictor being the size of the varices [1]. Other predictors are decompensated cirrhosis and endoscopic evidence of red wale sign [1,5]. Bleeding can stop spontaneously in up to 40% of patients, but is still associated with a mortality of at least 20% at 6 weeks [1].

The main factor determining variceal rupture is likely to be variceal wall tension, with vessel diameter being one of the major determinants. Another determinant of wall tension is the pressure in the varix, which is directly related to the HVPG. Therefore, patients whose HVPG decreases to <12 mmHg or at least 20% from baseline levels ('HVPG responders') have a lower probability of developing recurrent variceal haemorrhage [1] and a lower risk of developing ascites, spontaneous bacterial peritonitis (SBP), and death [1].

Diagnosis

The gold standard for diagnosing GEV is oesophagogastroduodenoscopy (OGD). GEV are generally classified by size—small, medium, and large. Recommendations for medium-sized varices are the same as for large [1]. Cirrhotic patients with GEV have a higher rate of death and risk of decompensation than those without. The frequency of surveillance endoscopies in patients with no or small varices depends on their natural history. Initial screening should be done when the diagnosis of cirrhosis is established [5]. In compensated cirrhosis with no varices on screening endoscopy, the OGD should be repeated in 2–3 years [5,6]. In those with small varices, the OGD should be repeated in 1–2 years while, in decompensated cirrhosis, it should be repeated yearly [5,6].

OGD also remains the main method for diagnosing variceal haemorrhage. This diagnosis is made when endoscopy shows one of the following: active bleeding from a varix, a 'nipple' over the varix, clots overlying the varix, or varices with no other source of bleeding [1]. Less invasive methods such as capsule endoscopy are currently being evaluated. However, the accuracy of evaluating the presence and size of varices and red wale marks is suboptimal, and has moderate sensitivity for diagnosing portal hypertensive gastropathy (PHG) and not suitable to diagnose GV [1].

Management

Management of varices is divided into three main areas: primary prophylaxis, acute haemorrhage treatment and management, and secondary prophylaxis. Pharmacological therapy currently consists of splanchnic vasoconstrictors (e.g. vasopressin, somatostatin), non-selective β-blockers (NSBB)) and venodilators (nitrates). Vasoconstrictors act by reducing portal venous inflow via splanchnic vasoconstriction. NSBB affect portal flow via both β-1 blockade, which decreases cardiac output, and β-2 blockade, producing splanchnic vasoconstriction [1]. Venodilators decrease intrahepatic and/or portocollateral resistance. However, the decrease in portal pressure appears more related to systemic hypotensive effects (i.e. a decrease in flow). Endoscopic therapies have no effect on either portal flow or resistance. Endoscopic procedures include banding (variceal ligation), sclerosing agents (variceal sclerotherapy), or tissue adhesives (variceal obturation). Shunting (either radiological or surgical) markedly reduces portal pressure by bypassing the increased resistance.

Primary prophylaxis

In patients with cirrhosis and no varices, expert consensus panels do not support the universal use of NSBB, but agree that surveillance endoscopies should be performed every 2–3 years, and annually with decompensation [6]. A large multicenter trial failed to show benefit from NSBB in patients with HVPG >5 mmHg at baseline, but no varices [7]. NSBB also did not prevent the development of varices [7].

For patients with small varices that have not bled, NSBB prophylaxis should be used in high-risk patients, such as advanced liver disease and the presence of red wale sign on the varices [8]. Non-high-risk patients can receive NSBB to delay variceal growth, although long-term benefits are not well established [9]. For those not taking NSBB, expert panels suggest surveillance OGD every 2 years, and annually with decompensation [1,6]. Two placebo-controlled studies assessing the efficacy of NSBB in preventing growth of small varices had conflicting results [9,10]. As with other such studies, a high percentage of patients on β-blockers had to be withdrawn due to side effects (11% versus 1% in the placebo group).

Both NSBB and endoscopic variceal ligation (EVL) are effective in preventing the first variceal bleed in patients with medium/large varices that have not bled. A meta-analysis comparing NSBB to no treatment or placebo showed a reduction of risk of first variceal bleed (14% in the NSBB group versus 30% for placebo) [1]. Mortality was also reduced in the NSBB group [1].

A decrease in HVPG <12 mmHg eliminates the risk of haemorrhage and improves survival [1], while decreases >20% from baseline (or even 10%) significantly decreased the risk of first variceal haemorrhage [1,7]. Therapy is titrated to maximal tolerated doses (propranolol 20 mg bd, nadolol 40 mg od). A reduction in heart rate does not correlate with a reduction in HVPG. Prophylactic therapy needs to be continued indefinitely, as risk of bleeding recurs with NSBB cessation [11].

Meta-analyses [12] have shown that EVL had a small, but significant lower incidence of first variceal bleeding when compared to NSBB. However, there was no mortality benefit. Although the EVL group had fewer adverse events (4% versus 13%), these events were more severe. The choice should be based on patient characteristics, preferences, and local resources and expertise.

Acute variceal haemorrhage

Improved management over the last two decades has led to decreasing mortality rates [1]. Initial resuscitation efforts involve basic measures, including evaluating the 'ABC's' to achieve haemodynamic stability. In patients with a low or intermediate risk (Child class A or B, HVPG <20 mmHg), standard therapy should be started. This includes the combination of a vasoconstrictor (e.g. octreotide, terlipressin) started on admission and maintained for 2–5 days, plus endoscopic therapy [1,8] together with prophylactic antibiotics. The goals of blood volume resuscitation should be maintaining haemodynamic stability and haemoglobin levels of 7–8 g/dL [1,8]. More aggressive resuscitation can lead to increases in portal pressures, and to more bleeding and mortality.

Despite the lack of evidence supporting correction of coagulopathy and thrombocytopenia, many endoscopists (including our own) target a platelet count >50,000/μL and an International Normalized Ratio (INR) <2. A multicentre placebo-controlled trial of recombinant factor VIIa (rFVIIa) in actively bleeding cirrhotic patients failed to show benefit over conventional management [13]. However, a **post hoc analysis** suggested that rFVIIa reduced the failure rate in controlling bleeding in Child–Pugh B and C patients; further studies are needed.

There is a high risk of developing SBP and other infections in variceal haemorrhage, leading to an early recurrence of bleeding and greater mortality [14]. Bacterial infections may initiate the bleeding episode via impaired haemostasis and increased portal pressures [1,2,14]. Short-term prophylaxis with antibiotics in variceal haemorrhage (and all types of GI bleeding in cirrhotics) decreases the rate of bacterial infections and increases survival. Therefore, prophylaxis should be considered standard practice in all acute variceal haemorrhage [1,8]. Antibiotics should be chosen based on the institution's antibiotic resistance patterns, and continued for seven days.

Pharmacological therapy should be considered first-line treatment for variceal bleeding based on a recent meta-analysis of 15 trials comparing sclerotherapy and pharmacological treatment (vasopressin +/– glyceryl trinitrate, somatostatin or octreotide) [15]. NSBB should not be used acutely as they may cause worsening hypotension and blunt the tachycardia response.

Vasopressin is the most potent splanchnic vasoconstrictor which, in turn, leads to decreases in portal flow and pressure. However, its clinical usefulness is limited by side-effects including cardiac and peripheral ischaemia, arrhythmias, hypertension, and bowel ischaemia [1]. Terlipressin is a synthetic analogue of vasopressin with a longer biological activity and less side-effects. It is effective in controlling acute variceal haemorrhage and is associated with decreased mortality [1]. At present, it is not available in the United States.

Somatostatin and analogues such as octreotide also cause splanchnic vasoconstriction. Advantages include safety and that they can be used continuously for five days or longer; however, meta-analysis are controversial [1]. Octreotide may be a useful adjunct to endoscopic therapy [8,16] and is continued for 5 days in our institution.

After patient stabilization, OGD should be performed as soon as possible, enabling endoscopic therapy if the source is confirmed (Fig. 178.1) [8]. A meta-analysis of 10 randomized controlled trials shows an almost significant benefit of EVL in initial control of bleeding when compared to sclerotherapy [12]. One study involved in the meta-analysis showed that HVPG increased after both EVL and sclerotherapy, but decreased in the EVL group after 48 hours. EVL is therefore the preferred from endoscopic treatment for acute bleeding [1,8].

Despite all measures, variceal bleeding may not be controlled or recurs early in about 10–20% of patients. An HVPG >20 mmHg is predictive of treatment failure [1]. Shunts, most commonly TIPS, are clinically effective as rescue therapy for those patients who fail to respond to endoscopic or pharmacological therapy [1]. Early TIPS (within 24–48 hours of admission) offers significant survival benefits among high-risk patients in two randomized controlled trials [1]. TIPS within 72 hours of variceal bleeding, in addition to EBL, has been recently shown to be highly effective in preventing recurrent bleeding and improved short- and long-term survival in patients with Child's C or Child's B cirrhosis with active bleeding during endoscopy [17]. Notably, there was no increase in encephalopathy, heart failure nor any other complications in the TIPS-treated patients compared to EBL alone. Balloon tamponade is effective in temporarily controlling haemorrhage in over 80% of patients [1]. Its use should be restricted to patients with uncontrollable bleeding where more definitive therapy (e.g. TIPS) is planned within 24 hours, as potentially lethal complications can occur. Complications include aspiration, migration, and necrosis/perforation of the oesophagus with mortality rates as high as 20% (Fig. 178.2).

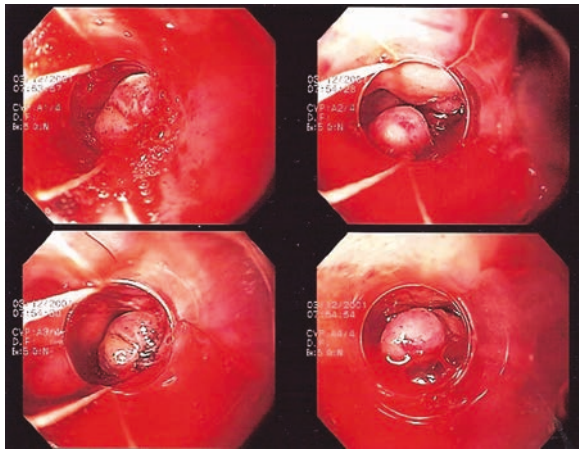


Fig. 178.1 Bleeding oesophageal varix being banded.

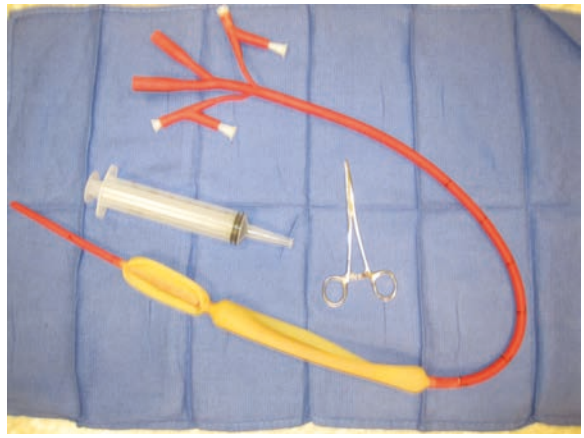


Fig. 178.2 Minnesota tube.

Gastric varices

The approach to gastric varices depends on the type of varices. Gastric varices are classified into four categories: GOV1, GOV2, IGV1, and IGV2 [18] (see Fig. 178.3). GOV1 and GOV2 are gastric varices that extend from oesophageal varices across the gastroesophageal

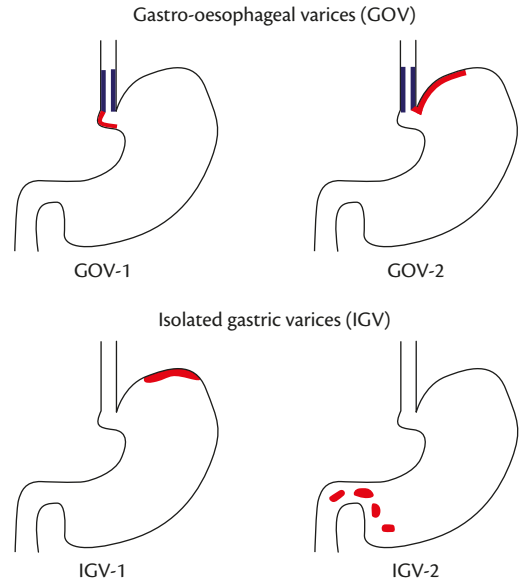


Fig. 178.3 The Sarin classification of gastric varices.
Reproduced from Sarin SK et al., 'Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertensive patients', *Hepatology*, **16**, pp. 1343–9, Copyright © 1992 American Association for the Study of Liver Diseases, with permission from John Wiley and Sons..

junction. In GOV1, they only extend 5 cm or less, while in the GOV2 group, the varices extend into the fundus. IGV refers to isolated gastric varices. IGV1 are varices found only in the fundus and IGV2 are isolated non-fundic varices. Type 1 gastric varices (GOV1) are the most common, accounting for 74% [16]). They are an extension of EV along the lesser curve of the stomach, and their management should be the same. GOV are present in 20% of cirrhotic patients, either isolated or combined. Bleeding is more severe and carries a higher rate of death [16] (Fig. 178.4). Limited data exist for the management of bleeding from fundal varices. Acute fundal gastric variceal bleeding is more effectively controlled with tissue adhesives (e.g. N-butyl-cyanoacrylate, isobutyl-2-cyanoacrylate, or thrombin) [1,16] than EVL. A large randomized trial compared gastric variceal obturation (GVO) with N-butyl-cyanoacrylate versus EVL in patients with acute gastric variceal haemorrhage. It demonstrated that control of active bleeding was similar in both groups, but rebleeding was less frequent with GVO [1]. The use of these agents is preferred in endoscopic therapy of fundal varices; if unavailable, TIPS should be considered first-line therapy. TIPS is also more effective in preventing recurrent bleeding [1] versus endoscopic therapy. Several studies have shown bleeding control rates of over 90% with TIPS for gastric varices. A prospective study showed equal efficacy in controlling gastric fundal and oesophageal variceal bleeding [1] with salvage TIPS. Treatment should be based on local expertise.

Secondary prophylaxis

The median rebleeding rate in untreated individuals is approximately 60% within 1–2 years of the index haemorrhage, with a mortality of 33% [1]. Prevention of recurrent VH is key in managing these patients, and secondary prophylaxis should be initiated as soon as possible after the initial episode. Those patients who required shunt surgery or TIPS would not require further preventative measures. NSBB or sclerotherapy decreases the rebleeding rate to around 42–43% [1], although sclerotherapy has a higher incidence of side-effects.

The combination of NSBB and nitrates has a synergistic effect on reducing portal pressure, and is theoretically more effective than BB alone [1,19]. However, clinical trials have shown the combination is no different from NSBB alone when looking at rebleeding rates and mortality. Only one study directly compared a combination versus propranolol alone in prior variceal haemorrhage [1], showing. A non-statistically significant benefit from combination therapy. Data from other randomized clinical trials show that the median rebleeding rate in those treated with combination therapy is approximately 35% [1], lower than BB alone. However, combination therapy has more side-effects and is poorly tolerated.

EVL is the endoscopic method of choice for preventing variceal rebleeding, and is superior to sclerotherapy. A median rebleeding rate in patients treated with EVL in different randomized clinical trials is around 32% [1]. EVL sessions are repeated at 7–14-day intervals. Once gone, OGD is usually repeated every 3–6 months. Complications of EVL occur in about 14% of cases and are minor.

The most rational approach would appear to be a combination endoscopy plus pharmacological therapy since NSBB protects against rebleeding prior to EVL. Two randomized trials demonstrate the benefit of combined treatment versus EVL alone, with rebleeding rates of 23 and 14% in EVL + BB versus 47 + 38% in EVL alone [20]. These results support combination therapy, even though consensus conferences recommend EVL or BB + nitrate as first line therapy [8].

The lowest rate of rebleeding (~10%) is in HVPG responders [1,3]. These are patients in whom pharmacological therapy (NSBB alone or BB + nitrate) leads to a decrease in HVPG <12 mmHg or a reduction >20% from baseline [1,3]. Shunt surgery effectively prevents rebleeding. However, this option carries a marked increase in the risk of hepatic encephalopathy with no effect on survival [1].

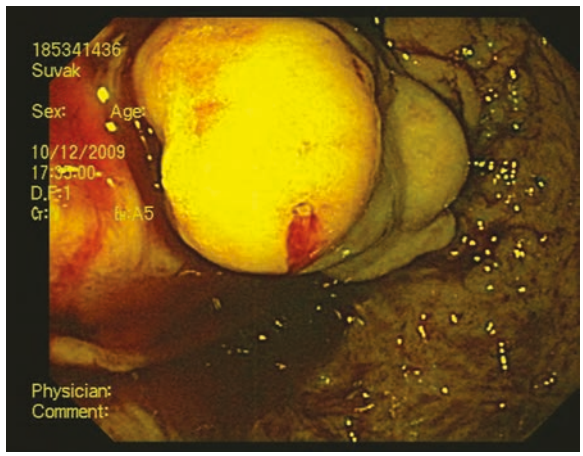


Fig. 178.4 Bleeding gastric varix.

References

1. Garcia-Tsao G, Sanyal A, Grace N, and Carey W. (2007). AASLD Practice Guidelines: Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology*, **46**, 922–38.
2. Thalheimer U, Triantos C, Goulis J, and Burroughs AK. (2011). Management of varices in cirrhosis. *Expert Opinion in Pharmacotherapy*, **12**, 721–35.
3. D'Amico G, Garcia-Pagan JC, Luca A, and Bosch J. (2006). Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systemic review. *Gastroenterology*, **131**, 1611–24.
4. D'Amico G, Garcia-Tsao G, and Pagliaro, L. (2006).Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *Journal of Hepatology*, **44**, 217–31.
5. Grace, ND, Groszmann RJ, Wagner JL, et al. (1998). Portal hypertension and variceal bleeding: an AASLD single topic symposium. *Hepatology*, **28**, 868–80.
6. De Franchis R. (2000). Updating Consensus in portal hypertension: Report of the Baveno III consensus workshop on definitions, methodology and therapeutic strategies in portal hypertension. *Journal of Hepatology*, **33**, 846–52.
7. Groszmann RJ, Garcia-Tsao G, Gao H, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis.
8. De Franchis R. (2005). Evolving consensus in portal hypertension: Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *Journal of Hepatology*, **43**, 167–76.
9. Merkel C, Marin R, Torboli P, et al. (2004). A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. *Gastroenterology*, **127**, 476–84.
10. Cales P, Oberti F, Payen J, et al. (1999). Lack of effect of propranolol in the prevention of large oesophaeal varices in patients with cirrhosis: a randomized trial. *European Journal of Gastroenterology and Hepatology*, **11**, 741–5.

11. Abraczinskas DR, Ookubo R, Grace NG, et al. (2001). Propranolol for the prevention of first esophageal variceal hemorrhage: A lifetime commitment? *Hepatology*, **34**, 1096–102.
12. Khuroo, M, Khuroo N, Farahat K, Khuroo Y, Sofi A, and Dahab S. (2005). Meta-analysis: endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleeding. *Alimentary Pharmacology & Therapy*, **21**, 347–61.
13. Bosch J, Thabut D, Bendtsen F, et al. (2004). Recombinant Factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology*, **2127**, 1123–30.
14. Goulis J, Armonis A, Patch D, Sabin C, Greenslade L, and Burroughs AK. (1998). Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology*, **27**, 1207–12.
15. D'Amico G, Pietrosi G, Tarantino I, and Pagliaro L. (2003). Emergency sclerotherapy versus vasoactive drugs for variceal bleeding in cirrhosis: a Cochrane meta-analysis. *Gastroenterology*, **124**, 1277–91.
16. Ryan BM, Stockbrugger RW, and Ryan JM. (2004). A pathophysiologic, gastroenterologic, and radiologic approach to the management of gastric varices. *Gastroenterology*, **126**, 1175–89.
17. Garcia-Pagan JC, Caca K, Bosch J, et al. (2010). Early use of TIPS in patients with cirrhosis and variceal bleeding. *New England Journal of Medicine*, **362**, 2370–9.
18. Sarin SK, Lahoti D, Saxena SP, Murthy NS, and Makwana UK. (1992). Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertensive patients. *Hepatology*, **16**, 1343–9.
19. Minano C and Garcia-Tsao G. (2010). Clinical pharmacology of portal hypertension. *Gastroenterology Clinic New America*, **39**, 681–95.
20. Lo G, Lai K, Cheng J, et al. (2000). Endoscopic variceal ligation plus nadolol and sucralfate compared with ligation alone for the prevention of variceal rebleeding: a prospective, randomized trial. *Hepatology*. **32**, 461–5.

CHAPTER 179

Pathophysiology and causes of lower gastrointestinal haemorrhage

Leslie M. Kobayashi and Raul Coimbra

Key points

- Lower gastrointestinal bleeding is less common than upper gastrointestinal bleeding, but is increasing in frequency, is a common cause of hospitalizations and results in significant utilization of health care resources.
- Acute lower gastrointestinal bleeding primarily presents with haematochezia or bright red blood per rectum, and melena; upper gastrointestinal bleeding may present with similar symptoms/signs in up to 9% of cases and must be ruled out in all patients.
- Diverticulosis is the most common cause of lower gastrointestinal bleeding in Western populations, and is increasing in frequency, likely due to the increasing numbers of elderly patients.
- Haemorrhoids are one of the most common causes of lower gastrointestinal bleeding in the younger patient. However, more proximal concomitant source of bleeding and malignancy should be ruled out in all symptomatic patients.
- Neoplastic lesions including polyps and carcinomas account for a significant minority of lower gastrointestinal bleeding cases, and are of particular concern among patients ≥50 years of age; with a family history of malignancy; or associated symptoms such as weight loss, pain, and change in bowel habits.

Presentation

Lower gastrointestinal bleeding (LGIB) can be defined as any gastrointestinal (GI) haemorrhage whose origin exists beyond the ligament of Treitz, although more modern classification systems differentiate LGIB due to colorectal sources from mid gut bleeding due to sources in the small bowel [1]. LGIB occurs when mucosal irritation/inflammation, friable masses, arteriovenous malformations (AVMs), or trauma to the colon or rectum causes intraluminal shedding of blood. Peristalsis then propels this blood along the faecal stream where it may result in haematochezia or melena. Haematochezia is the passage of bright red blood from the rectum and is the most common presenting symptom of LGIB [1]. Haematochezia primarily occurs if bleeding sources are located in the distal portions of the GI tract. However, bleeding may occasionally arise from more proximal sources and remain bright red due to the cathartic effects of large amounts of intra-luminal blood. Melena, the passage of dark, black, or tarry stools occurs if sources of bleeding are higher in the GI tract, allowing the oxidation of haematin.

Bleeding, presenting as either haematochezia or melena can range from low volume intermittent losses to massive haemorrhage with haemodynamic instability. Alternatively, LGIB may be detected in asymptomatic patients by faecal occult blood testing for work-up of anaemia or during routine screening. As upper GI bleeding (UGIB) may present in a similar fashion to LGIB in up to 9% of cases, UGIB should be ruled out as a cause of presenting symptoms [2]. This can be done simply in the acute setting by nasogastric lavage and return of bilious non-bloody fluid. If no bile is noted, more thorough examination with upper GI endoscopy is required to reliably rule out UGIB as a cause of symptoms.

Incidence

LGIB is quite common, with an annual incidence of 20–45 cases per 100,000 population [3,4]. It is a frequent cause of emergency department visits, hospitalizations, and healthcare expenditure. LGIB accounts for 0.5% of hospitalizations, or 120/100,000 cases in the United States; diverticular bleeding alone cost one billion dollars in 2001 [4]. LGIB is responsible for 23–33% of all GIB (3-4). In contrast to UGIB which has been decreasing in frequency over time with the introduction of acid-suppressing medications and *Helicobacter pylori* treatment, LGIB is increasing in incidence/frequency [3]. LGIB is even more frequent among the elderly, occurring in 181/100,000 among persons aged 45–64, and as high as 1,871/100,000 for those aged ≥85 [3]. Age is the main risk factor associated with LGIB, with the elderly accounting for 65% of hospitalizations [3-5]. There are multiple reasons for an increased risk of LGIB among the elderly, including increased incidences of diverticulosis, AVM, and neoplasia, as well as the frequent usage of medications that increase bleeding risk such as antiplatelet agents, anticoagulants, and non-steroidal anti-inflammatories (NSAIDs) [5,6]. The number of patients on such medications who present with LGIB is increasing significantly, affecting up to 54% [1,7]. These agents are associated with

more severe bleeding episodes, longer hospital stays, more frequent need for blood transfusion and in-hospital complications [6,8]. Approximately 28.4% of patients with LGIB present with some haemodynamic instability [7].

Aetiologies

The three commonest causes of LGIB in the US include diverticulosis, haemorrhoids, and masses such as (benign) polyps and (malignant) tumours [1,9]. Inflammation and infection can cause generalized friability of the colonic mucosa resulting in LGIB, e.g. ischaemic and inflammatory bowel disease (IBD) and haemorrhagic diarrhoea. Other less common causes include AVMs, solitary rectal ulcers, and radiation proctitis. As the majority of LGIB resolves spontaneously, the source may not be identified in 2.5–30.3% of cases [1,10,11]. Multiple sources may be present in up to 40% of cases [11].

Diverticulosis

Colonic diverticulae are outpouchings of the intestinal mucosa through the muscular wall of the intestine (Fig. 179.1). They occur near the origin of nutrient vessels where the bowel wall is relatively weak. Diverticulosis is found commonly among Western populations with a prevalence ranging from 17–45%, and increases in frequency with age, being present in over half of those aged ≥50 years [5]. Approximately 17% of patients with diverticulosis will experience an episode of bleeding, and it accounts for 30–57% of LGIB [1,2,4]. While diverticulae are more commonly found in the left colon, right-sided lesions have a higher tendency to bleed and account for 50–60% of diverticular bleeds [2,4,12]. The incidence of diverticular LGIB is increasing over recent years, and may be due in part to our aging population [1]. Bleeding due to diverticular disease may result in severe or massive haemorrhage in up to a quarter of patients with risk factors including hypotension, anaemia, coagulopathy, (INR ≥1.5) and use of antihypertensive medications [13].

Haemorrhoids

Haemorrhoids are the commonest cause of LGIB in non-elderly patients. Its prevalence ranges from 4–10% in the general population [5,14]. They account for 20–24% of LGIB cases; and this incidence appears to be stable over time [1,9], but can increase to as high as 54–96% in low-risk patients (age <55, no family history of malignancy or inflammatory bowel disease, no other abdominal

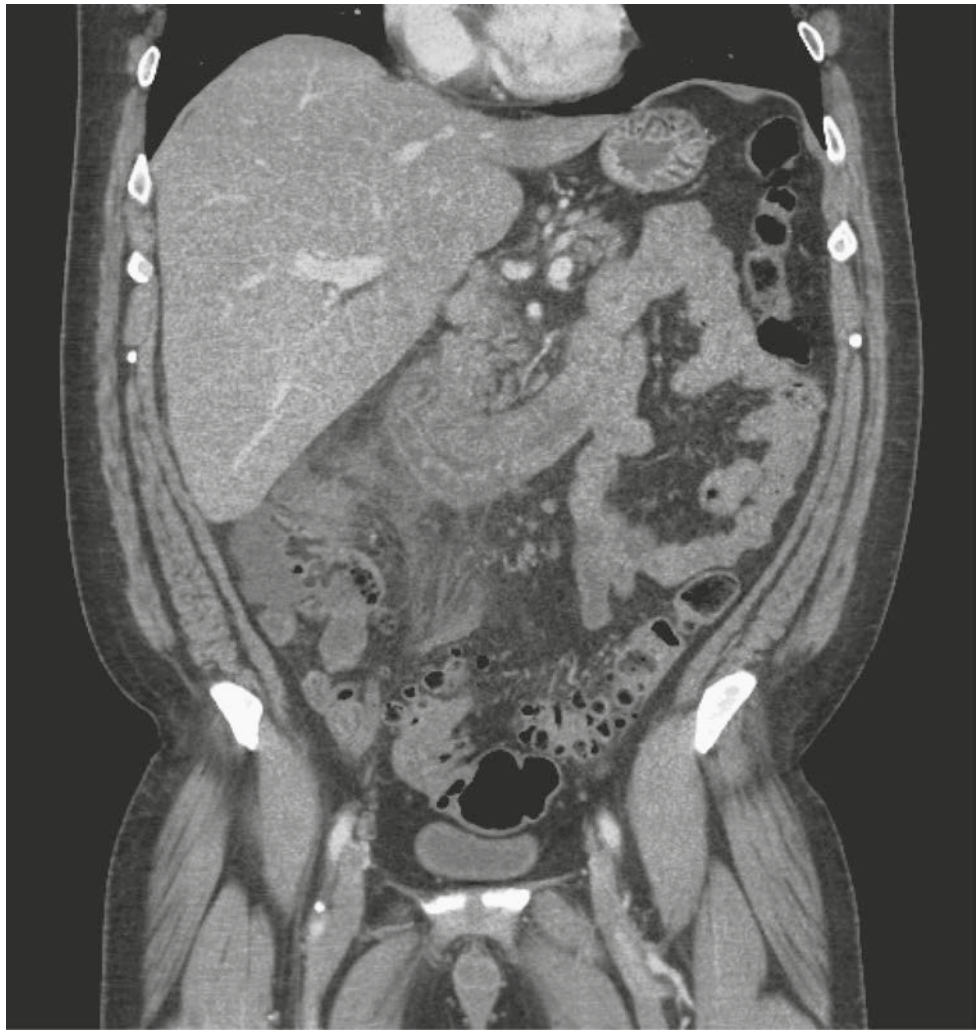


Fig. 179.1 Coronal CT image showing sigmoid diverticulosis.

or bowel symptoms) [15,16]. While haemorrhoids and other benign anal disorders such as fissures and fistula-in-ano are common causes of LGIB, and haematochezia in particular, patients may also harbour more proximal concomitant bleeding lesions or malignancies.

Masses

Spontaneous bleeding from neoplastic colorectal lesions (Fig. 179.2) accounts for 2–33% of LGIB cases; the frequency of a malignant source increases with patient age. Benign polyps account for 5–13% of cases and biopsy or polypectomy for 1–6% [2,9]. The rate of post-procedural bleeding decreases as endoscopic technology improves, and if patients are kept off anticoagulant, antiplatelet, and NSAID medications following their procedure [2].

Arteriovenous malformations

These include vascular ectasias, angiomas, and angiodysplasias. AVMs can be found throughout the GI tract, but are most often seen in the right colon and small bowel. AVMs can be classified based on angiographic characteristics, location, patient age, and history [17]. Type 1 lesions are solitary right-sided colonic lesions, primarily occurring in the elderly. These are likely acquired lesions forming as a result of chronic obstruction of submucosal veins and eventually resulting in arteriovenous communication. In contrast Type 2 AVMs are congenital, are larger than Type 1 lesions, and occur primarily in the small bowel. Type 3 lesions are punctate angiomas [17]. AVMs occur with a wide range of frequencies depending on the patient population, but are rare in the overall population accounting for only 2–5% of LGIB cases [1,2]. They are more frequent among the elderly, occurring in 2–37% of cases [4,5].

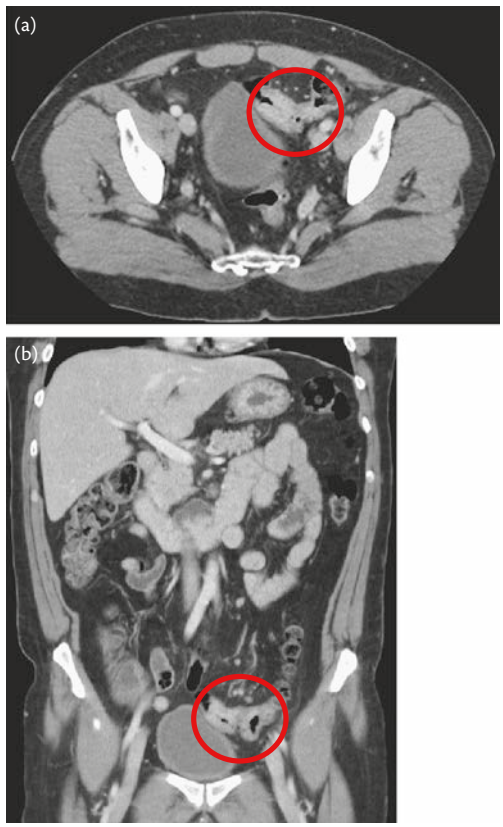


Fig. 179.2 (a) Axial and (b) coronal CT images of a near obstructing sigmoid colon cancer.

Inflammation

Colitis due to inflammatory, ischaemic, or infectious causes are responsible for 9–21% of cases of LGIB. Crohn's disease and ulcerative colitis are most common among younger male patients and cause 2–8% of cases of LGIB [2,10]. Ischaemic colitis is relatively rare in the general population, but is one of the commonest causes (up to 30% of cases) among the critically ill [2]. These patients often present with severe cramping abdominal pain out of proportion to examination findings; among the critically ill they may present with severe haemorrhage. The most common infectious organisms associated with haemorrhagic diarrhoea include *Salmonella, Histoplasma, Shigella, Campylobacter, Yersinia*, and enterohaemorrhagic *Escherichia coli* strains, as well as cytomegalovirus.

Radiation proctitis is a relatively rare cause of LGIB, accounting for 1–5% of cases, but occurs in up to 20% of patients undergoing radiation therapy [18]. It is likely to become increasingly important as the use of radiation therapy to treat pelvic malignancies continues to rise. Radiation causes endothelial cell swelling, vacuolization, and thrombosis as well as mucosal telangiectasias resulting in haematochezia, tenesmus and diarrhoea. LGIB due to radiation proctitis can be severe and recurrent [2].

Unusual causes

Solitary rectal ulcer syndrome (SRUS) occurs when chronically prolapsing mucosa causes local trauma and transient ischaemia resulting in formation of a benign ulcerative lesion in the mid-rectum. In addition to haematochezia, patients often complain of constipation, difficulty with defecation, and tenesmus. While an uncommon cause of LGIB in the ambulatory population, SRUS is more common among ICU patients, accounting for 21–31% of cases occurring after ICU admission [19].

Small bowel pathology is responsible for 1–9% of LGIB [1,5]. The commonest cause of small bowel LGIB is Meckel's diverticulum [11]. Other small bowel causes include IBD, intussusception, vascular ectasia, AVMs, tumours and polyps, and celiac disease.

In discussing the aetiology of LGIB it is important to distinguish between non-elderly and elderly populations, as well as the hospitalized patient. Benign anorectal disorders and IBD are more frequent among younger patients [20], while diverticulosis of both the right and left colon, angiodysplasia, and malignancy are much more common among the elderly [4]. In patients hospitalized for other causes prior to demonstrating signs or symptoms of LGIB, intestinal ischaemia, and SRUS, rarely encountered entities among ambulatory patients, are among the commonest causes of LGIB. The aetiology of LGIB slightly differs among non-Western civilizations where malignancy is more common and diverticular disease much less common. A meta-analysis of over 53,000 Chinese patients found colorectal cancer, polyps, and colitis to be the commonest aetiologies of LGIB, while diverticulosis accounted for only 1.1% of cases [10].

References

1. Gayer C, Chino A, Lucas C, et al. (2009). Acute lower gastrointestinal bleeding in 1,112 patients admitted to an urban emergency medical center. *Surgery*, **146**, 600–6.

2. Zuckerman GR and Prakash C. (1999). Acute lower intestinal bleeding. Part II: etiology, therapy, and outcomes. *Gastrointestinal Endoscopy*, **49**, 228–38.
3. Zhao Y and Encinosa W. (2006). *Hospitalizations for Gastrointestinal Bleeding in 1998 and 2006: Statistical Brief #65*. Rockville, MD: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs.
4. Longstreth GF. (1997). Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: a population-based study. *American Journal of Gastroenterology*, **92**, 419–24.
5. Zuccaro G. (2008). Epidemiology of lower gastrointestinal bleeding. *Best Practice Research in Clinical Gastroenterology*, **22**, 225–32.
6. Hashash JG, Shamseddeen W, Skoury A, Aoun N, and Barada K. (2009). Gross lower gastrointestinal bleeding in patients on anticoagulant and/or antiplatelet therapy: endoscopic findings, management, and clinical outcomes. *Journal in Clinical Gastroenterology*, **43**, 36–42.
7. Arroja B, Cremers I, Ramos R, et al. (2011). Acute lower gastrointestinal bleeding management in Portugal: a multicentric prospective 1-year survey. *European Journal on Gastroenterology and Hepatology*, **23**, 317–22.
8. Ahsberg K, Hoglund P, Kim WH, and von Holstein CS. (2010). Impact of aspirin, NSAIDs, warfarin, corticosteroids and SSRIs on the site and outcome of non-variceal upper and lower gastrointestinal bleeding. *Scandinavian Journal in Gastroenterology*, **45**, 1404–15.
9. Strate LL, Ayanian JZ, Kotler G, and Syngal S. (2008). Risk factors for mortality in lower intestinal bleeding. *Clinical Gastroenterology and Hepatology*, **6**, 1004–10.
10. Bai Y, Peng J, Gao J, Zou DW, and Li ZS. (2011). Epidemiology of lower gastrointestinal bleeding in China: single-center series and systematic analysis of Chinese literature with 53,951 patients. *Journal in Gastroenterology and Hepatology*, **26**, 678–82.
11. Lee J, Costantini TW, Coimbra R. (2009). Acute lower GI bleeding for the acute care surgeon: current diagnosis and management. *Scandinavian Journal in Surgery*, **98**, 135–42.
12. Lewis M and NDSG. (2008). Bleeding colonic diverticula. *Journal of Clinical Gastroenterology*, **42**, 1156–8.
13. Lee KK, Shah SM, and Moser MA. (2011). Risk factors predictive of severe diverticular hemorrhage. *International Journal of Surgery*, **9**, 83–5.
14. Johanson JF and Sonnenberg A. (1990). The prevalence of hemorrhoids and chronic constipation. An epidemiologic study. *Gastroenterology*, **98**, 380–6.
15. Mehanna D and Platell C. (2001). Investigating chronic, bright red, rectal bleeding. *Australia and New Zealand Journal of Surgery*, **71**, 720–2.
16. Nikpour S and Ali Asgari A. (2008). Colonoscopic evaluation of minimal rectal bleeding in average-risk patients for colorectal cancer. *World Journal of Gastroenterology*, **14**, 6536–40.
17. Moore JD, Thompson NW, Appelman HD, and Foley D. (1976). Arteriovenous malformations of the gastrointestinal tract. *Archives of Surgery*,**111**, 381–9.
18. Rustagi T and Mashimo H. (2011). Endoscopic management of chronic radiation proctitis. *World Journal of Gastroenterology*, **17**, 4554–62.
19. Lin CK, Liang CC, Chang HT, Hung FM, and Lee TH. (2011). Acute hemorrhagic rectal ulcer: an important cause of lower gastrointestinal bleeding in the critically ill patients. *Digestive Diseases and Sciences*, **56**, 3631–7.
20. Hoedema RE and Luchtefeld MA. (2005).The management of lower gastrointestinal hemorrhage. *Disease of the Colon & Rectum*, **48**, 2010–24.

CHAPTER 180

Diagnosis and management of lower gastrointestinal haemorrhage in the critically ill

Leslie M. Kobayashi and Raul Coimbra

Key points

- Initial management of all lower gastrointestinal bleeding should begin with establishment of adequate intravenous access, fluid resuscitation with balanced crystalloid solution, and judicious use of transfusion of blood and blood products to ensure haemodynamic stability.
- Early urgent colonoscopy following rapid bowel preparation with polyethylene glycol solution is safe and well tolerated in most patients, and results in accurate diagnosis.
- In patients unable to tolerate endoscopy or bowel preparation, in those with inadequate or non-diagnostic endoscopy, and those with very fast or very slow haemorrhage, alternative diagnostic techniques include angiography, computed tomography (CT) scanning, and tagged red blood cell (RBC) scanning.
- A small proportion of patients with lower gastrointestinal bleeding have a small bowel source; in these patients capsule endoscopy, single- and double-balloon enteroscopy, and CT scanning are the most effective diagnostic modalities.
- Most cases of lower gastrointestinal bleeding stop spontaneously and do not recur. In patients requiring therapeutic intervention, endoscopy is the preferred modality as it is effective and associated with a low rate of recurrent bleeding and complications.

Resuscitation

The first step in the management of lower gastrointestinal bleeding (LGIB) is resuscitation. Haemodynamically unstable patients should be treated immediately with placement of large bore intravenous (iv) access, either two large peripheral cannulae or a central line. Isotonic fluids and transfusion of blood and blood products should be utilized for intravascular volume repletion. A Foley catheter should be placed to monitor urine output. Consideration should be given to placing an arterial line for continuous invasive haemodynamic monitoring and repeat blood sampling. Routine lab tests should include blood group type and screen, complete blood count, arterial blood gas, coagulation parameters, and thromboelastography, if available. For stable patients, it is still important to measure baseline lab values, establish good peripheral iv access, and consider placing a Foley catheter for strict monitoring of fluid balance. After stabilizing the patient, a careful history should be taken, with special emphasis on use of anticoagulant, antiplatelet, and non-steroidal anti-inflammatory drugs (NSAIDs); symptoms of anaemia or hypovolaemia; personal or family history of malignancy or inflammatory bowel disease (IBD), and change in bowel habit. In patients on anticoagulants with evidence of haemodynamic instability, active or ongoing bleeding, reversal of the agent should be undertaken immediately as part of their general resuscitation. Reversal may include transfusion of fresh frozen plasma or platelets; agents such as desmopressin, activated factor VIIa or prothrombin complex concentrates; and haemodialysis. Patients should have a complete abdominal examination, seeking any stigmata of liver disease such as caput medusae, hepatosplenomegaly and ascites; and digital rectal exam for haemorrhoids, fissures, masses, strictures, and gross blood.

Diagnosis

LGIB stops spontaneously in the majority of cases so an exact source for bleeding may not be found in patients whose symptoms do not recur. Patients who present with haemodynamic instability, have continued evidence of bleeding, persistent or worsening anaemia, or associated abdominal symptoms should undergo further work-up to determine the etiology and possibly undergo treatment once stabilized [1]. As upper GI bleeding (UGIB) may present in a similar fashion as LGIB in ~9% of cases, diagnostic manoeuvers to exclude an UGIB source must be undertaken prior to diagnosis or treatment of LGIB [2]. Nasogastric lavage should be performed as a first-line diagnostic modality. If bilious non-bloody fluid returns, UGIB can be confidently excluded. If not, or if blood is noted, upper GI endoscopy is required.

Once UGIB has been ruled out, colonoscopy should be the initial diagnostic study of choice, and performed as quickly as possible. Timing should ideally be performed within the first 12–24 hours, as earlier examination results in a higher diagnostic yield, is associated with decreased hospital length of stay, and may contribute to decreased cost of care [3–7]. The diagnostic accuracy ranges widely from 48–100% depending on timing, indication, patient demographics, and type/use of bowel preparation [1,3–8]. Bowel preparation in

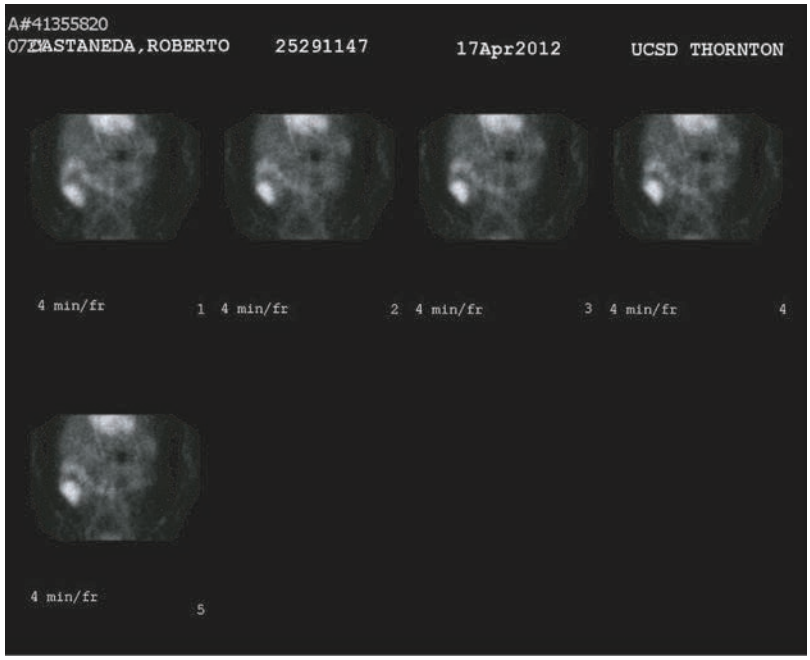


Fig. 180.1 Tagged red blood cell scan revealing abnormal uptake in the right hemi-abdomen suggestive of right colonic source of haemorrhage.

the setting of acute onset LGIB was felt to be dangerous and technically difficult. However, a growing body of evidence suggests that, if performed appropriately, it is safe, feasible, and improves diagnostic yield [4]. Most current protocols utilize a polyethylene glycol solution delivered via nasogastric tube followed rapidly by colonoscopy within the first 12 hours of presentation. This protocol accurately diagnoses LGIB in 74–100% of cases, a pooled analysis of six recent studies found an overall diagnostic yield of 91% [4,7].

If a bleeding source cannot be identified on colonoscopy, or endoscopy is not possible due to lack of availability, patient intolerance or instability, or is non-diagnostic due to poor bowel preparation or massive bleeding, other diagnostic methods include angiography, computed tomography (CT), and tagged red blood cell (RBC) scan. Angiography requires blood loss of at least 0.5–1 mL/min to be detectable, but has the benefit of being both diagnostic and therapeutic [6]. Its diagnostic yield ranges widely (25–87%), increasing in haemodynamically unstable patients and those with ongoing blood loss [4,6]. CT is another diagnostic option, with recent technological improvements resulting in improved detection rates. In one small prospective study CT angiography outperformed even colonoscopy in its ability to localize bleeding (100% versus 52.9%), and diagnose the etiology (88.2% versus 52.9%) [9]. Overall, CT has a sensitivity ranging from 79–100% [4,6,9,10]. CT angiography has higher yields in patients with evidence of active bleeding, but animal models suggest it can detect bleeding as slow as 0.3–0.5 mL/min; unlike other diagnostic modalities it can identify extra-luminal sources of haemorrhage [11,12]. Tagged RBC scan is most useful in detecting blood loss as low as 0.1–0.5 mL/min [6,13]. Unfortunately, the diagnostic yield ranges from 23–88%. Sensitivity does appear to be higher for LGIB (Fig. 180.1) as compared with UGIB, but can still result in false localization in 22% of cases [1,13]. Direct comparisons of endoscopy to radiographic studies are few, but suggest that overall endoscopy has a higher diagnostic yield than angiography or scintigraphy [3,4,14].

Small bowel lesions are the source of LGIB in a minority of cases. These lesions are mainly vascular in nature, followed in frequency by neoplasms and inflammatory lesions [6]. The commonest methods to investigate the small bowel include push enteroscopy, single- or double-balloon enteroscopy, and capsule endoscopy. Small bowel lesions may also be visualized on CT scan, tagged RBC scan, and angiography. The highest diagnostic yields are found with capsule or balloon enteroscopy, and CT scan in patients with active haemorrhage.

Treatment

Once a source for LGIB has been identified, treatment options include endoscopic or angiographic intervention and surgery. If a bleeding source cannot be identified and the patient is unstable, requiring ongoing transfusion, or has massive blood loss, emergent surgery is the only option.

Endoscopic therapies for LGIB include band ligation; injection of epinephrine, sclerosants, or ethanol; thermal contact, argon plasma coagulation, and placement of haemoclips. Which technique is used depends on the location, type, and characteristics of the lesion and operator experience with the different devices. Injection techniques affect haemostasis by causing chemical vasoconstriction and volume tamponade. Coagulation haemostasis can be achieved with contact devices such as heater probes and bipolar cautery, or non-contact devices such as the argon plasma coagulator. This is particularly useful for diffuse or multifocal sources of haemorrhage. Clips and band ligation use physical tamponade of the bleeding source to create haemostasis. They are particularly effective with diverticular and haemorrhoidal causes. Endoscopic therapies are generally successful with effective haemorrhage control in 80–96% of patients [4,15]. Re-bleeding rates range from 23–30% [3,4]. Complication rates are generally low, ranging from 0–2% and include perforation, sepsis, aspiration, and cardiac complications [1,4].

Angiographic therapies include embolization with microcoils (Fig. 180.2), polyvinyl alcohol particles, or gelfoam; and continuous infusion of vasopressin. Embolization can control haemorrhage successfully in 76–100% of patients [4,16,17]. Efficacy of intra-arterial vasopressin ranges from 62–100%, and may be slightly higher for colonic as compared to small bowel lesions [2]. The highest rates of haemorrhage control following angiographic intervention are found with caecal, ileal, and jejunal lesions, and bleeding of diverticular origin. Re-bleeding rates following angio-embolization range from 8–24%, while recurrence rates following vasopressin infusion are higher (40–50%) [2,4,16–18]. Risk factors for recurrent bleeding include post-procedural, post-operative or post-traumatic bleeding, non-diverticular source, multisystem organ failure, co-morbidities, transfusion requirements ≥6 units, shock, and coagulopathy or anticoagulant use. Complications following coil embolization are generally low, ranging from 5–17%, compared to 9–21% with vasopressin (2,4,6,15). Complications following angio-intervention include arrhythmias, myocardial ischaemia, pulmonary oedema, abdominal pain, fevers, access site complications such as pseudo-aneurysm, dissection or haematoma, contrast-induced nephropathy, and allergy. The most feared complication is bowel ischaemia. Fortunately, this is quite rare in most modern series, particularly if using microcoil embolization with super-selective catheterization. Minor and major ischaemic complications occur in 4.5–7% and 0–1.4% of cases, respectively [17,18]. As technology has improved, ischaemic complication rates have decreased, while the popularity of embolization over vasopressin infusion has increased [2]. In patients failing endoscopic management, angiographic

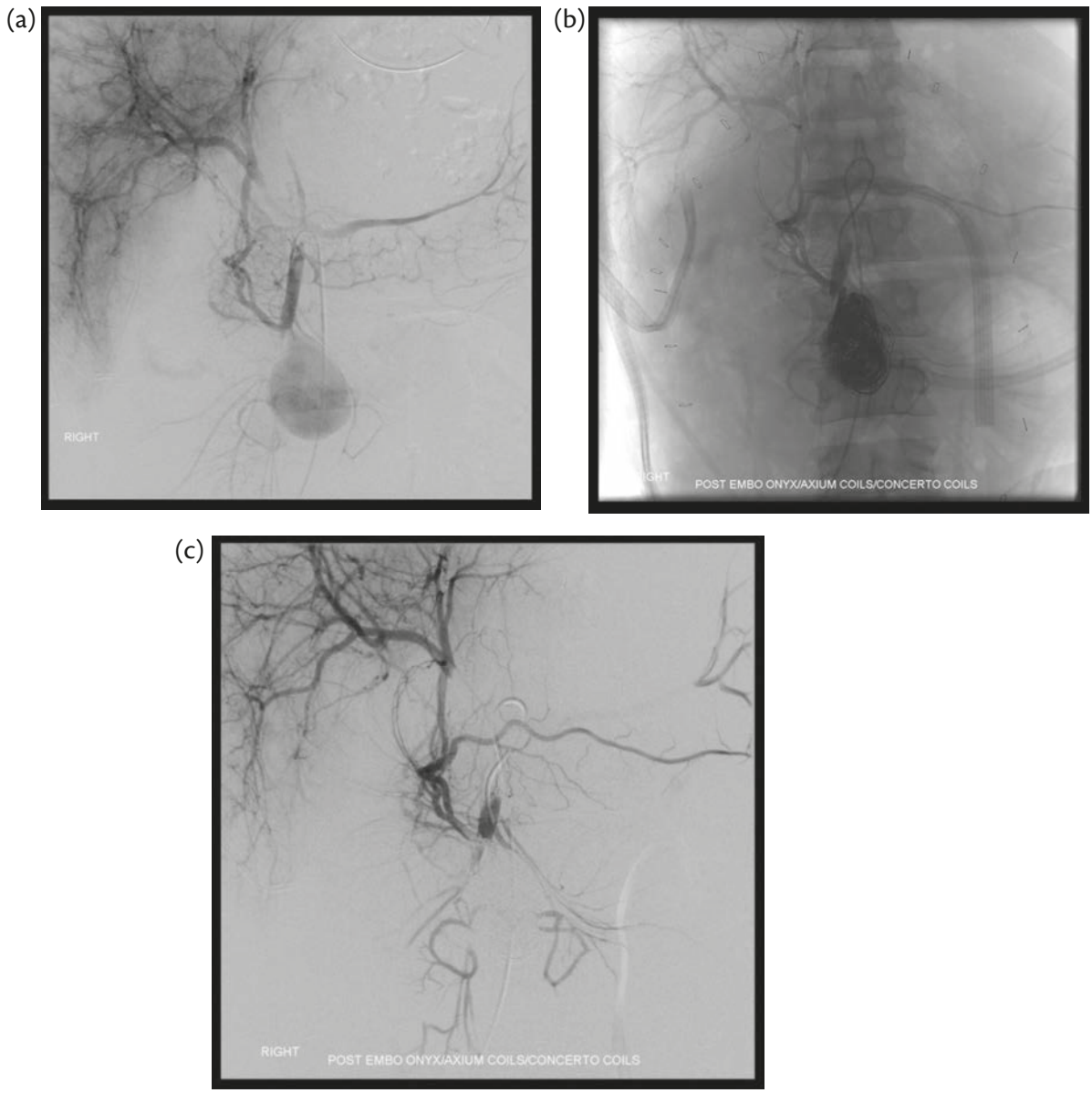


Fig. 180.2 Angiography revealing large proximal superior mesenteric artery pseudo-aneurysm. (a) Before coiling. (b) During coil placement. (c) Post-coiling angiogram with cessation of flow into aneurysm.

treatment appears to be similar to surgery in efficacy and complication rates. It should be considered an adjunct, or alternative to surgical treatment, particularly among high risk patients.

Outcomes following endoscopic and angiographic intervention vary with regard to efficacy and re-bleeding rates. Few trials have directly compared the two diagnostic and therapeutic modalities, though there is some suggestion that endoscopy results in better diagnostic yields, higher percentages of patients amenable to intervention, fewer complications, and shorter lengths of stay [3,4]. These comparisons primarily utilized older angiographic techniques; direct comparison of modern endoscopic interventions to super-selective coil embolization are lacking.

Surgery

The need for operative control of bleeding is decreasing as endoscopic and angiographic intervention improves, dropping from 20–25% to 8–16% [5,15,17]. Indications for surgery include excessive blood transfusion (≥4–10 units), haemodynamic instability, poor response to resuscitation, and failure to control bleeding by other means. Prior to surgery, localization of bleeding is key to success and minimization of risk of recurrence. The rate of re-bleeding is understandably higher with blind resection, up to 42%, compared with 14% following resection with accurate localization with endoscopy or radiographic imaging [2]. Accurate pre-operative localization also allows safer resection, improves rates of haemostasis, and is associated with significant decreases in post-operative morbidity and mortality [2]. If a source of bleeding cannot be localized pre-operatively the bowel can be serially clamped intra-operatively to localize bleeding if successful segmental resection is an option. If not, blind subtotal colectomy is the only therapeutic option. Blind segmental resection should not be performed as its morbidity and mortality is as great or greater than that following blind subtotal colectomy, with higher re-bleeding rates [2]. Excluding recurrent bleeding, the morbidity associated with surgical treatment of LGIB is high, with complications occurring in up to 23% of patients [15]. Overall surgical mortality ranges from 2.9–20% [8,19], but can be significantly increased following blind resection [2].

Outcomes

Morbidity and mortality are particularly high among the elderly who may have additional co-morbidities, poor physiological reserve, and are frequently on medications that worsen or prolong bleeding such as aspirin, NSAIDs, and anticoagulant and antiplatelet agents. LGIB has historically been associated with a lower mortality than UGIB, but results in longer hospitalizations and more resource utilization [20].

Overall morbidity for LGIB ranges from 6.4 to 21%; a recent review of 20 studies found a 26% rate of minor complications and 17% for major complications [4,5,17]. These complications include cardiac (e.g. myocardial infarction, exacerbation of heart failure), pulmonary (e.g. pneumonia, aspiration), abdominal pain, bowel ischaemia, access site (pseudo-aneurysm, dissection, haematoma, thrombosis or embolism), and allergic reaction. Risk factors for morbidity include associated co-morbidities, advanced age, and need for surgical treatment [5].

Mortality rates range from 3.6–25% with most large studies reporting mortality of 3–5% [5,6,8,20,12]. Patients presenting with active bleeding or haemodynamic instability, and those requiring urgent or emergent surgery have the highest risk of dying. Other risk factors include advanced age, intestinal ischaemia, coagulopathy, requirement for blood transfusion, severe co-morbidities, and male gender [5,12].

References

1. Zuckerman GR and Prakash C. (1998). Acute lower intestinal bleeding: part I: clinical presentation and diagnosis. *Gastrointestinal Endoscopy*, **48**, 606–17.
2. Zuckerman GR and Prakash C. (1999). Acute lower intestinal bleeding. Part II: etiology, therapy, and outcomes. *Gastrointestinal Endoscopy*, **49**, 228–38.
3. Strate LL and Syngal S. (2005). Predictors of utilization of early colonoscopy vs. radiography for severe lower intestinal bleeding. *Gastrointestinal Endoscopy*, **61**, 46–52.
4. Strate LL and Naumann CR. (2010). The role of colonoscopy and radiological procedures in the management of acute lower intestinal bleeding. *Clinic in Gastroenterology and Hepatology*, **8**, 333–43
5. Rios A, Montoya MJ, Rodriguez JM, et al. (2007). Severe acute lower gastrointestinal bleeding: risk factors for morbidity and mortality. *Langenbecks Archive Surgery*, **392**, 165–71.
6. Lee J, Costantini TW, and Coimbra R. (2009). Acute lower GI bleeding for the acute care surgeon: current diagnosis and management. *Scandinavian Journal in Surgery*, **98**, 135–42.
7. Lhewa DY and Strate LL. (2012). Pros and cons of colonoscopy in management of acute lower gastrointestinal bleeding. *World Journal in Gastroenterology*, **18**, 1185–90.
8. Garcia-Osogobio S, Remes-Troche JM, Takahashi T, Barreto Camilo J, and Uscanga L. (2002). Surgical treatment of lower digestive tract hemorrhage. Experience at the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran. *Revista de Investigacion Clinica*, **54**, 119–24.
9. Frattaroli FM, Casciani E, Spoletini D, et al. (2009). Prospective study comparing multi-detector row CT and endoscopy in acute gastrointestinal bleeding. *World Journal of Surgery*, **33**, 2209–17.
10. Yoon W, Jeong YY, Shin SS, et al. (2006). Acute massive gastrointestinal bleeding: detection and localization with arterial phase multi-detector row helical CT. *Radiology*, **239**, 160–7.
11. Miller M, Jr and Smith TP. (2005). Angiographic diagnosis and endovascular management of nonvariceal gastrointestinal hemorrhage. *Gastroenterology Clinics of North America*, **34**, 735–52.
12. Strate LL, Ayanian JZ, Kotler G, and Syngal S. (2008). Risk factors for mortality in lower intestinal bleeding. *Clinical Gastroenterology and Hepatology*, **6**, 1004–10.
13. O'Neill BB, Gosnell JE, Lull RJ, et al. (2000). Cinematic nuclear scintigraphy reliably directs surgical intervention for patients with gastrointestinal bleeding. *Archives of Surgery*, **135**, 1076–81.
14. Dell'Abate P, Del Rio P, Soliani P, Sianesi M. (2002). Value and limits of emergency colonoscopy in cases of severe lower gastrointestinal haemorrhage. *Chirurgia italiana*, **54**, 123–6.
15. Arroja B, Cremers I, Ramos R, et al. (2011). Acute lower gastrointestinal bleeding management in Portugal: a multicentric prospective 1-year survey. *European Journal in Gastroenterology and Hepatology*, **23**, 317–22.
16. Kaltenbach T, Watson R, Shah J, et al. (2012). Colonoscopy with clipping is useful in the diagnosis and treatment of diverticular bleeding. *Clinical Gastroenterology and Hepatology*, **10**, 131–7.
17. Koh DC, Luchtefeld MA, Kim DG, et al. (2009). Efficacy of transarterial embolization as definitive treatment in lower gastrointestinal bleeding. *Colorectal Disease*, **11**, 53–9.
18. Kuo WT, Lee DE, Saad WE, Patel N, Sahler LG, Waldman DL. (2003). Superselective microcoil embolization for the treatment of lower gastrointestinal hemorrhage. *Journal of Vascular Interventional Radiology*, **14**, 1503–9.
19. Zhao Y and Encinosa W. (2006). *Hospitalizations for Gastrointestinal Bleeding in 1998 and 2006: Statistical Brief #65*. Rockville, MD: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs.
20. Lanas A, Garcia-Rodriguez LA, Polo-Tomas M, et al. (2009). Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. *American Journal of Gastroenterology*, **104**, 1633–41.

PART 6.4

Disordered gastric motility

CHAPTER 181

Vomiting and large nasogastric aspirates in the critically ill

Tong J. Gan and John T. Lemm

Key points

- A wide range of conditions can cause nausea and vomiting, making it a common occurrence in the critically ill.
- A deeper understanding of the pathophysiology of vomiting has led to the emergence of effective anti-emetics, each targeting a specific neurotransmitter in the emetic pathway.
- Serotonin antagonists are the first line anti-emetic of choice for most cases of nausea and vomiting due to their efficacy and favourable side effect profile.
- Large nasogastric aspirates must be managed aggressively in order to prevent delays in enteral nutrition.
- Management of large gastric aspirates involves gastric drainage, prokinetic agents, and if necessary, post-pyloric feeding.

Introduction

A common manifestation of critical illness is alteration in normal gastric function, ranging from delayed gastric emptying to severe episodes of nausea and vomiting. While seemingly benign, perturbations in gastric function can have severe consequences, including electrolyte disturbances, aspiration, and even vomiting-induced mechanical injury. Furthermore, as the beneficial role of early enteral feeding in the critically ill has become firmly established, effective means of managing altered gastric function are paramount.

Nausea and vomiting

A vast number of conditions are associated with nausea and vomiting, and not surprisingly, these symptoms are common among the critically ill (Table 181.1). Nausea is an unpleasant sensation, perceived prior to the active phases of retching and vomiting. This contrasts with the passive regurgitation of gastric contents that may occur silently, typically has no prodromal symptoms, and can be relieved with a head-up posture. Differentiating between these two processes is crucial, as their pathophysiology and treatments are markedly different.

Pathophysiology

While the act of vomiting is regulated by the brainstem, the pathophysiology of nausea is much less clear. The cerebral cortex appears to process various afferent inputs from lower centres, such as the chemoreceptor trigger zone and the vestibular system, as well as higher centres supplying emotional states, pain, and olfaction into the sensation of nausea. Importantly, nausea is a distinct process that may not always precede vomiting, although it can be as or more distressing than vomiting. The conscious experience of nausea is typically accompanied by autonomically-mediated vasomotor activity.

Recent research demonstrates not one, but several, medullary structures that work in concert to produce the vomiting reflex, defined as the 'central pattern generator for vomiting' [1]. One main afferent limb of this system involves serotonin-releasing enterochromaffin cells of the gastrointestinal tract. The serotonin binds 5-HT_3 receptors activating vagal afferent from the gastrointestinal tract that terminate across the medulla. Another critical afferent input involves the area postrema, a blood–brain barrier free structure that acts as a chemoreceptor zone, sensing stimuli such as drugs or toxins. Additional inputs supplying the medulla include consciously perceived noxious stimuli from the cerebral cortex, the vestibular system, and the cranial nerve-mediated gag reflex. Research into these afferent pathways has elucidated the neurotransmitters responsible for emetic effects and has facilitated the development of anti-emetic agents. Histaminergic H_1 and cholinergic muscarinic M_1 receptors are principally responsible for the vestibular vomiting pathway, while gastrointestinal vagal pathways are predominantly mediated by serotonin 5-HT3 receptors. Other neurotransmitter systems involved include dopaminergic D_2 receptors and neurokinin (NK_1) receptors.

Once a critical threshold of afferent input is reached, the efferent limb of the vomiting reflex is mediated via several brainstem nuclei. Simultaneous contraction of the abdominal wall, diaphragm, and intercostal muscles against a closed glottis result in the act of retching. Vomiting then occurs when the upper oesophageal sphincter relaxes and the pressure gradient from these muscular contractions promotes oral ejection of gastric contents. Post-dromal symptoms include pain, diaphoresis, shivering, and generalized weakness.

Vomiting in the critically-ill patient

Nausea and vomiting are manifestations of a wide range of disease states, and are exceedingly common in the critically ill. Intensivists should not discount emesis as innocuous, as even short periods of vomiting can result in catastrophic injury. Mild complications include emotional distress, increased post-surgical pain and mild dehydration. More severe harm may occur in the form of wound dehiscence, esophageal rupture, severe dehydration, electrolyte

Table 181.1 Conditions associated with nausea and vomiting

Gastrointestinal illness	Non-gastrointestinal illness	Metabolic disorders	Drugs/toxins
Gastroenteritis	Vestibular disorders	Pregnancy	Post-operative nausea and vomiting
GI obstruction	Elevated ICP	Diabetic ketoacidosis	Opiates
Pseudo-obstruction	Intracranial haemorrhage	Uraemia	Antibiotics
Gastroparesis	Migraine headache	Hypercalcaemia	Chemotherapy agents
Intestinal ischaemia	Psychogenic vomiting	Hyponatraemia	Radiation therapy
Peptic ulcer disease	Bulimia	Thyroid disorders	Dopamine agonists
Biliary colic/cholecystitis	Myocardial infarction	Parathyroid disorders	Hypoglycaemics
Appendicitis	Cardiomyopathy	Liver failure	Anti-arrhythmics
Hepatitis	Severe pain	Adrenal insufficiency	Ethanol
Pancreatitis	Cough	Porphyria	Envenomations
Cyclic vomiting syndrome		Acute mountain sickness	Food poisoning
Functional vomiting syndrome			

disturbances and metabolic alkalosis. Perhaps the most devastating of all vomiting complications in the ICU setting is pulmonary aspiration of gastric contents. While any ICU patient may suffer from nausea and vomiting, two patient subsets are at highest risk: the acute post-operative patient, and those with neurological disease.

Post-operative nausea and vomiting

Post-operative nausea and vomiting (PONV) are among the commonest complications following anaesthesia, with an overall incidence estimated at 30%, and up to 80% in high-risk patients. Patient-related risk factors include female gender, non-smokers, and a history of motion sickness or previous PONV. Anaesthesia-related predictors include duration of anaesthesia and administration of nitrous oxide, opiates, and volatile anaesthetics. Surgical procedures such as strabismus correction, ear, nose, and throat, major abdominal, breast, and neurosurgery are all associated with higher rates of PONV. In addition to the risk of physical harm imposed by PONV, its associated emotional distress should not be discounted. Post-surgical patients have stated that they would spend up to $100 USD to avoid PONV [2].

Management of PONV begins with pre-operative risk-stratification and associated levels of escalating anti-emetic prophylaxis. The intensivist should have a thorough understanding of this strategy and identify the exact anti-emetics administered intra-operatively. Repeating an anti-emetic from the same class within 6 hours is a common, expensive, and ineffective method of PONV treatment in the ICU setting; other classes of anti-emetics should be supplemented instead. Finally, heightened awareness of pulmonary aspiration is necessary due to impaired levels of consciousness commonly found in post-operative patients.

Vomiting in neurological disease

Neurological disease represents another common aetiology of nausea and vomiting in the ICU setting. Subarachnoid haemorrhage, migraine headache, vestibular disease, and conditions that raise intracranial pressure (ICP) are associated with an incidence of vomiting as high as 80%. Prompt treatment is paramount in this setting, as protracted vomiting can further raise ICP and exacerbate the pathology. Furthermore, vomiting in this setting is another risk factor for pulmonary aspiration, as such patients commonly have impaired levels of consciousness [3].

Management of nausea and vomiting

Proper management of nausea and vomiting should begin, if possible, with preventative measures. Nausea can be a harbinger of vomiting and should be aggressively treated with anti-emetics to prevent the complications of vomiting. A differential diagnosis as to the aetiology of vomiting is necessary; surgically correctable causes must be identified and dealt with early.

Clinicians now have an array of anti-emetic choices at their disposal. While many patients readily respond to one drug class, a more effective strategy will require multi-modal techniques. The astute intensivist requires knowledge of each anti-emetic class type, as well as their benefits and drawbacks. The patient may still require management of dehydration and electrolyte disturbances. Basic chemistry panels will guide electrolyte supplementation, while dehydration is typically managed with balanced crystalloid infusions.

Serotonin antagonists

With availability of generic ondansetron, the 5-HT_3 receptor antagonists have become a mainstay in anti-emetic therapy due to their effectiveness and favourable side-effect profile. Exerting their effects at both serotonin receptors in the gastrointestinal tract and brain they are particularly effective treatments for chemotherapy-induced nausea and vomiting (CINV) and PONV. While ondansetron is the most widely available, dolasetron, granisetron, and palonosetron all have similar efficacy. Palonosetron, with a half-life of nearly 40 hours is of particular use in preventing delayed nausea and vomiting seen after chemotherapy. Contrary to common belief, 5-HT_3 antagonists have very similar efficacy compared with dexamethasone and droperidol. The widespread use of serotonin antagonists as a first-line anti-emetic stems from their relatively positive side-effect profile compared with these other agents [4,5].

Dopamine-D_2 antagonists

Dopamine antagonists have established anti-emetic efficacy and are readily available in most settings. The three main classes of dopamine

antagonists include prokinetics such as metoclopramide, phenothiazines, and the butyrophenone droperidol, all of which are believed to act on the chemoreceptor trigger zone. Regardless of class, all dopamine antagonists can cause anti-serotonergic and extrapyramidal side-effects at high doses. Metoclopramide mediates its anti-emetic effect through prokinetic activity in addition to dopamine receptor antagonism. A 10-mg intravenous dose is typically used for management of vomiting, however, while this dose is effective in emptying the stomach, it has weak anti-emetic properties. Higher doses may possess greater anti-emetic properties, but at the expense of extrapyramidal side-effects. Alternative D_2 antagonists that also act on histamine and cholinergic receptors include phenothiazines, e.g. promethazine and prochlorperazine. Lower doses have adequate anti-emetic properties (promethazine 6.25 mg; prochlorperazine 10 mg), while higher doses increase the risk of sedation.

Droperidol is a highly effective anti-emetic that has fallen out of favour due to a somewhat controversial FDA black box warning regarding its QTc prolongation effects. Droperidol increases QTc, in a dose-dependent manner. Doses from 0.625 to 1.25 mg possess anti-emetic effects. At this low dose, QTc rose on average only 15-msec, smaller than the 20-msec rise associated with 4 mg of ondansetron [4]. All controversy aside, the ICU setting provides a suitable environment for the 2–3 hours of continuous ECG monitoring recommended by the FDA after droperidol administration, although it should be avoided in patients with a history of QTc prolongation or torsade de pointes.

Antihistamines

Histamine antagonists mediate their anti-emetic effect primarily via blocking the vestibular vomiting pathways, making them particularly suited for motion sickness or patients with vestibular dysfunction. Diphenhydramine and dimenhydrinate are effective anti-emetics, but commonly lead to drowsiness. The sedative side-effects of the antihistamine class must be considered before administration to patients with already altered levels of consciousness.

Anticholinergics

Hyoscine is an effective anti-emetic typically administered via a transdermal patch to prolong its duration of action. Like the antihistamine class, it mediates its effects primarily through the vestibular pathways. Commonly used to prevent PONV, the patch is applied pre-operatively and provides up to 72 hours of anti-emetic coverage. Side-effects include sedation, blurred vision, and dry mouth, and elderly patients are at higher risk of anti-cholinergic mediated agitation. A recent meta-analysis did not show an increased risk of the various anticholinergic side effects when used in the peri-operative setting, other than visual disturbances [6].

Dexamethasone

Dexamethasone is another effective anti-emetic. However, given its slower onset of action, it is much better when administered as a prophylactic agent. While many providers use anti-emetic doses upwards of 10 mg, doses as low as 4 mg are as effective, with a duration of 24 hours [7]. Caution must be applied when administering dexamethasone to diabetics or patients with head injury as it may precipitate a rise in serum glucose levels [8]. Another potential complication includes immunosuppression, although this has not been reported with a single anti-emetic dose.

Neurokinin antagonists

While other classes of anti-emetics have targeted the afferent vomiting pathways, the neurokinin antagonists represent a breakthrough in targeting efferent pathways. Neurokinin-1 (NK1) has long been known to elicit emetic activity, but only recently have selective NK1 receptor antagonists come to fruition. Aprepitant and its intravenous form, fosaprepitant, are currently the only available drugs in this class, with several others under development. Their relatively long half-life makes them excellent preventative agents for CINV and PONV. When 4 mg ondansetron was compared with 40 and 125 mg of aprepitant for PONV prevention, the incidences of vomiting were 26, 10, and 5%, respectively [9].

Large nasogastric aspirates

Critical illness commonly impairs gastric motility and leads to intolerances or delays in enteral feeding. Gastric aspirates, otherwise known as gastric residual volumes (GRV), have become the default measurement in which to assess tolerance to enteral feeding, yet practice varies widely. As a consequence, GRV cut-offs ranging from 150 to 500 mL are commonly used to define tolerance of enteral nutrition [10]. While numerous complications stemming from large gastric residual volumes have been postulated, the greatest threat to the patient is interruption in enteral feeding. A recent meta-analysis demonstrates reduced mortality when enteral nutrition is provided within the first 24 hours of ICU admission, while another study found an association with increased ventilator-free ICU days [11,12]. A thorough appreciation of excessive GRV and its management are therefore critical to prevent delayed enteral nutrition in the critically ill [13].

Pathophysiology

Gastrointestinal motility is the result of orchestration between the enteric nervous system, enteric endocrine cells, and gastrointestinal smooth muscle. The central nervous and systemic endocrine systems then provide additional modulation, and as in nausea and vomiting, wide arrays of neurotransmitter systems are responsible for coordination of this activity [14]. The final result is a co-ordinated process by which gastrointestinal smooth muscle relaxes in order to accept food, then contracts to propel it further along the tract. The stomach relies on this complex pattern of relaxation and contraction, not only to propel food, but also to grind solids before they pass into the small intestine. Stomach motility is exquisitely sensitive to perturbations induced during critical illness, and drugs such as opioids, sedatives, and vasopressors may amplify these disturbances. Traumatic brain injury is another common cause of gastric retention and has proven especially resistant to conservative management with prokinetic agents. Fortunately, post-pyloric feeding is generally tolerated by the critically ill, and represents a simple means of managing gastric dysmotility.

Complications

Intensivists have long known that large gastric residual volumes are not innocuous, yet until recently, aspiration pneumonia was

believed to be the most severe side-effect of gastrointestinal dysmotility. Recent studies do not support this belief and, indeed, show no difference in pneumonia rates between liberal and conservative GRV thresholds [15]. Interruptions in enteral feeding represent a much greater threat. Minor complications from large GRV include gastric dilatation, nausea and vomiting, and electrolyte disturbances. Acute gastric dilatation is a manifestation of large GRV and is associated with patient discomfort. Acid-base status and electrolyte panels should be monitored as hypochloraemic alkalosis commonly occurs with chronic loss of large nasogastric aspirates.

Management

Reversible causes of dysmotility should be sought and corrected. Medications with known anti-motility side-effects, such as opioids and anticholinergics, should be avoided. Inadequate pain control can be effectively managed with non-opioid analgesics, while suspected gastrointestinal obstruction warrants a surgical consult. When reversible causes have been addressed, gastric dysmotility should be managed with a combination of drainage, prokinetic agents, and post-pyloric feeding.

Gastric drainage

Symptomatic gastric dilatation requires drainage, either intermittent or continuous in severe cases. More protracted episodes require crystalloid solutions and electrolyte supplementation to replace the volumes drained.

Prokinetic agents

Metoclopramide is a dopamine antagonist that has prokinetic properties primarily in the upper gastrointestinal tract. An intravenous regimen of 10 mg every 6 hours improves antropyloroduodenal co-ordination, although demonstrating benefit in critically-ill patients has been modest at best [16]. High-dose erythromycin (100–200 mg tid) is another agent that augments gastric motility and has a synergistic effect when prescribed alongside metoclopramide. Recent concerns over bacterial resistance and cardiac arrhythmias have limited its widespread use.

Post-pyloric feeding

Patients that fail conservative management strategies, or those perceived to be at high risk for gastric dysmotility, require post-pyloric feeding, either via nasogastric tube or jejunostomy. Fine-bore, 8 Fr soft nasogastric tubes with wire stylets are the most commonly used for this purpose. For post-pyloric placement, a tube length of at least 100 cm is optimal. Successful placement is most readily achieved using fluoroscopy, either at the bedside or in interventional radiology suites. Magnetically-guided systems (e.g. Cortrak) are gaining popularity as they show promise to speed placement and minimize radiation exposure. Blind placement should be avoided if fluoroscopy or magnetically-guided placement is available, as success rates are low. Prokinetic agents, such as metoclopramide may assist blind passage across the pylorus, but radiographic confirmation should always precede commencement of feeding if blind techniques are used. For patients that fail nasogastric feeding tube placement, or who require chronic, post-pyloric feeding, a surgically-placed jejunostomy is required.

References

1. Diemunsch P, Joshi GP, and Brichant JF. (2009). Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting. *British Journal of Anaesthesia*, **103**, 7–13.
2. Gan TJ, Sloan F, de L Dear G, El-Moalem HE, and Lubarsky DA. (2001). How much are patients willing to pay to avoid postoperative nausea and vomiting? *Anesthesia and Analgesia*, **92**, 393–400.
3. Fontanarosa PB. (1989). Recognition of subarachnoid hemorrhage. *Annals of Emergency Medicine*, **18**, 1199–205.
4. White PF, Song D, Abrao J, Klein KW, and Navarette B. (2005). Effect of low-dose droperidol on the QT interval during and after general anesthesia: a placebo-controlled study. *Anesthesiology*, **102**, 1101–5.
5. Apfel CC, Korttila K, Abdalla M, et al. (2004). A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *New England Journal of Medicine*, **350**, 2441–51.
6. Apfel CC, Zhang K, George E, et al. (2010). Transdermal scopolamine for the prevention of postoperative nausea and vomiting: a systematic review and meta-analysis. *Clinical Therapy*, **32**, 1987–2002.
7. Wang J-J, Ho S-T, Tzeng J-I, and Tang C-S. (2000). The effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting. *Anesthesia and Analgesia*, **91**, 136–9.
8. Hans P, Vanthuyne A, Dewandre PY, Brichant JF, and Bonhomme V. (2006). Blood glucose concentration profile after 10 mg dexamethasone in non-diabetic and type 2 diabetic patients undergoing abdominal surgery. *British Journal of Anaesthesia*, **97**, 164–70.
9. Gan TJ, Apfel CC, Kovac A, et al. (2007). A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting. *Anesthesia and Analgesia*, **104**, 1082–9.
10. Ridley EJ and Davies AR. (2011). Practicalities of nutrition support in the intensive care unit: the usefulness of gastric residual volume and prokinetic agents with enteral nutrition. *Nutrition*, **27**, 509–12.
11. Doig G, Heighes P, Simpson F, Sweetman E, and Davies A. (2009). Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. *Intensive Care Medicine*, **35**, 2018–27.
12. Alberda C, Gramlich L, Jones N, et al. (2009). The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Medicine*, **35**, 1728–37.
13. Martindale RG, McClave SA, Vanek VW, et al. (2009). Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: Executive Summary. *Critical Care Medicine*, **37**, 1757–61.
14. Herbert MK and Holzer P. (2008). Standardized concept for the treatment of gastrointestinal dysmotility in critically ill patients—current status and future options. *Clinical Nutrition*, **27**, 25–41.
15. McClave SA, Lukan JK, Stefater JA, et al. (2005). Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. *Critical Care Medicine*, **33**, 324–30.
16. Jooste CA, Mustoe J, and Collee G. (1999). Metoclopramide improves gastric motility in critically ill patients. *Intensive Care Medicine*, **25**, 464–8.

CHAPTER 182

Ileus and obstruction in the critically ill

Philip Stevens and Paul Dark

Key points

- Obstruction is the commonest cause of acute intestinal failure in critical care.
- Management is dependent upon whether the obstruction is adynamic (paralytic) or mechanical in origin.
- Mechanical obstruction is more likely to require surgery and must be presumed present until actively excluded.
- Seventy per cent of post-operative small bowel mechanical obstruction is adhesional and likely to settle within 7 days of conservative management.
- Nutritional support should be considered when acute intestinal failure lasts >5 days.

Introduction

Intestinal obstruction results either from physical blockage (mechanical obstruction) or failure of propulsive motor activity (adynamic obstruction), the latter being synonymous with 'ileus' in common usage. Together, these represent the most frequent cause of acute intestinal failure in critical care that, in turn, may be either a consequence of, or a driver for, multiple organ dysfunction. Levels of evidence are graded according to definitions of the Oxford Centre for Evidence-based Medicine [1].

Physiology of gastrointestinal motility

Gut activity is controlled by the enteric nervous system and co-ordinated by autonomic innervation, hormonal, and chemical mediators. Specialized smooth muscle cells generate slow-wave electrical rhythmicity with decreasing frequency from duodenum to ileum. In the fasted state, mechanical activity is characterized by periods of phasic contractions known as Phase 3 of the migrating motor complex (MMC). This housekeeping activity clears debris from the small intestine. Loss of Phase 3 contractions is associated with the development of bacterial overgrowth and feed intolerance.

In the fed state, contractile activity results in segmentation that enhances mixing. Short segments of peristalsis allow aboral movement of food, the rate of which is regulated by humoral feedback mechanisms such that, within 1–2 hours, meals are cleared from the small intestine. Less is known about colonic contraction, which largely produces segmentation with mass movements up to three times a day resulting in transport of waste material [2].

Ileus

Epidemiology and aetiology

Clinically significant loss of small bowel motility is often a transient event secondary to abdominal surgery. It occurs in up to 15% of intestinal resections [3]. Other causes of paralytic ileus or pseudo-obstruction are less common (Table 182.1).

Pathogenesis

Sympathetic tone and inflammatory mediators (TNF-α, IL-1ß, IL-6, prostaglandins, nitric oxide) have an enterostatic effect. This is exacerbated by pharmacological effects, such as stimulation of peripheral μ-opioid receptors (PAMORs). Clinical features depend on the region of bowel affected. Gastroparesis or pyloric dysfunction results in vomiting or failure to tolerate nasogastric feed. Small bowel ileus is associated with varying degrees of feed intolerance or abdominal distension. Colonic pseudo-obstruction results in cessation of bowel movements or flatus. Consequences of ileus include acute intestinal failure, resulting in failure of substrate supply during the increased demand of catabolism, and intestinal ischaemia with evidence suggestive of bacterial translocation or perforation.

Management of ileus

Adynamic obstruction is managed conservatively with correction of any electrolyte disturbance, nutritional support, and minimization of enterostatic drug use. Rarely, surgical decompression may be necessary if ileus arises in the context of abdominal compartment syndrome. The pattern of recovery depends upon the segment of bowel involved, with small bowel recovering more quickly than stomach or colon. Return of colonic motility, however, seems to be a key factor in the clinical resolution of ileus [4].

Pharmacological management of ileus has largely focused on stimulation of motility by reduction of sympathetic tone. Prokinetic agents (e.g. metoclopramide, tegaserod, erythromycin, atilmotin) have not been shown to reduce ileus in clinical trials. Anti-inflammatory effects of cyclo-oxygenase-2 inhibitors have shown promise in the prevention of post-operative ileus, although their use in critical illness may be limited by microcirculatory disturbances and renal dysfunction. Anticholinesterase inhibitors (e.g. edrophonium, bethanechol) have been reported to be effective, but trials are lacking and clinical application is limited by cholinergic side effects [5]. Endoscopic pacing has only been described to date in animal models.

Table 182.1 Causes of acute intestinal failure

Cause	Mechanism	Examples
Adynamic (Ileus)	Acquired	Post-abdominal surgery
	Neurogenic	Spinal or head injury/hip fracture
	Inflammatory/infective:	Chagas' disease
	◆ Intestinal	Post-operative scleroderma
	◆ Intraperitoneal	Abscess/peritonitis
	◆ Retroperitoneal	Pancreatitis/malignant infiltration (Ogilvie's)
	◆ Systemic	SIRS/MODS/shock/myocardial infarction/stroke
	Infiltrative	Amyloidosis
	Pharmacological	Anticholinergics
	Metabolic	Opiates
	Over distension	Calcium channel blockers
	Congenital	Ganglion blockers
	Myopathic or neuropathic	Hypokalaemia/hypomagnesaemia
		Hypoxia/uraemia/diabetes/myxoedema
		Advanced mechanical obstruction
		Chronic intestinal pseudo-obstruction
		MELAS, MMIHS, MNGIE
Mechanical (obstruction)	Intraluminal	Gallstone ileus, foreign body
	Intramural	Tumour/intussuscepting polyp
	Extramural	Adhesions/hernia/extrinsic compression
Mucosal disease	Primary defects of absorption	Infective enteritis
		Inflammatory bowel disease
		Radiotherapy/chemotherapy

MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MMIHS, megacystis microcolon intestinal hypoperistalsis syndrome; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; MODS, multiple organ dysfunction syndrome.

Cisapride, a 5-HT4 receptor antagonist, promotes post-ganglionic acetylcholine release in the myenteric plexus, increasing the number and amplitude of duodenal contractions post-prandially. However, widespread clinical application has been limited by concerns regarding cardiovascular toxicity. Consequently, its application is largely restricted to post-operative ileus and feed intolerance in children with short bowel syndrome (**level 4**) [6].

Opioid effects on gastrointestinal motility are well documented. The balance between analgesic suppression of sympathetic activity and direct inhibition of gastrointestinal motility has been the focus of much interest in enhanced recovery programmes. Regional infiltration of local anaesthetics reduces demand for systemic opioids and PAMOR antagonists mitigate opioid-induced enterostasis. However, evidence to date for these agents has been from trials in chronic degenerative illnesses (methylnaltrexone) [7], or post-operative ileus (alvimopan) [8] (**level 1b**). Data on their utility in critical illness are lacking.

Neostigmine is an anticholinesterase inhibitor that promotes parasympathetic tone in the gut wall. Cholinergic side effects, including bradycardia, vomiting, excessive salivation and abdominal cramps, may be mitigated by glycopyrronium bromide or atropine. Epidural neostigmine has reduced time to restoration of bowel function in elective abdominal aortic surgery (**level 1b**) [9], and is moderately effective in relieving acute colonic pseudo-obstruction in critical illness (**level 1b**) [10]. However, its usefulness in small bowel ileus is less clear. Pyridostigmine is a similar drug that may prevent recurrent pseudo-obstruction (**level 4**) [11], although its efficacy in critically-ill patients is unknown.

Colonoscopic decompression may be required when conservative management fails. However, repeated procedures may be necessary with a 2% risk of perforation each time (**level 4**) [12]. Recurrence may be less likely with the osmotic laxative, polyethylene glycol, although data are limited (**level 1b**) [13]. As a stimulant laxative, bisacodyl has potential for maintenance use but, again, clinical evidence is lacking.

Obstruction

Definition

Mechanical obstruction indicates occlusion of the lumen in a normally motile segment of bowel. It may be complete or incomplete (i.e. allowing passage of minimal volume with proximal distension; also known as **subacute** obstruction), and simple or strangulated (depending on whether the obstructed segment has compromised perfusion). A closed-loop obstruction occurs when the obstructed loop has no proximal means of decompression, such as an obstructed hernia or colon with a competent ileocaecal valve. Closed-loops are more likely to progress to perforation if untreated.

Epidemiology

Up to 10% of patients undergoing abdominal surgery will develop significant post-operative mechanical obstruction [14]. Post-operative small bowel obstruction is most likely to occur following open abdominal surgery in the infracolic compartment, especially colectomy or ileo-anal pouch surgery, or emergency surgery, particularly following perforated appendicitis [15]. In contrast, small bowel obstruction is less common following laparoscopic surgery [16]. Nevertheless, mechanical obstruction is more likely than ileus following laparoscopic surgery, in which a low threshold for re-operation should be maintained [17].

Aetiology

Eighty per cent of mechanical obstruction occurs in the small bowel, most commonly by adhesions, hernias or intra-abdominal neoplasia (in descending order). Large bowel obstruction is more commonly due to tumours, diverticular stricture or volvulus (in the case of the caecum and sigmoid colon). Causes of mechanical obstruction can be classified according to their origin in relation to the bowel wall as intra-luminal, intra-mural, or extra-mural.

Pathogenesis

Stretch receptors stimulate the intestine-intestinal reflex, via extrinsic nerves, such that distension results in reflex relaxation of distal bowel and stimulation of increased contractions proximally. In the presence of static mechanical obstruction, this increases peristalsis resulting in colicky abdominal pain. As intraluminal pressure increases the bowel distends, increasing transmural tension and compressing the vasculature. If the obstruction is not overcome, the proximal bowel is eventually overridden by inhibition of

motor activity. Strangulation occurs if reflex relaxation occurs after ischaemic injury is established, or if mesenteric blood flow is interrupted by direct vascular occlusion as with volvulus, intussusception or hernia sac entrapment. Uncorrected, ischaemia leads to loss of mucosal barrier function and the potential for bacterial translocation or necrosis with perforation, resulting in sepsis.

Symptoms

These vary from predominant vomiting to painful distension depending on whether the level of obstruction is high or low (i.e. proximal or distal bowel). Initially, vomiting is typical of gastric or upper small bowel involvement. Stagnation and bacterial overgrowth occur later in obstruction, resulting in effortless feculent vomiting. Failure to pass flatus or faeces is a hallmark of complete obstruction and occurs earlier with more distal obstruction.

The hallmark of obstruction is colicky pain, characterized by an inability to settle in a position of minimal pain, in contrast to the peritonitic patient, who lies still to minimize pain. Signs of peritonitis in the presence of obstruction indicate late presentation with possible perforation or necrosis of the underlying bowel. However, these features may be absent in sedated patients so clinical suspicion should remain high in critically-ill patients intolerant of enteral feeding.

Management

Urgent operative resolution is important if there are signs of peritonitis, severe sepsis, strangulation, or a closed-loop obstruction. Complete large bowel obstruction with caecal tenderness or volvulus also requires prompt operative correction due to the risk of imminent perforation. However, 70% of post-operative small bowel obstruction is due to adhesions and will usually settle with nasogastric drainage and nutritional support, usually via a peripheral cannula or percutaneously inserted central catheter (PICC line). Obstruction after laparoscopic surgery, on the other hand, is much more commonly the result of port-site herniation (**level 4**) [16]; early laparotomy should be considered in order to avoid strangulated obstruction.

Patients who settle with conservative management tend to do so within seven days (**level 4**) [14]. The risk of strangulation within this time is negligible in the absence of closed-loop obstruction and severe sepsis (**level 3a**) [15]. Re-operation for those who do not settle becomes particularly hazardous as, within 10–14 days of surgery, obliterative peritonitis may convert the peritoneal cavity into an impenetrable fused block, precluding safe dissection. Early surgical involvement is therefore essential. When indicated, re-operation for obstruction should be performed by a senior, experienced surgeon. Great care is necessary to avoid inadvertent intestinal injury and creation of gastrointestinal fistulae (**level 2b**) [18].

Differentiating a dynamic from mechanical obstruction

In comparison with mechanical obstruction, pain is not a significant feature of adynamic obstruction. However, it can be difficult to differentiate between them in the sedated, post-operative or spinally-injured critically-ill patient. Deep sedation, neuromuscular blockade, and steroid therapy can all contribute to masking clinical signs. Hyper-echoic bowel sounds may be absent in long-standing mechanical obstruction. More subtle clinical features, such as intolerance of tube feeding, or alteration of bowel or stoma output, may be the first signals of impending serious intra-abdominal pathology.

Plain abdominal radiography may be helpful with identifying sigmoid or caecal volvulus, hernial obstruction, foreign body ingestion, or gallstone ileus. However, sensitivity is limited by the possible failure to identify fluid-filled, distended loops. Urgent surgical opinion is recommended where clinical suspicion remains. Erect abdominal radiography has been superseded by contrast-enhanced studies. Water-soluble contrast may be both diagnostic and therapeutic as hyperosmolar gastrografin stimulates peristalsis. Plain films demonstrating passage of contrast into the large bowel within 2 hours effectively excludes small bowel ileus. Contrast enemas can also rule out distal obstruction in colonic pseudo-obstruction. Double contrast CT scans will identify 95% of obstructions, delineate the level and cause of obstruction, and provide information regarding bowel viability. Critically-ill patients must be stable for transfer. When doubt remains despite imaging, an exploratory laparotomy may be necessary.

Nutritional support

A pragmatic definition of acute intestinal failure applicable to the bedside is an inability to tolerate 80% of estimated nutritional requirements delivered enterally for a minimum of 48 hours [19]. Intolerance of enteral feeding expected to last ≥5 days is generally seen as an indication for parenteral nutrition, although controversy exists over the ideal timing of its introduction in critically-ill patients [20].

Conclusion

In general, if a patient has obstructive symptoms, a surgical opinion is essential to assist in consideration of the underlying cause and the realistic chances of resolution. Decide early if further investigation is required—look for and treat correctable systemic factors. Regardless of cause, consider whether nutritional support is required until resolution of acute intestinal failure is achieved.

References

1. Howick JP, Phillps B, Ball C, et al. (2012). *Oxford Centre for Evidence-based Medicine: Levels of Evidence*. Oxford: CEBM. Available at: http://www.cebm.net/index.aspx?o=1025 (accessed 29 March 2012).
2. Weisbrodt NW. (2007). Motility of the large intestine. In: Johnson LR (ed.) *Gastrointestinal Physiology*, pp. 49–56. Philadelphia: Mosby Elsevier.
3. Wolff BG, Viscusi ER, Delaney CP, Du W, and Techner L. (2007). Patterns of gastrointestinal recovery after bowel resection and total abdominal hysterectomy: pooled results from the placebo arms of alvimopan phase III North American clinical trials. *Journal of the American College of Surgery*, **205**, 43–51.
4. Behm B and Stollman N. (2003). Post-operative ileus: etiologies and interventions. *Clinical Gastroenterology and Hepatology*, **1**, 71–80.
5. Lewis TD, Daniel EE, Sarna SK, Waterfall WE, and Marzio L. (1978). Idiopathic intestinal pseudoobstruction. Report of a case, with intraluminal studies of mechanical and electrical activity, and response to drugs. *Gastroenterology*, **74**, 107–11.
6. Raphael BP, Nurko S, Jiang H, et al. (2011). Cisapride improves enteral tolerance in pediatric short-bowel syndrome with dysmotility. *Journal of Pediatric Gastroenterology and Nutrition*, **52**, 590–4.

7. Yuan CS, Wei G, Foss JF, O'Connor M, Karrison T, and Osinski J. (2002). Effects of subcutaneous methylnaltrexone on morphine-induced peripherally mediated side effects: a double-blind randomized placebo-controlled trial. *Journal of Pharmacology and Experimental Therapy*, **300**, 118–23.
8. Delaney CP, Weese JL, Hyman NH, et al., for the Alvimopan Postoperative Ileus Study Group (2005). Phase III trial of alvimopan, a novel, peripherally acting, mu opioid antagonist, for postoperative ileus after major abdominal surgery. *Diseases of the Colon and Rectum*, **48**, 1114–25.
9. Caliskan E, Turkoz A, Sener M, Bozdogan N, Gulcan O, and Turkoz R. (2008). A prospective randomized double-blind study to determine the effect of thoracic epidural neostigmine on postoperative ileus after abdominal aortic surgery. *Anesthesia and Analgesia*, **106**, 959–64.
10. van der Spoel JI, Oudemans-van Straaten HM, Stoutenbeek CP, Bosman RJ, and Zandstra DF. (2001). Neostigmine resolves critical illness-related colonic ileus in intensive care patients with multiple organ failure—a prospective, double-blind, placebo-controlled trial. *Intensive Care Medicine*, **27**, 822–7.
11. O'Dea CJ, Brookes SJH, and Wattchow DA. (2009). The efficacy of treatment of patients with severe constipation or recurrent pseudo-obstruction with pyridostigmine. *Colorectal Diseases*, **12**, 540–8.
12. Geller A, Petersen BT, and Gostout CJ. (1996). Endoscopic decompression for acute colonic pseudo-obstruction. *Gastrointestinal Endoscopy*, **44**, 144–50.
13. Sgouros SN, Vlachogiannakos J, Vassiliadis K, et al. (2006). Effect of polyethylene glycol electrolyte balanced solution on patients with acute colonic pseudo obstruction after resolution of colonic dilation: a prospective, randomised, placebo controlled trial. *Gut*, **55**, 638–42.
14. Ellozy SH, Harris MT, Bauer JJ, Gorfine SR, and Kreel I. (2002). Early postoperative small-bowel obstruction: a prospective evaluation in 242 consecutive abdominal operations. *Diseases of the Colon and Rectum*, **45**, 1214–17.
15. Sajja SBS and Schein M. (2004). Early post-operative small bowel obstruction. *British Journal of Surgery*, **91**, 683–91.
16. Duron JJ, Hay JM, Msika S, et al. (2000). Prevalence and mechanisms of small intestinal obstruction following laparoscopic abdominal surgery: a retrospective multicenter study. *Archives of Surgery*, **135**, 208–12.
17. Augestad KM and Delaney CP. (2010). Postoperative ileus: impact of pharmacological treatment, laparoscopic surgery and enhanced recovery pathways. *World Journal of Gastroenterology*, **16**, 2067–74.
18. Van der Krabben AA, Dijkstra FR, Nieuwenhuijzen J, Reijnen MM, Schaapveld M, and Van Goor H. (2000). Morbidity and mortality of inadvertant enterotomy during adhesiotomy. *British Journal of Surgery*, **87**, 461–71.
19. Gatt M and MacFie J. (2010). Randomised clinical trial of gut-specific nutrients in critically ill surgical patients. *British Journal of Surgery*, **97**, 1629–36.
20. Casaer MP, Mesotten D, Hermans G, et al. (2011). Early versus late parenteral nutrition in critically ill adults. *New England Journal of Medicine*, **365**, 506–17.

CHAPTER 183

Diarrhoea and constipation in the critically ill

Geoffrey J. Dobb

Key points

- All except short-term intensive care unit patients should have a bowel management plan.
- Severe diarrhoea can rapidly induce dehydration and electrolyte imbalance with significant mortality, especially in infants, debilitated or malnourished children and adults, and in developing countries.
- *Clostridium difficile* is now the most cause of infectious diarrhoea in hospitals in Europe and North America.
- Constipation is very common in patients needing intensive care.
- Faecal impaction can complicate any form of constipation and must be excluded by rectal examination.

Introduction

Disordered gastrointestinal function is common in the critically ill. Diarrhoea and constipation both have major adverse effects on patient comfort and dignity. Both also have secondary effects that may impact on outcomes. Normal stool consistency can be defined as type 3 or 4 on the Bristol stool form scale [1]. All except short-term intensive care unit (ICU) patients should have a bowel management plan though, in practice, these are used less often than other ICU process of care plans [2]. When used, they appear to reduce the frequency of diarrhoea and constipation [3].

Diarrhoea

Diarrhoea is an increase in the frequency, quantity, and liquidity of faeces. The circumstances of intensive care make quantitative definitions based on weight or volume of stool hard to implement, and the process of measurement has implications for infection control when the cause is unknown. More pragmatically, diarrhoea is often defined as passage of ≥3 liquid stools in a day.

Diarrhoea can be the predominant symptom of severe systemic illness, especially in infants, but is also a common complication of hospital-acquired infection or drug treatments. Depending on definition used and setting, the reported frequency is 40–90% [4]. While most diarrhoea episodes do not have an infectious cause, the potential severity and infection control implications of infectious diarrhoea are increasingly recognized as important issues for the critically ill.

Pathophysiology

Approximately 1500 mL of liquid intestinal content reach the caecum each day, but only 100–200 mL water is normally lost in faeces. The colon can absorb up to 4500 mL water a day. Increased water loss with diarrhoea occurs if the fluid volume entering the caecum exceeds the maximum absorption capacity of the colon, if colonic absorption is impaired, or there is net loss of water into the colon.

Absorption of water in the colon is closely linked to electrolyte absorption. Energy-dependent active transport of electrolytes across the colonic mucosa draws water into the extracellular space. The colon can transport water against an osmolar gradient of up to 50 mOsmol/L, unlike the ileum where absorbed electrolytes are accompanied by iso-osmolar amounts of water. Water absorption is greater in the ascending colon than descending colon or rectum.

Rapid colonic transit times through the proximal colon, associated for example with some neuro-endocrine tumours or carcinoid, limit the potential for water absorption and cause diarrhoea.

Normal intestinal secretion, absorption and motility are maintained by highly complex interactions of >30 hormones and hormone-like peptides, plus sympathetic and parasympathetic nervous systems. Secretion and activity are altered during critical illness; in addition, many inflammatory mediators released during sepsis and other inflammatory syndromes affect gut function. In animal studies, pro-inflammatory cytokines are secreted into the gut lumen during endotoxaemia [5].

Other non-infectious factors contributing to diarrhoea include splanchnic vasoconstriction as a physiological response to hypotension or exogenous vasoconstriction (e.g. noradrenaline, vasopressin) with reduced supply of energy substrates needed for reabsorption of salt and water, reduced enteral feeding (the colonic mucosa normally receives 60–70% of energy needs from the gut lumen), altered gut flora as a result of proton pump inhibitors or H_2 antagonists allowing colonization of the upper gastrointestinal tract or antibiotic use, and reduced bile acid re-absorption, increasing the amount reaching the colon and causing water and electrolyte secretion. Hypoalbuminaemia is common in the critically ill and has been associated with an increased frequency of diarrhoea, but studies are inconclusive.

Infectious diarrhoea

In many developing countries 25–50% of childhood mortality is associated with diarrhoea l disease. Malnutrition is a risk factor for mortality. In adults dehydration, electrolyte imbalance and

weight loss tend to be proportionately less severe but can still be life-threatening, especially in the severely malnourished, debilitated and those with severe end-stage disease, e.g. AIDS. Pneumonia and septicaemia are common concurrent infections in those who die.

Causes

Bacteria causing diarrhoea in developed countries include *Salmonella, Shigella, Yersinia, Campylobacter, Clostridium perfringens, Clostridium difficile*, and *Staphylococcus aureus*. These are commonly transmitted by food, but in hospital and intensive care, the potential for faecal transmission requires strict infection control procedures, including care with disposal of liquid faeces, soiled linen, and cleaning materials. *Salmonella, Shigella, Yersinia*, and *Campylobacter* are invasive, causing an inflammatory diarrhoea that can be associated with fever and abdominal pain. Stools are usually watery, but can contain blood or mucus.

Enterotoxins are the cause of diarrhoea associated with *Staphylococcus aureus, Bacillus* spp., some *Escherichia coli* and *Clostridium perfringens*. Enterotoxin-induced diarrhoea usually lasts about 24 hours. Enterotoxins act in varying ways, but the diarrhoea is non-inflammatory and mediated by reduced water and electrolyte absorption. *Clostridium perfringens* type C, mainly found in South East Asia, causes enteritis necroticans.

Escherichia coli form part of the normal intestinal flora, but six pathogenic strains are associated with diarrhoea:

- Shiga toxin-producing *E.coli*, also referred to as enterohaemorrhagic *E. coli*. This is the strain most commonly associated with *E. coli* food-borne diarrhoeal illness. The strain causing the 2011 European outbreak was O104:H4, and the commonest in the USA is O157:H7.
- Enterotoxingenic *E.coli.*
- Enteropathogenic *E.coli.*
- Enteroaggregative *E. coli.*
- Entero-invasive *E .coli.*
- Diffusely adherent *E. coli.*

The *Shigella* toxin-producing *E. coli* causes a variable illness mimicking *Shigella* infection with abdominal pain, diarrhoea (sometimes bloody), and vomiting. Illness duration is usually 5–7 days. Approximately 5–10% of patients, mainly children, develop the life-threatening complication of haemolytic uraemic syndrome with renal failure, micro-angiopathic anaemia and thrombocytopenia.

Cholera is an acute diarrhoeal illness caused by *Vibrio cholera.* It is estimated to cause over 100,000 deaths a year worldwide out of 3–5 million cases. Perhaps 75% of those infected are symptom-free. Of those who develop symptoms, 80% have mild-to-moderate illness and 20% develop acute watery diarrhoea causing dehydration. It can kill within hours of onset. Two serogroups, O1 and O139, cause outbreaks. It is a disease of poor sanitation and a risk after natural disasters in endemic areas.

Clostridium difficile is the commonest cause of infectious diarrhoea in North American and European hospitals, and is increasing in both frequency and severity [6]. The virulent BI/NAP1/027 strain has been associated with some hospital outbreaks. It produces considerably more A and B toxins that cause intestinal mucosal inflammation. While its presence in the colon can be asymptomatic or associated with only mild diarrhoea, it is the major cause of antibiotic-associated colitis and pseudomembranous colitis. Toxic megacolon is an uncommon, but severe complication of pseudomembranous colitis. It should be suspected when a patient who is on, or has recently received, antibiotics develops increasing abdominal pain, distention, and fever. Approximately half the patients with toxic megacolon present with shock, and need intensive care and surgical review. Failure to respond to medical treatment—fluids, vasopressor support, vancomycin 125–500 mg (depending on severity) enterally 6-hourly plus metronidazole 500 mg intravenously 8-hourly, with increasing abdominal pain and colonic distention is an indication for subtotal colectomy.

Norovirus and rotavirus are well-recognized forms of hospital- or ICU-acquired diarrhoea. Rotavirus predominantly affects young children and is endemic worldwide. It causes both watery diarrhoea and vomiting that lasts 3–8 days, so dehydration and electrolyte loss can be severe and cause death, especially in malnourished and debilitated infants and young children. Norovirus is one of the commonest causes of diarrhoea worldwide. It causes outbreaks in nursing homes and hospitals. Importantly, it is easily transmitted to health care workers with a very short incubation time, in part because it survives well in faeces and vomitus.

Giardia lamblia, Cryptosporidiosis, and *Entamoeba histolytica* are important causes of severe diarrhoea in developing countries. Reactivation of *Strongyloides stercoralis* can be precipitated by critical illness and cause diarrhoea.

Management

Infectious diarrhoea is generally highly transmissable from patient-to-patient, or via health care workers. Many are notifiable diseases and managing outbreaks is an important public health function. ICU patients with diarrhoea should be isolated, and extreme care taken with disposal of faeces and vomitus. Strict adherence to hand hygiene is extremely important; patient-to-patient transmission of pathogens often indicates that this has failed. Any outbreak of diarrhoea in an ICU requires involvement of infection control staff, microbiology expertise to determine the cause, patient isolation or cohorting, and environmental cleaning.

Health care workers assigned to international aid agencies and those travelling to endemic areas can be immunized against cholera, but this is less than 100% effective. Careful ICU design including use of single rooms can limit the risk of patient-to-patient transmission. Innovative approaches, such as using copper on ICU surfaces may also have a role.

A good history is important to determine if there are chronic diseases present that are associated with diarrhoea. Other important questions relate to recent and past travel, drug history, family health, and exposure to others with diarrhoeal illness.

Physical examination should assess signs of dehydration, body temperature, pulse and blood pressure, and abdominal examination for signs of distention, tenderness, guarding, and bowel sounds. Rectal examination is important to exclude constipation with overflow of liquid faeces. Signs are non-specific, but can give an indication of severity. The nature of the stool including liquidity, and the presence of blood or mucus are also non-specific.

Stool samples should be sent for culture and sensitivity testing. The scope can be guided by the clinical setting and information obtained from history and examination. During outbreaks, individual pathogens should be sought, e.g. *Escherichia coli* O157-H7, norovirus. ICU patients should always have their stool checked for

the presence of *Clostridium difficile* toxins. Abdominal X-rays have a low yield except to detect severe colonic distention in toxic megacolon associated with, for example, *C. difficile* or ulcerative colitis.

Sigmoidoscopy has a limited role, but can provide diagnostic information if there is a flare-up of chronic colitis, an invasive colitis, or if the typical pseudomembranes of pseudomembranous colitis are present.

Laboratory investigation should include plasma electrolytes, magnesium, urea, creatinine, and phosphate. A high haematocrit suggests dehydration. A stool osmotic gap >100 mosmol/kg (2 × stool $[Na^+ + K^+]$ minus plasma osmolality) demonstrates osmotic diarrhoea or malabsorption.

Treatment should be directed at any known and treatable underlying cause. Many drugs have diarrhoea as a side-effect; review and cessation of all non-essential medications may stop the diarrhoea. Many ICU patients are given laxatives and the cumulative effects of these should not be overlooked. Medication given as elixirs through feeding tubes can contain large amounts of sorbitol and be responsible for osmotic diarrhoea.

Enteral feeds are often blamed for diarrhoea, although evidence is limited. Implicated predisposing factors, include high feed osmolality, lactose intolerance, bacterial contamination, bolus (as opposed to continuous) feeding, lack of dietary fibre, and re-feeding syndrome. Most modern commercially available feeds are lactose-free, contain a source of fibre, and are given through closed systems that limit the risk of bacterial contamination.

Avoidance and correction of dehydration and electrolyte imbalance are the mainstays of treatment. Except for severe dehydration, oral rehydration therapy (ORT) is sufficient, either orally or through a nasogastric tube. The WHO recommends glucose or rice water-based fluids with an osmolarity of 200–310 mOsmol/L and sodium 60–90 mmol/L [7]. WHO oral rehydration salts contain (in mmol/L) sodium 75, chloride 60, potassium 20, citrate 10, and glucose 75; total osmolarity is 245mosmol/L. The addition of zinc has been recommended in developing countries. Carbonated drinks, diluted cordial, and fruit juices are not suitable. Commercial ORT solutions are readily available in developed countries. Mild-to-moderate dehydration is corrected by 50–100 mL/kg body weight of ORT over 4 hours with ongoing replacement of losses at approximately 120 mL ORT for every watery stool or vomit. Severe dehydration may need intravenous balanced salt solution until peripheral perfusion and urine output return to normal, followed by ongoing ORT for replacement of losses.

Antibiotics have a limited role in treating infectious diarrhoea. Most are viral or self-limiting. Some options for antibiotic treatment are shown in Table 183.1, using the cheapest available.

Anti-motility agents (e.g. loperamide 4 mg initially followed by 2 mg after each loose stool to a maximum of 16 mg in 24 hours for adults, or codeine phosphate) are relatively contraindicated in infectious diarrhoea and may prolong shedding of infectious organisms, but are often used for symptomatic relief or prolonged diarrhoea.

Probiotics are advocated to reduce the frequency of antibiotic-associated diarrhoea, including that caused by *Clostridium difficile*. A meta-analysis of trials assessing *Saccharomyces boulardii* suggested a 50% risk reduction; *Lactobacillus GG* also appears effective [8]. There is insufficient evidence to recommend probiotics for prevention/treatment of *C. difficile*-induced diarrhoea [8]. While there is no clear increase in adverse events associated with probiotics, the evidence is insufficient to be certain.

Constipation

Constipation is the most common disorder of intestinal motility. In the general community its prevalence is estimated at 3–17%

Table 183.1 Antibiotic options for bacterial infectious diarrhoea

Organism	Antibiotic	Comment
Bacillus spp.	Not indicated	
Campylobacter spp.	Erythromycin	Reduces duration of diarrhoea and shedding of organism
Clostridium difficile	Metronidazole, vancomycin	See text
Clostridium perfringens	Not indicated	
Escherichia coli	Trimethoprim-sulphmethoxazole	
	3rd generation cephalosporin	For systemic complications
Salmonella spp.	Not indicated unless high risk	Prolong carrier state, risk of relapse
	Trimethoprim-sulphmethoxazole	For high risk patients, severe diarrhoea
	3rd generation cephalosporin	Invasive disease, typhoid
Shigella spp.	Trimethoprim-sulphmethoxazole	
	3rd generation cephalosporin	For bacterial resistance, invasive disease
Staphylococcus aureus	Not indicated	Enterotoxin
Vibrio cholerae	Doxycycline	
	Erythromycin	2nd line
Yersinia spp.	Trimethoprim-sulphmethoxazole	Only for high risk, complicated disease
	3rd generation cephalosporin	

depending on definition and population studied. A period of constipation is very common in critically-ill patients. Contributing factors include immobility, drug side effects, reduced food intake, abdominal surgery, and neurohumoral changes.

Chronic constipation is generally defined as less than two bowel movements a week, persisting in the absence of obstruction, and despite medical treatment and a high fibre diet. Constipation has three forms:

- **Slow transit**: reduced colonic motility slows stool transit through the colon resulting in hard faeces and infrequent bowel actions.
- **Normal transit**: normal colonic motility, but small bulk results in hard faeces and straining.
- **Pelvic floor dysfunction**: incomplete evacuation and obstruction.

Faecal impaction can complicate any form of constipation. The patient cannot pass faeces spontaneously. Faeces are hard and abdominal discomfort common. It is an important cause of faecal incontinence.

The frequency of constipation in ICU patients depends on the definition and the population studied; most studies report between 20 and 58% [9,10] but 83% has been reported [11]. A PaO_2/FIO_2 ratio <150 and hypotension increase the risk of constipation. Having constipation is associated with adverse outcomes and a prolonged ICU stay.

Constipation must be differentiated from mechanical obstruction, pseudo-obstruction and ileus.

Pathophysiology

Defecation is usually under a high level of voluntary control to prevent incontinence. During normal rectal emptying, rectal pressure, and intra-abdominal pressure increase accompanied by inhibition of the smooth and striated muscle of the rectal sphincter. During rectal emptying the pelvic floor descends, followed by increased pelvic floor muscle activity as it returns to the resting position at the end of defecation.

Colonic motor activity is mainly localized to short segments and occurs in an uncoordinated way at irregular intervals through the day. Several times a day, most commonly after wakening or in the late post-prandial period, high-pressure contractions propagate as a peristaltic wave over a long length of colon (mass movements), and transport colonic content distally. These contractions are accompanied by an urge to defaecate or precede defaecation during consciousness. Sleep, sedation, and abdominal incisions inhibit colonic motor activity. Peristaltic contractions are less frequent in constipated patients.

Colonic muscle is innervated by the myenteric plexus, which includes cholinergic and peptidergic neurons sensitive to vasoactive intestinal peptide, substance P, encephalin, somatostatin, and other mediators. It is also innervated by the autonomic nervous system and influenced by gastrointestinal hormones. The parasympathetic supply to the proximal and distal colon are from the vagus nerve and pelvic nerves, respectively. The sympathetic supply to the proximal and distal colon comes from splanchnic or lumbar nerves arising from the superior and inferior mesenteric ganglia, respectively. Catecholamines inhibit colonic muscle contraction. Loss of the pelvic parasympathetic nerve supply interferes with reflex control of defecation.

Disordered motility and bowel distention cause abdominal discomfort and pain in conscious patients. More severe distention contributes to raised intra-abdominal pressure with its associated adverse effects [12].

Causes

Main causes of constipation are summarized in Box 183.1. Constipation is also almost invariable in patients with circulatory shock as a consequence of splanchnic hypoperfusion. Most patients given narcotic analgesics and sedatives become constipated. The role of altered food intake and dietary fibre remain unclear despite multiple investigations.

Constipation is more common in the elderly. Women are also more prone to constipation, particularly during pregnancy.

Management

Clinical history and examination may provide evidence of any reversible cause. A detailed drug history should be taken, and a rectal examination performed to exclude faecal impaction and to inform the patient's bowel management plan.

If the rectum is full, a suggested management pathway is shown in Fig. 183.1. Suppositories are dissolved into a liquid at body temperature. Glycerine suppositories draw water into the faeces by osmosis, while stimulant suppositories (e.g. bisacodyl) stimulate colonic peristalsis and secretion of fluid into the lumen. Small volume (5 mL) sodium citrate enemas or larger volume sodium phosphate enemas (133 mL) contain poorly absorbed ions including magnesium, phosphate, sulphate, and citrate that draw water into faeces by osmosis. Retention of larger volume enemas may contribute to fluid overload and electrolyte imbalance. These are also risks associated with colonic lavage. Manual evacuation is generally a last resort and needs to be performed with care to avoid anal or rectal trauma. It can cause parasympathetic stimulation with extreme bradycardia, especially in patients with spinal injury. Once the rectum is empty, patients can revert to the standard care pathway outlined in Fig. 183.1.

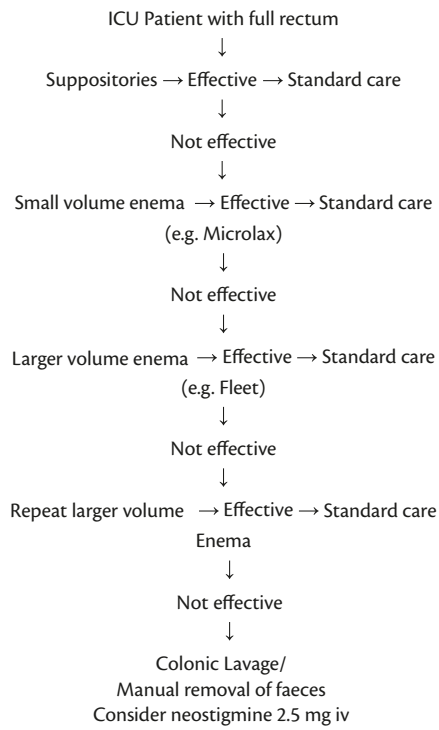


Fig. 183.1 Management plan for constipated ICU patients with a full rectum.

Box 183.1 Causes of constipation

- **Environmental**: need for bedpans, commode, lack of privacy, noise, unfamiliar toileting environment.
- **Neurological**: head injury, spinal injury with quadriplegia or paraplegia, multiple sclerosis, autonomic neuropathy, pelvic surgery.
- **Psychiatric**: depression, dementia, anorexia nervosa.
- **Drug-induced**: opiates, sedatives, catecholamines, antidepressants, antipsychotics, anticholinergics, aluminium-containing antacids, antihypertensives, diuretics, oral iron supplements, laxative abuse.
- **Endocrine**: hypothyroidism, pregnancy, hypercalcaemia, diabetic neuropathy.
- **Metabolic**: hypercalcaemia, lead poisoning, acute porphyria, dehydration.
- **Nutritional**: reduced food intake, altered diet, reduced dietary fibre.
- **Abdominal surgery.**

If the rectum is empty, a staged response is recommended. In patients who are eating or on enteral feeds, ensure that sufficient dietary fibre is being given. If deficient, it can be supplemented by bulking agents, e.g. ispaghula husk, guar gum. If constipation persists, stimulant laxatives can be added, e.g. senna, bisacodyl. These are not recommended for long-term use. Persisting constipation with an empty rectum after 2 days can be treated by adding an osmotic laxative, e.g. sorbitol, lactulose, magnesium salts. These can cause diarrhoea when constipation resolves. Macrogol 3350 is an alternative. Constipated patients should have a rectal examination at least every 2 days and be treated as per Fig. 183.1 if the rectum is full.

Conclusion

Emulsified paraffin is no longer recommended for treating constipation in ICU patients. Methylnaltrexone has been investigated as a specific treatment for opioid-induced constipation and appeared effective [13]. Neostigmine has been used for refractory constipation in both adults and children with success in anecdotal reports.

References

1. Lewis SJ and Heaton KW. (1997). Stool form scale as a useful guide to intestinal transit time. *Scandinavian Journal of Gastroenterology*, **32**, 920–4.
2. Hewson-Conroy KM, Burrell AR, Elliott D, et al. (2011). Compliance with processes of care in intensive care units in Australia and New Zealand: a point prevalence study. *Anaesthesia Intensive Care*, **39**, 926–35.
3. McPeake, J, Gilmour, H., and MacIntosh, G. (2011). The Implementation of a bowel management protocol in an adult intensive care unit. *Nursing Critical Care*, **16**, 235–42.
4. Bobo LD and Dubberke ER. (2010). Recognition and prevention of hospital-associated enteric infections in the intensive care unit. *Critical Care Medicine*, **38**(Suppl.), S324–34.
5. Sonnier DI, Bailey SR, Schuster RM, Gangidine MM, Lentsch AB, and Pritts TA. (2012). Proinflammatory chemokines in the intestinal lumen contribute to intestinal dysfunction during endotoxemia. *Shock*, **37**, 63–9.
6. Bobo LD, Dubberke ER, and Kollef M. (2011). *Clostridium difficile* in the ICU: the struggle continues. *Chest*, **140**, 1643–53.
7. WHO Drug information (2014).Vol. 16, No. 2, *Current Topics: New Formula Oral Rehydration Salts*. Available at: http://apps.who.int/medicinedocs/en/d/Js4950e/2.4.html (accessed 18th February 2014).
8. Morrow LE, Gagineni V, and Malesker MA. (2012). Probiotic, prebiotic and synbiotic use in critically ill patients. *Current Opinions in Critical Care*, **18**, 186–91.
9. Nguyen T, Frenette AJ, Johanson E, et al. (2013). Impaired gastrointestinal transit and its associated mortality in the intensive care unit. *Critical Care*, **28**, 11–17.
10. Gacouin A, Carnus C, Gros A, et al. (2010). Constipation in long-term ventilated patients: associated factors and impacts on intensive care unit outcomes. *Critical Care Medicine*, **38**, 1933–8.
11. Mostafa SM, Bhandari S, Ritchie G, Gratton N, and Wenstone R. (2003). Constipation and its implications in the critically ill patient. *British Journal of Anaesthesia*, **91**, 815–19.
12. Malbrain ML and De Iaet I. (2009). It's all in the gut: introducing the concept of acute bowel injury and acute intestinal distress syndrome. *Critical Care Medicine*, **37**, 365–6.
13. Sawh SB, Selvaraj IP, Danga A, Cotton AL, Moss J, and Patel PB. (2012). Use of methylnaltrexone for the treatment of opioid-induced constipation in critical care patients. *Mayo Clinic Proceedings*, **87**, 255–9.

PART 6.5

The acute abdomen in the ICU

CHAPTER 184

Pathophysiology and management of raised intra-abdominal pressure in the critically ill

Inneke E. De laet and Manu L. N. G. Malbrain

Key points

- The diagnosis of intra-abdominal hypertension/abdominal compartment syndrome (IAH/ACS) relies on accurate intra-abdominal pressure (IAP) measurement. The current gold standard for measurement is intermittently every 4–6 hours via the bladder, using ≤25 mL of instillation volume, in a completely supine position, using the mid-axillary line as a zero reference point.
- IAP monitoring should be performed in all critically ill or injured patients exhibiting ≥1 risk factors for the development of IAH, and continued until risk factors are resolved and IAP has remained normal for 24–48 hours.
- IAH and ACS cause organ dysfunction through direct compression of the heart, compression of both arterial and venous perfusion of the abdominal organs, and abdominothoracic pressure transmission. All organ systems are affected by IAH-induced injury.
- The WSACS medical management algorithm contains several minimally invasive techniques aimed at decreasing IAP and sustaining adequate systemic and regional perfusion. These can be applied in a stepwise fashion until IAP is decreased. Current evidence to support these techniques is rather low, but since there are no reports on adverse effects and there is a possible therapeutic benefit, some of them were retained as weak recommendations in the guidelines.
- Standard surgical treatment of established ACS not responding to non-invasive management consists of decompressive laparotomy via midline or transverse incision. Promising alternative surgical strategies like subcutaneous linea alba fasciotomy (SLAF) are being developed to avoid the complications of the open abdomen. Prophylactic open abdomen (OA) treatment is currently only recommended for trauma damage control surgery. Critically ill patients with an OA are preferentially treated with NPT.

Introduction

The negative effects of increased intra-abdominal pressure (IAP) on organ function were known to the pioneers of physiology centuries ago. However, Kron, et al. coined the term 'abdominal compartment syndrome' (ACS) in the 1980s and launched the modern revival of interest in this phenomenon. Initially, researchers and clinicians were mainly focused on overt ACS, a dramatic complication seen mostly in emergency surgical or trauma patients that almost invariably leads to death when untreated, and which carries a guarded prognosis even when treated (by decompressive laparotomy). Gradually, interest has shifted to more moderate forms of raised IAP termed intra-abdominal hypertension (IAH), which has proved to be more amenable to prevention and treatment. IAH was also more frequently seen in non-trauma surgical patients and medical patients, mainly in those requiring massive fluid resuscitation. This led to increased awareness among both the surgical and critical care communities, and the birth of the World Society of the Abdominal Compartment Syndrome (WSACS, www.wsacs.org) in 2004. From 2006, WSACS has published guidelines for definition, diagnosis and management of IAH/ACS [1,2]. In 2012, the guidelines were updated based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system in order to provide better consistency in identifying and rating the quality of available evidence and strength of management suggestions and recommendations [3]. This chapter briefly summarizes basic concepts relating to IAH/ACS and reflects the essentials of the current 2013 WSACS guidelines.

Definitions

Table 184.1 summarizes the current WSACS consensus definitions regarding IAH and ACS [3]. Since the standard treatment for ACS is still decompressive laparotomy (DL), which leaves the patient with an open abdomen (OA), a new classification for OA was also proposed.

Although the physiopathology of raised IAP in children is quite similar to adults, cut-off values for definitions and IAP measurement technique differ somewhat [4]. Definitions amended for

Table 184.1 Definitions regarding IAP according to the 2013 WSACS guidelines update

Intra-abdominal pressure (IAP)	Steady-state pressure concealed within the abdominal cavity
Abdominal perfusion pressure (APP)	APP = MAP – IAP
'Normal' IAP	Approximately 5–7 mmHg in critically ill adults
Intra-abdominal hypertension (IAH)	Sustained or repeated pathological elevation in IAP ≥12 mmHg
IAH grading	IAH is graded as follows: ◆ Grade I, IAP 12–15 mmHg ◆ Grade II, IAP 16–20 mmHg ◆ Grade III, IAP 21–25 mmHg ◆ Grade IV, IAP > 25mmHg
Abdominal compartment syndrome (ACS)	Sustained IAP > 20 mmHg (± APP < 0 mmHg) that is associated with new organ dysfunction/failure
Primary IAH/ACS	Condition associated with injury or disease in the abdominopelvic region that frequently requires early surgical or interventional radiological intervention
Secondary IAH/ACS	Conditions that do not originate from the abdominopelvic region
Recurrent IAH/ACS	When IAH/ACS redevelops following previous surgical or medical treatment of primary or secondary IAH/ACS
IAP measurement	The reference standard for intermittent IAP measurements is via the bladder with a maximal instillation volume of 25 mL of sterile saline. IAP should be expressed in mmHg and measured at end-expiration in the completely supine position after ensuring abdominal muscle contractions are absent and with the transducer zeroed at the level of the mid-axillary line
Polycompartment syndrome	Condition where two or more anatomical compartments have elevated compartmental pressures
Abdominal compliance	Abdominal compliance quantifies the ease of abdominal expansion, is determined by elasticity of the abdominal wall and diaphragm, and expressed as the change in intra-abdominal volume per change in intra-abdominal pressure in L/mmHg
Open abdomen (OA)	Any abdomen requiring temporary abdominal closure due to skin and fascia not being closed after laparotomy. The technique of temporary abdominal closure should be explicitly described
OA classification	Classified by the following grading system: **1 – No fixation** 1A: clean, no fixation. 1B: contaminated, no fixation. 1C: enteric leak, no fixation. **2 – Developing fixation** 2A: clean, developing fixation. 2B: contaminated, developing fixation. 2C: entero-atmospheric/cutaneous fistula, developing fixation. **3 and 4 – Frozen abdomen** 3: frozen abdomen, no fistula. 4: frozen abdomen with entero-atmospheric/cutaneous fistula.
Lateralization of the abdominal wall	Phenomenon whereby musculature and fascia of the abdominal wall, most well seen in rectus abdominis muscles and their enveloping fascia, move laterally away from the midline with time

MAP, mean arterial pressure.

Adapted with permission from Kirkpatrick AW et al., 'Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome', *Intensive Care Medicine*, 39, 7, pp. 1990–1206, Copyright © 2013 Kirkpatrick et al., with permission.

paediatric use are listed in Table 184.2 otherwise non-listed definitions given in Table 184.1 also apply to children.

Pathophysiology and epidemiology

Since the abdominal compartment is surrounded by a combination of rigid (spine, rib cage, and bony pelvis) and semi-rigid borders (the muscular abdominal wall, diaphragm, and pelvic muscles), it is vulnerable to the development of raised compartmental pressure. When intra-abdominal volume (IAV) increases, the compliant abdominal wall initially expands, keeping IAP constant over a relatively wide range of IAV [5]. However, when abdominal wall expansion reaches its maximum, or when abdominal compliance is impaired by internal (e.g. oedema) or external (e.g. restrictive bandages or sutures) causes, any increase in IAV leads to a rapid increase in IAP. Therefore, any condition associated with increased IAV and/or decreased abdominal compliance can lead to IAH and/or ACS. The WSACS has published a list of risk factors that

Table 184.2 Definitions regarding IAP for paediatric use according to the 2013 WSACS guidelines update [13]

IAP measurement	Reference standard for intermittent IAP measurement in children is via the bladder using 1 mL/kg as an instillation volume, a minimal instillation volume of 3 mL and a maximum installation volume of 25 mL of sterile saline.
'Normal' IAP	In critically ill children is approximately 4–10 mmHg.
IAH	In children defined by a sustained or repeated pathological elevation in IAP >10 mmHg.
ACS	In children defined as a sustained elevation in IAP of >10 mmHg associated with new or worsening organ dysfunction that can be attributed to elevated IAP.

Adapted with permission from Kirkpatrick AW et al., 'Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome', *Intensive Care Medicine*, 39, 7, pp. 1990–1206, Copyright © 2013 Kirkpatrick et al., with permission.

Table 184.3 Risk factors for development of IAH and/or ACS according to the WSACS [2]

Risk factors
Age*
Increased APACHE II or SOFA score*
Acidaemia*
Hypothermia*
Coagulopathy
Sepsis/bacteraemia*
Shock or hypotension*
Mechanical ventilation*
PEEP >10 cmH_2O or the presence of auto-PEEP*
Pneumonia
Major burns
Major trauma*
Massive fluid resuscitation or positive fluid balance*
Polytransfusion*
Liver dysfunction/cirrhosis with ascites
Intra-abdominal infection/abscess*
Peritonitis
Abdominal surgery*
Haemoperitoneum/pneumoperitoneum or intra-peritoneal fluid collections*
Gastroparesis/gastric distention/ileus*
Volvulus
Obesity or increased body mass index*
Intra-abdominal or retroperitoneal tumours
Increased head of bed angle*
Prone positioning*
Massive incisional hernia repair
Acute pancreatitis*
Damage control laparotomy
Laparoscopy with excessive inflation pressures
Peritoneal dialysis

*Indicates primary literature support.

APACHE II, Acute Physiology and Chronic Health Evaluation-II; PEEP, positive end expiratory pressure; and SOFA, Sequential Organ Failure Assessment.

Adapted from ***Intensive Care Medicine*, 32**(11), pp. 1722–32, 'Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions', Malbrain ML et al., copyright 2006, European Society of Intensive Care Medicine and the European Society of Paediatric and Neonatal Intensive Care, with kind permission of Springer Science and Business Media.

are partly supported by literature data and partly based on physiopathological common sense [2]. A modified version is presented in Table 184.3.

Due to increased awareness, primarily in surgeons, the incidence of overt ACS (specifically primary ACS) is decreasing as concepts such as damage-control surgery and prophylactic use of the OA have found their way into the routine surgical management of critical abdominal trauma or injury. At the same time, aggressive fluid resuscitation for sepsis, burns, and trauma have led to an increased incidence of IAH, especially secondary IAH. The incidence for IAH in the critically ill varies across populations, but ranges from 25% in the general ICU population [6] to 75% in patients with septic shock. This is a worrying development since the mortality of secondary IAH is even higher than that of primary IAH [5]. A critical factor in the development of secondary IAH appears to be the iatrogenic effect of massive fluid resuscitation [7]. In some populations, e.g. postoperative patients after major abdominal surgery, a direct correlation between fluid balance and IAP was found. Better targeting of fluid resuscitation and fluid balance control currently offer the best hope for lowering the incidence of IAH in the critically ill [8].

The effect of IAH on organ function

The impact of IAH on the cardiovascular system is multifactorial. Cephalad displacement of the diaphragm leads to direct compression of the heart and decreased contractility. Compression of the systemic arterial circulation increases afterload, while reduced venous return from the lower half of the body due to inferior vena cava compression decreases preload. All these changes usually lead to a decreased cardiac output, which can temporarily be corrected by fluid loading although this, in turn, can lead to further increases in IAP [9]. Cephalad displacement of the diaphragm is also associated with abdominothoracic pressure transmission. This leads to a 'cosmetic' (i.e. not reflecting a true physiologic change) increase in all pressures measured intrathoracically (such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP)), but also to clinically relevant physiological phenomena [10]. The increased thoracic pressure leads to increases in CVP and intrajugular pressure, impaired venous outflow from the brain, and increased intracranial pressure (ICP). This association between IAP and ICP is important to consider when treating patients with IAH at risk of brain injury [5].

Increased IAP leads to dysfunction of all abdominal organs due to compromise of arterial blood flow, venous outflow obstruction, and impaired microcirculatory flow. Kidney failure is the most

often and consistently described organ failure associated with IAH though hepatic, adrenal, and gastrointestinal dysfunction have also been repeatedly reported [5,11]. Notably, IAH can lead to increased bacterial translocation, lending truth to the adage 'the gut is the motor of sepsis' [1].

IAP monitoring

Since clinical examination is unreliable for detecting raised IAP in critically ill patients, the diagnosis of IAH and ACS hinges on accurate measurement of IAP [5]. Theoretically, IAP can be measured intermittently or continuously, directly in the peritoneal cavity or indirectly through hollow viscera, most frequently bladder or stomach [12]. The WSACS recommends routine measurement of IAP through the bladder in critically ill or injured patients when any known risk factor for IAH/ACS is present [2,3].

Currently, the most adopted form of IAP monitoring involves intermittent IAP measurement through the bladder every 4–6 hours using no more than 25 mL of instillation volume, starting when at least one risk factor (Table 184.3) for IAH is present. This is continued until the risk factor(s) have resolved and IAP has remained normal for 24–48 hours [13]. Gastric IAP measurement techniques are mainly used when the bladder is not available for catheterization, a localized increase in pelvic pressure is suspected (e.g. due to a pelvic haematoma), or monitoring of the upper abdominal compartment is deemed useful (e.g. in severe acute pancreatitis).

Management of intra-abdominal hypertension and abdominal compartment syndrome

Since the modern revival of ACS as a real concern in critically ill or injured patients, surgery (DL) has been considered the ultimate treatment. Initially, when overt primary ACS was the only clinical entity considered, DL was even considered the only treatment option, even though outcomes were poor in terms of mortality [14]. Over the years, as focus shifted towards earlier and more moderate stages of increased IAP (mostly secondary IAH), more attention was diverted towards non-invasive techniques to decrease IAP [15]. A medical management algorithm has been produced by the WSACS [16], see Fig. 184.1.

Medical management

Bearing in mind the mechanisms through which IAH develops, it is evident that IAP can be lowered by decreasing IAV, increasing abdominal compliance or combining both. The WSACS medical management algorithm is essentially a collection of non-invasive techniques that were proposed to reach these goals, either after small clinical studies or based on a pathophysiological rationale. They are organized into five major categories (evacuating intraluminal contents, evacuating extraluminal intra-abdominal contents, improving abdominal wall compliance, managing fluid balance, and optimizing systemic and regional perfusion) [15]. In each of these categories, techniques are arranged into steps of increasing invasiveness (and presumed efficacy). The algorithm is designed to be used by experienced clinicians with a certain degree of flexibility, ascertaining which is the most likely mechanism of IAH in an individual patient, carefully selecting the physiological category most likely to benefit that patient, and applying the corresponding measures in a stepwise fashion until IAP decreases. Flexibility, allowing the clinician to tailor the treatment to the patient, is one of the algorithm's most defining features. This also means that its efficacy is largely dependent on user knowledge and experience.

Another downside to the algorithm is that evidence supporting many of the techniques is low at best. The last revision (2013) of the WSACS guidelines using the GRADE methodology made weak recommendations for using a protocol to avoid sustained IAH, using sedation and analgesia for pain and anxiety relief, for brief trials of neuromuscular blockers for patients with IAH, consideration of body position in patients with IAH, gastric or colonic decompression using tubes for patients with gastric or colonic dilatation and IAH, and the use of neostigmine for established refractory colonic ileus [13]. A weak recommendation was made to avoid a positive cumulative fluid balance in critically-ill patients with, or at risk of, IAH, after the acute resuscitation phase has been completed and the inciting issues/source control have been addressed [13]. The WSACS also suggested that an enhanced ratio of plasma/packed red blood cells should be used for resuscitation of massive haemorrhage versus low or no attention to plasma/packed red blood cell ratios. Paracentesis or percutaneous catheter drainage (PCD) is another minimally invasive procedure frequently advocated for treating IAH [17]. The WSACS eventually made a weak recommendation to use PCD to remove fluid (in the setting of obvious intra-peritoneal fluid) in those with IAH/ACS when technically possible, compared to doing nothing [13]. It also recommended that PCD be used to remove fluid (in the setting of obvious intra-peritoneal fluid) in those with IAH/ACS when technically possible compared to immediate DL, as this may remove the need for DL. Both recommendations were again based on low quality evidence [13]. Due to lack of evidence, the WSACS consensus conference could not make any recommendations on using APP as a resuscitation target, the use of diuretics to mobilize fluids, the use of renal replacement therapy or administration of albumin to mobilize fluids, [13].

The fifth column of the medical management algorithm ('optimize systemic/regional perfusion') deserves extra attention. The measures described here are not designed to decrease IAP, but to optimize the general ICU management of patients with IAH/ACS [18]. In particular, haemodynamic management should be adapted to the increased IAP in patients with IAH. Due to abdomino-thoracic pressure transmission, cardiac filling pressures (mainly CVP and PAOP) are 'falsely' increased, i.e. poorly reflect cardiac preload [10]. Abdomino-thoracic pressure transmission depends on abdominal wall compliance and can be estimated by obtaining a simultaneous CVP and IAP pressure tracing, inducing IAH by putting a small weight on the abdomen and measuring the resulting CVP increase. This allows for correction of CVP (transmural CVP) to better reflect cardiac preload. An alternative strategy is to use volumetric monitoring, using parameters such as left ventricular end-diastolic volume index) or global end-diastolic volume index that are less affected by IAH [9]. Due to decreased venous return from the inferior vena cava, IAH can mimic a state of increased fluid responsiveness [19]. Although, if necessary, fluid loading can be used temporarily to correct this state, this can also exacerbate IAH. In most patients, increasing efforts to decrease IAP is probably a better strategy in terms of long-term improvement.

Abdominothoracic pressure transmission also causes decreased compliance of the thoracic wall, while lung compliance remains mostly constant. Therefore, in order to achieve similar tidal

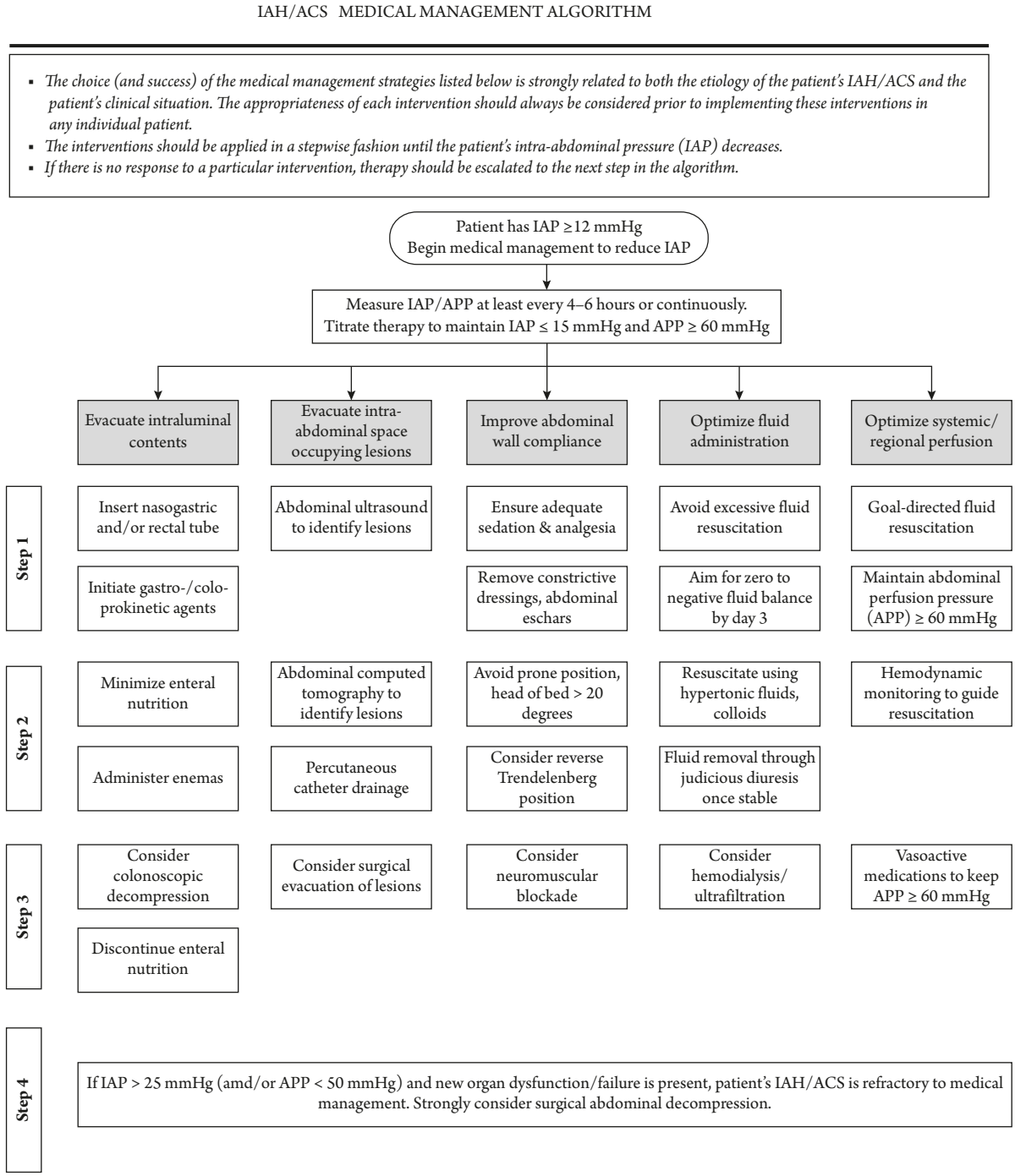


Fig 184.1 Medical management of IAH/ACS.
Reproduced with kind permission from WSACS – The Abdominal Compartment Society, www.wsacs.org.

volumes, higher ventilation pressures are needed in the presence of IAH. Higher than normal positive end-expiratory pressure (PEEP) is recommended to preserve alveolar recruitment since IAH causes increased atelectasis and decreased functional residual capacity [18].

Surgical management

When the different options contained in the medical management algorithm have been exhausted and the IAP is still critically elevated, surgery becomes unavoidable. DL through a midline incision is still the most standard approach to abdominal decompression. Dramatic improvements in organ function and immediate decreases in IAP have been reported consistently after DL. However, DL is associated with a high risk of complications and mortality remains high afterwards [14]. To address these issues some less invasive surgical techniques were developed, most notably subcutaneous linea alba fasciotomy (SLAF). SLAF appears to be a promising alternative with a sustained effect on IAP and

decreased morbidity when compared with full DL, but these findings need further confirmation.

Standard DL leaves the patient with an open abdomen, needing temporary abdominal closure (TAC). Several techniques for TAC have been developed in the past (e.g. Bogota bag, Wittmann patch, zipper closure, non-absorbable mesh), but all are associated with a high complication rate (particularly enterocutaneous fistula and large ventral hernia) and significantly longer ICU and hospital stays [5]. Recently, negative pressure therapy (NPT) has significantly changed OA management [15]. Treatment with NPT dressings specifically designed for use in the abdominal cavity appears to reduce the typical complications associated with TAC. Additionally, NPT may successfully remove inflammatory mediators along with peritoneal fluid from the peritoneal space, leading to lower cytokine levels, both in peritoneal fluid and plasma [20], possibly leading to improved organ function. The WSACS 2013 recommendations made a strong recommendation to use NPT in critically ill patients with an OA, albeit based on low grade evidence [13]. It is important to note that no outcome comparisons have yet been made on the various types of NPT (commercially available vs home-made, different types of commercially available NPT dressings).

Instead of closing the abdomen after a primary surgical procedure and monitoring IAP, many authors suggested using the OA prophylactically to avoid the development of IAH/ACS and its complications. Naturally, it is important to consider that some patients, who would not have developed ACS had their abdomen been closed, are needlessly exposed to the complications associated with OA. The 2013 recommendations advocate prophylactic OA only for trauma patients with 'physiological exhaustion' [13].

Even though the evidence base for both surgical and medical management of IAH/ACS is currently weak, Cheatham, et al, have shown that a global approach, including prophylactic use of the open abdomen, early abdominal decompression, negative pressure therapy and the medical management algorithm can achieve, in the hands of experienced clinicians, better outcomes in terms of primary closure rates, time to closure, and even survival [15].

References

1. Cheatham ML, Malbrain ML, Kirkpatrick A, et al. (2007). Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. II. Recommendations. *Intensive Care Medicine*, **33**, 951–62.
2. Malbrain ML, Cheatham ML, Kirkpatrick A, et al. (2006). Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. *Intensive Care Medicine*, **32**, 1722–32.
3. Kirkpatrick AW, Roberts DJ, and De Waele J. (2013). Intra-abdominal Hypertension and the Abdominal Compartment Syndrome: Updated Consensus Definitions and Clinical Practice Guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Medicine*, **39**, (7),1190–206.
4. Ejike JC, Bahjri K, and Mathur M. (2008). What is the normal intra-abdominal pressure in critically ill children and how should we measure it? *Critical Care Medicine*, **36**, 2157–62.
5. Malbrain ML and De laet IE. (2009). Intra-abdominal hypertension: evolving concepts. *Clinical Chest Medicine*, **30**, 45–70.
6. Malbrain ML, Chiumello D, Pelosi P, et al. (2005). Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. *Critical Care Medicine*, **33**, 315–22.
7. De laet IE, De Waele JJ, and Malbrain MLNG. (2008). Fluid resuscitation and intra-abdominal hypertension. In: Vincent JL (ed.) *Yearbook of Intensive Care and Emergency Medicine*, pp. 536–48. Berlin: Springer-Verlag.
8. Balogh ZJ and Malbrain M. (2011). Resuscitation in intra-abdominal hypertension and abdominal compartment syndrome. *American Surgery*, **77**(1), 31–3.
9. Cheatham ML and Malbrain ML. (2007). Cardiovascular implications of abdominal compartment syndrome. *Acta Clinica Belgica*, **62**(Suppl.), 98–112.
10. Malbrain ML and Wilmer A. (2007). The polycompartment syndrome: towards an understanding of the interactions between different compartments! *Intensive Care Medicine*, **33**, 1869–72.
11. De laet I, Malbrain ML, Jadoul JL, Rogiers P, and Sugrue M. (2007). Renal implications of increased intra-abdominal pressure: are the kidneys the canary for abdominal hypertension? *Acta Clinica Belgica*, **62**(Suppl), 119–30.
12. Malbrain ML. (2004). Different techniques to measure intra-abdominal pressure (IAP): time for a critical re-appraisal. *Intensive Care Medicine*, **30**, 357–71.
13. Malbrain ML and De Laet I. (2008). AIDS is coming to your ICU: be prepared for acute bowel injury and acute intestinal distress syndrome. *Intensive Care Medicine*, **34**, (9), 1565–9.
14. De Waele JJ, Hoste EA, and Malbrain ML. (2006). Decompressive laparotomy for abdominal compartment syndrome—a critical analysis. *Critical Care*, **10**, R51.
15. Cheatham ML and Safcsak K. (2010). Is the evolving management of intra-abdominal hypertension and abdominal compartment syndrome improving survival? *Critical Care Medicine*, **38**, 402–7.
16. De Keulenaer BL, De Waele JJ, and Malbrain ML. (2011). Nonoperative management of intra-abdominal hypertension and abdominal compartment syndrome: evolving concepts. *American Surgery*, **77**(1), S34–41.
17. Cheatham ML and Safcsak K. (2011). Percutaneous catheter decompression in the treatment of elevated intraabdominal pressure. *Chest*, **140**, 1428–35.
18. De laet I and Malbrain ML. (2007). ICU management of the patient with intra-abdominal hypertension: what to do, when and to whom? *Acta Clinica Belgica*, **62**, 190–9.
19. Malbrain ML and de Laet I. (2009). Functional hemodynamics and increased intra-abdominal pressure: same thresholds for different conditions …? *Critical Care Medicine*, **37**, 781–3.
20. Kubiak BD, Albert SP, Gatto LA, et al. (2010). Peritoneal negative pressure therapy prevents multiple organ injury in a chronic porcine sepsis and ischemia/reperfusion model. *Shock*, **34**, 525–34.

CHAPTER 185

Perforated viscus in the critically ill

Ori D. Rotstein

Key points

- The patient with an 'acute abdomen' requires timely and accurate investigation to direct appropriate management; among imaging modalities CT scanning has assumed a dominant position.
- Various pathological processes can lead to loss of gastrointestinal (GI) wall integrity including inflammation, neoplasm, infarction due to compromised blood supply, and mechanical causes including trauma and obstruction.
- The commonest causes of abdominal visceral perforation are appendicitis, diverticulitis, and perforated peptic ulcer.
- The major principles of management comprise stabilization of patient physiology, timely administration of appropriate antimicrobial therapy, and adequate source control.
- Antibiotic selection should take into account patient physiology, severity of the pathological process, and an increased likelihood of multi-resistance following hospital-acquired perforation.

Introduction

An 'acute abdomen' is defined as the rapid onset of severe abdominal pain that comes to medical attention, usually in an Emergency Department setting, and requires timely and accurate investigation to direct appropriate management. Approximately 4% of patients presenting to US Emergency Departments have a primary diagnosis of abdominal pain, making it the 4th commonest presenting complaint [1]. Most patients presenting with an acute abdomen have symptoms related to an intra-abdominal process, although pulmonary or cardiac events can sometimes manifest with acute abdominal symptoms. Within the abdomen, diseases of the gastrointestinal (GI) tract, genitourinary tract, and vascular system can all present acutely and be labelled as an 'acute abdomen'. This chapter will focus on gastrointestinal tract diseases, in particular those leading to a perforated viscus as the underlying pathological entity.

Aetiology of perforated viscus

By definition, perforation of a hollow viscus requires transmural disruption of the GI tract wall. Several pathological processes can lead to loss of GI wall integrity including inflammation, neoplasm, infarction due to compromised blood supply, and mechanical causes including trauma and obstruction. Table 185.1 lists common aetiological entities by GI tract level and was compiled by review of operative reports where visceral perforation was found [2]. Appendicitis was the most frequent diagnosis, followed by diverticulitis and perforated peptic ulcer. Transmural disruption due to malignant ulceration/necrosis is relatively rare, although malignancy causing proximal obstruction and perforation is well described. Similarly, intestinal obstruction can cause perforation when there is vascular compromise, e.g. closed loop obstruction. Intestinal ischaemia followed by gangrene also leads to loss of bowel wall integrity.

Diagnosis of perforated viscus

This is based on clinical examination supported by laboratory investigation and diagnostic imaging. Most patients look unwell, are in acute distress and may be febrile. Pathological processes leading to the perforation and the local peritoneal response dictate both the clinical symptom complex and imaging results. Under ideal circumstances, local host defences contain the spread of GI content though the peritoneal cavity by physically walling off the perforation with bowel and omentum. Presumably, this localization occurs more frequently when the intestinal disruption is small and insidious, e.g. diverticulitis, perforated Crohn's disease, appendicitis. Here, pain and tenderness are localized and occasionally associated with an abdominal mass. The abdomen distant from the site of maximum tenderness may be soft and non-tender, and bowel sounds are usually present. By contrast, free spillage of gastrointestinal content without localization leads to diffuse peritoneal irritation. This is manifest by pain that is steady, severe, and aggravated by movement. Physical examination reveals diffuse tenderness, abdominal wall rigidity and guarding, with accompanying anorexia and nausea. Intra-abdominal infection from a perforated viscus may also exhibit signs of septic shock, characterized by hypo- or hyperthermia, tachycardia, and hypotension. Haemodynamically, these patients may have an increased cardiac output and reduced peripheral vascular resistance.

Abnormal laboratory data, particularly leukocytosis >11,000 cells/mm^3 or profound leukopenia, may be observed. Blood chemistry is generally undisturbed, but may reveal evidence of dehydration with elevated blood urea nitrogen levels and a metabolic acidosis. Urinalysis is essential to rule out urinary tract causes such as pyelonephritis and renal colic.

Table 185.1 Aetiology of perforated viscus and probability of free air on CT scan/plain radiographs

Cause	Total (*n*)	Percentage of all perforation
Appendicitis	38	34
Diverticulitis	12	12
Peptic ulcer	11	10
Bowel ischaemia	10	9
Trauma	10	9
Malignancy	9	8
Post-surgical	4	4
Endoscopic injury	4	4
Biliary source	3	2
Other	11	10
Total	**114**	**100**

Reproduced from Kumar et al., 'The etiology of pneumoperitoneam in the 21st century', *Journal of Trauma and Acute Care Surgery*, **73**(3), pp. 542–8, copyright 2012, with permission from Wolters Kluwer Health.

Medical imaging will hopefully confirm the diagnosis and potentially point to the underlying pathology. Plain abdominal X-rays are invariably performed, but do not always show free air in the peritoneal cavity nor do they frequently help to elucidate the aetiology. The presumed *sine qua non* for visceral perforation is the presence of free air. This is only observed when a large amount of free air is present, such as might occur with perforated peptic ulcer disease (~70%) [2]. Furthermore, plain radiographs do not reveal locules of air that might be observed with localized visceral perforations, e.g. locally-perforated appendicitis or diverticulitis. Other imaging modalities are routinely used to aid diagnosis and management, ultrasonography and CT scanning being the most frequent. Ultrasonography is mainly useful in equivocal cases of right lower quadrant pain, with a view to diagnosing acute appendicitis. Perforated appendicitis may also manifest as a localized abscess in the peri-appendiceal region. For the purpose of managing the patient with an 'acute abdomen', CT scanning has assumed a dominant position. In diagnosing acute appendicitis, the sensitivity and specificity of CT scanning was superior to ultrasonography [3]. However, the ability to specifically diagnose locally-perforated appendicitis is not consistent. The presence of peri-appendiceal air locules is uncommon, and localized fluid collections may represent inflammatory fluid/phlegmon collections rather than discrete abscesses indicative of perforation.

CT scanning is useful in defining other pathological abnormalities including focal defects in the bowel wall, bowel wall thickening, perivisceral fat stranding, free abdominal fluid, the transition point of an obstruction, and the presence of metastatic disease in the peritoneum and/or distant organs. Together, these help to direct the treating physician to both the location and nature of the pathological process. Multi-detector CT scanning predicted the site of perforation in 85% of patients, with the presence of extraluminal air bubbles, segmental bowel wall thickening, and focal defects in the bowel wall being most predictive [4]. A recent meta-analysis of the use of multi-detector CT in the diagnosis of acute mesenteric ischaemia also showed a high degree of sensitivity and specificity for detecting and excluding this entity. This is highly relevant in the ICU patient where mesenteric ischaemia as a cause of an abdominal catastrophe is relatively common [5]. Here, the diagnosis of peritonitis may be challenging because of underlying patient factors which preclude accurate clinical examination. This cause of 'acute abdomen' is particularly lethal because delayed diagnosis may permit progression to infarction and perforation. In addition to CT scanning, several adjunctive diagnostic modalities including peritoneal lavage and bedside laparoscopy have been suggested.

Management

The major principles underlying management related to perforated viscus are:

- Stabilization of patient physiology.
- Timely administration of appropriate antimicrobial therapy.
- Initiation of source control manoeuvres, i.e. addressing the underlying pathological process.

Stabilization

Spillage of gastrointestinal content into the abdominal cavity induces an inflammatory response, with peritoneal fluid sequestration. The magnitude of response usually correlates with peritonitis severity, ranging from minor haemodynamic perturbations after local perforation to profound haemodynamic instability following free perforation of the GI tract with diffuse peritoneal infection. Specifics of managing resuscitation in the latter setting are addressed elsewhere.

Antimicrobial therapy

Timely and appropriate antimicrobial therapy is essential to optimize outcome. Empiric selection of antimicrobial therapy is based on the likely pathogens found in the infection. For GI tract disruption causing intra-abdominal infection, the recovered flora are polymicrobial, consisting of a mixture of Gram-positive aerobic bacteria, Gram-negative facultative anaerobic bacteria and anaerobes. The commonest microbes recovered include *Escherichia coli, Bacteroides fragilis,* and *Enterococcus faecalis*. Antimicrobial therapy should include agents with activity against Gram-negative facultative anaerobic bacteria (e.g. *E.coli)* and anaerobes (e.g. *B. fragilis*) [6]. In straightforward cases of intra-abdominal infection, antimicrobial coverage of *Enterococcus* is unnecessary [6]. Using this general principle, a number of antimicrobial regimens have been compared and shown to be effective, although the need for patient stratification was cited as a flaw in many trials [7].

Recent consensus guidelines have considered the importance of patient factors in making recommendations regarding the choice of antimicrobial regimen [6]. These guidelines stratify patients according to their risk of treatment failure, i.e. low- or high-risk, with a view to tailoring antimicrobial coverage. Decision-making around antimicrobial selection is partly based on data showing that factors such as patient physiology, severity of the pathological process, and healthcare-associated infection can influence the microbial flora of infections. For example, Table 185.2 illustrates the change towards more multi-resistant microbes when comparing patients with 'off-the-street' community-acquired peritonitis

Table 185.2 Changes in microbial flora recovered in patients with community-acquired peritonitis compared to postoperative peritonitis

Strain	Community-acquired	Post-operative
Enterococci	5	21
Escherichia coli	36	19
Enterobacter spp.	3	12
Bacteroides sp.	10	7
Klebsiella sp.	7	7
Staphylococcus aureus	1	6
Coagulase negative taphylococci	1	5
Candida sp.	7	4
Pseudomonas sp.	2	6
Streptococci	14	4
Haemolytic streptococci	3	0
Other	11	9

Reproduced from Roehrborn A et al., 'The microbiological of postoperative peritonitis', *Clinical Infectious Diseases*, 2001, **33**(9), pp. 1513–19, by permission of Oxford University Press and Infectious Diseases Society of America.

Table 185.3 Recommendations for antimicrobial treatment of community-acquired intra-abdominal infections

Mild/moderate infections	High-severity infections
Single agent regimen	
◆ Cefoxitin ◆ Ticarcillin/clavulanic acid ◆ Ertapenem ◆ Moxifloxacin ◆ Tigecycline	◆ Piperacillin/tazobactam ◆ Imipenem/cilastatin ◆ Meropenem ◆ Doripenem
Combination regimen	
Cefazolin, cetriaxone, cefuroxime, cefotaxime. fluoroquinolone (FQ)-based therapy + metronidazole	◆ Ceftazidime, cefepime plus metronidazole ◆ FQ + metronidazole

Adapted from Solomkin et al., 'Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America', *Clinical Infectious Diseases*, 2010, **50**(2), pp. 133–64, by permission of Oxford University Press and Infectious Diseases Society of America.

to post-operative peritonitis due to disruption of a surgical anastomosis [8]. Guidelines separate patients into those with community-acquired or health care associated infection. The former is further subdivided into 'mild-to-moderate severity' and 'high severity' where high-risk defines patients at increased risk of treatment failure. Box 185.1 lists factors causing patients to be designated 'high-risk'. Based on this separation, the authors recommend specific treatment regimens (Table 185.3). In the 'mild-to-moderate' group, agents which cover enteric Gram negative aerobic and facultative bacilli and enteric Gram-positive *streptococci* are recommended, with the addition of anti-anaerobe coverage if the perforation is in the colon or in obstructed or paralytic small bowel. Broader-spectrum agents including anti-enterococcal treatment are indicated for 'high risk' patients, given the higher probability of multi-resistant organisms. Importantly, refinement of antimicrobial agents should be made based on cultures taken at surgery.

Box 185.1 Factors which define patients as being high-risk for treatment failure

- High severity of illness (i.e. physiological derangement as defined by APACHE II).
- Advanced age.
- Co-morbidity and degree of organ dysfunction.
- Immunological suppression (including malnutrition, malignancy, immunosuppressive agents).
- Diffuse peritonitis.
- Poor control of underlying pathological process.
- Prolonged preoperative hospital stay.
- Prior use of antimicrobial agents.

Adapted from Solomkin et al., 'Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America', *Clinical Infectious Diseases*, 2010, **50**(2), pp. 133–64, by permission of Oxford University Press and Infectious Diseases Society of America.

Finally, patients developing peritonitis in the health care setting are likely to harbour multi-resistant bacteria. In essence, antibiotic selection should be similar to those for 'high severity' community-acquired infections plus addition/replacement of agents based upon susceptibility patterns at the individual Institution. The regimen should be tailored to culture and sensitivity data derived from the infection, including anti-fungal therapy as indicated.

Until recently, treatment duration for perforated viscus was based on retrospective studies where defervescence and normalization of leukocyte count correlated with low probability of recurrent infection following antibiotic discontinuation [9]. Treatment for 4–7 days was usually required for this response. Recently, a National Institutes of Health-sponsored prospective randomized clinical trial evaluating duration of antimicrobial use for intra-abdominal infection was published [10]. This study reported that a fixed duration of four days of antimicrobial therapy resulted in equivalent outcomes to the traditional approach of using physiological parameters to dictate antimicrobial duration. Finally, short-duration (<24 hours) antimicrobial therapy is recommended for patients with perforated peptic ulcer or traumatic perforation of the GI tract [6].

An intravenous route is preferred for initial antimicrobial treatment. Switchover to oral antibiotics with good bioavailability is acceptable once the GI tract has resumed function [6].

Source control

This describes physical measures employed to remove or limit the focus of infection, and to mitigate local factors that promote

recurrent or residual infection [11]. Adequate source control is essential for successful management, the incidence of inadequate source control as a cause for treatment failure in eight clinical trials studying anti-infective therapy ranged from 5–29% [12]. Inadequate source control resulted in a two-fold increase in post-operative length of stay and ~55% increase in mortality [13].

Depending on the ability of the host peritoneal defence mechanisms to contain the perforation, visceral perforation is manifested as either localized abscess or diffuse peritoneal infection. Abscesses may also develop following surgery for diffuse peritonitis (e.g. after surgery for an anastomotic disruption) when residual infection is localized by peritoneal host defences. As previously noted, diffuse contamination and contained infection are usually clinically distinguishable, CT can reliably distinguish between a well-demarcated fluid collection for abscess, and less well-defined fluid 'collections' for diffuse peritoneal soiling.

Intra-abdominal abscesses

Percutaneous drainage (PCD) is the preferred technique for management of intra-abdominal abscesses as it is a safe, effective alternative to surgical intervention [14].

Criteria for the use of PCD have broadened as experience has evolved. There are few absolute contraindications, although efficacy may be limited when thick abscess contents preclude drainage, or there are early post-operative collections, indicative of diffuse infection. The weight of evidence, albeit not methodologically robust, suggests that PCD should be used for initial management of discrete intraperitoneal fluid collections.

Management of diffuse peritonitis due to visceral perforation

Treatment should focus on reducing the bacterial burden and necrotic material, managing the underlying pathological process responsible for leaking GI content, and preventing residual or recurrent infection.

Purulent, faecal and necrotic material should be aspirated and debrided. This lessens bacterial burden and reduces the presence of adjuvant materials known to promote bacterial growth (e.g. haemoglobin) and impair local host defence mechanisms (e.g. particulate faecal matter). Surgical options include closing and/or patching the defect, resecting the pathology + primary anastomosis of the bowel ends, or exteriorizing the defect. Decision-making should take into account the organ affected, the underlying pathological process, local conditions within the abdomen, and the patient's general status. The following paragraphs briefly address the commonest causes of GI tract perforation (Table 185.1).

Appendicitis

Perforated appendicitis is usually managed by appendectomy. Both open and laparoscopic appendectomy are effective in managing the appendicitis, but the latter appears superior with respect to hospital length of stay, post-operative complications and return to work [15]. A recent meta-analysis suggested that laparoscopic appendectomy was associated with increased fetal loss during pregnancy, although included studies were of poor quality [16].

Sigmoid diverticulitis

For patients with purulent or faecal peritonitis (Hinchey class III and IV), a two-stage procedure (i.e. Hartmann's procedure) is performed whereby the diseased sigmoid is resected, an end-sigmoid stoma and rectal stump created, and delayed reconstruction planned. Intestinal continuity may be safely restored by a primary anastomosis (PA) at the time of the initial emergency surgery with or without proximal diversion [17]. There has been recent enthusiasm for laparoscopic lavage and drainage for managing Hinchey III-perforated diverticulitis, although the quality of studies was evaluated as low [18].

Perforated peptic ulcer disease

The management of perforated peptic ulcer disease is dictated by the manifestations of the perforation. In some patients, the perforation is well walled off and can be managed conservatively with antibiotics alone. In others, the perforation has been localized, but there is an abscess present which is amenable to PCD. Finally, perforation with diffuse spread of gastroduodenal contents throughout the peritoneal cavity usually warrants surgical intervention. At surgery, the defect is managed by direct closure when the defect is small with easily opposable edges, reinforced by patching of the defect with vascularized omentum. Intraoperative lavage of GI content and particulate matter should be performed. A laparoscopic approach to this procedure is comparable to open surgery, with a modest reduction in the requirement for pain medication in the former [19].

Perforated small intestine due to mesenteric ischaemia

Here, the perforation is a manifestation of loss of wall integrity at ≥1 sites within a segment of infarcted small intestine. The demarcation sites between live and dead bowel is usually obvious for mesenteric vascular embolus or intestinal volvulus. In non-occlusive mesenteric ischaemia, gangrenous perforation may occur at ≥1 sites with intervening areas where the bowel looks dusky (i.e. ischaemic, but not necrotic). Here, one should resect the obviously gangrenous parts of intestine (which presumably include the sites of perforation), and plan for a second-look laparotomy 24–48 hours later when any residual ischaemic/infarcted bowel should be resected. A primary intestinal anastomosis after the second-look should take into consideration local factors in the peritoneal cavity and systemic factors such as patient haemodynamics and comorbidities.

Prevention of residual or recurrent infection

Lavage of the peritoneal cavity is generally repeated at the end of surgery. There is no benefit to including antibiotics in the solution nor is there a role for continuous post-operative peritoneal lavage through indwelling catheters placed intra-operatively. 'Scheduled repeat laparotomy', where a laparotomy is performed by protocol every 24–48 hours for peritoneal lavage is not superior to 'on-demand' laparotomy [20]. Similarly, leaving the fascia open (i.e. the 'open abdomen') with frequent laparotomy for peritoneal lavage is not superior to planned re-intervention based on clinical criteria of infection.

Conclusion

Visceral perforation presents with either localized or diffuse abdominal pain and tenderness depending on the ability of the peritoneal host defence mechanisms to contain the spread of GI content from the site of perforation. The diagnosis is based on clinical symptoms and signs, supported by appropriate imaging. CT scanning is an accurate method of diagnosing perforation and can

provide information about the underlying pathological process. The principles of treatment include adequate physiological support, appropriate antimicrobial therapy and intervention to control the source of infection and prevent its recurrence.

References

1. McCaig LF and Burt CW. (2002). National Hospital Ambulatory Medical Care Survey: 2001 emergency department summary. *Advance Data*, **340**, 1–29.
2. Kumar A, Muir MT, Cohn SM, Salhanick MA, Lankford DB, and Katabathina VS. (2012). The etiology of pneumoperitoneum in the 21st century. *Journal of Trauma*, **73**, 542–48.
3. van Randen A, Bipat S, Zwinderman AH, Ubbink DT, Stoker J, and Boermeester MA. (2008). Acute appendicitis: meta-analysis of diagnostic performance of CT and graded compression ultrasonography related to prevalence of disease. *Radiology*, **249**, 97–106.
4. Hainaux B, Agneessens E, Bertinotti R, et al. (2006). Accuracy of MDCT in predicting site of gastrointestinal perforation. *American Journal of Radiology*, **187**, 1179–83.
5. Gajic O, Urritia LE, Sewani H, Schroeder DR, Cullinane DC, and Peters SG. (2002). Acute abdomen in the medical intensive care unit. *Critical Care Medicine*, **30**, 1187–90.
6. Solomkin JS, Mazuski JE, Bradley JS, et al. (2010). Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clinical Infectious Diseases*, **50**, 133–64.
7. Wong PF, Gilliam AD, Kumar S, Shenfine J, O'Dair GN, and Leaper DJ. (2008). Antibiotic regimens for secondary peritonitis of gastrointestinal origin in adults (Review) *Cochrane Collaborative Reviews*, **18**, 1–213.
8. Roehrborn A, Thomas L, Potreck O, et al. (2001). The microbiology of postoperative peritonitis. *Clinical Infectious Diseases*, **33**, 1513–19.
9. Lennard ES, Dellinger EP, Wertz MJ, and Minshew BH. (1982). Implications of leukocytosis and fever at conclusion of antibiotic therapy for intra-abdominal sepsis. *Annuals on Surgery*, **195**, 19–24.
10. Sawyer RG1, Claridge JA, Nathens AB, et al. (2015). Trial of short-course antimicrobial therapy for intraabdominal infection. New England Journal of Medicine, **372**(21), 1996–2005.
11. Marshall JC, Maier RV, Jiminez M, and Dellinger EP. (2004). Source control in the management of severe sepsis and septic shock: an evidence-based review. *Critical Care Medicine*, **32**, 513–26.
12. Solomkin JS, Ristagno RL, Das AF, et al. (2013).Source control review in clinical trials of anti-infective agents in complicated intra-abdominal infections. *Clinical Infectious Diseases*, **56**, 1765–73.
13. Christou NV, Barie PS, Dellinger EP, Waymack JP, and Stone HH. (1993). Surgical Infection Society intra-abdominal infection study. Prospective evaluation of management techniques and outcome. *Archives of Surgery*, **128**,193–8.
14. Politano AD, Hranjec T, Rosenberger LH, Sawyer RG, and Tache Leon CA. (2011). Differences in morbidity and mortality with percutaneous versus open surgical drainage of post-operative intra-abdominal infections: a review of 686 cases. *American Surgery*, **77**, 862–7.
15. Sauerland S, Lefering R, and Neugebauer EAM. (2004). Laparoscopic versus open surgery for suspected appendicitis. *Cochrane Collaborative Reviews*, **10**, 1–144.
16. Wilasrusme C, Sukrat B, McEvoy M, Attia J, and Thakkinstian A. (2012). Systematic review and meta-analysis of safety of laparoscopic versus open appendectomy for suspected appendicitis in pregnancy. *British Journal of Surgery*, **99** 1470–9.
17. Cirocchi R, Trastulli S, Desiderio J, et al. (2012). Treatment of Hinchey stage III–IV diverticulitis: a systematic review and meta-analysis. *International Journal in Colorectal Disease*, **28**, 447–57.
18. Afshar S and Kurer MA. (2012). Laparoscopic peritoneal lavage for perforated sigmoid diverticulitis. *Colorectal Disease*, **14**, 135–42.
19. Sanabria AE, Morales CH, and Villegas MI. (2013). Laparoscopic repair for perforated peptic ulcer disease. *Cochrane Database of Systematic Reviews* (updated), **2**, 1–38.
20. van Ruler O, Mahler CW, Boer KR, et al. (2007). Comparison of on-demand vs planned relaparotomy strategy in patients with severe peritonitis: a randomized trial. *Journal of the American Medical* Association, **298**, 865–72.

CHAPTER 186

Ischaemic bowel in the critically ill

A. G. Peppelenbosch and Martijn Poeze

Key points

- The cause of acute mesenteric ischaemia, i.e. occlusion of visceral arteries, thrombosis of the mesenteric veins, and non-occlusive mesenteric ischaemia influences survival.
- A high index of suspicion is necessary and should be followed by administering therapeutic low molecular weight heparins (LMWH) or systemic heparin infusion. Newer laboratory detection techniques may become available in the near future.
- Resuscitation and support are essential, but should not delay further diagnosis.
- Emergency CT angiography (CTA) for visualizing visceral arteries, with emergency percutaneous transluminal angioplasty (PTA) and stenting of the superior mesenteric artery (SMA) is a priority.
- Thereafter, laparotomy should be performed with resection of necrotic bowel without anastomoses, followed, if possible, after 24–48 hours by a second-look laparotomy and bowel anastomoses.

Introduction

As visceral arteries have an extended collateral network, occlusion of one branch may occur without any symptoms. This is probably the reason for the low incidence rate of acute mesenteric ischaemia (AMI), which is reported to be as low as 0.63 cases per 100,000 person years [1]. However, this incidence rate is probably an underestimate. In an autopsy study an incidence of 8.6 per 100,000 person years was reported [2] even higher than that of ruptured abdominal aortic aneurysm (5.6 per 100,000 person years).

Aetiology

Three different pathways can cause AMI. The first consists of an occlusion of the visceral artery, arteries, or its outflow tract (Fig. 186.1). Usually, the superior mesenteric artery (SMA) is involved. Involvement of ≥2 arteries was previously considered essential in order to develop AMI, but several reports with only one artery involvement make this assumption less likely.

The second pathway involves thrombosis of the mesenteric veins or its outflow tract causing a rise in mean venous pressure, thereby jeopardizing inflow through the mesenteric arteries, and finally inducing bowel ischaemia.

The third pathway is called non-occlusive mesenteric ischaemia (NOMI). This is based on the theory that flow in the visceral arteries becomes too low to sustain adequate mucosal blood flow. The pathogenesis for such a critically low flow state involves a wide variety of conditions of non-mesenteric related origin such as failure of organ function during sepsis, multiple organ failure, cardiogenic and haemorrhagic shock.

The relative occurrence of these three main causes of intestinal ischaemia varies, with non-thrombotic ischaemia reported in 15.4–60% of cases, embolism in 30–38%, thrombus (superimposed on a stenosis) in 36–40%, and venous occlusion in 5–26% [2–4].

Symptoms and signs

Presenting symptoms are usually non-specific. Classically, acute intestinal ischaemia presents with severe abdominal pain out of proportion to objective physical signs. However, especially in

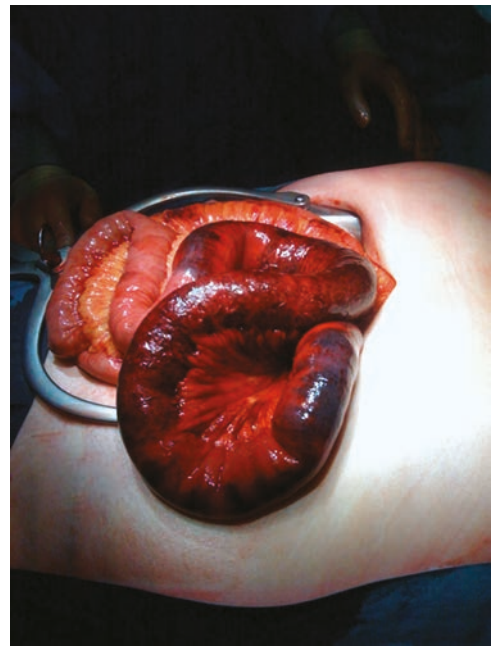


Fig. 186.1 Intra-operative view of acute small bowel ischaemia during laparotomy due to occlusion of the superior mesenteric artery. Note the clear demarcation between viable and ischaemic intestine. Pre-operative revascularization was performed with resection of the demarcated necrotic small bowel.

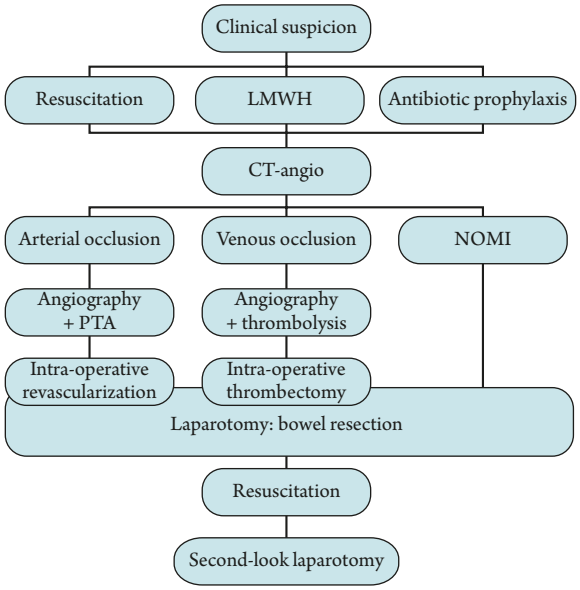


Fig. 186.2 Treatment flow chart for patients with acute intestinal ischaemia. LMWH, low molecular weight heparin; PTA, percutaneous transluminal angioplasty; NOMI, non-occlusive mesenteric ischaemia; CT, computed tomography.

critically-ill (ventilated) patients, the signs and symptoms (of NOMI) are usually inconclusive. Likewise, in elderly patients the clinical symptoms and signs of acute occlusive intestinal ischaemia leading to peritonitis can be very deceptive. Irrespective of the initial presentation, the clinical features during transmural ischaemia will inevitably progress to dysfunction of multiple organs, with tachycardia, hypotension, respiratory distress, oliguria, and, finally, cardiorespiratory arrest.

Diagnosis and surgical treatment

Treatment should start promptly when there is a clinical suspicion of AMI (Fig. 186.2). Even before the diagnosis is confirmed, therapeutic dose LMWH should be administered [5]. Resuscitation is commenced based on clinical signs, especially in patients with organ failure and peritonitis. This is guided by haemodynamic profile and urine output, with replacement of fluid, electrolytes, and protein losses. A broad-spectrum antibiotic should be administered based upon hospital guidelines. Animal studies suggest that antibiotics may have a beneficial effect on outcome [5].

At present blood sampling is not of critical importance in the diagnosis, but is used to evaluate the extent of metabolic acidosis and organ dysfunction. New biomarker developments indicate that products of intestinal cell damage may be useful in diagnosing acute intestinal ischaemia, increased urine concentrations of intestinal fatty-acid binding protein have an excellent likelihood ratio in diagnosing and excluding mesenteric ischaemia in patients suspected of having this condition [6].

The second step is to perform arterial and late venous phase CTA expeditiously. With current scanners, a total-body CT scan takes less than 1 minute. Therefore, in our opinion, scans should include the thorax and abdomen, and extend down to the groins. When there is a clear occlusion of the origin of the SMA and/or coeliac trunk (Cx) with signs of bowel infarction, the next step should be a revascularization procedure. Nowadays it is common practice to perform an endovascular revascularization of the SMA and to stent its origin. In case of multi-vessel involvement in chronic mesenteric ischaemia one vessel revascularization (SMA) is as good as two vessel revascularization (SMA and Cx) [7]. In patients with AMI, revascularization and stenting of the SMA alone is suggested to minimize the time of the procedure and to get the patient as quickly as possible to the third step. After revascularization, or in the absence of occlusion of the SMA or Cx, an expeditious laparotomy should follow.

The third step is a laparotomy to diagnose the (amount of) ischaemia and to resect any necrotic bowel without anastomoses. If angiographic revascularization of the SMA is not successful, a surgical revascularization procedure is of the utmost importance although this will substantially increase the complexity and length of the operation. One option is to identify the SMA, cannulate it, and then revascularize the occluded stenotic artery retrogradely by angioplasty. If the occlusion is caused by an embolus, the SMA can be transversely incised and an embolectomy performed. If this fails, a bypass operation (preferably venous) is the only other option, but this will significantly prolong the operation.

Another advantage of stenting prior to operation is that the bowel has time to recompensate, which probably results in less necrotic bowel to resect.

Any patchy segments of bowel should not be resected, but left *in situ*. The patient should then be transported to the ICU for further stabilization. A second look can be performed after 24–48 hours, during which a re-assessment of the viability of the patchy segments should be performed. Bowel continuation can now be performed with an anastomosis if the patient is stable and vasoactive support minimized.

Treatment of a venous occlusion is aimed at restoring the outflow. This can be performed by administering thrombolytic therapy directly with an angiography catheter placed in the SMA [5]. The patient is subsequently monitored carefully and, if deterioration occurs, surgery must be performed to check for necrotic bowel. Another option is to perform a venous thrombectomy. If necrotic bowel is suspected a laparotomy should be performed with resection, but without any intestinal anastomoses. Similarly, a second look operation should be performed after 24–48 hours. However, the literature is scarce as to what constitutes the best treatment option [3].

The treatment of NOMI is to treat the underlying cause. Surgery is only aimed at resecting any necrotic bowel, after which a stoma is usually placed primarily as the affected patients are generally severely ill and not expected to recover within 24–48 hours to allow bowel anastomoses to be performed. Therefore, any patchy segments are also directly resected. Some advocate papaverine infusion directly into the SMA [5], but no good clinical evidence is currently available.

Intensive care treatment

Patients with AMI are severely ill and should be monitored and treated on the ICU. The point of ICU admission and the treatment policy can both vary depending on the patient's clinical condition. If a patient is admitted to ICU after an assumption of AMI, but before CT scan confirmation, the treatment strategy should be initially focused upon patient stabilization. This includes providing LMWH in a therapeutic dose, inserting central venous and arterial

lines, urinary catheterization, administering fluid and antibiotics, taking blood samples, and providing respiratory and haemodynamic support, as needed. However, as none of these strategies is life-saving without bowel revascularization, there should be no delay in performing CT angiography and undertaking endovascular revascularization or surgery, as necessary.

Once the first three steps have been performed, the ICU and surgical staff should decide when to perform the second-look operation as the fourth step. This depends on any haemodynamic instability and other signs of deterioration of organ function. It may thus be advisable to perform this second look operation earlier, preferably in the operating theatre, but in case of gross instability, on the ICU. If vasoactive support is reduced, the second look operation may be delayed a little longer than 48 hours to allow bowel anastomosis without the need for a stoma.

Outcome

The time a patient spends on the ICU depends on many issues and is therefore unpredictable. An open revascularization may lead to pancreatic problems, e.g. (necrotic) pancreatitis and pseudocysts. The necrotic bowel can produce abscesses while suture dehiscence may occur with bowel anastomoses. The revascularization procedure can fail and create new bowel necrosis or hepatic insufficiency/necrosis. With an atherosclerotic aetiology underlies the AMI, other organs may also be affected such as the heart, kidneys, and peripheral arterial system.

If the AMI is secondary to NOMI, the options are more limited. Necrotic bowel should be resected since this causes a systemic inflammatory reaction. Again, no anastomoses are performed and, usually, stomata are directly fashioned. By observing the stoma any new ischaemia can be seen although this is a weak follow-up tool. If new bowel ischaemia is suspected, a second look operation should be performed, even in the absence of a necrotic stoma.

The overall in-hospital mortality of AMI in patients receiving supportive care is 74%. However this varies greatly, from 44% in venous thrombosis and 71% in SMA embolism to 87% in SMA thrombosis and 80% in NOMI [8]. In this systematic review there were suggestions that an aggressive approach of early diagnosis, early restoration of perfusion to the intestine, resection of necrotic bowel, second-look laparotomy, and ICU treatment has improved outcomes for arterial embolism and venous thrombosis, whereas mortality rates following treatment for arterial thrombosis and NOMI had not changed [8].

References

1. Huerta C, Rivero E, Montoro MA, and Garcia-Rodriguez L.A. (2011). Risk factors for intestinal ischaemia among patients registered in a UK primary care database: a nested case-control study. *Alimentary Pharmacology & Therapy*, **33**, 969–78.
2. Acosta S. (2010). Epidemiology of mesenteric vascular disease: clinical implications. *Seminars in Vascular Surgery*, **23**, 4–8.
3. Endean ED, Barnes SL, Kwolek C, et al. (2001). Surgical management of thrombotic acute intestinal ischaemia. *Annual of Surgery*, **233**, 801–8.
4. Dahlke MH, Asshoff L, Popp FC, et al. (2008). Mesenteric ischaemia-outcome after surgical therapy in 83 patients. *Digestive Surgery*, **25**, 213–19.
5. Frishman WH, Novak S, Brandt LJ, et al. (2008). Pharmacologic management of mesenteric occlusive disease. *Cardiology in Review*, **16**, 59–68.
6. Thuijls G, van Wijck K, Grootjans J, et al. (2011). Early diagnosis of intestinal ischemia using urinary and plasma FABPs. *Annals of Surgery*, **253**, 303–8.
7. Malgor RD, Oderich GS, McKusick MA, et al. (2010). Results of single- and two-vessel mesenteric artery stents for chronic mesenteric ischaemia. *Annals of Vascular Surgery*, **24**, 1094–101.
8. Schoots IG, Koffeman GI, Legemate DA, Levi M, and van Gulik TM. (2004). Systematic review of survival after acute mesenteric ischaemia according to disease aetiology. *British Journal of Surgery*, **91**, 17–27.

CHAPTER 187

Intra-abdominal sepsis in the critically ill

Jeffrey D. Doyle and John C. Marshall

Key points

- Intra-abdominal infection encompasses a broad group of infections arising both within the peritoneal cavity and the retroperitoneum.
- The likely bacteriology reflects patterns of normal and pathologic colonization of the gastrointestinal tract, anaerobic bacteria are found in the distal small bowel and colon.
- The duration of antibiotic therapy depends on the success of source control, and can be very short when source control is successful.
- Source control measures—drainage of fluid, debridement of infected tissue, and definitive control of the source of contamination—are needed for most intra-abdominal infections.
- In an unstable patient, damage control measures and a staged surgical approach can be life-saving.

Introduction

The abdomen is the second most common site of infection leading to sepsis in critically-ill patients [1]. Intra-abdominal infections can be complex to manage and require excellent collaboration between intensivists, diagnostic and interventional radiologists, surgeons, and sometimes gastroenterologists, and infectious disease specialists. Prompt diagnosis, appropriate antimicrobial coverage, and timely source control are the cornerstones of successful management. The spectrum of pathological conditions responsible for intra-abdominal infection is broad. However, some common biological features facilitate an understanding of their diagnosis and management.

Biological considerations

Anatomy and physiology of the peritoneal cavity

The peritoneal cavity is a continuous space created by the layer of mesothelial cells that covers most of the abdominal viscera [2]. In health, the potential space contains approximately 50–100 mL of protein-rich fluid, as well as scattered peritoneal macrophages. This fluid is produced continuously, circulates superiorly as a consequence of negative pressure created by diaphragmatic movements, and is resorbed into the lymphatics through specialized fenestrations at the diaphragm.

Bacteria, damaged tissues, or other damage-associated molecular patterns (DAMPs) activate the resident peritoneal macrophage population and incite a vigorous local inflammatory response. Chemo-attractants such as interleukin-8 from the macrophage induce a robust influx of neutrophils, while up-regulation of tissue factor on the macrophage surface activates coagulation factors in the peritoneal fluid, resulting in fibrin deposition. Together these processes serve to contain the threat through the creation of an abscess—a fibrin-encased structure containing neutrophils, bacteria, and tissue fluid (Fig. 187.1). The peritoneal membrane is exquisitely pain-sensitive, and inflammation results in pain and tenderness localized to the site of the inflammatory response.

The abdominal viscera, on the other hand, do not have visceral pain fibres, and visceral pain is experienced as localized to the vascular supply of the organ and its embryological origin as the **foregut** (supplied by the coeliac axis and extending from the gastro-oesophageal junction to the duodenum), the **mid-gut** (supplied by the superior mesenteric artery and extending from the duodenojejunal flexure to the splenic flexure of the colon), or the **hindgut** (supplied by the inferior mesenteric artery and extending from the splenic flexure to the rectum). Visceral pain is experienced in the midline, with foregut pain in the epigastrium, midgut pain in the peri-umbical region, and hindgut pain in the suprapubic region. The nature and location of abdominal pain is highly informative in establishing a diagnosis. Colicky epigastric pain suggests obstruction of a foregut organ, most commonly the gall bladder. Constant severe peri-umbilical pain suggests ischaemia, for example from an acute superior mesenteric artery thrombosis, while localized left lower quadrant pain and tenderness is characteristic of the peritoneal inflammation resulting from acute diverticulitis.

Microbiology of the gastrointestinal tract

The lumen of the gastrointestinal tract houses an enormously dense and complex flora, and it is these organisms that emerge as the dominant infecting species in intra-abdominal infections. Numerically, bacterial cells in the gut exceed the total number of host cells by a factor of 10:1, and current estimates are that there are at least as many as 1000 distinct microbial species present in the human gastrointestinal tract [3]. Anaerobic organisms are uncommon in the upper gastrointestinal tract, which is typically lightly colonized by Gram-positive species, and occasional Gram-negative organisms, the latter being more common when gastric acid secretion is reduced. The diversity of the flora increases in a

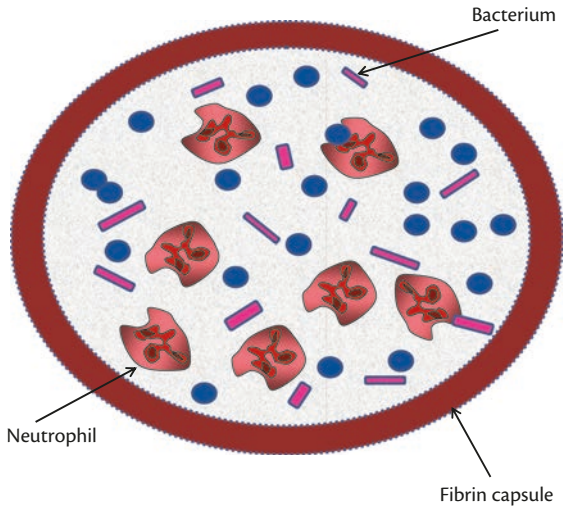


Fig. 187.1 The anatomy of an abscess. An abscess consists of a collection of inflammatory cells (predominantly neutrophils), bacteria, and tissue fluid, enclosed within a fibrin capsule whose formation is triggered by local activation of coagulation.

caudal direction, and anaerobes predominate in the distal small bowel and colon.

The indigenous flora plays a key role in normal host homeostasis, including the development of the gut epithelium, the digestion of intraluminal nutrients, and the maturation of the innate and adaptive immune systems. Critical illness is associated with striking changes in both the composition and the virulence of the gut flora, changes that contribute to the complications of severe intra-abdominal infection. Microbial overgrowth and a reduction in the numbers of anaerobic organisms promote the passage of intact, viable organisms across the gut mucosa—a process known as bacterial translocation [4]. Changes in the luminal environment of the gastrointestinal tract can promote the expression of virulence factors in bacteria such as *Pseudomonas* [5].

Definitions and classification

The term, 'intra-abdominal infection' encompasses a heterogenous group of infectious processes, associated with differing approaches to clinical management and strikingly different outcomes. While the patient with acute appendicitis may be managed by appendectomy and a very brief hospital stay, or the patient with acute diverticulitis may respond to outpatient antibiotic therapy alone, similar patients with infected peri-pancreatic necrosis or intestinal infarction typically face a substantial risk of mortality and a prolonged stay in the intensive care unit (ICU).

Intra-abdominal infection denotes any infectious process occurring within the abdomen, between the diaphragm superiorly and the pelvic cavity inferiorly. These infections may arise within the peritoneal cavity or in the retroperitoneal space, e.g. in pancreas or kidneys. Peritonitis refers to inflammation of the peritoneal cavity, and may result from sterile insults such as an early perforated duodenal ulcer, as well as from intra-abdominal infection. Peritonitis can further be classified as **primary**, **secondary**, or **tertiary** [6]. **Primary peritonitis** arises spontaneously, in the absence of a breach of the gastrointestinal tract. It is characteristically caused by a single micro-organism, such as occurs in young women with streptococcal infection, and in cirrhotics with spontaneous bacterial peritonitis. **Secondary peritonitis** is peritonitis arising from disruption of the gastrointestinal tract, with contamination of the peritoneal space with gut micro-organisms. It is typically polymicrobial in nature, the microbial flora reflecting normal patterns of colonization of the GI tract where the perforation occurred. **Tertiary peritonitis** is defined as peritonitis recurring or persisting after apparently adequate treatment of primary or secondary peritonitis. The infecting species in tertiary peritonitis are generally resistant organisms such as yeast, *Enterococcus* species, coagulase-negative *Staphylococcus* and multi-resistant Gram-negative bacilli [7].

Intra-abdominal infections can be further classified on the basis of the organ involved and whether the infection is **uncomplicated** (associated with minimal physiological derangement and amenable to successful treatment by surgical resection or systemic antibiotics) or **complicated** (associated with significant physiological derangement, and less readily managed using simple source control measures).

Diagnosis

The diagnosis of intra-abdominal infection in patients initially presenting to hospital is usually quite straightforward, based on the results of a comprehensive history and physical examination, supported by findings on diagnostic imaging. The history is of sentinel importance. The location of the abdominal pain, and its radiation and aggravating and relieving factors, all point to a diagnosis that may be definitive, even in the absence of laboratory data or diagnostic imaging. Physical findings support the impression derived from the history, tenderness associated with localized pain suggests a localized inflammatory process, whereas pain in the absence of tenderness suggests ischaemia in the absence of inflammation of the overlying peritoneum. Imaging modalities such as ultrasonography and computerized tomography (CT) scanning can confirm the diagnosis, although clinical findings of peritonitis with instability, or simple radiographic findings such as free air on plain films, may render more sophisticated imaging studies unnecessary.

In contrast, patients who develop intra-abdominal infection in the ICU are more difficult to evaluate. The history and physical examination are challenging. Signs of infection may be masked by co-existing disease processes or immunosuppression, while manifestations such as leukocytosis and metabolic acidosis are prevalent in the critically-ill patient and thus non-specific for the identification of intra-abdominal infection. The clinical context is key. Has the patient had a prior abdominal procedure? Has he or she had a prior episode of significant hypotension that could result in mesenteric ischaemia? Does the patient have risk factors such as peripheral vascular disease, atrial fibrillation, recent myocardial infarction, or a hypercoagulable state? Physical examination will often reveal focal tenderness, even in the presence of moderate analgesia or sedation. However, most patients who are haemodynamically stable should undergo abdominal imaging to clarify the diagnosis. Imaging also facilitates a more targeted approach to source control, including non-operative management or minimally invasive approaches, such as percutaneous drainage. Ultrasonography is particularly useful in evaluating the gall bladder and biliary tree. However, the primary diagnostic imaging modality is CT, with oral and/or intravenous contrast. A diagnosis—at least indicating a

Table 187.1 Empiric antimicrobial therapy of community-acquired intra-abdominal infection

	Mild-to-moderate severity	High risk or severity
Single agent	Cefoxitin, ertapenem, moxifloxacin, tigecycline, or ticarcillin-clavulanic acid	Imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam
Combination	Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole	Cefepime, ceftazidime, ciprofloxacin, or levofloxacin, each in combination with metronidazole

problem for which source control is indicated—is usually possible, and exploratory laparotomy in the absence of radiographic support should be uncommon in the contemporary ICU patient.

Management

Successful management of intra-abdominal infection in the critically-ill patient is grounded in three principles—adequate haemodynamic resuscitation, appropriate antibiotic therapy, and effective source control. The principles of haemodynamic resuscitation do not differ from those applied to any cause of haemodynamic instability, and will not be discussed further here.

Antibiotic therapy

Despite the complexity of the indigenous gut flora that is responsible for secondary bacterial peritonitis, animal studies reveal that adequate antibiotic therapy can be achieved using agents that target enteric Gram negative organisms such as *E. coli* and obligate anaerobes such as *B. fragilis*; the utility of agents directed against common Gram positive organisms such as the *Enterococcus* is uncertain. Based on these principles, a number of antibiotic regimens are available, and none show clear evidence of superiority Table 187.1 [8]. Hospital-acquired infections and tertiary peritonitis typically yield resistant species, and so the initial selection of empiric therapy must reflect the expanded spectrum of infecting organisms. Initial therapy with an agent or combination that is recommended for high-risk community-acquired infection is appropriate. However the selection must be tailored based on prior patterns of patient colonization and resistance patterns within the institutional environment. Antibiotics should be administered as soon as the diagnosis is entertained as delay in initiating appropriate therapy is associated with an increase in mortality [9].

Although identification of *Enterococcus* in peritoneal samples is correlated with worse outcomes, it is not clear whether *Enterococcus* is a pathogen or simply a marker of more complicated disease [10]. Specific anti-enterococcal therapy should be considered in the immunocompromised patient or in the patient with a prosthetic heart valve or other implanted intravascular device [11]. Fungi are common isolates from patients with health care-associated infections and recurrent gastrointestinal perforations. While systemic antifungal therapy is the standard of care, the benefits of treatment are difficult to establish [12].

The optimal duration of antibiotics for intra-abdominal infection is unknown, although most recommend treatment for no more than 4–7 days if source control has been successful [8], and even less for uncomplicated infections such as appendicitis or perforated peptic ulcer disease. Patients who manifest persistent signs of infection at 4–7 days post-operatively should be re-evaluated for the adequacy of source control.

Source control

The phrase '**source control**' encompasses all physical measures that are undertaken to eliminate a source of infection, control ongoing contamination, and restore optimal anatomy and function [13]. Source control measures are particularly important in the management of intra-abdominal infection. While laparotomy has been the classical approach to achieve source control in intra-abdominal infections, laparoscopy, percutaneous drainage for contained intra-abdominal abscesses, or endoscopic decompression for ascending cholangitis are less invasive approaches that are the preferred mode of intervention in specific circumstances.

Methods of source control

Source control measures include drainage, debridement, device removal, and definitive measures.

Drainage is the creation of a controlled *fistula* (an abnormal communication between two epithelial-lined surfaces) or *sinus* (a communication between a closed space and a single epithelial surface) in order to externalize a focus of invasive infection. Drainage can be achieved through surgical intervention, however, image-guided percutaneous drainage provides safe and effective source control for many intra-abdominal infections. Percutaneous drainage does not require general anaesthesia, results in minimal physiologic disruption, and maximizes the options for later definitive measures. Moreover, it can be performed at the bedside in the ICU. Percutaneous drainage should be considered as an initial modality for source control whenever possible. It is, however, not effective for patients with generalized peritonitis or diffuse free fluid or free air on imaging, and its effectiveness of drainage may be limited by highly viscous material or multiloculated abscesses. Patients with ongoing enteric drainage from their percutaneous drains will often need subsequent operative management, but this can be safely deferred until the patient is more stable.

Debridement is the physical removal of solid infected or necrotic material. As a general principle, surgical excision of infected necrotic tissue, for example, in the patient with intestinal infarction, is an emergency that should be undertaken as quickly as possible. The exception to this principle is infected peripancreatic necrosis. Case series and a randomized trial have shown that delayed surgical intervention is associated with improved survival, because intervention before the infected retroperitoneal necrosis has adequately demarcated from adjacent viable tissue runs the risk of uncontrollable retroperitoneal bleeding [14]. An approach that combines earlier percutaneous drainage of peripancreatic fluid collections with delayed, minimally invasive debridement of infected peripancreatic necrosis has been demonstrated to minimize the complications of intervention, and to maximize survival [15] (Fig. 187.2).

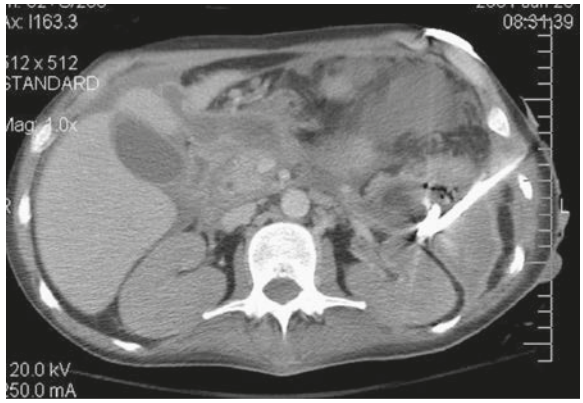


Fig. 187.2 A step-up approach for the management of infected peripancreatic necrosis. A complex retroperitoneal infection arising in a focus of necrotic peripancreatic tissue was managed by early percutaneous drainage to evacuate the liquid component of the infection and reduce the pressure within the infectious focus (black arrow), followed several weeks later by a minimally-invasive pancreatic necrosectomy, inserting the camera through the tract created by the percutaneous drain.

For complex intra-abdominal infections in the unstable critically-ill patient, a **damage control** approach is commonly used—draining or debriding the responsible focus, but deferring reconstruction and abdominal wall closure until the patient has been stabilized in the ICU. For example, a segment of gangrenous intestine can be resected, leaving the ends of the viable bowel stapled off, any areas of persistent bleeding packed, and the abdomen temporarily closed. Re-exploration in 24–72 hours enables evaluation of the viability of the remaining bowel, re-anastomosis or creation of a stoma, and definitive abdominal wall closure (Fig. 187.3).

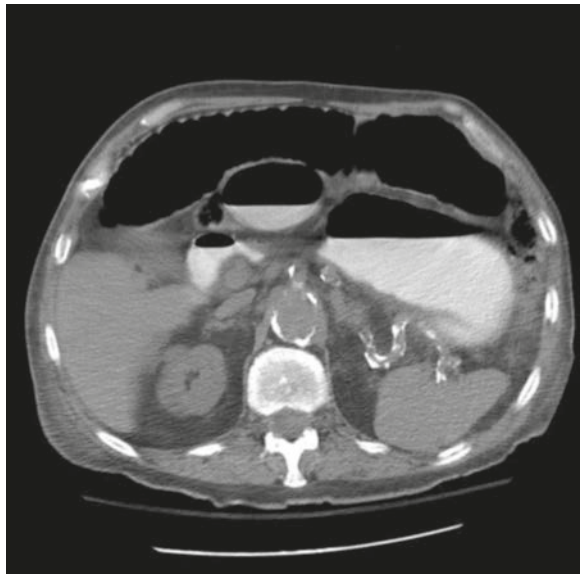


Fig. 187.3 Damage control laparotomy. This 57-year-old man with coronary artery disease and dialysis-dependent chronic renal failure presented with septic shock and CT evidence of right colon ischaemia. He was managed emergently by laparotomy to resect the ischaemic colon, leaving the ends of the viable intestine stapled off, and the abdomen open. Two days later, and following haemodynamic stabilization, re-exploration was undertaken, and an anastomosis created between the two ends of defunctional bowel. A further 2 days later the abdomen was closed.

If at all possible, it is preferable to avoid open abdomen management of intra-abdominal infection. Moreover, planned relaparotomy has not been proven to improve outcomes when compared to laparotomy on demand [16]. An open abdomen approach may be necessary in the setting of damage control surgery, for the treatment of intra-abdominal compartment syndrome, or when there has been extensive loss of the abdominal wall. It also simplifies management in patients for whom re-exploration is planned—most commonly patients with intestinal ischaemia or infarction.

Conclusion

Intra-abdominal infections make up an anatomically and clinically heterogeneous group of potentially life-threatening illnesses. Adequate source control is key to their successful management, and close collaboration between the intensivist, surgeon, and interventional radiologist is key to a maximally successful outcome. Advances in diagnostic imaging and in the understanding of host-microbial interactions are facilitating focused and more minimally disruptive management strategies—specifically image-guided source control and short duration focused antibiotic therapy. Nonetheless, for some patients, a staged or damage control approach provides the simplest solution to a complex problem.

References

1. Vincent JL, Sakr Y, Sprung CL, et al. (2006). Sepsis in European intensive care units: results of the SOAP study. *Critical Care Medicine*, **34**, 344–53.
2. van der Wal JB and Jeekel J. (2007). Biology of the peritoneum in normal homeostasis and after surgical trauma. *Colorectal Disease*, **9**(2), 9–13.
3. Sommer F and Backhed F. (2013). The gut microbiota—masters of host development and physiology. *Nature Review Microbiology*, **11**, 227–38.
4. Marshall JC, Charbonney E, and Gonzalez PD. (2008). The immune system in critical illness. *Clinical Chest Medicine*, *29*, 605–16.
5. Wu L, Estrada O, Zaborina O, et al. (2005). Recognition of host immune activation by Pseudomonas aeruginosa. *Science*, **309**, 774–7.
6. Rotstein OD and Meakins JL. (1990). Diagnostic and therapeutic challenges of intraabdominal infections. *World Journal of Surgery*, **14**, 159–66.
7. Nathens AB, Rotstein OD, and Marshall JC. (1998), Tertiary peritonitis: Clinical features of a complex nosocomial infection. *World Journal of Surgery*, **22**, 158–63.
8. Solomkin JS, Mazuski JE, Bradley JS, et al. (2010). Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clinical Infectious Diseases*, **50**, 133–64.
9. Kumar A, Roberts D, Wood KE, et al. (2006). Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Critical Care Medicine*, **34**, 1589–96.
10. Sotto A, Lefrant JY, Fabbro-Peray P, et al. (2002). Evaluation of antimicrobial therapy management of 120 consecutive patients with secondary peritonitis. *Journal of Antimicrobial Chemotherapy*, **50**, 569–76.
11. Harbarth S and Uckay I. (2004). Are there patients with peritonitis who require empiric therapy for enterococcus? *European Journal of Clinical Microbiology & Infectious Diseases*, **23**, 73–7.
12. Montravers P, Mira JP, Gangneux JP, Leroy O, and Lortholary O. (2011). A multicentre study of antifungal strategies and outcome of

Candida spp. peritonitis in intensive-care units. *Clinical Microbiology and Infection*, **17**, 1061–7.
13. Marshall JC, Maier RV, Jimenez M, and Dellinger EP. (2004). Source control in the management of severe sepsis and septic shock: an evidence-based review. *Critical Care Medicine*, **32**(11), 513–26.
14. Mier J, Leon EL, Castillo A, Robledo F, and Blanco R. (1997). Early versus late necrosectomy in severe necrotizing pancreatitis. *American Journal of Surgery*, **173**, 71–5.
15. van Santvoort HC, Besselink MG, Bakker OJ, et al. (2010). A step-up approach or open necrosectomy for necrotizing pancreatitis. *New England Journal of Medicine*, **362**, 1491–502.
16. Van Ruler O, Mahler CW, Boer KR, et al. (2007). Comparison of on-demand vs planned relaparotomy strategy in patients with severe peritonitis: a randomized trial. *Journal of the American Medical Association*, **298**, 865–72.

CHAPTER 188

Acute acalculous cholecystitis in the critically ill

Vanessa P. Ho and Philip S. Barie

Key points

- Acute acalculous cholecystitis should be suspected in every critically-ill patient with sepsis in whom the source of infection cannot be found immediately.
- Suspicion should be especially high if the patient is injured, has undergone recent major surgery, has had a period of hypotension or hypoperfusion for any reason, or becomes jaundiced.
- The preferred diagnostic modality is ultrasound, which is inexpensive, non-invasive, and can be brought to the bedside of the unstable patient.
- Once diagnosed, the treatment of choice is percutaneous cholecystostomy, but if the response to drainage is not prompt and favourable, an alternative diagnosis must be considered and abdominal exploration may be required.
- If percutaneous drainage is successful and a cholangiogram verifies that there are no gallstones present, then the catheter may be removed after resolution of the disease with no further treatment.

Introduction

Acute acalculous cholecystitis (AAC) is the development of acute inflammation of the gallbladder in the absence of gallstones. The development of AAC is not limited to surgical or injured patients, or even to the intensive care unit, although it is generally considered to be a complication of serious medical and surgical illnesses [1,2]. It is especially related to patients with trauma, burns, sepsis, prolonged fasting, or total parenteral nutrition. The diagnosis may be elusive as the clinical symptoms of fever, leukocytosis, and abnormal liver function tests are nonspecific in this population, even abdominal pain is not necessarily a reliable symptom. Despite the diagnostic difficulties, more cases of AAC are being identified as a result of increased numbers of critically-ill patients, increased physician awareness, and improved imaging modalities [3]. The mortality rate remains at least 30% because, the diagnosis of AAC remains challenging to make, the affected patients are already critically ill, and the disease itself can progress rapidly owing to the high prevalence of gangrene (~50%) and perforation (~10%) [4].

Clinical patterns of acute acalculous cholecystitis

AAC may occur in surgical or injured patients, critically-ill patients, and systemically ill patients. Reports of acute cholecystitis complicating surgery, multiple trauma, or burn injury are widespread and well-described [5,6]. The incidence of AAC following open abdominal aortic reconstruction is 0.7–0.9%, and has also been reported to complicate endovascular aortic reconstruction. After cardiac surgery, the incidence of acute cholecystitis is 0.12%, with an overall mortality rate of 45% [4].

Among medical patients, a variety of systemic diseases have been associated with the development of AAC. Diabetes mellitus, abdominal vasculitis, congestive heart failure, cholesterol embolization of the cystic artery, and resuscitation from haemorrhagic shock or cardiac arrest have been associated with AAC [2,4]. AAC has also been described in patients with end-stage renal disease, cancer, bone marrow transplant recipients, and autoimmune deficiency syndrome.

Acalculous cholecystitis may also develop as a secondary infection of the gallbladder during systemic sepsis for a wide range of infections. Small case series and case reports have described AAC associated with disseminated candidiasis, leptospirosis, *Salmonella* spp., cholera, tuberculosis, malaria, brucellosis, and dengue fever [4,7]. Extrahepatic biliary obstruction can also cause AAC from infectious or non-infectious causes. Obstructive infectious causes include ascariasis and echinococcus; non-infectious obstructive causes include haemobilia, choledochal cyst, and ampullary stenosis [4].

Children may also be affected, especially following a viral illness. Acute acalculous cholecystitis represents 50–70% of all cases of acute cholecystitis in children [7]. Acalculous cholecystitis is recognized in young children and neonates, as well as older children. Dehydration is a common precipitant, as are acute bacterial infections and viral illnesses such as hepatitis and upper respiratory tract infections [8]. Portal lymphadenitis with extrinsic cystic duct obstruction may be aetiological in viral infections.

Pathogenesis

The pathogenesis of AAC is complex and multifactorial. Ischaemia and the associated pro-inflammatory response and oxidative tissue stress is likely the initial insult resulting in microvascular occlusion of the gallbladder, this is likely potentiated by bile stasis, which allows bile and bacterial infiltration into the gallbladder wall [9]. Gallbladder specimen arteriography supports the theory that vascular occlusion is an important step in pathogenesis, arteriography after AAC shows multiple arterial occlusions and minimal-to-absent venous filling. In contrast, gallbladder specimen arteriography in gallstone-related disease is markedly different with arterial dilatation and extensive venous filling [10].

Box 188.1 Imaging Criteria for the Diagnosis of AAC [7,12,13,20]

Ultrasound

Either two major, or one major criterion and two minor criteria, satisfy the ultrasound diagnosis of AAC.

Major criteria

- Gallbladder wall thickening >3.5 mm.
- Striated gallbladder (i.e. gallbladder wall oedema).
- Sonographic Murphy sign (inspiratory arrest during deep breath, while gallbladder is being insonated; unreliable if patient is obtunded or sedated).
- Pericholecystic fluid.
- Mucosal sloughing.
- Intramural gas.

Minor criteria

- Gallbladder distension (>5 cm in transverse diameter).
- Echogenic bile (sludge).

Computed tomography (CT)

Either two major, or one major criterion and two minor criteria, satisfy the CT diagnosis of AAC.

Major criteria

- Gallbladder wall thickening >3 mm.
- Subserosal halo sign (intramural lucency caused by oedema).
- Pericholecystic infiltration of fat.
- Pericholecystic fluid (absent either ascites or hypoalbuminaemia).
- Mucosal sloughing.
- Intramural gas.

Minor criteria

- Gallbladder distension (>5 cm in transverse diameter).
- High-attenuation bile (sludge).

Hepatobiliary scintigraphy

- Non-visualization or questionable visualization of the gallbladder 1 hour after administration of 5 mCi of a ^{99m}Tc iminodiacetic acid derivative, in the presence of adequate hepatic uptake of tracer, and excretion into the duodenum.
- Morphine sulphate, 0.04–0.05 mg/kg intravenously, may be given after 30–40 minutes of non-visualization to increase specificity at 1 hour.
- Enhanced accumulation of radiotracer in the gallbladder fossa may be indicative of gallbladder gangrene or perforation.

Data from: Barie PS and Eachempati SR, 'Acute acalculous cholecystitis', *Current Gastroenterology Reports*, 2003, **5**, pp. 302–9; Mirvis SE et al., 'The diagnosis of acute acalculous cholecystitis: a comparison of sonography, scintigraphy, and CT', *American Journal of Roentgenology*, 1986, **147**, pp. 1171–5; Deitch EA and Engel JM, 'Acute acalculous cholecystitis. Ultrasonic diagnosis', *American Journal of Surgery*, 1981, **142**, pp. 290–2; Hopfer K and Ziessman H, 'Nuclear medicine hepatobiliary imaging (cholescintigraphy)', *Gastrointestinal Endoscopy*, 2011, **74**, pp. 375–7.

Bile stasis is also an important risk factor for the development of AAC. Volume depletion from dehydration or lack of oral intake leads to concentration of bile, which can inspissate in the absence of a stimulus for gallbladder emptying. Opioid analgesics lead to increased biliary pressure secondary to spasm of the sphincter of Oddi; ileus and mechanical ventilation may also contribute to bile stasis. Bile stasis potentially contributes to the development of AAC by two separate mechanisms. Firstly, bile stasis may alter the chemical composition of bile allowing for local gallbladder mucosal injury. Secondly, stasis may potentiate gallbladder ischaemia by increasing intraluminal pressure and increasing gallbladder wall tension, which would allow bacterial invasion of ischaemic tissue as a secondary phenomenon. Reperfusion may lead to further injury [4].

Fasting and bile stasis may be potentiated by the administration of total parenteral nutrition (TPN) in the pathogenesis of AAC [11]. Parenteral nutrition is associated with both gallstone formation and acalculous cholecystitis in both adults and children. The incidence of AAC during long-term TPN may be as high as 30%. Formation of gallbladder 'sludge' occurs among 50% of patients on long-term TPN at 4 weeks and is ubiquitous at 6 weeks. However, neither stimulation of gallbladder emptying with cholecystokinin nor enteral alimentation can prevent AAC among critically-ill patients [11].

Although bacterial infection is likely a secondary phenomenon, the host response to Gram-negative bacteraemia or splanchnic ischaemia/reperfusion injury may also be an important contributor to the disease. In several non-human mammalian experiments, intravenous injection of *Escherichia coli* lipopolysaccharide (LPS), a potent stimulus of inflammation and coagulation that mimics clinical sepsis, produces AAC as well as decreased gallbladder contractility and mucosal injury. Cholecystitis has also been induced by factors that lead to cystic artery spasm in experimental models. The inflammation appears to be mediated by pro-inflammatory eicosanoids as it is inhibited by non-specific cyclooxygenase inhibitors [7].

Diagnosis

AAC poses major diagnostic challenges. Most afflicted patients are critically ill and unable to communicate their symptoms. Cholecystitis is but one of many potential causes in the differential diagnosis of the systemic inflammatory response syndrome or sepsis in such patients. Rapid and accurate diagnosis is essential, as gallbladder ischaemia can progress rapidly to gangrene and perforation. Acalculous cholecystitis is sufficiently common that the diagnosis should be considered in every critically ill or injured patient with a clinical picture of sepsis or jaundice and no other obvious source.

Physical examination and laboratory evaluation are unreliable. Fever is generally present, but other physical findings cannot be relied upon, particularly physical examination of the abdomen. Leukocytosis and jaundice are commonplace, but non-specific in the setting of critical illness. The differential diagnosis of jaundice in the critically-ill patient is complex and context-sensitive, including intrahepatic cholestasis from sepsis or drug toxicity and 'fatty liver' induced by TPN, in addition to AAC. Other biochemical assays of hepatic enzymes are of little help. The diagnosis of AAC thus often rests on radiologic studies.

Radiological studies

Three radiological modalities (ultrasound, CT, hepatobiliary scanning) are generally used for the diagnosis of AAC Box 188.1. Only a single retrospective study has compared all three modalities [12], ultrasonography and CT were comparably accurate and superior to hepatobiliary imaging. Ultrasound of the gallbladder is generally the first-line modality for the diagnosis of AAC in the critically-ill patient as it is rapid, low-risk, and portable. In calculous cholecystitis, ultrasonography is useful for detecting gallstones and measuring biliary duct diameter; in AAC, these measurements are not valuable. Thickening of the gallbladder wall is the single most reliable criterion, with reported specificities of 90% at 3.0 mm and 98.5% at 3.5 mm wall thickness, and sensitivities of 100% at 3.0 mm and 80% at 3.5 mm [13]. Accordingly, gallbladder wall thickness ≥3.5 mm is generally accepted to be diagnostic of AAC. Other helpful ultrasonographic findings for AAC include pericholecystic fluid, the presence of intramural gas, or a sonolucent intramural layer, or 'halo', which represents intramural oedema. Distension of the gallbladder of more than 5 cm in transverse diameter has also been reported [2,13]. False-positive ultrasound examinations may occur in particular when conditions including sludge, non-shadowing stones, cholesterolosis, hypoalbuminaemia, or ascites mimic a thickened gallbladder wall [12,13].

CT appears to be as accurate as ultrasound in the diagnosis of AAC. Diagnostic criteria for AAC by CT are similar to those described for ultrasonography Box 188.1. Low cost and the ability to perform ultrasonography rapidly at the bedside make it the preferred diagnostic modality in possible AAC in the ICU setting. Preference may be given to CT if other thoracic or abdominal diagnoses are under consideration. While technetium ^{99m}Tc iminodiacetic acid imaging is approximately 95% accurate to diagnose acute calculous cholecystitis, it is less useful for the diagnosis of AAC in the setting of critical illness [14]. Intravenous morphine (0.05 mg/kg) given after initial non-visualization of the gallbladder may increase the accuracy of cholescintigraphy among critically-ill patients, by enhancing gallbladder filling due to an increase in bile secretory pressure [14].

Laparoscopy

Bedside laparoscopy has been used with success for the diagnosis and therapy of AAC [15]. However, bringing the equipment to the ICU bedside is cumbersome. Laparoscopy can be performed under local anaesthesia and intravenous sedation at the bedside, and is possible in patients who have undergone recent abdominal surgery if 'gasless' techniques are used. Diagnostic accuracy is high, and both laparoscopic cholecystostomy and cholecystectomy have been performed if AAC is diagnosed, although no randomized trial data have been published. It may be reasonable to perform laparoscopy in critically-ill patients in whom AAC is suspected, but cannot be ruled out, and would otherwise require an exploratory laparotomy for diagnosis.

Therapy

Historically, the treatment for AAC was cholecystectomy, owing to the ostensible need to inspect the gallbladder and perform a resection if gangrene or perforation was discovered. Open cholecystostomy may be accomplished under local anaesthesia through a short right subcostal incision, but the ability to visualize elsewhere in the abdomen is limited. A laparotomy or laparoscopy would be required to drain distant fluid collections or identify other pathology that may mimic acute cholecystitis in the case of a misdiagnosis (e.g. perforated ulcer, cholangitis, pancreatitis). Currently, percutaneous cholecystostomy is now established as a life-saving, minimally-invasive alternative [16]. Percutaneous cholecystostomy controls the AAC in 70–90% of patients [17,18]. The gallbladder is usually intubated under ultrasonographic (occasionally laparoscopic) control via an anterior or anterolateral transhepatic approach (through the right hepatic lobe) in order to minimize leakage of bile, but transperitoneal puncture has been described [16,18]. Rapid improvement should be expected when percutaneous cholecystostomy is successful. Cholecystostomy will not decompress the common bile duct if cystic duct obstruction is present, therefore the common duct must be decompressed by some manner, e.g. endoscopic retrograde cholangiopancreatography [ERCP] with sphincterotomy, laparoscopic, or open common bile duct exploration, if cholangitis is suspected.

If percutaneous cholecystostomy does not lead to rapid improvement, the tube may be malpositioned or not draining properly, or the patient may have gangrenous cholecystitis. Other reported causes of failure include catheter dislodgement, bile leakage with peritonitis, or an erroneous diagnosis. Perforated ulcer, pancreatic abscess, pneumonia, and pericarditis have been discovered in the aftermath of percutaneous cholecystostomy when patients failed to improve. Reported major complications occur after 8–10% of procedures, including dislodgment of the catheter, acute respiratory distress syndrome (ARDS), bile peritonitis, haemorrhage, cardiac arrhythmia, and hypotension due to procedure-related bacteraemia [17,18]. An open cholecystostomy or cholecystectomy may be required if other sources of sepsis are ruled out and the patient continues to deteriorate. The 30-day mortality rates of percutaneous and open cholecystostomy are similar, and influenced heavily by the underlying severity of illness.

Empiric percutaneous cholecystostomy has been advocated for patients who have sepsis, but lacking a demonstrable source. In one report of 24 patients receiving vasopressor therapy for septic shock, 14 patients (58%) improved as a result of cholecystostomy [19]. Pneumonia was diagnosed subsequently in three of the ten non-responders, but an infection was never found in the other seven patients. Such an approach is not recommended routinely, but the importance of considering AAC in the differential diagnosis of occult sepsis is underscored.

Antibiotic therapy does not substitute for drainage of AAC, but is an important adjunct. The most common bacteria isolated from bile in acute cholecystitis are *E. coli, Klebsiella,* spp., and *Enterococcus faecalis,* thus antibiotic therapy should be directed against these organisms [4,17,19]. However, critical illness and prior antibiotic therapy alter host flora, and resistant or opportunistic pathogens may be encountered. *Pseudomonas,* staphylococci (including methicillin-resistant strains), *Enterobacter* and related species, anaerobic organisms (e. g. *Clostridium* spp., *Bacteroides* spp.), or fungi may be recovered [4]. Anaerobes are particularly likely to be isolated from bile of patients with diabetes mellitus, in those older than 70 years of age, and from patients whose biliary tracts have been instrumented previously.

Complications

The prevalence of gallbladder gangrene in AAC exceeds 50%, and leads to additional morbidity, including gallbladder perforation.

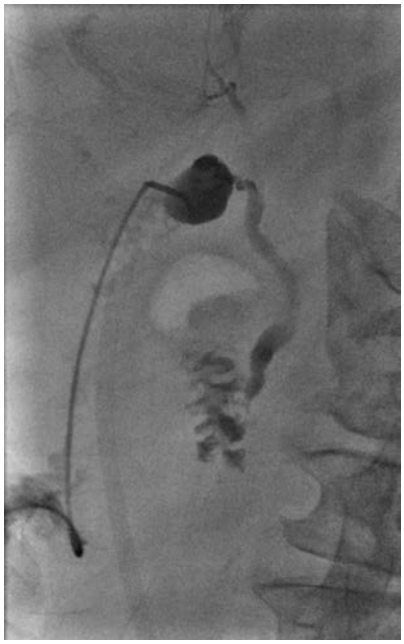


Fig. 188.1 Cholangiogram following percutaneous cholecystostomy, demonstrating a patent cystic duct and no gallstones present.

One variant—emphysematous cholecystitis—is particularly associated with gangrene and perforation. Crepitus to palpation of the right upper abdomen or radiographic identification of gas in patients with acute cholecystitis mandates immediate cholecystectomy in view of the fulminant nature of untreated emphysematous cholecystitis as percutaneous cholecystostomy does not achieve reliable source control. *Clostridium* spp., rather than aerobic Gram-negative bacilli, are isolated most commonly in emphysematous cholecystitis (45% of cases). Antimicrobial therapy specific for *Clostridium* (such as penicillin G) may be added to agents directed against the typical bacterial flora of acute cholecystitis.

Perforation of the gallbladder occurs in 10% or more of cases of AAC [3,4], either localized into the subhepatic space or free perforation with generalized peritonitis. Perforation into the liver or biliary tract has been reported rarely in AAC, as has perforation into the retroperitoneum with iliopsoas abscess. Rare causes of death from gallbladder perforation in AAC include haemorrhage from the liver, and pulmonary bile embolism. Serious complications of gallbladder gangrene without perforation include acute pancreatitis, colon perforation, and obstruction of the common hepatic duct. Empyema of the gallbladder may also complicate AAC.

Follow-up

Patency of the cystic duct can be determined immediately after the cholecystostomy is performed by tube cholangiography (Fig. 188.1). This should be performed again after the patient has recovered to determine the presence of gallstones that may have not been detected initially. If gallstones are present, an elective cholecystectomy is usually recommended, with the drainage tube remaining in place during the inter-procedure interval. For patients without gallstones, interval cholecystectomy is usually not indicated, and the cholecystostomy tube can be removed after tube cholangiography confirms that gallstones are absent. Recurrent episodes warrant cholecystecomy.

References

1. Glenn F and Becker CG. (1982). Acute acalculous cholecystitis. An increasing entity. *Annals of Surgery*, **195**, 131–6.
2. Huffman JL and Schenker S. (2010). Acute acalculous cholecystitis: a review. *Clinical Gastroenterology and Hepatology*, **8**, 15–22.
3. Kalliafas S, Ziegler DW, Flancbaum L, et al. (1998). Acute acalculous cholecystitis: incidence, risk factors, diagnosis, and outcome. *American Surgery*, **64**, 471–5.
4. Barie PS and Eachempati SR. (2010). Acute acalculous cholecystitis. *Gastroenterology Clinics of North America*, **39**, 343–57.
5. Crichlow L, Walcott-Sapp S, Major J, et al. (2012). Acute acalculous cholecystitis after gastrointestinal surgery. *American Surgery*, **78**, 220–4.
6. Pelinka LE, Schmidhammer R, Hamid L, et al. (2003). Acute acalculous cholecystitis after trauma: a prospective study. *Journal of Trauma*, **55**, 323–9.
7. Barie PS and Eachempati SR. (2003). Acute acalculous cholecystitis. *Current Gastroenterology Reports*, **5**, 302–9.
8. Tsakayannis DE, Kozakewich HP, and Lillehei CW. (1996). Acalculous cholecystitis in children. *Journal of Pediatric Surgery*, **31**, 127–30.
9. McChesney JA, Northup PG, and Bickston SJ. (2003). Acute acalculous cholecystitis associated with systemic sepsis and visceral arterial hypoperfusion: a case series and review of pathophysiology. *Digestive Disease Science*, **48**, 1960–7.
10. Hakala T, Nuutinen PJ, Ruokonen ET, et al. (1997). Microangiopathy in acute acalculous cholecystitis. *British Journal of Surgery*, **84**, 1249–52.
11. Bower R, Mrdeza MA, and Block GE. (1990). Association of cholecystitis and parenteral nutrition. *Nutrition*, **6**, 125–30.
12. Mirvis SE, Vainright JR, Nelson AW, et al. (1986). The diagnosis of acute acalculous cholecystitis: a comparison of sonography, scintigraphy, and CT. *American Journal of Roentgenology*, **147**, 1171–5.
13. Deitch EA and Engel JM. (1981). Acute acalculous cholecystitis. Ultrasonic diagnosis. *American Journal of Surgery*, **142**, 290–2.
14. Ziessman HA. (2010). Nuclear medicine hepatobiliary imaging. *Clinical Gastroenterology and Hepatology*, **8**, 111–16.
15. Ceribelli C, Adami EA, Mattia S, et al. (2012). Bedside diagnostic laparoscopy for critically ill patients: a retrospective study of 62 patients. *Surgical Endoscopy and Other Interventional Techniques*, **26**, 3612–15.
16. Lo LD, Vogelzang RL, Braun MA, et al. (1995). Percutaneous cholecystostomy for the diagnosis and treatment of acute calculous and acalculous cholecystitis. *Journal Vascular Interval Radiology*, **6**, 629–34.
17. Joseph T, Unver K, Hwang GL, et al. (2012). Percutaneous cholecystostomy for acute cholecystitis: ten-year experience. *Journal of Vascular Interval Radiology*, **23**, 83–8, e81.
18. McLoughlin RF, Patterson EJ, Mathieson JR, et al. (1994). Radiologically guided percutaneous cholecystostomy for acute cholecystitis: long-term outcome in 50 patients. *Cancer Association Radiology Journal*, **45**, 455–9.
19. Lee MJ, Saini S, Brink JA, et al. (1991). Treatment of critically ill patients with sepsis of unknown cause—value of percutaneous cholecystostomy. *American Journal of Roentgenology*, **156**, 1163–6.
20. Hopfer K, and Ziessman H. (2011). Nuclear medicine hepatobiliary imaging (cholescintigraphy). *Gastrointestinal Endoscopy*, **74**, 375–7.

CHAPTER 189

Management of the open abdomen and abdominal fistulae in the critically ill

Philip Stevens and Gordon Carlson

Key points

- Leaving the abdomen open when it is possible to close it confers no benefit and may increase morbidity.
- 50–80% of enterocutaneous fistulae close spontaneously, compared to only 10% of colonic fistulae.
- Entero-atmospheric fistulae are associated with significant mortality and prevention is paramount.
- Controversy exists regarding the risk of entero-atmospheric fistula with negative pressure wound therapy.
- Refistulation rates are high despite operative repair of gastrointestinal fistulae.

Introduction

Management of the open abdomen and intestinal fistulae remain significant challenges. Most patients will initially be critically ill and morbidity and mortality are significant. Management is best undertaken within an adequately equipped and experienced multidisciplinary team. Management priorities are discussed in the following sections, accompanied with levels of evidence and grading of recommendations according to the Oxford Centre for Evidence-based Medicine definitions [1].

The open abdomen

Indications

The abdomen may be left open deliberately at the end of a laparotomy (laparostomy) as part of a 'damage control' strategy in an unstable patient with abdominal trauma, or in other conditions in which it may be impossible to close the abdomen because swollen intestinal loops, retroperitoneal haematoma or oedema may lead to Abdominal Compartment Syndrome Table 189.1.

It may also be inappropriate to close the abdomen when there has been infection which cannot be readily controlled, for example, by resecting or exteriorising the source, or where there have been multiple previous surgical attempts to deal with intra-abdominal infection (tertiary peritonitis).

Pathogenesis

Conditions necessitating management with an open abdomen are invariably emergencies. Patients are (or frequently become) profoundly catabolic and malnourished. Protection of exposed and inflamed viscera is vital in order to avoid fistulation, which increases the complexity of management, delays recovery and may increase mortality.

Management

Leaving the abdomen intentionally open should be undertaken with an explicit strategy of either closing the abdomen as soon as the patient's condition allows (delayed primary closure) or leaving the abdomen to heal by secondary intention. Viscera should be covered by the omentum to reduce the likelihood of injury.

Temporary abdominal closure

Temporary closure may be achieved by patch interposition, negative pressure wound therapy (NPWT), silos (such as the Bogota bag), or by simple application of a non-adhesive 'sandwich' dressing. The aim is to protect the bowel from mechanical injury, allow removal of exudate and prevent the loss of 'domain' which otherwise occurs as a result of lateral retraction of the rectus muscles. Preservation of the domain into which the oedematous loops of bowel can be returned is essential if delayed primary closure is planned.

Patch techniques involve securing prosthetic material over the exposed viscera, usually with sutures. The artificial bur (Wittmann patch®) involves an interposition patch with hook-and-loop fastening in the midline. Absorbable mesh (e.g. polyglactin) is popular and inexpensive, allows the escape of exudate, and can be left in place to allow healing by secondary intention, granulation or later skin grafting, with late ventral hernia formation.

Silo techniques also employ synthetic material sutured to the abdominal wall. The 'Bogota bag' involves suture of an opened sterile, fluid irrigation bag circumferentially around the abdominal wall. Transparency of the bag allows inspection of viscera through a non-adherent protective barrier.

NPWT simplifies nursing care, avoiding the need for frequent changes of dressing and leakage. There is no evidence that

Table 189.1 Indications for open abdominal management

Intra-abdominal sepsis/ tertiary peritonitis/severe pancreatitis (**level 2b** evidence) [2,3]	Inability to defunction or exteriorise septic foci Technically impossible to close
Abdominal compartment syndrome (**level 3b** evidence) [4]	Intra-abdominal pressure >20 mmHg and evidence of organ dysfunction
Trauma/damage control laparotomy (**level 3b** evidence) [5]	No clear recommendations, but an inability to defunction, close or risk of ACS mandates laparostomy
Intracranial hypertension (**level 5** evidence) [6]	Observations of reduced intracranial pressure following decompressive laparostomy require further evaluation before recommendations can be made

Data from various sources (see references).

it enhances wound healing. Direct application against exposed bowel is not recommended because of the risk of fistulation, which may be considerably higher when NPWT is used for abdominal infection rather than trauma [7]. A recent large observational study has suggested that NPWT seems safe, although the rate of delayed primary closure was reduced (**level 2b**) [8]. The rate of fistulation confirmed the findings of an underpowered prospective randomized study that failed to demonstrate clear benefit from NPWT (**level 2b**) [9].

Nutritional support in the open abdomen

In many cases in which the abdomen has been left open, intestinal dysfunction or fistulation will preclude satisfactory enteral feeding, in which case parenteral nutrition is required. Where possible, enteral nutrition is preferable to promote intestinal adaptation and maintenance of gastrointestinal function. Early enteral feeding (within 4 days of operation) has been associated with a significant reduction in fistula rate, earlier primary abdominal closure and lower treatment costs compared with delayed enteral feeding (**level 3b**) [10].

Fistulae

A fistula is an abnormal communication between two epithelial surfaces. Nomenclature reflects the organs involved; 'enterocutaneous' indicating communication between intestine and skin, and 'enterovesical' from intestine to bladder. Although strictly a misnomer, 'entero-atmospheric' neatly describes the disturbing appearance of intestinal mucosa in the open abdominal wound.

Epidemiology

Post-operative intestinal fistulae are associated with considerable morbidity and mortality. Eradication of sepsis, improved wound and skin care, safe nutritional support and appropriate timing of surgical intervention have reduced mortality with from 65% to <10% over the last 30 years [11]. However, mortality from fistulation within the open abdomen has remained disturbingly high [12–14]. and may exceed 5%, even in highly selected patients treated under optimal conditions in specialist centres [15].

Aetiology

Fistulae are classified as primary or secondary, according to whether they result from the underlying disease, or as a complication of subsequent treatment. Primary fistulae are rare and arise largely in the context of Crohn's disease. They are also seen with diverticular disease, radiation enteritis, or malignancy. Secondary fistulae are much commoner and usually arise as a consequence of surgical management due to accidental injury to the gut or anastomotic leakage. The overwhelming majority of post-operative fistulae arise from the small intestine. Almost half follow surgery where no bowel resection has occurred, but the bowel has been injured and repaired.

Pathogenesis

Gastrointestinal fistulae result in catabolism due to a combination of sepsis and reduced nutrient intake. Fistulae are the commonest cause of severe acute intestinal failure (i.e. inability to maintain nutritional status in the absence of artificial nutritional support). Fistulae are described as simple or complex, the latter indicating the presence of multiple fistula tracks, an associated abscess cavity, or involvement of other organs. Fistulae are also described as 'high' output when volume excreted exceeds 500 mL per day (>200 mL per day for pancreatic fistulae). High output fistulation is strongly predictive of catabolism and mortality.

Management

General management principles are summarized by the four 'R's (Box 189.1).

Resuscitation

Initial management must address resuscitation to ensure adequate oxygenation, hydration, and perfusion, with escalation to a higher level of care as appropriate.

Restitution

Sepsis

Most deaths in patients with intestinal fistulae are caused by inadequate treatment of sepsis, so effective management of sepsis is a priority [15]. This requires early imaging and drainage of abscess cavities, which should be undertaken percutaneously with the support of a radiologist, in order to avoid further laparotomy and the potential for bowel injury. When laparotomy is required, intestinal suture lines should be avoided as further fistulation is likely.

Box 189.1 Management of fistulae

- **R**esuscitation.
- **R**estitution:
  - **S** Sepsis, skin.
  - **N** Nutrition.
  - **A** Assessment.
  - **P** Plan.
- **R**econstruction.
- **R**ehabilitation.

Exteriorization of fistulating bowel, and delayed intestinal reconstruction until after the patient's condition has improved, are crucial in reducing mortality.

Skin care

Contaminated effluent macerates and burns skin, perpetuating the catabolic response and causing severe discomfort. Management of fistulation into the open abdomen is especially difficult. The Eakin bag is a large stoma appliance, secured around the wound edges with adhesive and often connected to a drainage system. It may occasionally be preferable to fashion a proximal stoma in the upper abdomen to protect the wound from uncontrollable fistula effluent.

Nutrition

Safe, complication-free nutrition is essential once sepsis is controlled. This may necessitate parenteral nutrition until it is clear that enteric defects are not feeding undrained abscess cavities, or if insufficient length remains for adequate enteral absorption. There is no evidence that parenteral nutrition expedites spontaneous closure of fistulae through 'bowel rest'. Enteral nutrition can be delivered orally, via a feeding tube (nasogastric, gastrostomy, or jejunostomy), or via a gastrostomy tube inserted into the distal limb of a proximally situated fistula (fistuloclycis), provided integrity of the distal gastrointestinal tract has first been confirmed by contrast study and more than 150 cm of small bowel remains (**level 4**) [16].

Assessment

Once restitution is established with control of sepsis and safe nutrition, systematic assessment of gastrointestinal anatomy with contrast studies is required to rule out distal obstruction and to plan definitive management. These are best performed from the proximal gastrointestinal tract first.

Plan

Between 50–80% of small bowel enterocutaneous fistulae will close spontaneously with conservative management (Box 189.2). Retrospective series suggest only 10% of colonic fistulae close spontaneously (**level 4**) [17]. Fistulae in the open abdomen require surgical intervention to facilitate closure. Premature attempts at surgical repair risk further enterostomy and fistulation. Retrospective data support the suggestion that definitive surgery should be postponed for at least 6 months after the index event and resuscitation (**level 4**) [18]. This will allow resolution of obliterative peritonitis, fistula maturation, neoperitonealization (demonstrable by stomal prolapse on coughing) and optimization of nutritional status.

Reconstruction

Recurrence rates following surgical closure of intestinal fistulae are high. A review of 205 cases reported a 20.5% recurrence of fistulae within three months of surgery. This was lowest with resection compared with simple closure of enteric defects, which is almost invariably doomed to fail (**level 4**) [18]. Recurrence is also higher in stapled versus hand-sewn techniques (**level 4**) [19]. The method used for reconstruction of the abdominal wall is an important determination of outcome in patients with large defects associated with intestinal fistulation. Replacement of abdominal wall defects with prosthetic mesh is associated with a considerably higher rate of refistulation than simple suture repair (**level 4**) [20].

Box 189.2 Factors predictive of spontaneous closure

- No distal obstruction.
- No intrinsically diseased bowel underlying the fistula.
- No abscess cavity associated with fistula.
- No foreign body.
- Absence of mucocutaneous/atmospheric continuity.

Rehabilitation

The disruption of physical, mental, and social well-being that follows gastrointestinal fistulation can be catastrophic for patients and their families. Specialized nursing care and dedicated psychological support are essential for adjustment.

Conclusion

If at all possible, the abdomen should be closed at the end of surgery as leaving it open appears to confer no benefit and may increase morbidity (**level 2b**) [2]. Techniques to reduce the risk of entero-atmospheric fistula in the open abdomen include coverage of hollow viscera with omentum, avoidance of serosal injury and closure of fascia or skin as soon as possible. The choice of temporary abdominal closure should be individualized, based on the disease process and the surgeon's familiarity with the technique. Enteral nutrition should be provided when possible. Reconstruction should be undertaken only when the patient's condition has been optimized. Management of intestinal fistulation, particularly when associated with the open abdomen, should preferably be undertaken by experienced multidisciplinary teams.

References

1. Howick JP, Phillips B, Ball C, et al. (2009). Oxford Centre for Evidence-based Medicine: Levels of Evidence. Available at: http://www.cebm.net/index.aspx?o=1025 (accessed 29 March 2012).
2. Robledo FA, Luque-de-Leon E. Suarez R, et al. (2007). Open versus closed management of the abdomen in the surgical treatment of severe secondary peritonitis: a randomized clinical trial. *Surgery Infections*, **8**, 63–72.
3. Carlson GL and Dark P. (2010). Acute intestinal failure. *Current Opinions in Critical Care*, **16**, 347–52.
4. Malbrain ML, Cheatham ML, Kirkpatrick A, et al. (2006). Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome: I. definitions. *Intensive Care Medicine*, **32**, 1722–32.
5. Diaz JJ Jr, Cullinane DC, Dutton D, et al. (2010). The management of the open abdomen in trauma and emergency general surgery: part 1-damage control. *Journal of Trauma*, **68**, 1425–38.
6. Scalea TM, Bochicchio GV, Habashi N, et al. (2007). Increased intra-abdominal, intrathoracic, and intracranial pressure after severe brain injury: multiple compartment syndrome. *Journal of Trauma*, **62**, 647–56.
7. Rao M, Burke D, Finan PJ, and Sagar PM. (2007). The use of vacuum-assisted closure of abdominal wounds: a word of caution. *Colorectal Disease*, **9**, 266–8.
8. Anderson O, Putnis A, Bhardwaj R, et al. (2011). Short- and long-term outcome of laparostomy following intra-abdominal sepsis. *Colorectal Disease*, **13**, 20–32.
9. Bee TK, Croce MA, Magnotti, LJ, et al. (2008). Temporary abdominal closure techniques: a prospective randomized trial comparing

polyglactin 910 mesh and vacuum-assisted closure. *Journal of Trauma*, **65**, 337–42.
10. Collier B, Guillamondegui O, Cotton, B et al. (2007). Feeding the open abdomen. *Journal of Parenteral and Enteral Nutrition*, **31**, 410–15.
11. Datta V, Engledow A, Chan S, Forbes A, Cohen CR, and Windsor A. (2010). The management of enterocutaneous fistula in a regional unit in the United Kingdom: a prospective study. *Disease of Colon and Rectum*, **53**, 192–9.
12. Adkins, AL, Robbins J, Villalba M, Bendick P, and Shanley CJ. (2004). Open abdomen management of intra-abdominal sepsis. *American Surgery*, **70**, 137–40.
13. Mastboom WJ, Kuypers HH, Schoots FJ, and Wobbes T. (1989). Small-bowel perforation complicating the open treatment of generalized peritonitis. *Archives of Surgery*, **124**, 689–92.
14. Sitges-Serra A, Jaurrieta E, and Sitges-Creus A. (1982). Management of postoperative enterocutaneous fistulas: the roles of parenteral nutrition and surgery. *British Journal of Surgery*, **69**, 147–50.
15. Dellinger RP, Levy MM, Carlet JM, et al. (2008). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Medicine*, **34**, 17–60.
16. Teubner A, Morrison K, Ravishankar HR, Anderson ID, Scott NA, and Carlson GL. (2004). Fistuloclysis can successfully replace parenteral feeding in the nutritional support of patients with enterocutaneous fistula. *British Journal of Surgery*, **91**, 625–31.
17. LaBerge JM, Kerlan RK Jr, Gordon RL, and Ring EJ. (1992). Nonoperative treatment of enteric fistulas: results in 53 patients. *Journal of Vascular and Interventional Radiology*, **3**, 353–7.
18. Lynch AC, Delaney CP, Senagore AJ, Connor JT, Remzi FH, and Fazio VW. (2004). Clinical outcome and factors predictive of recurrence after enterocutaneous fistula surgery. *Annals of Surgery*, **240**, 825–31.
19. Brenner M, Clayton JL, Tillou A, Hiatt JR, and Cryer HG. (2009). Risk factors for recurrence after repair of enterocutaneous fistula. *Archives of Surgery*, **144**, 500–5.
20. Connolly, PT, Teubner A, Lees NP, Anderson ID, Scott NA, and Carlson GL. (2008). Outcome of reconstructive surgery for intestinal fistula in the open abdomen. *Annals of Surgery*, **247**, 440–4.

PART 6.6

Pancreatitis

CHAPTER 190

Pathophysiology, diagnosis, and assessment of acute pancreatitis

James R. A. Skipworth and Stephen P. Pereira

Key points

- The incidence of acute pancreatitis continues to increase, but the attendant mortality has not decreased for >30 years.
- The pathogenesis remains poorly understood, but the initial mechanism appears to be intracellular activation of pancreatic enzymes, with micro- and macrovascular dysfunction, in conjunction with a systemic inflammatory response acting as a key propagating factor and determinant of severity.
- A multitude of causes or initiators exist, but there is a common pathophysiologic pathway.
- The use of conventional scoring systems, combined with repeated clinical and laboratory assessment, remain the optimal method of predicting early severity and organ dysfunction.
- Death occurs in a biphasic pattern with early mortality (<2 weeks) secondary to SIRS and MODS; and late deaths (>2 weeks) due to superinfection of pancreatic necrosis. Assessment of severity should reflect this, with early severity being diagnosed in the presence of organ failure for >48 hours, and late severity defined by the presence of pancreatic and peripancreatic complications on CT or other appropriate imaging modalities.

Introduction

The revised Atlanta classification system (2008) defines acute pancreatitis (AP) as 'an acute inflammatory process of the pancreas, with variable involvement of regional tissues or remote organ systems' [1]. It is diagnosed if ≥2 of the following features are identified:

- Abdominal pain characteristic of AP.
- Serum amylase (or lipase) ≥3 times the upper limit of normal.
- Characteristic findings of AP on ultrasonography (USS) or CT.

Mild and self-limiting in many cases, up to a quarter will suffer severe disease. In Western societies, approximately 80% are secondary to cholelithiasis or ethanol abuse, although many other causes exist (Box 190.1). It is a common condition, affecting twice as many men as women. Although the incidence per 100,000 population per year varies throughout the developed world (9.8 UK, 15.9 Netherlands, 19.7 Germany, 43.8 USA), it continues to rise in Europe and North America, especially in females under the age of 35 [2–6]. Associated mortality has not decreased [2], and up to 10% still die [2].

Pathophysiology

AP initiation and propagation

Precise mechanisms driving pancreatic inflammation remain poorly understood. However, the initial insult results in increased intracellular calcium, which leads to conversion of the inactive proenzyme trypsinogen to active trypsin within pancreatic acinar cells. Premature trypsin activation triggers a cascade of digestive proenzyme activation resulting in pancreatic vacuolization and auto digestion, allowing dissemination of enzymes to act directly on both surrounding acinar cells and local extra-pancreatic structures (see Fig. 190.1). Vascular endothelial barriers are similarly disrupted, increasing vascular permeability and allowing further propagation of activated enzymes.

Significant cellular destruction follows, releasing reactive oxygen species and various pro-inflammatory mediators including TNF-α, IL-6 and IL-8. A systemic inflammatory response syndrome is subsequently triggered with characteristic micro- and macrovascular changes resulting in a hyperdynamic circulation, capillary leak, and significant third space fluid losses. Without intervention, hypovolemia, hypotension, and secondary organ dysfunction and failure occur.

Organ failure

Pulmonary dysfunction

This represents the commonest form of secondary organ dysfunction in AP. Hypoxemia secondary to ventilation/perfusion mismatch and right-to-left intrapulmonary shunting occurs in 50–60% of cases, often before radiographic abnormalities can be seen [7]. Atelectasis (to which decreased surfactant production, and diaphragmatic splinting contribute) is commonly encountered [7]. Pleural effusions occur secondary to increased capillary permeability, blockage of trans-diaphragmatic lymph channels, or formation of pancreaticopleural fistulae following retroperitoneal pancreatic duct disruption, and their presence is an independent predictor of severity and prognosis. An acute respiratory distress syndrome (ARDS) can result in approximately 33% of patients with severe AP, leading to death in >50% of those affected [7].

Cardiovascular dysfunction

This results primarily from hypovolaemia and decreased cardiac preload, but is further exacerbated by vasodilatation secondary to SIRS, and cytokine-mediated direct myocardial depression.

Box 190.1 Common causes of acute pancreatitis

- Post-procedure: e.g. ERCP/surgery.
- Alcohol.
- Neoplastic: e.g. pancreatic/ampullary.
- Cystic fibrosis and genetic disorders: e.g. hereditary pancreatitis.
- Rheology: e.g. vasculitis/hypoperfusion/hypothermia.
- Ischaemia: intra-abdominal surgery/CABG/embolic.
- Endocrine/autoimmune: e.g. hypercalcaemia/SLE.
- Anatomical and functional abnormalities/obstruction: e.g. pancreatic cancer/ampullary tumour/pancreas divisum/sphincter of Oddi dysfunction/ascariasis.
- Triglyceridaemia/hyperlipidaemia.
- Idiopathic and iatrogenic: drugs, e.g. steroids/NSAIDs/ACE-inhibitors/azathioprine/metronidazole/Furosemide/oestrogen/tetracyclines/tamoxifen/sulphonamides.
- Traumatic.
- Infections: e.g. mumps/EBV/CMV/Coxsackie/HIV/adenovirus.
- Stones (Cholelithiasis / Microlithiasis / Choledocholithiasis).

ERCP, endoscopic retrograde cholangiopancreatography; SLE, systemic lupus erythematosus; NSAIDs, non-steroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme; EBV, Epstein–Barr virus; CMV, cytomegalovirus; CBD, common bile duct; HIV, human immunodeficiency virus; CABG, coronary artery bypass graft.

Monitoring of cardiac preload and output are often required to guide both fluid and inotrope administration.

Renal dysfunction

Renal dysfunction can follow circulatory failure and reduced perfusion, or occur via raised intra-abdominal pressure [8]. Acute renal failure occurs in 15% of patients with AP, a higher incidence than other causes of ICU admission [9], and when present it is associated with a mortality of 50% [10]. Careful circulatory support and the avoidance (where possible) of intravenous contrast, and other potential nephrotoxic insults, is crucial to reduce this risk.

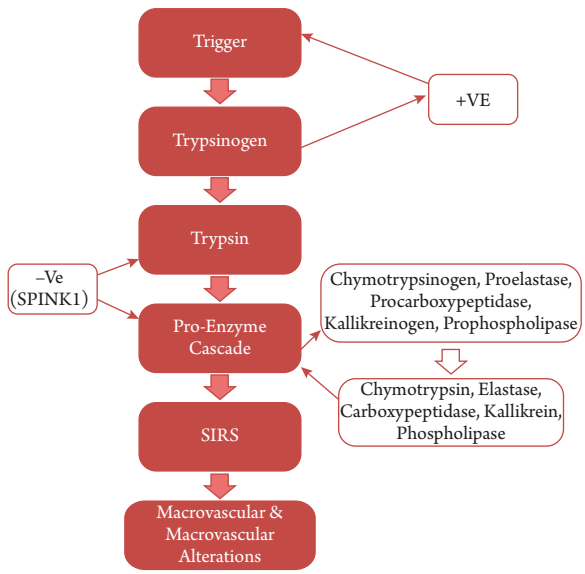


Fig. 190.1 Pathogenesis of acute pancreatitis.

Coagulation dysfunction

Coagulation dysfunction can also follow on from AP-induced SIRS. Raised levels of fibrinogen, D-dimers and activated platelets, as well as coagulation cascade abnormalities can result in a coagulopathy and secondary haemorrhage. Significant coagulation abnormalities occur in up to 50% of patients. D-dimer levels >414 mcg/L are associated with organ failure in AP [11].

Pancreatic consequences

Pancreatic necrosis

The pancreas is particularly susceptible to ischaemic injury: each lobule is supplied by an end vessel so reductions in local pancreatic perfusion are disproportionately greater than those in global cardiac output. Pancreatic necrosis appears early (72–96 hours), starts peripherally and proceeds in a lobular pattern. Over the subsequent 3–4 weeks, necrotic tissue usually remains sterile. Complete resolution can occur via liquefaction and reabsorption. However, necrotic tissue can become infected with diverse species in up to 50%, with translocation of intestinal Gram-negative organisms or *Staphylococcus* species being particularly predominant. Differentiating sterile from infected necrosis remains challenging, as both are characterized by the presence of SIRS. However, confirmation of infection is associated with a significantly increased incidence of multi-organ failure and mortality. Super-infection should be clinically suspected in the presence of fever, hypotension, and tachycardia with raised inflammatory markers. It usually develops at least 2 weeks following AP onset and is identified on CT by the presence of retroperitoneal gas in non-enhancing areas in the presence of infection with Gram-negative organisms. In some centres fine needle aspiration is utilized for the diagnosis of infected necrosis, for which it has a high sensitivity and specificity combined with an infection risk <1%. Other centres confirm infection via microbiological assessment of blood or drain cultures to avoid even this low potential risk of introducing infection into a previously sterile collection.

Pancreatic collections and pseudocysts

Acute peripancreatic fluid collections, rich in inflammatory fluid and pancreatic enzymes, often form within anatomical boundaries (often in the lesser sac). The majority resolve spontaneously as the disease process settles, but in approximately 10% a well-defined wall of fibrous or granulation tissue forms over a 3–4 week period, encapsulating sterile fluid to form a pseudocyst [12,13]. Up to 85% of pseudocysts resolve spontaneously, but those that are large, expanding rapidly or causing complications (e.g. pain, secondary infection, haemorrhage, bile duct, or duodenal obstruction) often require treatment via percutaneous, endoscopic or surgical drainage [12,13].

Pseudo-aneurysms

These form as proteolytic enzymes weaken peripancreatic vascular walls, especially within pseudocysts, and can be multiple. While some remain stable, others can rupture directly into the peritoneal cavity or gastrointestinal tract, resulting in death from

haemorrhagic shock in up to 20% [14]. Presentation can thus be with a pulsatile abdominal mass, haematemesis or melena, or cardiovascular instability related to occult bleeding. CT angiography is the optimal imaging method and should be performed prior to oesophagogastroduodenoscopy in patients with AP and evidence of gastrointestinal bleeding.

Diagnosis

Clinical presentation

AP is characterized by the presence of acute epigastric pain, which can be referred through to the back, and is often associated with nausea and vomiting (see Box 190.2). There may be evidence of hypovolemia due to third space losses, and fever due to SIRS. Jaundice may occur secondary to biliary obstruction whether primary, or secondary to ampullary oedema. Rarely, exudates from pancreatic necrosis can track along the falciform ligament and into the retroperitoneum, resulting in bruising and discoloration in the peri-umbilicus (Cullen's sign) or flank (Grey–Turner's sign). Extension of inflammatory exudates from the peripancreatic region to the diaphragm may also result in shallow respiration and increased respiratory frequency.

Serum diagnostic markers

Given the substantial variation in clinical presentation, enzymes derived from pancreatic acinar cells are used as biochemical markers to confirm diagnosis.

Serum amylase

Serum amylase is considered the gold-standard diagnostic test for AP, with 91–100% sensitivity and 71–98% specificity [15]. Levels usually rise sharply within the first 12 hours after symptom onset, but can return to normal within three days and, therefore, may be falsely low in patients with a delay between symptom onset and presentation. Levels may also be normal in patients with pancreatic insufficiency (e.g. chronic pancreatitis, cystic fibrosis), raised (in the absence of pancreatitis) in those with impaired renal clearance, perforated duodenal ulcer, acute cholecystitis, shock, and macroamylasemia, and low in hypertriglyceridaemia.

Serum lipase

This marker has a sensitivity (85–100%) and specificity (95–99%) higher than serum amylase for the diagnosis of AP [15]. Levels may remain elevated and detectable for up to 14 days, thereby providing greater accuracy in patients with a delayed presentation. However, falsely high levels may be seen in patients with other intra-abdominal pathology or renal insufficiency and it is less readily available than serum amylase.

Box 190.2 Clinically important differential diagnosis of acute pancreatitis

- **Acute coronary syndrome**: particularly inferior myocardial infarction.
- **Peptic ulcer disease**: particularly perforated peptic ulcer.
- **Symptomatic cholelithiasis**.
- **Mesenteric or intestinal ischaemia**.
- **Small bowel obstruction**.
- **Aortic aneurysm**.

Trypsinogen-2

This pro-enzyme can be measured by serum immunofluorometric assay or bedside urine dipstick. It has a reported sensitivity and specificity of 86–100% for the diagnosis of AP [16], but is not widely available.

Imaging

Ultrasonography

Useful in documenting the presence of gallstones and bile duct dilatation, and for assessment of pancreatic oedema. It has a false negative rate of 20–40% for detecting common bile duct stones, particularly in patients with a high body mass index or those with overlying air-filled bowel loops.

Computed tomography

Contrast-enhanced CT is the imaging procedure of choice under circumstances of inconclusive clinical, ultrasonographic, and biochemical findings. It can assess the presence and extent of any pancreatic necrosis or local complications, and also rule out the presence of alternate abdominal pathology.

Magnetic resonance imaging

Rarely used for diagnosis, but can be helpful in further elucidating the presence of microlithiasis or choledocholithiasis not confirmed on ultrasound, or in patients with impaired renal function.

Assessment of severity

Clinical course

Most patients develop a self-limiting, mild, oedematous-interstitial pancreatitis. This is associated with minimal organ dysfunction and usually improves within 48–72 hours following conservative management. However, up to a third of patients develop severe disease, characterized by pancreatic necrosis, organ failure, acute fluid collections, and later pseudocyst or pseudo-aneurysm formation. Mortality follows a biphasic pattern: early deaths (<2 weeks) occur as a result of multi-organ dysfunction syndrome, while later deaths (>2 weeks) are generally secondary to sepsis associated with infected necrosis or complications of sterile necrosis.

Definition of severity

The revised Atlanta classification [1] defines mild AP as pancreatitis without the presence of SIRS, organ failure, pancreatic necrosis, or other acute complications. However, the definition of severity is complicated by the biphasic nature of AP mortality. Severe disease during the early phase is classified as the persistence of organ failure for >48 hours as characterized by a suitable scoring system such as the Marshall Score (Table 190.1), which can be repeated on a daily basis for evaluation of progress. Severe late disease is defined by the presence of peripancreatic complications (that may give rise to systemic symptoms), reflecting the predominant cause of mortality in this time period. This should be assessed by contrast-enhanced CT to identify morphologic abnormalities of the pancreatic and peripancreatic region.

Predictors of severity

Common diagnostic markers such as serum amylase have no value in the early assessment of disease severity or prognosis.

Table 190.1 Marshall Scoring System for the determination of AP severity in the early phase of disease (score ≥ 2 for organ failure)

Score	0	1	2	3	4
Respiratory system PO_2/FiO_2	>400	301–400	201–300	101–200	<101
Renal system serum creatinine (μmol/L)	134	134–169	170–310	311–439	>439
Cardiovascular system systolic blood pressure (mmHg)	>90	<90 Fluid responsive	<90 Not fluid responsive	<90 pH <7.3	<90 pH <7.2

Reproduced from Marshall JC et al., 'Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome', *Critical Care Medicine*, **23**(10), pp. 1638–52, copyright 1995, with permission from Wolters Kluwer Health and Society of Critical Care Medicine.

Table 190.2 Scoring systems for the prediction of severity in acute pancreatitis

Variable	Ranson Score (At 0 and 48 hours)		Glasgow (within 48 hours)	APACHE II (on admission and then daily)
Age (years)	>55		–	+
				Premorbid illnesses
WCC ($\times 10^9$/L)	>16		>15	+
Blood glucose (mmol/L)	>11.1		>10	
AST (U/L)	>250		>200	
LDH (U/L)	>350		>600	
Serum urea (mmol/L) (despite hydration)		>1.8 Increase	>16	Renal failure
Serum Ca (mmol/L)		<2	<2	
Serum albumin (g/L)			<32	
PaO_2 (mm/Hg)		>60	<60	Pulmonary insufficiency ≤60
Base deficit		>4		Arterial pH
Fluid sequestration (mL)		>6 000		
Packed cell volume (%)		<10 Decrease		+
Serum sodium				+
Serum potassium				+
Temperature				+
Mean arterial BP (mmHg)				Shock < 90
Heart rate				+
Respiration rate				+
Glasgow coma scale				+
Total number of criteria	11		8	14
Threshold value for severe acute pancreatitis	≥3		≥3	≥8
	1 point per positive variable			Points per variable range from 0 (normal) to +4 (very abnormal) Minimum total score: 0 Maximum total score: 71

WCC, white cell count; AST, aspartate transaminase; LDH, lactate dehydrogenase; Ca, calcium; BP, blood pressure.

Ranson Score: reproduced from Ranson JH et al., 'Prognostic signs and the role of operative management in acute pancreatitis', *Surgery, Gynaecology & Obstetrics*, 1974, **139**(1), pp. 69–81. Reprinted with permission from the Journal of the American College of Surgeons, formerly Surgery Gynecology & Obstetrics. Glasgow criteria: reproduced from *Gut*, Blamey SL et al., 'Prognostic factors in acute pancreatitis', **25**(12), pp. 1340–6, copyright 1984, with permission from BMJ Publishing Group Ltd. APACHE II score: reproduced from Knaus WA et al., 'APACHE II: A severity of disease classification system', *Critical Care Medicine*, **13**(10), pp. 818–29, copyright 1985, with permission from Wolters Kluwer Health.

Development of severe AP is therefore predicted in the first 48 hours following presentation, utilizing various clinical and laboratory scoring systems, supplemented by inflammatory markers. However, specific mechanisms underlying progression from SIRS to organ failure remain poorly elucidated. Although the use of scoring systems to allow swift identification of patients likely to benefit from early, aggressive treatment is likely to improve outcome, such scoring systems have limited accuracy and clinical value (up to 69% positive predictive value) and do not replace careful and repeated clinical assessment and examination [17] (Table 190.2).

Ranson's or modified Glasgow score (Imrie)

These scoring systems were developed specifically for the assessment of pancreatitis and are the most commonly utilized. They are easy to perform, utilizing routinely assessed blood tests. A score ≥3 in both of these scoring systems has a high negative predictive value for severe AP [18].

Apache II score

This assesses 12 physiologic variables, age and chronic health status, and can be used at hospital admission unlike the 'Ranson' and 'Glasgow' criteria that can only be fully utilized after 48 hours. It is more complex to perform and not specific to pancreatitis, but remains the most accurate tool for predicting mortality [17].

Panc 3 score

This simple assessment method reflects the findings that an elevated haematocrit (>44 mg/dl) due to hypovolemia, pleural effusion, and body mass index >30 kg/m^2 (mechanism unknown) are independent predictors of AP severity [19]

Inflammatory markers

Serum C-reactive protein (CRP) levels are useful in predicting both AP severity (CRP≥150 mg/l at 36 hours) and super-infection of pancreatic necrosis (CRP >81 mg/l). An elevated white cell count (>13x10^9/L) is also an indicator of pancreatic superinfection [20].

Table 190.3 CT severity index

CT severity index (time not specified)	Points
Pancreatic morphology	
(A) Normal pancreas	**0**
(B) Pancreatic enlargement (oedema)	**1**
(C) Pancreatic inflammation and/ or peripancreatic changes	**2**
(D) Single peripancreatic fluid collection	**3**
(E) Two or more fluid collections and/or retroperitoneal air	**4**
Plus	
Necrosis (% of pancreatic parenchyma)	
0%	**0**
<30%	**2**
30–50%	**4**
>50%	**6**
Total (Minimum score 0; Maximum score 10)	

Reproduced from Balthazar EJ. Acute pancreatitis: assessment of severity with clinical and CT evaluation. *Radiology*, 2002, **223**(3), with permission from the Radiological Society of North America.

Table 190.4 Balthazar score

Grade	CT findings
A	Normal pancreas
B	Pancreatic enlargement
C	Pancreatic and/or peripancreatic fat inflammation
D	Single peripancreatic fluid collection
E	Two or more fluid collections and/or retroperitoneal air

Reproduced from Reproduced from Balthazar EJ. Acute pancreatitis: assessment of severity with clinical and CT evaluation. *Radiology*, 2002, **223**(3), with permission from the Radiological Society of North America.

Novel biomarkers

Several have been associated with AP severity, e.g. the acute phase serum reactant, procalcitonin; the pro-inflammatory cytokine IL-6 which is one of the main inducers of hepatic CRP synthesis and peaks earlier than CRP; or elastase, an enzyme released by activated polymorphonuclear leukocytes. However, these remain research tools requiring further validation at present, and are yet to be established in routine clinical practice.

Radiological imaging for assessment of severity

Computed tomography

CT remains the mainstay of severity assessment late in the course of disease. Mild AP is identified by the presence of enhancing but

Table 190.5 Extra-pancreatic inflammation on CT (EPIC) score

Sign of extra-pancreatic inflammation	Points
Pleural effusion	
None	0
Unilateral	1
Bilateral	2
Ascites (Perisplenic or perihepatic, interloop, pelvic)	
None	0
1 Location	1
>1 Location	2
Retroperitoneal inflammation	
None	0
Unilateral	1
Bilateral	2
Mesenteric inflammation	
Absent	0
Present	1

Reproduced from De Waele J et al., 'Extrapancreatic inflammation on abdominal computed tomography as an early predictor of disease severity in acute pancreatitis: evaluation of a new scoring system', *Pancreas*, **34**(2), pp. 185–90, copyright 2007, with permission from Wolters Kluwer Health and American Pancreatic Association.

oedematous pancreatic parenchyma, whereas severe AP is associated with non-enhancing pancreatic parenchyma or peripancreatic tissues, indicative of necrosis, with or without peripancreatic fluid collections, pseudocysts and pseudo-aneurysms. The degree of necrosis is usually quantified as comprising <30%, 30–50% or >50% of the total pancreatic parenchyma.

Radiological scores such as the CT severity index (CTSI), Balthazar score and 'extra-pancreatic inflammation on CT' (EPIC) score (Tables 190.3, 190.4, and 190.5) can quantify pancreatic and peripancreatic morphology and provide a repeatable assessment of patient progress. The CTSI is based upon the degree of pancreatic inflammation and necrosis seen at initial CT; a CTSI score ≥3 is associated with a poor prognosis.

Magnetic resonance imaging

MRI is capable of accurately delineating pancreatic and biliary duct disruption, and is comparable to CT in the assessment of severity, while avoiding the risks associated with radiation exposure. It has a particular role in assessing pancreatic ductal anatomy prior to planned intervention, and in follow-up of patients requiring multiple sequential imaging.

Acknowledgements

Text credit for Atlanta classification: Reproduced from Gut, Banks PA et al., for the Acute Pancreatitis Classification Working Group, 'Classification of acute pancreatitis - 2012: revision of the Atlanta classification and definitions by international consensus', 62, 1, pp. 102–111, Copyright 2013, with permission from BMJ Publishing Group Ltd.

References

1. Banks PA Bollen TL, Dervenis C, et al. (2013). Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*, **62**, 102–11.
2. Goldacre, MJ and Roberts SE. (2004). Hospital admission for acute pancreatitis in an English population, 1963–98: database study of incidence and mortality. *British Medical Journal*, **328**, 1466–9.
3. Roberts SE, Williams JG, Meddings D, and Goldacre MJ. (2008). Incidence and case fatality for acute pancreatitis in England: geographical variation, social deprivation, alcohol consumption and aetiology—a record linkage study. *Aliment Pharmacology Therapy*, **28**, 931–41.
4. Frey CF, Zhou H, Harvey DJ, and White RH. (2006). The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994–2001. *Pancreas*, **33**, 336–44.
5. Stimac D, Mikolasevic I, Krznaric-Zrnic I, Radic M, and Milic S. (2013). Epidemiology of acute pancreatitis in the North Adriatic region of Croatia during the last ten years. *Gastroenterology Research in Practice*, **2013**, 956149.
6. Lankisch PG, Karimi M, Bruns A, Maisonneuve P, and Lowenfels AB. (2009). Temporal trends in incidence and severity of acute pancreatitis in Luneburg County, Germany; a population-based study. *Pancreatology*, **9**, 420–6.
7. Browne GW and Pitchumoni CS. (2006). Pathophysiology of pulmonary complications of acute pancreatitis. *World Journal of Gastroenterology*, **12**, 7087–96.
8. Pavlidis TE, Pavlidis ET, and Sakantamis AK. (2010). Advances in prognostic factors in acute pancreatitis: a mini-review. *Hepatobiliary Pancreatic Disease International*, **9**, 482–6.
9. Lin HY, Lai JI, Lai YC, Lin PC, Chang SC, and Tang GJ. (2011). Acute renal failure in severe pancreatitis: A population-based study. *Uppsala Journal of Medical Science*, **116**, 155–9.
10. Zhang XP, Wang L, and Zhou YF. (2008). The pathogenic mechanism of severe acute pancreatitis complicated with renal injury: a review of current knowledge. *Digestive Disease Science*, **53**, 297–306.
11. Radenkovic D, Bajec D, Ivancevic N, et al. (2009). D-dimer in acute pancreatitis: a new approach for an early assessment of organ failure. *Pancreas*, **38**, 655–60.
12. Baillie J. (2004). Pancreatic pseudocysts (Part I). *Gastrointestinal Endoscopy*, **59**, 873–9.
13. Baillie J. (2004). Pancreatic pseudocysts (Part II). *Gastrointestinal Endoscopy*, **60**, 105–13.
14. Balachandra S and Siriwardena AK. (2005). Systematic appraisal of the management of the major vascular complications of pancreatitis. *American Journal of Surgery*, **190**, 489–95.
15. Yadav D, Agarwal N, and Pitchumoni CS. (2002). A critical evaluation of laboratory tests in acute pancreatitis. *American Journal of Gastroenterology*, **97**, 1309–18.
16. Andersen AM, Novovic S, Ersbøll AK, Jorgensen LN, and Hansen MB. (2010). Urinary trypsinogen-2 dipstick in acute pancreatitis. *Pancreas*, **39**, 26–30.
17. Gravante G, Garcea G, Ong SL, et al. (2009). Prediction of mortality in acute pancreatitis: a systematic review of the published evidence. *Pancreatology*, **9**, 601–14.
18. Mounzer R, Langmead CJ, Wu BU, et al. (2012). Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. *Gastroenterology*, **142** 1476–82.
19. Brown A, James-Stevenson T, Dyson T, and Grunkenmeier D. (2007). The panc 3 score: a rapid and accurate test for predicting severity on presentation in acute pancreatitis. *Journal of Clinical Gastroenterology*, **41**, 855–8.
20. Pongprasobchai S, Jianjaroonwong V, Charatcharoenwitthaya P, et al. (2010). Erythrocyte sedimentation rate and C-reactive protein for the prediction of severity of acute pancreatitis. *Pancreas*, **39**, 1226–30.

CHAPTER 191

Management of acute pancreatitis in the critically ill

Rajkumar Rajendram

Key points

- Acute pancreatitis (AP) can be divided into three broad categories: mild, moderately severe AP (SvAP) and necrotizing SvAP. The severity determines the management stratagem.
- Monitoring and support of pulmonary, renal, circulatory, and hepatobiliary function may minimize the systemic consequences of SvAP.
- Adequate pain control requires administration of intravenous opiates (e.g. fentanyl), usually as patient-controlled analgesia.
- In SvAP, initiate enteral nutrition early (within 72 hours) via a nasogastric tube (Grade 1B evidence). If the target rate is not achieved within 48–72 hours and SvAP has not resolved, parenteral nutrition should be considered.
- For gallstone pancreatitis, perform ERCP and sphincterotomy early if there is cholangitis or a high suspicion of cholestasis (Grade 1B evidence). Cholecystectomy should be performed after recovery in all patients with gallstone pancreatitis.

Introduction

The main causes of morbidity and mortality in acute pancreatitis are organ dysfunction and infection of necrotic tissue. The likelihood of these complications depends upon the severity of pancreatitis which is subdivided into three broad categories [1]:

- Mild acute pancreatitis.
- Moderately severe acute pancreatitis.
- Necrotizing severe acute pancreatitis.

While acute pancreatitis is usually mild and recovers within seven days, severe acute pancreatitis (SvAP) occurs in about 20% and is associated with significant morbidity and mortality. In the absence of major co-morbidities patients with mild pancreatitis do not require admission to intensive care. Early (fulminant) SvAP causes extensive pancreatic necrosis, multiple organ dysfunction syndrome, and results in a high mortality (25–30%) [1]. Moderately severe acute pancreatitis only causes local complications so the mortality is low, but the morbidity is similar to that of necrotizing SvAP [1].

The aims of management are to prevent, or to diagnose and treat, the complications of pancreatic inflammation and any predisposing factors to avoid recurrence. The systemic consequences of SvAP may be reduced by admission to an intensive care unit (ICU) for monitoring and organ support.

Supportive care

Medical management is essentially supportive with supplemental oxygen, fluid resuscitation, analgesia, and correction of metabolic abnormalities. Patients can recover and resume oral intake with supportive treatment alone.

Fluid and electrolyte replacement

Necrotizing pancreatitis causes vascular leak and hypovolemia which exacerbate damage to the pancreatic microcirculation thus worsening necrosis. Inadequate resuscitation results in hypotension and acute kidney injury, and may exacerbate pancreatic necrosis. Faster initial fluid resuscitation reduces mortality [2].

Although several approaches to fluid resuscitation have been described, data on the type and amount of fluids required are limited. Fluid resuscitation is best guided by haemodynamic variables and urine output (>0.5 mL/kg/hour). The serum urea level on admission and the trend over the next 24 hours can predict mortality [3]. Maintenance rates >300 mL/hour may be required for 48 hours to reduce the urea level and the raised haematocrit. Fluid balance should be optimized if the urea does not improve. However, if oliguria reflects acute kidney injury rather than hypovolemia, aggressive fluid replacement may cause oedema without improving renal function.

Serum electrolytes should be measured frequently in patients with electrolyte and metabolic disturbances. Hypocalcaemia should be corrected if the ionized calcium is low. Hypomagnesaemia can cause hypocalcaemia and should also be treated.

Hyperglycaemia may be caused by insulin resistance, increased gluconeogenesis, reduced metabolism of glucose, and parenteral nutrition (PN). Hyperglycaemia may increase secondary pancreatic infections. Blood glucose should be measured hourly and insulin used to control blood glucose.

Analgesia

Fluid resuscitation can improve the pain from ischaemic pancreatitis due to hypovolemia. However, adequate analgesia often requires intravenous opiates. Pethidine has traditionally been preferred to morphine. However, the half-life of pethidine is short and repeated doses can lead to accumulation of norpethidine; a toxic metabolite. Although morphine increases sphincter of Oddi pressure, it does

not cause nor exacerbate pancreatitis or cholecystitis. Fentanyl may be safer, particularly in patients with renal impairment, and can be given in boluses, as an infusion or as patient-controlled analgesia.

Nutrition

Mild pancreatitis can often be managed with intravenous fluids alone as patients usually recover and resume oral intake within a week. However, patients with SvAP are unlikely to resume oral intake for 5–7 days and so nutritional support should be provided early.

Enteral nutrition

Enteral nutrition (EN) maintains the intestinal barrier and prevents bacterial translocation from the gut. Translocation of organisms is a major cause of secondary infection. Raised pancreatic enzymes or fluid collections are not absolute contraindications to EN. Even partial gastric outlet obstruction can resolve as inflammation can subside and fluid collections mature, becoming drainable while EN is being administered. Enteral nutrition avoids the complications of PN; in comparison, EN significantly reduces mortality, multiple organ failure, systemic infections, and the need for surgery [4,5].

A controlled trial comparing nasogastric and nasojejunal feeding found no significant difference in APACHE II score, C-reactive protein, pain or analgesic use [6]. Post-pyloric feeding is thus not required if nasogastric feeding is tolerated. However, EN—whether oral, gastric or post-pyloric—can cause pain, recurrence of pancreatitis, or increase fluid collections. This often occurs in patients with disrupted pancreatic ducts and fluid collections. It may be possible to resume enteral nutrition after drainage of collections. If the collections are not drainable or the target rate of EN is not achieved within 72 hours, PN is required.

Parenteral nutrition

While patients intolerant of EN should receive PN, supplementing EN with PN may be harmful. A randomized multicentre trial of 4640 critically-ill adults showed that early PN supplementation (within 48 hours of ICU admission) increased the incidence of new infections and the duration of mechanical ventilation, ICU admission, and hospital admission [7].

Resumption of oral intake

In SvAP, oral intake is limited by postprandial pain, nausea, or vomiting as gastroduodenal inflammation and/or extrinsic fluid collections cause gastric outlet obstruction. Enteral or parenteral nutrition is required until oral intake is tolerated. Patients traditionally progress from clear fluids to solid food.

Infection

Approximately a third of patients with SvAP develop infection of the necrotic pancreas. This often occurs late (>10 days) and is a common cause of morbidity and mortality. Most infections (about 75%) are monomicrobial. Causative organisms are predominantly gut-derived, e.g. *Escherichia coli, Pseudomonas, Klebsiella*, and *Enterococci*. Infection with fungi or Gram-positive organisms is unusual, but more likely if prophylactic antibiotics are administered for >10 days. Fungal infections occur in approximately 10%, but it is not yet clear if fungal infection *per se* increases mortality [8].

Treatment of infections includes systemic antimicrobials, EN, percutaneous aspiration, and/or necrosectomy (surgical debridement of pancreatic necrosis).

Antibiotics

Antibiotics should be given if there is clinical or microbiological evidence of infection. The role of prophylactic antibiotics is controversial. Although a systematic review concluded that prophylactic antibiotics decreased mortality in SvAP, but not the rate of infected pancreatic necrosis [9], a subsequent meta-analysis found no mortality benefit or reduction in the rate of infected necrosis [10]. Although the American Association of Gastroenterology recommends antibiotic prophylaxis if >30% of the pancreas is necrotic, prophylactic antibiotics are associated with selection of resistant organisms and fungal infection [8].

Percutaneous CT-guided aspiration

Acute pancreatic fluid collections do not require drainage unless infected or obstructing bowel. Conservative management allows organization of necrotic fluid collections. Endoscopic or percutaneous minimally invasive debridement can then clear any necrotic debris. CT-guided percutaneous aspiration should be considered for microscopy and culture should infected pancreatic necrosis be suspected [11], or if there is no improvement after a week of empirical antibiotics in a patient with >30% pancreatic necrosis and clinical signs of infection without any other obvious source [12].

If the aspirate is sterile, conservative treatment should continue for 4–6 weeks. However, a negative fine needle aspiration does not exclude infection. If signs of systemic toxicity persist >5–7 days, repeat aspiration may be required. If there is evidence of bacterial infection, antibiotics should be changed according to culture and sensitivity results and necrosectomy considered [13].

Necrosectomy

Indications include infected pancreatic necrosis and symptomatic sterile pancreatic necrosis preventing oral intake. Necrosectomy can be performed endoscopically, percutaneously, or as an open procedure. Compared with open necrosectomy, a minimally invasive step-up approach consisting of percutaneous drainage followed, if necessary, by open necrosectomy, reduces morbidity and mortality in patients with infected necrotizing SvAP [14].

Abdominal compartment syndrome

Patients with SvAP may develop intra-abdominal hypertension. Contributory factors include tissue oedema from aggressive fluid resuscitation, peripancreatic inflammation, ascites, and ileus. Abdominal compartment syndrome (ACS) is a life-threatening complication that occurs when intra-abdominal pressure rises >20 mmHg causing ischaemia and tissue necrosis. Most patients who develop ACS are critically ill and unable to communicate so intra-abdominal pressures should be monitored with serial measurement of urinary bladder pressures. However, nearly all patients with a significant ACS have a tensely distended abdomen, progressive oliguria and increased ventilatory requirements.

If ACS is confirmed, either percutaneous catheter or surgical decompression may be considered [15]. Surgical decompression typically requires a midline laparotomy. Following decompressive laparotomy, temporary abdominal closure is used until the laparotomy is no longer required. The abdomen is then closed primarily, functionally, or using skin grafts.

Splenic vein thrombosis

Splenic vein thrombosis occurs in nearly 20% of patients with acute pancreatitis [16]. Anticoagulation may be necessary if the thrombus compromises liver or bowel perfusion by extension into the portal or superior mesenteric vein. However, the thrombosis may resolve spontaneously with treatment of pancreatitis while anticoagulation increases the risk of haemorrhage into areas of pancreatic necrosis or into collections [16]. Variceal bleeding is uncommon in patients with splenic vein thrombosis due to SvAP so prophylactic splenectomy is not required [16].

Treatment of gallstone pancreatitis

Any predisposing factors require treatment. Gallstones are the commonest cause of pancreatitis that requires specific treatment. As removal of stones may reduce the severity of pancreatitis, an endoscopic retrograde cholangiopancreatography (ERCP) should be performed within 72 hours if there is co-incident cholangitis or it is likely that a stone is obstructing the bile duct or ampulla of Vater (i.e. visible common bile duct stone on non-invasive imaging, persistently dilated common bile duct, jaundice or worsening liver biochemistry). Placement of a biliary stent reduces the risk of post-ERCP pancreatitis.

The role of ERCP in the absence of cholangitis or suspicion of a persistent common bile duct stone conflict is unclear. Two meta-analyses found that early ERCP in patients without cholangitis reduced the risk of overall complications and mortality regardless of the predicted severity [17]. In another meta-analysis of five prospective randomized trials (702 patients), early ERCP reduced complications, but not mortality in SvAP; there was also no benefit in mild pancreatitis [18].

Patients with biliary pancreatitis can undergo ERCP before cholecystectomy in the absence of persistent bile duct stones, cholangitis, persistently abnormal liver biochemistry, or worsening liver biochemistry. However, endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MRCP) can determine the need for ERCP if the patient is pregnant; too unstable to allow timely laparoscopic cholecystectomy and intraoperative cholangiography; if ERCP is likely to be difficult (altered surgical anatomy or coagulopathy); if the probability of a retained common bile duct stone is intermediate; and if the patient is too unstable for cholecystectomy with cholangiography.

Cholecystectomy

Patients should have a cholecystectomy after recovery from gallstone pancreatitis. The risk of recurrent pancreatitis, cholecystitis, or cholangitis is 30% within 18 weeks if cholecystectomy is not performed [19]. This risk is highest in patients who have not had a sphincterotomy.

Cholecystectomy can be performed within seven days of recovery from mild pancreatitis. In a randomized study of 50 patients with mild gallstone pancreatitis, laparoscopic cholecystectomy within 48 hours of admission reduced admission more than cholecystectomy performed after resolution of pain and biochemical abnormalities [20]. However, the risk of post-operative infection is increased by SvAP so delaying cholecystectomy for over 3 weeks after SvAP may be appropriate.

If the clinical suspicion of common bile duct stones is high, pre-operative ERCP is the investigation of choice because therapeutic intervention (sphincterotomy, stone extraction) will probably be required. However, if the suspicion of persistent common bile duct stones is low (e.g. if liver biochemistry returns to normal), MRCP, EUS or an intra-operative cholangiogram during cholecystectomy can be used to avoid the risks of ERCP.

Conclusion

Effective management of acute pancreatitis requires a co-ordinated multidisciplinary approach. The mainstay of management is supportive with analgesia, intravenous fluids, nutrition, prevention, and treatment of complications, infection and organ failure to avoid or delay surgery. A minimally invasive step-up approach including conservative therapy with percutaneous drainage of infected collections followed, only if absolutely necessary, by open necrosectomy, reduces morbidity and mortality [14]. The diagnosis and treatment of the cause of pancreatitis is important to prevent recurrence of pancreatitis and the long-term consequences of pancreatic failure.

References

1. Banks PA, Bollen TL, Dervenis C, et al. (2013). Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. *Gut*, **62**, 102–11.
2. Gardner TB, Vege SS, Chari ST, et al. (2009). Faster rate of initial fluid resuscitation in severe acute pancreatitis diminishes in-hospital mortality. *Pancreatology*, **9**, 770–6.
3. Wu BU, Johannes RS, Sun X, Conwell DL, and Banks PA. (2009). Early changes in blood urea nitrogen predict mortality in acute pancreatitis. *Gastroenterology*, **137**, 129–35.
4. Mirtallo JM, Forbes A, McClave SA, et al. (2012). International Consensus Guideline Committee Pancreatitis Task Force. International consensus guidelines for nutrition therapy in pancreatitis. *Journal of Parenteral and Enteral Nutrition*, **36**, 284–91.
5. Al-Omran M, Albalawi ZH, Tashkandi MF, and Al-Ansary LA. (2010). Enteral versus parenteral nutrition for acute pancreatitis. *Cochrane Database System Reviews*, CD002837.
6. Eatock FC, Chong P, Menezes N, et al. (2005). A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. *American Journal of Gastroenterology*, **100**, 432–9.
7. Casaer MP, Mesotten D, Hermans G, et al. (2011). Early versus late parenteral nutrition in critically ill adults. *New England Journal of Medicine*, **365**, 506–17.
8. Gloor B, Müller CA, Worni M, et al. (2001). Pancreatic infection in severe pancreatitis: the role of fungus and multiresistant organisms. *Archives of Surgery*, **136**, 592–6.
9. Villatoro E, Bassi C, and Larvin M. (2010). Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database of Systematic Reviews*, CD002941.
10. Bai Y, Gao J, Zou DW, and Li ZS. (2008). Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in acute necrotizing pancreatitis: evidence from a meta-analysis of randomized controlled trials. *American Journal of Gastroenterology*, **103**, 104–10.
11. Mortelé KJ, Girshman J, Szejnfeld D, et al. (2009). CT-guided percutaneous catheter drainage of acute necrotizing pancreatitis: clinical experience and observations in patients with sterile and infected necrosis. *American Journal of Roentgenology*, **192**, 110–16.
12. Freeny PC, Hauptmann E, Althaus SJ, Traverso LW, and Sinanan M. (1998). Percutaneous CT-guided catheter drainage of infected acute necrotizing pancreatitis: techniques and results. *American Journal of Roentgenology*, **170**, 969–75.
13. Yasuda T, Ueda T, Takeyama Y, et al. (2007). Treatment strategy against infection: clinical outcome of continuous regional arterial infusion, enteral nutrition, and surgery in severe acute pancreatitis. *Journal of Gastroenterology*, **42**, 681–9.

14. van Santvoort HC, Bakker OJ, Bollen TL, et al. (2011). A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology*, **141**, 1254–63.
15. Radenkovic DV, Bajec D, Ivancevic N, et al. (2010). Decompressive laparotomy with temporary abdominal closure versus percutaneous puncture with placement of abdominal catheter in patients with abdominal compartment syndrome during acute pancreatitis: background and design of multicenter, randomised, controlled study. *BMC Surgery*, **10**, 22.
16. Heider TR, Azeem S, Galanko JA, and Behrns KE. (2004). The natural history of pancreatitis-induced splenic vein thrombosis. *Annals of Surgery*, **239**, 876–82.
17. Tse F and Yuan Y. (2012). Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. *Cochrane Database of Systematic Reviews*, CD009779.
18. Moretti A, Papi C, Aratari A, et al. (2008). Is early endoscopic retrograde cholangiopancreatography useful in the management of acute biliary pancreatitis? A meta-analysis of randomized controlled trials. *Digestive Liver Disease*, **40**, 379–85.
19. Hernandez V, Pascual I, Almela P, et al. (2004). Recurrence of acute gallstone pancreatitis and relationship with cholecystectomy or endoscopic sphincterotomy. *American Journal of Gastroenterology*, **99**, 2417–23.
20. Aboulian A, Chan T, Yaghoubian A, et al. (2010). Early cholecystectomy safely decreases hospital stay in patients with mild gallstone pancreatitis: a randomized prospective study. *Annals of Surgery*, **251**, 615–19.

PART 6.7

Jaundice

CHAPTER 192

Pathophysiology and causes of jaundice in the critically ill

Anand D. Padmakumar and Mark C. Bellamy

Key points

- Jaundice is commonplace in the intensive care unit (ICU) patient with a prevalence as high as 30–55% in specific patient subgroups.
- Severity of jaundice is proportional to the number of failing organs and mortality.
- Commonly used therapies, such as vasopressors, positive end-expiratory pressure (PEEP), and parenteral nutrition, can increase the risk of ICU jaundice.
- A lag phase exists between hepatocyte injury and elevation of serum markers.
- An unselective battery of tests often confuses the clinical picture; therefore a systematic and logical diagnostic approach should be used to identify the aetiology of jaundice.

Introduction

This chapter focuses only on the acutely jaundiced adult intensive care unit (ICU) patient. Detailed discussion encompassing chronic and neonatal jaundice is beyond the scope of this chapter.

Jaundice is defined as a serum bilirubin concentration >2 mg/dL (40 μmol/Ll). It becomes clinically recognizable when above 3 mg/dL (60 μmol/L). Clinically, it can be identified as yellowish discoloration of skin, lateral aspect of conjunctiva and sublingual mucosa.

Jaundice is common in the ICU and is often the only symptom of liver dysfunction or other systemic disease. The prevalence of hyperbilirubinaemia has been quoted as high as 30–55% in various ICU patient subgroups (trauma, post-cardiac surgery, shock, sepsis) [1]. The median onset time is approximately three days. Risk factors include hypotension, severe sepsis, Gram negative infections and major surgery; these increase the risk of developing liver dysfunction by 3–4-fold [2]. Overall mortality for liver dysfunction alone has been reported at 56%, and 61% for liver dysfunction following sepsis or major surgery. Strassburg introduced the concept of 'shock liver', a term used collectively to describe deranged liver function tests (LFTs) or clinical evidence of liver dysfunction, varying degrees of which have been identified in about 50% of ICU patients [3].

Commonly used interventions such as positive end-expiratory pressure (PEEP), vasopressors and parenteral nutrition are also risk factors for the development of jaundice [4]. It remains unclear whether these associations are causative. Elevated liver enzymes and bilirubin are markers of hepatocyte damage. Although uncommon, isolated hyperbilirubinaemia can occur as a result of intra- or extrahepatic causes (e.g. haemolysis, Gilbert's syndrome). Derangement of liver function can be closely monitored as part of routine ICU blood testing. However, there is usually a lag phase of several days between the development of hepatocyte damage and a rise in serum markers.

At physiologic levels, bilirubin exerts beneficial effects due to its anti-oxidant properties [4,5]. However, when levels are elevated, it causes more harm than good. See Table 192.1.

Severity of jaundice has a direct relationship with the number of failing organs and mortality [6]. Animal studies have shown that obstructive jaundice may also have a direct cardiac depressant effect (bradycardia, hypotension, diminished catecholamine responsiveness) [7]. Therefore, it is crucial to request appropriate investigations (guided by clinical presentation) and to interpret biochemical abnormalities accurately in order to detect hepatocellular damage early on. In addition to good general supportive therapy, this offers opportunities for improved patient management and outcome.

Metabolism of bilirubin

To appreciate the causes of jaundice and have a rationale for ordering specific investigations, an understanding of bilirubin metabolism is essential [8]. Bilirubin is a tetrapyrrole, lipophilic molecule derived as an end-product of haeme catabolism. It undergoes a complex conjugation process within the liver to be excreted in bile and urine (Fig. 192.1).

Most of the haeme (80–85%) is derived from senescent red blood cells (RBC) by microsomal haeme oxygenase present in reticuloendothelial cells of the spleen. The remainder is derived

Table 192.1 Pathophysiological effects of bilirubin

Beneficial effects	Harmful effects
◆ Reduces risk of coronary artery disease.	◆ Reduces cell survival due to increased oxidative stress.
◆ Reduces cancer-related mortality.	◆ Causes red blood cell lysis.
◆ Protection against pulmonary fibrosis and cyclosporin-induced nephrotoxicity	◆ In sepsis, it is an independent predictor of mortality from and development of acute respiratory distress syndrome

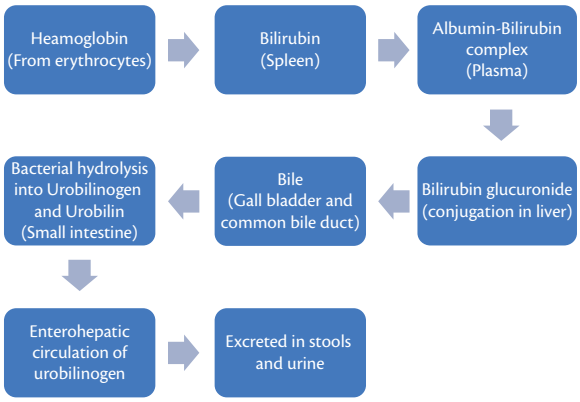


Fig. 192.1 Summary of metabolism of bilirubin and enterohepatic circulation.

from cytochrome P450 and some immature erythrocytes from the spleen and bone marrow. Haeme is initially converted to biliverdin (water-soluble) that, in turn, is reduced to bilirubin (lipid-soluble) by biliverdin reductase. This unconjugated bilirubin is bound to plasma albumin and transported to the liver.

Hepatocytes have specialized functions that uptake bilirubin (after separating albumin), then conjugate it by glucuronidation, and finally excrete it as water-soluble bile into the biliary canaliculi. Bile is stored within the gall bladder and excreted into the second part of duodenum (via the ampulla of Vater) through the common bile duct. In the colon, conjugated bilirubin is again rendered lipid-soluble by colonizing bacteria that produce urobilinogen and urobilin that are excreted in the stool and urine. There is some reabsorption and recirculation through the enterohepatic circulation.

Pathophysiologic classification of jaundice

A multiplicity of aetiological factors has been identified which can be classified into three main pathophysiological domains—prehepatic, intrinsic hepatic, and post-hepatic Table 192.2.

Pathophysiological mechanisms

Current understanding of the pathophysiology of hyperbilirubinaemia is predominantly derived from animal studies. Exact mechanisms remain incompletely elucidated. Hawker has classified intrahepatic causes of liver dysfunction (LD) in the ICU into two main syndromes—ischaemia-related hepatic injury and 'ICU jaundice'. The characteristic feature of **ischaemic hepatitis** is a raised level of serum (aspartate- and alanine-) aminotransferases (AST, ALT) that usually occurs within the first day of insult. Bilirubin levels can be normal or mildly elevated. Other abnormalities such as hepatomegaly, deranged clotting and acidosis have also been linked to injury secondary to low-flow states. In contrast, **ICU jaundice** has a much slower onset with a significantly higher and proportional increase in bilirubin and bile salts compared to AST and ALT levels. Histopathologically, centrilobular necrosis is typically seen in ischaemic hepatitis while most patients with ICU jaundice show intrahepatic cholestasis [9].

Hepatocytes are highly susceptible to hypoxic damage, especially in low-flow states. This could be multi-factorial and accurate measurement of variables such as liver blood flow can be difficult. Pathogenetic mechanisms leading to LD in the ICU are shown in Table 192.3 [4,10,11].

Once LD is identified, clinicians should also actively explore and treat its potential knock-on effects [10] such as:

- **Immunosuppression**: possibly mediated by Kupffer cell activation, and depression of cell-mediated immunity.
- **Altered drug pharmacokinetics**: loss of cytochrome P450 enzyme activity can significantly alter drug handling; reduced liver blood flow can affect uptake and breakdown of certain drugs.
- **Multi-organ dysfunction**: LD can predispose to many systemic effects involving multiple organs (heart, lung, kidney, brain). This may be related to Kupffer cell activation and release of inflammatory mediators into the systemic circulation.

Table 192.2 Classification of jaundice

Classification	Mechanisms	Etiology
Prehepatic (UCB)	Increased production of unconjugated bilirubin	**Haemolysis** ◆ *Intravascular*: hereditary spherocytosis, malaria, G6PD deficiency, mismatched transfusion, autoimmune haemolysis, drug-related ◆ *Extravascular*: trauma, haematoma, splenic sequestration (sickle cell crisis)
Intrahepatic (UCB +/− CB)	◆ Reduced uptake of bilirubin ◆ Hepatocellular damage ◆ Reduced conjugation	◆ *Infection*: hepatitides, sepsis ◆ *Inherited*: Gilbert's, Crigler–Najjar syndromes ◆ *Infiltration*: malignancy ◆ *Ischaemia*: coronary (heart failure), hepatic ◆ *Injury*: trauma, drug-induced (rifampicin, chemotherapy), alcohol-induced cirrhosis
Post-hepatic (CB)	◆ Obstruction to flow of bile ◆ Leakage of bile due to injury to hepatocytes	◆ *Infection:* AIDS, parasites, TB, hepatitides ◆ *Inherited*: Dubin–Johnson and Rotor syndrome ◆ *Inflammation:* cholecystitis, cholangitis, NASH ◆ *Infiltration:* carcinoma (gall bladder, pancreas) ◆ *Injury:* trauma, surgery, alcohol-related, drugs ◆ *Impaction and impingement:* gall stone disease, tumours

NB: UCB, unconjugated bilirubin; CB, conjugated bilirubin; G6PD, glucose-6-phosphate dehydrogenase deficiency; AIDS, acquired immunodeficiency syndrome; TB, tuberculosis; NASH, non-alcoholic steatohepatitis.

Table 192.3 Overview of possible pathogenetic mechanisms involved in ICU jaundice

Aetiology	Pathogenetic mechanisms
Ischaemia/low flow states	◆ Selective splanchnic vasoconstriction (vasopressors) ◆ Reduced bile flow/excretion of conjugated bilirubin from hepatocytes [13] ◆ Altered portohepatic haemodynamics as a result of increased right heart pressures (mechanical ventilation, PEEP, congestive heart failure, etc.) [4]
Sepsis	◆ Endotoxin/inflammatory mediators (bacterial translocation from gut) → failure of phagocytosis by Kupffer cells (drug induced/ischemic injury) → further cascading of inflammatory mediators (IL-1, IL-6, TNF) causing local and distant organ injury/dysfunction ◆ Endotoxin-mediated inhibition of Na-K-ATPase causing cholestasis (reduced secretion of bile) ◆ Inhibition of cytochrome-P450 enzymes by IL-1 (causing impaired drug metabolism)
Drug-induced	◆ Cholestasis (ACE-I, anticonvulsants, tricyclic antidepressants) ◆ Hepatocellular inflammation/death (paracetamol, NSAIDs, methyldopa) Both forms can be immune (indirect) or non-immune mediated (direct) hepatocellular or canalicular injury.
TPN	◆ **Steatosis:** due to perilobular deposition of fat (increased fatty acid synthesis due to reduced clearance of triglycerides and availability of excess free calories, possible local effects of insulin promoting lipogenesis, nutritional deficiencies, etc.) ◆ **Cholestasis:** reduced production of bile salts and enterohepatic circulation ◆ **Cholecystitis:** calculous (reduced gall bladder motility promotes formation of sludge and gallstones) or acalculous (biliary stasis, reduced CCK production) ◆ **Bacterial translocation:** prolonged disuse of intestines promotes bacterial overgrowth; endotoxin mediated injury
Congestive heart failure	◆ **Passive congestion of liver:** reduced hepatic flow, increased venous congestion, reduced oxygen delivery to hepatocytes (causing cell death) ◆ **Ischaemia:** due to oxygen demand supply mismatch ◆ **Ischaemia-reperfusion injury:** Kupffer cell and TNF-mediated cell injury

PEEP, positive end expiratory pressure;, IL, interleukin; TNF, tumour necrosis factor; ACE-I, angiotensin-converting enzyme inhibitor; NSAID, non-steroidal anti-inflammatory drug, CCK, cholecystokinin.

Data from: Minetti M et al., 'Bilirubin is an effective antioxidant of peroxy nitrite-mediated protein oxidation in human blood plasma', *Archives of Biochemistry and Biophysics*, 1998, **352**, pp. 165–74; Levinson MJ, 'Jaundice in the intensive care unit', *Hospital Practice*, 1993, **30**, pp. 51–60; Johnson EE et al., 'End-expiratory pressure ventilation and sulfobromophthalein sodium excretion in dogs', *Journal of Applied Physiology*, 1997, **43**, pp. 714–20.

◆ **Reduced synthetic function**:

- *Albumin*—can affect drug binding and transport, peripheral oedema due to alterations in tissue oncotic pressure.
- *Clotting factors*—can precipitate disseminated intravascular coagulation.
- *Glucose*—hypoglycaemia can be a presentation of 'shock liver'.

Prehepatic causes for unconjugated hyperbilirubinaemia arise from various sources, but are commonly due to transfusion-related haemolytic reactions, drug-induced haemolysis, and breakdown of excessive free or old erythrocytes. Hereditary conditions (e.g. spherocytosis, elliptocytosis, red cell fragility disorders, glucose-6-phosphate dehydrogenase deficiency) can lead to jaundice when exposed to certain stressful situations (exercise, hypoxia, hypothermia, acidosis, etc.). Reduced clearance of bilirubin due to other predisposing factors (pre-existing liver disease) can also predispose to unconjugated hyperbilirubinaemia. Acquired haemolytic conditions include paroxysmal nocturnal haemoglobinuria (Marchiafava–Micheli syndrome) and autoimmune haemolytic anaemia.

Diagnostic approach

A good understanding of the aetiology, pathogenesis, and impact of LD is key to developing a step-wise, logical diagnostic strategy. Many diagnostic dilemmas exist, e.g. what tests to order, their interpretation, and whether hyperbilirubinaemia should be investigated further. Such difficulties can impede prompt initiation of therapy, especially when there is limited guidance in the literature.

It is useful to have a system to explore potential causes. The importance of a good history and general physical and focused examination of the gastrointestinal system cannot be overemphasized. Bilirubin by itself is only one of many indicators of hepatocellular dysfunction, yet is commonly used in organ failure scoring systems [12,13]. A major limitation of using bilirubin as a marker of liver dysfunction is the time delay between the hepatocellular insult and the rise in serum levels [11]. This could be due to overcompensation by unaffected hepatocytes. There is a strong association between hyperbilirubinaemia and sepsis (up to 33% of patients); Franson et al. highlighted that if the rise in bilirubin levels has no obvious cause, then a septic source should be actively explored [14].

Ordering an unselective battery of tests can often generate unwanted results and confuse the clinical picture. The following flowcharts help to formulate a logical approach to the jaundiced ICU patient. In the acute setting, depending on presentation severity, initial stabilization is required before commencing a detailed evaluation of jaundice [15]. The aim is to prevent any secondary damage to vital organs, including the liver. In Stage 1 (Fig. 192.2) the aim is to generate basic information as a guide to planning further tests [16]. The second stage (Fig. 192.3) fine-tunes the diagnostic strategy. However, this general approach should be adapted using clinical judgement to individualize it to both patient and local

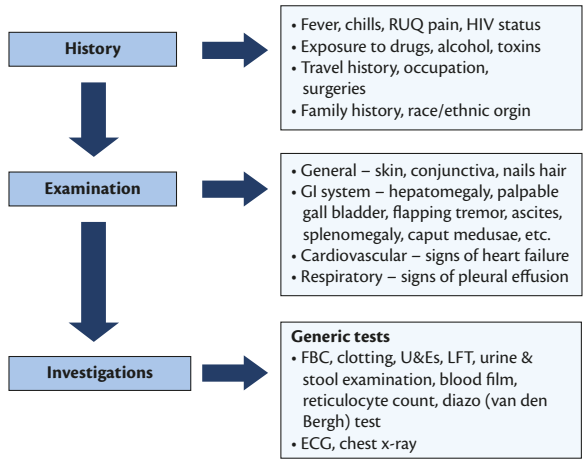


Fig. 192.2 Fundamental steps in initial evaluation of ICU jaundice.
RUQ, right upper quadrant; HIV, human immunodeficiency virus; GI, gastrointestinal; FBC, full blood count; U&Es, urea and electrolytes; LFT, liver function test; ECG, electrocardiogram.

guidelines. Early involvement of medical and surgical gastroenterology teams is crucial.

Hyperbilirubinaemia can occur when there is hepatocellular (prehepatic) disease or cholestatic (intra- and post-hepatic) conditions. Plasma levels of hepatic enzymes (e.g. AST, ALT) are variably affected. A diazo (van den Bergh) test can check the proportion of direct (conjugated) to indirect (unconjugated) bilirubin and should be considered in every patient presenting with jaundice [15].

Computer-assisted decision-support algorithms are gaining popularity [17]. However, while useful in improving efficiency by 'ordering the right test for the right patient', they are not without limitations, biases, and inconsistencies [18].

Nevertheless, by using some of these objective principles of probability and with the results from the initial (Stage 1) assessment, acutely jaundiced patients can be generally categorized into pathophysiologic subgroups (blue boxes in Fig. 192.3) [7]. This helps to plan definitive therapy. The practical difficulties of arranging further investigations and the severity of illness can preclude the possibility of undertaking certain tests. For example, transfer to the radiology department may compromise patient safety if the patient is haemodynamically unstable. If coagulation is deranged, invasive procedures may be relatively contraindicated. Therefore a pragmatic, multi-disciplinary team approach should be adopted in such circumstances. Where a specific line of diagnostic possibility is identified, appropriate specialist input from radiologists, gastroenterologists, hepatologists, and hepatobiliary surgeons should be sought. Wherever possible, less invasive procedures (preferably at the bedside) should be given priority over invasive tests (such as ERCP) in unstable patients. Demarcation into pathophysiological

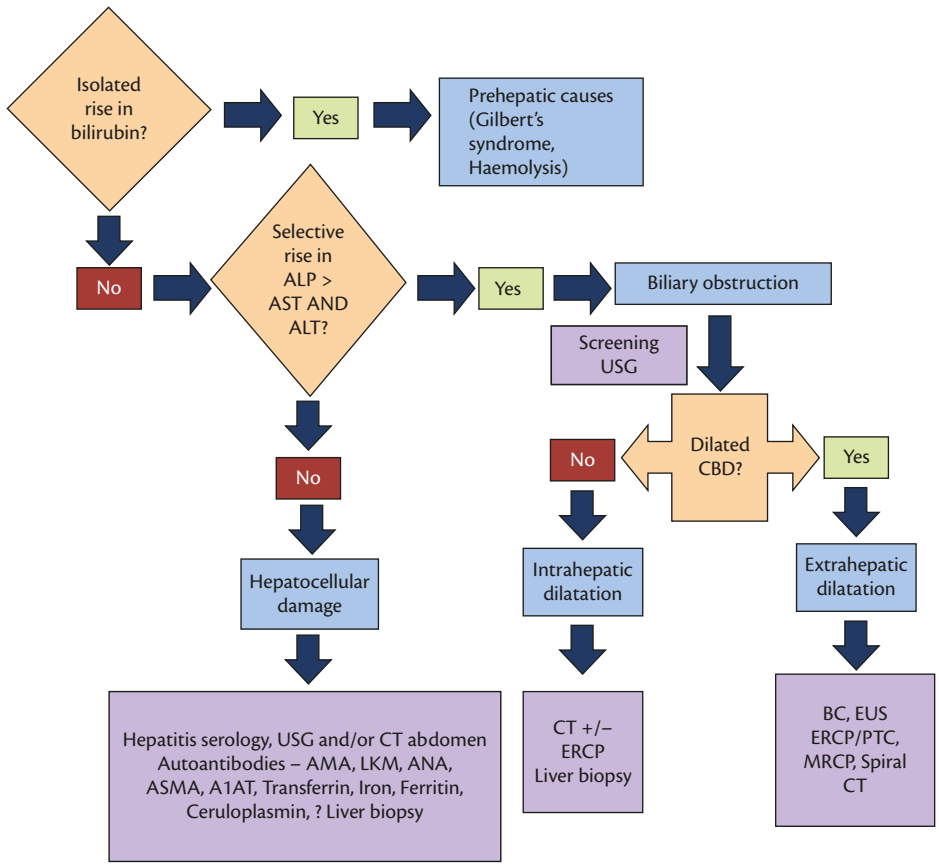


Fig. 192.3 Stage 2 investigations based on results of Stage 1 tests.
ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; USG, ultrasonography; CBD, common bile duct; CT, computed tomography; AMA, anti-mitochondrial antibody; LKM, liver kidney microsomal antibody; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; ERCP, endoscopic retrograde cholangiopancreatography; BC, blood culture; EUS, endoscopic ultrasonography; PTC, percutaneous transhepatic cholangiography; MRCP, magnetic resonance cholangiopancreatography.

subgroups may not always be clear-cut and there can be some overlap in both biochemical and clinical pictures.

Special considerations

Not uncommonly, patients are admitted to ICU with an unusual presentation. While many presentations of jaundice in ICU non-specifically reflect systemic disease, there are some specific causes such as a complication of pregnancy, paracetamol toxicity, and liver transplantation Table 192.4. Care must be taken to identify these high-risk patients early and tailor management accordingly. Any woman in the reproductive age group should have a pregnancy test to direct specific tests relevant to pregnancy itself and to identify rarer causes of jaundice. Drug dyscrasias, non-A non-B hepatitis and halothane hepatitis are discussed elsewhere.

Supplementary investigations

Based on presentation, some additional investigations may need to be ordered, e.g. [7,19]

- For haemolysis, a direct Coombs (antihuman globulin) test, lactate dehydrogenase and serum haptoglobulin may be required.
- Serum albumin and vitamin K-dependent clotting factors are markers of synthetic liver function.
- In obstructive jaundice, fat-soluble vitamins (A, D, E, K) are poorly absorbed. This may also impact on synthesis of the clotting factors II, VII, IX, X, and proteins C and S.
- Urine dipstick to check for the presence of bilirubin aids in diagnosis (negative test suggests cholestatic picture), and urine pregnancy testing to rule out pregnancy.
- Sepsis-related liver injury can cause jaundice and should be investigated with blood cultures, blood gas analysis, and measurement of serum lactate to assess severity of illness and guide further management.
- Diagnostic paracentesis (microscopy, cell count, cytology, cultures, serum ascites-albumin gradient, etc.) should be performed in all patients with ascites, especially in cirrhotic patients with encephalopathy, renal failure, signs of peritoneal infection, or if the source of sepsis is unclear.
- Serum amylase and leucocyte count may be elevated in pancreatic injury and can be suggestive of an obstructive cause for the jaundice (head of pancreas tumours, common bile duct stones, stricture at ampulla of Vater).

Table 192.4 Jaundice: special considerations and pathophysiology

Special consideration	Pathophysiology
Jaundice during pregnancy	◆ Intrahepatic cholestasis (3rd trimester) ◆ Acute fatty liver (3rd trimester) ◆ Hyperemesis gravidarum (usually 1st trimester) ◆ HELLP syndrome, PET (rare causes)
Paracetamol and salicylate overdose	Hepatocellular damage (check serum drug levels)
Post-liver transplantation	◆ Rejection ◆ Biliary obstruction/stenosis ◆ Hepatitis, delayed primary function, primary non-function, ischaemic biliopathy (vanishing bile duct syndrome)

O'Grady Classification: reprinted from *The Lancet*, **342**, 8866, Williams R et al., 'Acute liver failure: redefining the syndromes', pp. 273–5, copyright 1993, with permission from Elsevier. Bernaua Classification: reprinted from *The Lancet*, **342**, 8866, Bernuau J and Benhamou JP, 'Classifying acute liver failure', pp. 252–253, copyright 1993, with permission from Elsevier. Fujiwara Classification: reproduced from Springer and *Journal of Gastroenterology*, **37**(Suppl. 13), 2002, pp. 74–7, 'Indications and criteria for liver transplantation for fulminant hepatic failure', Fujiwara K and Mochida S, with kind permission from Springer Science and Business Media.

Novel diagnostic methods

Investigations such as bilirubin, ALP, ALT, and clotting studies are 'static' tests providing indirect evidence of liver dysfunction [20]. 'Dynamic' tests measure the ability of the liver to metabolize or eliminate substances such as indocyanine green (ICG), caffeine, galactose, or lidocaine. Of these, ICG has been most studied because of its physical properties (inert, water-soluble, anionic nature) and ability to be excreted in bile (without being metabolized). The rate of disappearance of serum ICG, measured at specific intervals after injection, may be used as a surrogate marker of dynamic liver function. Advantages of these novel experimental methods are offset by limitations such as their time-consuming nature and cost. Their use is generally limited to animal models; further research is needed to correlate them with improvement in outcome or reversibility of hepatic dysfunction.

Conclusion

Jaundice is not a disease in itself, but can be a frightening symptom for the patient and a diagnostic and therapeutic challenge for the ICU clinician. Establishing the underlying diagnosis with a systematic approach can lead to positive patient outcomes. This chapter reviews the various pathophysiological and aetiological considerations of an acutely jaundiced ICU patient. Recommendations are made for developing a diagnostic strategy based on literature review, and for future areas of research. As many of the studies reviewed have their own limitations and the very fact that technological advances in the health care industry are progressing so rapidly, it is impossible to have a rigid framework for investigating jaundice in a pre-set manner.

Critically-ill jaundiced patients could have a wide range of aetiologies. Special circumstances such as overdose, drug-induced liver injury, and pregnancy will need careful attention during the process of diagnosis and management. Newer diagnostic tools are on the horizon bringing newer promises, but a balanced view with good clinical evaluation should always underpin a meticulous investigation process of identifying the cause for jaundice. This, along with early involvement of specialist teams, can reduce morbidity and mortality. A secondary advantage is reduction in health care costs, not just by improving outcomes, but also by using resources wisely.

References

1. Bansal V and Schuchert VD. (2006). Jaundice in the intensive care unit. *Surgery Clinics of North America*, **86**, 1495–502.
2. Brienza N, Dalfino L, Cinnella G, et al. (2006). Jaundice in critical illness: promoting factors of a concealed reality. *Intensive Care Medicine*, **134**, 267–74.

3. Strassburg CP. (2003). Gastrointestinal disorders of the critically ill. Shock liver. *Best Practice Research: Clinical Gastroenterology*, **17**, 369–81.
4. Minetti M, Mallozzi C, Di Stasi AM, et al. (1998). Bilirubin is an effective antioxidant of peroxy nitrite-mediated protein oxidation in human blood plasma. *Archives of Biochemical Biophysics*, **352**, 165–74.
5. Polte T, Hemmerle A, Berndt G, et al. (2002). Atrial natriuretic peptide reduces cyclosporin toxicity in renal cells: role of cGMP and heme oxygenase-1. *Free Radical Biology Medicine*, **32**, 56–63.
6. te Boekhorst T, Urlus M, Doesburg W, et al. (1998). Etiologic factors of jaundice in severely ill patients. A retrospective study in patients admitted to an intensive care unit with severe trauma or with septic intra-abdominal complications following surgery and without evidence of bile duct obstruction. *Journal of Hepatology*, **7**, 111–17.
7. Binah O, Bomzon A, Blendis LM, et al. (1985). Obstructive jaundice blunts myocardial contractile response to isoprenaline in the dog: a clue to the susceptibility of jaundiced patients to shock? *Clinical Science*, **69**, 647–53.
8. Sherlock S, Dooley J. (2002). Jaundice. In: Sherlock S and Dooley J (eds) *Diseases of the Liver and Biliary System*, 11th edn, pp. 205–18. Oxford: Blackwell Science.
9. Hawker F. (1991). Liver dysfunction in critical illness. *Anaesthesia Intensive Care*, **19**, 165–81.
10. Levinson MJ. (1993). Jaundice in the intensive care unit. *Hospital Practice*, **30**, 51–60.
11. Johnson EE, Hedley-Whyte J, and Hall SV. (1997). End-expiratory pressure ventilation and sulfobromophthalein sodium excretion in dogs. *Journal of Applied Physiology*, **43**, 714–20.
12. Marshall JC, Cook DJ, Christou NV, et al. (1995). Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Critical Care Medicine*, **23**, 1638–52.
13. Vincent JL, Moreno R, Takala J, et al. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group of Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Medicine*, **22**, 707–10.
14. Franson Tr, Hierholzer MJ Jr, and LaBrecque DR. (1985). Frequency and characteristics of hyperbilirubinemia associated with bacteremia. *Reviews of Infectious Diseases*, **7**, 1–9.
15. Wheatley M and Heilpern KL. (2008). Jaundice: An emergency department approach to diagnosis and management. *Emergency Medicine Practice*, **10**, 1–24.
16. Wang, HD, Yamaya, M, Okinaga, S, et al. (2002). Bilirubin ameliorates bleomycin-induced pulmonary fibrosis in rats. *American Journal of Respiratory Critical Care Medicine*, **165**, 406–11.
17. Cammà C, Garofalo G, Almasio P, et al. (1991). A performance evaluation of the expert system 'Jaundice' in comparison with that of three hepatologists. *Journal of Hepatology*, **13**, 279–85.
18. Molino G, Marzuoli M, Molino F, et al. (2000). Validation of ICTERUS, a knowledge-based expert system for Jaundice diagnosis. *Methods in Infectious Medicine*, **39**, 311–18.
19. Frank BB. (1989). Clinical evaluation of jaundice. A guideline of the Patient Care Committee of the American Gastroenterological Association. *Journal of the American Medical Association*, **262**, 3031–4.
20. Faybik P and Hetz H. (2006). Plasma disappearance rate of indocyanine green in liver dysfunction. *Transplant Proceedings*, **38**, 801–2.

CHAPTER 193

Management of jaundice in the critically ill

Anand D. Padmakumar and Mark C. Bellamy

Key points

- Primary prevention of hepatic injury may not always be possible, but management principles should aim to reduce secondary insults.
- Definitive management should not delay initial resuscitation measures.
- Early categorization into the pre-, intra- and post-hepatic pathophysiological groups will help to channel therapy accordingly.
- Intensive care unit (ICU) jaundice is more commonly non-obstructive in nature, but obstructive causes should be actively excluded due to their high impact on morbidity and mortality.
- Novel strategies (pharmacological and extracorporeal methods) have shown some promise in the management of the jaundiced ICU patient.

Introduction

In the previous chapter we reviewed epidemiology, the diverse aetiopathogenesis, consequences and diagnostic conundrums of jaundice in the intensive care unit (ICU) patient. A systematic diagnostic strategy, guided by sound knowledge of pathophysiology and good clinical assessment, will help intensivists to provide better quality treatment and, potentially, to prevent mortality. Here we focus on management aspects related to the jaundiced *adult* ICU patient only.

Jaundice itself is not a diagnosis, however, arriving at a diagnosis of its cause will assist the overall management goals. Once done, generic and specific treatment can be guided accordingly, to target and, if possible, eliminate the source.

The management approach is divided into two main sections—*preventive* and *therapeutic* with an intention of providing a systematic approach to managing the acutely-ill jaundiced ICU patient.

Prevention strategies

The same principles of management can be applied outside the ICU setting, ideally prior to the onset of critical illness. However, in routine clinical practise, hyperbilirubinaemia often presents late. This could be due to the natural time delay for biochemical markers to rise following the actual insult or injury. Primary prevention may be impossible in such cases. However, it is possible to prevent secondary injury to the liver by providing well-rounded and meticulous supportive care. When biochemical or clinical evidence of hyperbilirubinaemia becomes obvious, expeditious planning and treatment should be undertaken. As discussed in the previous chapter, knowledge of factors that predispose to liver dysfunction (LD) plays a key role in effective prevention of secondary insults.

ICU jaundice is more commonly non-obstructive in nature. However, an obstructive cause should be actively excluded as any delay in treatment will significantly increase morbidity and mortality. The key principles of elimination of these precipitating factors include:

- Initial resuscitation.
- Monitoring.
- Supportive therapy.

Initial resuscitation

Resuscitation strategies should be guided by a focused history and examination and the acute clinical situation. These strategies should be in line with basic and advanced ICU management principles: securing a definitive airway, mechanical ventilation, appropriate and timely fluid resuscitation, use of vasopressors, etc. However, such measures can affect hepatoportal haemodynamics and carry the potential to cause secondary insult. Therefore cardiac output monitoring and frequent clinical re-assessment should guide resuscitation. The consequences of hypotension can be dire (compensatory reduction in splanchnic circulation leading to bacterial translocation from the gut may cause or worsen sepsis, cause 'shock liver' [1], etc.). Appropriate resuscitation may require transfusion of blood and its components [2].

Where an infective aetiology is suspected, Surviving Sepsis guidelines should be followed with appropriate antibiotics instituted early [3]. If a precipitating cause for the jaundice, e.g. a drug, is identified, its administration should be stopped immediately. Additionally, in cases of hepatocellular injury due to paracetamol (acetaminophen) overdose, acetylcysteine (N-acetylcysteine, NAC) should be commenced immediately (without waiting for blood levels) as risks are small and, historically, have been overstated.

Monitoring

Profound haemodynamic disturbances presenting either as a cause (sepsis, heart failure, chronic liver disease, severe trauma, drug

overdose, systemic inflammatory response, etc.) or effect of primary hepatic injury should be closely monitored to guide fluid and vasopressor management. While surrogate measures for liver blood flow are available in some specialist centres, such as indocyanine green clearance or the 'MEGX' test (based on lidocaine metabolism), liver blood flow is not accurately measured in daily clinical practice. Hence, cardiac output (CO) can be used as a surrogate marker of the adequacy of global organ perfusion [4]. It must be emphasized that CO monitoring devices have limitations, their degree of invasiveness must be balanced against the risks involved and the level of information necessary for optimizing treatment.

Supportive therapy

The fundamental goal of supportive therapy is to improve oxygen delivery to organelles within the cell, aiming to maintain homeostasis. Adequate hydration, glycaemic control, and correction of electrolyte disturbances play key roles in maintaining homeostasis.

Careful attention to nutrition, head-end elevation, prevention of venous thromboembolism, physiotherapy, stress ulcer prophylaxis (especially in the coagulopathic patient), selective decontamination of the oropharyngeal and digestive tract, bowel care, and so forth have been shown to improve outcome.

Therapeutic strategies

Treatment relies upon the underlying diagnosis. Strategies have been categorized into the following subsections:

- Treatment of associated symptoms.
- Treatment of associated complications.
- Treatment of underlying causes.
- Novel therapies.

Treatment of associated symptoms

Although there are few specific treatments for jaundice itself, several medical therapies are available for controlling symptoms associated with jaundice.

- **Itching** is a common complaint and can be treated with agents such as cholestyramine (bile salt binding resin), ursodeoxycholic acid, and anti-histamines (used mainly for its sedative effect). Rifampicin, phenobarbitone, naloxone, ondansetron, and steroids have been tried with a variable response and should be used cautiously in view of their potential side-effect profile. Phototherapy, plasmapheresis, and liver transplant may be necessary depending on the underlying pathology or in treatment-resistant cases [5].
- **Abdominal pain** (commonly right upper quadrant pain) can be associated with jaundice and should be addressed with appropriate analgesia. This is especially relevant in patients where the stress response caused by pain can cause or worsen an oxygen demand-supply mismatch, e.g. ischaemic heart disease or cerebrovascular injury.
- **Ascites** is a common presentation of cirrhosis [6]. Treatment involves dietary salt restriction, step-ladder diuretic therapy with spironolatone (first-line), furosemide (second-line), or amiloride, and therapeutic large-volume paracentesis with concomitant volume expansion with human albumin solution, approximately 100 mL of 20% albumin is required for every 3 L of ascitic fluid drained. There is no conclusive evidence to support the use of fluid restriction [7].

Surgical or radiological treatment of an obstructive cause will also help to relieve these symptoms.

Treatment of associated complications

Various physiologic and biochemical abnormalities can accompany ICU jaundice including coagulopathy, multi-organ dysfunction (including liver and renal failure), electrolyte abnormalities, and sepsis. Acute liver failure (ALF) carries a high mortality and management can be challenging. Detailed management strategies for ALF are discussed elsewhere.

- **Coagulopathy** in a jaundiced patient can be due to decompensated liver disease or disseminated intravascular coagulation due to sepsis. The lack of absorption of vitamin K-dependent clotting factors (II, VII, IX, X) in obstructive jaundice compounds the problem further. This may require correction if there is active haemorrhage, e.g. variceal, peptic ulcer, trauma. However, there is no evidence to support routine correction of deranged clotting parameters (with blood components) prior to invasive procedures such as central venous catheterization, chest drain, or tracheostomy insertion, unless there is active bleeding [8].
- **Multi-organ failure** is essentially managed by supportive therapy (as described elsewhere). Protecting the airway by intubating the trachea, mechanical ventilation, vasopressor support, and renal replacement therapy (RRT) are commonly used strategies for supporting various failing organs. Dietician team input, nutritional therapy, meticulous care of invasive catheters, physiotherapy, and early mobilization are also important.

Treatment of underlying causes

The three main pathophysiological categories of jaundice comprise pre-, intra-, and post-hepatic groups. Causes are myriad and, for reasons of brevity, the management strategy of only some causes in each of these three groups will be covered.

Prehepatic group

Haemolytic conditions cause unconjugated hyperbilirubinaemia and can be due to primary (e.g. autoimmune, hereditary spherocytosis, elliptocytosis, sickle cell disease) or acquired (e.g. trauma, mismatched blood transfusion, drug-induced) causes.

- **Diagnosis**: based on peripheral blood smear examination (schistocytes, raised reticulocyte count) and reduced haptoglobin levels, raised levels of unconjugated (indirect) bilirubin and lactate dehydrogenase (LDH) [9].
- **Therapy**: for congenital causes the mainstay is to prevent haemolytic or sickle cell crises by maintaining adequate hydration and analgesia, avoiding known triggers (drugs, acidosis, stress, hypothermia, etc.) and correcting electrolyte disturbances. The resultant haemolytic anaemia may require folic acid and iron supplementation, or rarely, blood transfusion if symptomatic or a history of ischaemic heart disease is obtained. Splenectomy may be indicated in haemolytic crisis secondary to hereditary spherocytosis [10].
- **Pitfalls**: with autoimmune aetiologies there is a risk of haemolysis with transfused blood, causing further hyperbilirubinaemia. Specific cross matching may be necessary. Transfusion should be

undertaken at a slower rate and there may be a role for corticosteroids and intravenous immunoglobulin. Such cases should be discussed early with a haematologist.

Intrahepatic group

Hepatitis can be caused by various conditions, e.g. infection, hypoperfusion or 'shock liver', drugs, alcohol, congestive heart failure. It may become evident through history and abnormal liver enzymes [9]. A viral aetiology often has pre-icteric, icteric and post-icteric phases.

- **Diagnosis**: the pattern of injury is characterized by a rapid and disproportionate rise (10–100 times normal) in serum aminotransferase levels in comparison to alkaline phosphatase (ALP), a slow rise in bilirubin levels, a plateau phase, and quick recovery to the normal range. Liver biopsy is not advisable until after recovery from acute critical illness, but may show centrilobular necrosis [9]. It is important to highlight that untreated hepatitis has a higher chance of progressing to chronic liver disease.
- **Therapy**: therapy for viral hepatitis depends upon the severity of symptoms and liver dysfunction. The British Society of Gastroenterology recommends interferon (IFN) and antiviral agents (ribavirin, lamivudine) either as mono- or combination therapy [11]. Immunosuppression with steroids is the mainstay of treatment for autoimmune hepatitis. Other agents such as azathioprine and tacrolimus may be considered when resistance is encountered to steroid therapy. Septic foci should be actively explored and eliminated (drainage of collections, antibiotics, etc.).
- **Pitfalls**: hypoglycaemia is common in patients with acute liver dysfunction and should be treated without delay. Signs of encephalopathy may be subtle; it is important to clinically rule out ALF [12].

Post-hepatic group

Cholestasis describes any interference with bile flow or formation, and can be extra- or intra-hepatic [5]. **Extrahepatic** cholestasis is due to mechanical obstruction due to gall stone disease or malignancy. In **intrahepatic** cholestasis, there is no physical blockage visible on ultrasonography or cholangiography; causes include drugs, infection, or sepsis and inflammatory conditions (primary sclerosing cholangitis). Patients may present with jaundice (usually late-onset), excessive itching, fever with chills, and rigors, right upper quadrant pain, and malabsorption. Benign post-operative intrahepatic cholestasis, total parenteral nutrition (TPN)-related cholestasis and inherited conditions (Dubin-Johnson and Rotor syndrome) are other, relatively uncommon, causes.

- **Diagnosis**: early screening ultrasonography will help differentiate between intra- and extra-hepatic cholestasis. This is important as further management will differ. Blood cultures and urgent endoscopic retrograde cholangiopancreatography (ERCP) are warranted in the extrahepatic group while, in the intrahepatic group, computed tomography (CT) of the liver, magnetic resonance cholangiopancreatography (MRCP), or ERCP and biopsy may be indicated. In both groups, serum biochemistry will show raised conjugated bilirubin, gamma glutamyl transpeptidase (GGT) and a more than three-fold rise in ALP. Peripheral blood smear may show 'target cells' due to deposition of cholesterol in red cells.
- **Therapy**:
  - Untreated patients may die within a very short time span. Therefore, initial resuscitation and appropriate antibiotic therapy (providing cover for Gram-negative organisms) are vital. The choice and degree of invasive therapy (i.e. surgical or medical management) relies heavily on the underlying cause.
  - ERCP-guided stent insertion is the treatment of choice for obstruction due to strictures or stenosis, although this carries the risk of causing pancreatitis and a systemic inflammatory response. ERCP/MRCP in an unwell patient may be challenging and the benefits must be weighed against the inherent risks of transfer to a remote site. Patients can destabilize during or just after transfer and help may not be immediately available. Equipment compatibility, limited resources during transfer and lack of familiarity are commonly encountered issues.
  - Appropriate antibiotic prophylaxis (presumed sepsis of biliary origin) and vitamin K supplementation may be necessary in coagulopathic patients prior to invasive procedures. Patients requiring multiple CT scans are at risk of contrast-induced nephropathy (CIN), which can worsen the clinical picture and outcome. The ideal preventive agent still remains elusive. The role of NAC in preventing CIN and improving outcomes has yet to be conclusively shown [13].
- **Surgery** in the form of open or laparoscopic cholecystectomy, radiological decompression (percutaneous transhepatic cholangiography) or drainage under CT guidance may be necessary in selected cases. Occasionally, in cases of neoplastic obstruction, biliary diversion with a Roux loop or bypass plus curative resection is the intervention of choice for the acutely ill jaundiced patient. Conclusive evidence of outcome benefit is still lacking to support the role of preoperative biliary drainage (for distal obstruction), the risk of wound infection and intra-abdominal sepsis due to bile leak may be increased [14].
- **Pitfalls**: failure to recognize pregnancy (where the cause of the jaundice may be intrahepatic cholestasis of pregnancy) can place both fetus and mother at risk. Furthermore, delay in identifying the cause for the cholestatic jaundice significantly increases morbidity and mortality. This is especially true for ascending cholangitis where prompt therapy with antibiotics could be life-saving. A small proportion may require biliary drainage [12].

Novel therapies

Refractory itching can be a debilitating symptom for a jaundiced ICU patient. This may be due to accumulation of various endogenous substances such as bile acids and lysophosphatidic acid. There is increasing interest in liver support systems for the treatment of severe pruritus [15]. This is mainly aimed at symptom control, but sometimes can be used as an alternative or 'bridge' therapy for patients awaiting liver transplantation as definitive therapy. These devices will be dealt with in more detail elsewhere [16,17]. Extracorporeal liver assist devices (ELADs) are chiefly used to take over two of the main functions of the liver: elimination of albumin-bound endogenous and exogenous toxins or drugs. These can be classified into **bio-artificial devices** (cell-based models) and **non-bio-artificial devices** (non-cell-based models using albumin dialysis). All devices have varying short-term efficacy and inherent shortcomings with limited outcome benefit.

The role of such advanced and expensive techniques has to be tailored to the individual jaundiced ICU patient.

Novel anti-endotoxin peptides (P6 and C1) have shown some promise in treating endotoxaemia related to obstructive jaundice in animal models [18]. Kupffer-cell blockade (using gadolinium chloride) and reducing thromoboxane (TX) levels (TX synthase inhibitors, cyclo-oxygenase inhibitors and TX-receptor antagonists) are other avenues being explored by researchers in cholestatic animal models [19,20].

Despite the high prevalence of jaundice in ICU patients, there is still a lack of robust randomized studies and evidence base for management strategies that have been clearly shown to improve outcomes. Clearly, there is scope for further research that can hopefully enable a halt in the progression of, and mortality from, liver injury.

Conclusion

In critically-ill patients, liver dysfunction significantly affects hospital length of stay and overall outcome. Regardless of the cause, the final common pathway of liver failure is not only difficult to manage, but carries a high mortality. Primary prevention of hepatic injury may not always be possible, but management principles should aim to reduce secondary insults.

Early categorization into the pre-, intra-, and post-hepatic pathophysiological groups will help in channelling therapy accordingly. For example, gallstone disease is the commonest cause of post-hepatic disease, but can have fatal complications if left untreated. Initial resuscitation and adherence to sepsis care bundles improve outcomes in acutely ill jaundiced patients. Prompt referral to appropriate medical, surgical, and radiology teams are also important measures that can positively change the course of the illness.

References

1. Strassburg CP. (2003). Gastrointestinal disorders of the critically ill. Shock liver. *Best Practice & Research: Clinical Gastroenterology*, **17**, 369–81.
2. Hawker F. (1991). Liver dysfunction in critical illness. *Anaesthesia Intensive Care*, **19**, 165–81.
3. Dellinger RP, Levy MM, Carlet JM, *et al*. (2008). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Critical Care Medicine*, **36**, 296–327.
4. Krenn C. (2012). Intraoperative monitoring. In: Wagener G (ed.) *Liver Anesthesiology and Critical Care Medicine*, pp. 101–2. New York, NY: Springer.
5. Sherlock S, and Dooley J.(2007). Cholestasis. In: Sherlock S and Dooley J (Eds) *Diseases of the Liver and Biliary System*, 11th edn, pp. 235–37. Oxford: Blackwell Science.
6. Gines P, Quintero E, Arroyo V, et al. (1987). Compensated cirrhosis: natural history and prognostic factors. *Hepatology*, **7**, 12–18.
7. Moore KP and Aithal G. (2006). Guidelines on the management of ascites in cirrhosis. *Gut*, **55**, 1–12.
8. Padmakumar AD and Bellamy MC. (2011). Review of current practice of blood and component transfusion: critical issues for the critically ill patient. *Journal of the Intensive Care Society*, **12**, 134–9.
9. Chung C and Buchman AL. (2002). Postoperative jaundice and total parenteral nutrition-associated hepatic dysfunction. *Clinical Liver Disease*, **6**, 1067–84.
10. Hamilton JW, Jones FG, and McMullin MF. (2004). Glucose-6-phosphate dehydrogenase Guadalajara—a case of chronic non-spherocytic haemolytic anaemia responding to splenectomy and the role of splenectomy in this disorder. *Hematology*, **9**, 307–9.
11. Booth JCL, O'Grady J, and Neuberger J. (2001). Clinical guidelines on the management of hepatitis C. *British Society of Gastroenterology*, **49**(1), 11–21. Available at: http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/liver/clinguidehepc.pdf.
12. Wheatley M and Heilpern KL. (2008). Jaundice: an emergency department approach to diagnosis and management. *Emergency Medicine Practice*, **10**, 1–24.
13. Sun Z, Fu Q, Cao L, Jin W, Cheng L, and Li Z. (2013). Intravenous n-acetylcysteine for prevention of contrast-induced nephropathy: a meta-analysis of randomized, controlled trials. *PLoS One*, **8**, e55124.
14. Garcea G, Chee W, Ong SL, and Maddern GJ. (2010). Preoperative biliary drainage for distal obstruction: the case against revisited. *Pancreas*, **39**, 119–26.
15. Fuhrmann V, Drolz A, and Trauner M. (2011). Extracorporeal artificial liver support systems in the management of intractable cholestatic pruritus. *Liver International*, **31**, (3), 31–3.
16. Rikker C. (2009). Liver support systems today. *Orvosi Hetilap*, **150**, 2299–307.
17. Wittebole X and Hantson P. (2011). Use of the molecular adsorbent recirculating system (MARS™) for the management of acute poisoning with or without liver failure. *Clinical Toxicology (Philadelphia)*, **49**, 782–93.
18. Jones C, Badger SA, Black JM, et al. (2012). The use of antiendotoxin peptides in obstructive jaundice endotoxemia. *European Journal of Gastroenterology and Hepatology*, **24**, 248–54.
19. Abrahám S, Szabó A, Kaszaki J, et al. (2008). Kupffer cell blockade improves the endotoxin-induced microcirculatory inflammatory response in obstructive jaundice. *Shock*, **30**, 69–74.
20. Yokoyama Y, Nimura Y, Nagino M, et al. (2005). Role of thromboxane in producing hepatic injury during hepatic stress. *Archives of Surgery*, **140**, 801–7.

PART 6.8

Acute hepatic failure

CHAPTER 194

Pathophysiology and causes of acute hepatic failure

Sameer Patel and Julia Wendon

Key points

- Acute liver failure (ALF) is a rare, life-threatening clinical syndrome occurring in a person with no prior history of liver disease.
- Several classifications exist incorporating time to encephalopathy from the onset of jaundice. O'Grady's classification is the most widely used.
- Viral hepatitis is the most common cause of ALF worldwide, with drug-induced liver failure the most common in the developed world.
- ALF is a multi-system disorder resulting in encephalopathy, coagulopathy, systemic inflammatory response syndrome, and multi-organ failure.
- Patients can be prothrombotic or have balanced coagulation disorders.

Introduction

Acute liver failure (ALF) is a rare, life-threatening, and unpredictable clinical syndrome consequent to a sudden and severe hepatic injury in a person with no prior history of liver disease, with subsequent loss of hepatic metabolic and immunologic function. Approximately 1–8 cases per million population occur per year in the developed world. This is likely to be much higher in developing countries where infective causes of ALF are more prevalent. Despite modern medical advances, mortality can still exceed 50%, notwithstanding the significant healthcare burden ALF represents.

ALF is characterized by hepatic encephalopathy and coagulopathy, occurring within days or weeks of symptom appearance, and is frequently associated with the development of progressive multi-organ dysfunction requiring ICU admission. The syndrome can be divided into hyperacute, acute, or subacute based on the development of encephalopathy from the time of onset of jaundice [1], or into fulminant and subfulminant categories [2]. O'Grady's description remains the most commonly used (Table 194.1).

Aetiology

Numerous causes of ALF exist (Table 194.2) and these vary in their course, severity, and outcome. Some patients, despite rigorous investigation, have no obvious precipitant and are classified as indeterminate or seronegative [4].

Viral infections

Acute viral infections are the predominant cause of ALF worldwide, principally affecting the developing world [5]. They constitute 40–70% of cases, with hepatitis A and E viruses (HAV and HEV) accounting for the majority. HAV and HEV are both transmitted via the faeco-oral route, and are endemic in the developing world with HEV the leading cause of ALF in the Indian and Southeast Asian subcontinents, China, and Africa. HAV, on the other hand, has become less prevalent following the introduction of vaccination worldwide. Infection with either HAV or HEV rarely leads to ALF, but typically follows a hyperacute or acute clinical course [5]. Less than 1% of HAV infection results in ALF. Pregnant women are susceptible to hepatitis E infection, especially in the third trimester [6].

Hepatitis B (HBV) is transmitted by exposure to contaminated blood or other bodily fluids. It runs an acute presentation typically resulting in viral clearance and immunity. HBV-induced ALF, presenting as seroconversion from chronic or inactive states, has a higher risk of developing liver failure with worse outcomes. As a preventable cause of ALF, patients should be screened for HBV carriage before institution of chemotherapy or high-dose steroids, as this may result in HBV-related ALF. If testing positive, patients should be treated with antivirals prior to instituting immunosuppressive or immunomodulatory therapy [7].

Other rare viral causes are shown in Table 194.2. These tend to be more prevalent in immunocompromised patients. Acute hepatitis C (HCV) is a very rare cause of ALF, more typically causing a chronic infection. Hepatitis D (HDV) is associated with superinfection in HBV carriers.

Drug-induced causes

Drug-induced ALF is the leading cause in the developed world and the second leading cause worldwide [5]. Drug-induced liver injury (DILI) may be idiosyncratic or dose-related, and may be attributable to the parent drug compound or its metabolites. Only rarely does this progress to liver failure. Paracetamol (acetaminophen) taken in excess is the most common culprit, either as deliberate self-harm or unintentionally, and either at a single time-point or over several days. It presents in the hyperacute form, often rapidly progressing to multi-organ failure. Toxicity is dose-dependent, and secondary to depletion of glutathione stores and accumulation of the toxic metabolite N-acetyl-P-benzoquinone-imine (NAPQI). Risk factors include extremes of age, regular alcohol consumption, concurrent administration of cytochrome p450 enzyme-inducing drugs

Table 194.1 Classifications of liver failure and causes

Classification	Time of onset jaundice to encephalopathy	Causes
O'Grady [1]		
Hyperacute	0–1 weeks	Paracetamol, ischaemia, recreational drugs, toxins (amanita)
Acute	1–4 weeks	Hepatitis B, A, and E
Subacute	4–26 weeks	Non-paracetamol drug-induced liver injury, seronegative hepatitis
Bernuau [2]		
Fulminant	<2 weeks	Viral hepatitis, paracetamol, toxins
Subfulminant	>2 weeks to several months	Viral infections, idiosyncratic drug reactions
Fujiwara [3]		
Acute	<10 days	Hepatitis A, B
Subacute	11 days–8 weeks	Asymptomatic hepatitis B carriers
Late onset hepatic failure (LOHF)	>8 weeks	Autoimmune hepatitis, seronegative

Encephalopathy should be Grade II or above, and PT ≤40% (i.e. prolonged) or INR ≥1.5.

O'Grady Classification: reprinted from *The Lancet*, **342**(8866), Williams R et al., 'Acute liver failure: redefining the syndromes', pp. 273–5, copyright 1993, with permission from Elsevier. Bernaua Classification: reprinted from *The Lancet*, **342**(8866), Bernuau J and Benhamou JP, 'Classifying acute liver failure', pp. 252–3, copyright 1993, with permission from Elsevier. Fujiwara Classification: Reproduced from Springer and *Journal of Gastroenterology*, **37**(Suppl. 13), 2002, pp. 74–7, 'Indications and criteria for liver transplantation for fulminant hepatic failure', Fujiwara K and Mochida S, with kind permission from Springer Science and Business Media.

(e.g. anticonvulsants), malnutrition, and staggered ingestion, often resulting in late presentation. Antimicrobial agents are a major class of drug associated with liver injury and failure. All classes of antibiotics have been implicated. Other recognized drug causes of ALF are listed in Table 194.2. Genetic polymorphisms are postulated as potential mechanisms for injury for many of these drugs.

Pregnancy-induced

Pregnancy-associated liver failure can be divided into three groups, which are widely considered to be part of one clinical and pathological spectrum: acute fatty liver of pregnancy (AFLP), HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome and pre-eclampsia/eclampsia [8]. AFLP usually occurs in the third trimester and is characterized by sudden onset jaundice, altered mentation, hypoglycaemia, elevated urate, and elevated transaminases. HELLP syndrome is characterized by the features inherent in the mnemonic. Pre-eclampsia is characterized by gestational hypertension, proteinuria, right upper quadrant or epigastric pain, and seizures in eclampsia. It occurs in 6–8% of pregnancies and is a leading cause of maternal death. Pre-eclampsia may be

Table 194.2 Aetiology of ALF

Classification	Causes
Viral	Hepatitis A,B,D,E, EBV, CMV, HSV-1 and II, VZV, Parvovirus B19, adenovirus, viral haemorrhagic fevers
Drug-induced	◆ **Antibiotics**: co-amoxiclav, erythromycin, septrin, nitrofurantoin, flucloxacillin ◆ **Antifungals**: fluconazole, itraconazole ◆ **Antituberculous**: isoniazid, rifampicin, pyrazinamide ◆ **Antivirals**: nelfinavir, nevirapine, abacavir, efavirenz ◆ **Chemotherapy**: thalidomide ◆ **Anticonvulants**: phenytoin, valproate, carbamazepine ◆ **Analgesics**: paracetamol, NSAIDs ◆ **Other**: total parenteral nutrition, statins, halothane, oral hypoglycaemics, β-interferon, herbal remedies, cocaine, MDMA (ecstasy), propylthiouracil, antipsychotics
Pregnancy-induced	AFLP, HELLP, pre-eclampsia, and eclampsia
Toxins	Amanita phalloides, industrial solvents, phosphorus, carbon tetrachloride, *Bacillus cereus*
Vascular	Budd–Chiari syndrome, ischaemic hepatitis, thromboembolism
Infiltrative	Lymphoma, carcinoma, metastases, haemophagocytic syndromes
Miscellaneous	Seronegative hepatitis, heatstroke, trauma, Acute Wilson's disease, AIH

associated with spontaneous liver rupture, presenting with pain and significant transaminitis. The subcapsular collection may progress, resulting in hepatic ischaemia and/or an obstructed outflow to the hepatic veins. Pregnancy-related disease is associated with good clinical outcomes. In all types, prompt delivery of the fetus is usually enough to reverse the process. However, liver transplantation may be necessary in some cases [9]. Consideration should always be given to microvascular thrombosis, and hepatic vein occlusion or thrombosis.

Miscellaneous

Autoimmune hepatitis (AIH), typically a chronic disease, can present acutely in a small proportion of cases, although rarely as an ALF. Ischaemia following severe hypovolaemia, sepsis, or low cardiac output states, often in association with right-sided cardiac dysfunction, presents as hypoxic or ischaemic hepatitis. Hepatic vein outflow obstruction results in acute Budd–Chiari syndrome, often associated with prothrombotic disease, while small vessel veno-occlusive disease may complicate chemotherapy. Malignant infiltration and acute presentations of Wilson's disease are other causes; these patients often have splenomegaly unlike other presentations of ALF.

Pathophysiology

Despite the numerous aetiologies of ALF, common to all presentations is the unpredictable clinical course. Disease progression can often be rapid, frequently resulting in multisystem organ failure making treatment extremely challenging. Presenting symptoms are often non-specific, and include malaise, anorexia, abdominal pain, and jaundice.

Encephalopathy

Encephalopathy is an essential component for the diagnosis of ALF. Time of onset defines the subtype and, with the aetiology, will help determine prognosis. It is a clinical spectrum graded 1–4 on the Modified Parsons-Smith Scale (Table 194.3) ranging from mild confusion to coma, with associated complications of cerebral oedema and intracranial hypertension in the higher grades. The aetiology is poorly understood. Various theories postulated include increased brain uptake of ammonia, γ-aminobutyric acid (GABA) and other endogenous factors, neurotransmitters, and hormones. Ammonia accumulation results in an associated increase in glutamine, with loss of cerebral function and autoregulation. Being osmotically active, accumulation results in astrocyte swelling and cerebral oedema.

Table 194.3 Modified Parsons-Smith Scale for hepatic encephalopathy

Score	Clinical features
I	Mild confusion, poor concentration, slurred speech, mild tremor, ataxia
II	Disorientation, lethargy, tremor
III	Drowsy, but rousable, significant confusion, incoherent
IV	Coma (GCS < 8), may exhibit decerebrate posturing

Reprinted from *The Lancet*, **270**(7001), Parsons-Smith BG et al., 'The electroencephalograph in liver disease', pp. 867–71, copyright 1957, with permission from Elsevier.

Arterial ammonia levels >150 μmol/L were associated with cerebral death in a cohort of ALF patients in grade III/IV coma [10]; levels >120 μmol/L were associated with poor prognosis in India while, more recently, levels >200 μmol/L were associated with worse outcome [11]. Importantly, with regard to prognosis, is the delta change in arterial ammonia level. This appears to be significant for the development of cerebral oedema. Those with a fall show no increase in intracranial pressure.

Coagulopathy

Coagulopathy (International Normalized Ratio, INR >1.5) also forms part of the definition for ALF. The degree of coagulopathy can be highly variable, and is determined by the extent to which clotting factor synthesis in the liver is depressed, plus the excessive consumption of platelets and prothrombotic factors. Factors II, V, VII, IX, and X are synthesized in the liver, and their loss or reduced production results in a prolonged prothrombin time (PT) or INR. Platelet consumption and low fibrinogen levels are observed secondary to increased fibrinolysis as part of the disseminated intravascular coagulation (DIC) syndrome. Despite significant coagulopathy, spontaneous haemorrhage is rare unless platelets fall below 20,000/mL. Even in the context of highly abnormal INR levels, patients can be prothrombotic or have balanced coagulation disorders [12]. To this end, routine correction of coagulopathy with fresh frozen plasma (FFP) is not advised unless the patient is actively bleeding or due to undergo invasive procedures with a high risk of bleeding. More importantly, however, correction with FFP masks the trajectory of liver failure, as the INR (or prothrombin time) forms one of the criteria required to determine prognosis, and the need for transplantation. Vitamin K deficiency, however, increases the likelihood and severity of coagulopathy, and correction is advocated.

Systemic inflammatory response syndrome (SIRS)/sepsis

Acute liver failure and hepatocellular injury causes a surge in cytokine release. This is associated with circulation of endotoxins and cytokines that are normally cleared by the liver, resulting in a SIRS and, subsequently, multisystem organ dysfunction. Associated infection and sepsis are frequent phenomena. Patients tend to be immunocompromised secondary to dysfunction of their reticuloendothelial and innate immune systems. The incidence of positive blood cultures in a recent study was 30% [13]. An inflammatory phenotype is associated with a poor prognosis irrespective of sepsis [14], while the severity of SIRS is associated with progression of encephalopathy and mortality [13]. A low threshold for sending septic screens is recommended whenever infection is suspected. Hygiene and prevention of nosocomial infection is essential in this population.

Cardiorespiratory

Significant hemodynamic changes are common in ALF patients. They characteristically develop a low systemic vascular resistance (SVR) with elevated cardiac output resulting in functional hypovolaemia often compounded by decreased fluid intake. Adrenal dysfunction is also thought to play a role in refractory hypotension [15], warranting consideration of hydrocortisone therapy when hypotension persists despite volume repletion. However, no survival benefit has been demonstrated with steroid therapy.

Respiratory embarrassment is usually due to atelectasis, pleural effusions, intrapulmonary shunts with resultant ventilation–perfusion (V/Q) mismatch and, rarely, development of hepatopulmonary syndrome, the latter having been described in ischaemic hepatitis. ARDS can ensue, contributing to or exacerbating any respiratory compromise. Raised intra-abdominal pressures can contribute to respiratory, cardiovascular, and renal compromise, and should be monitored.

Renal

Renal failure is an independent risk factor for mortality in intensive care [16]. In ALF its causes are multifactorial. It can be related to the underlying cause of ALF, as occurs in direct paracetamol (acetaminophen)-related renal toxicity, or due to the pathophysiological processes associated with ALF. Hypovolaemia and hypotension reduce renal perfusion pressure leading to renal injury. Hepatorenal syndrome (HRS) is diagnosed when no causal factors are identified for the development of acute kidney injury (AKI), i.e. it is a diagnosis of exclusion. It is thought to be a functional renal failure associated with intrarenal vasoconstriction, and is rare in ALF as compared with cirrhosis.

Metabolic

Homeostatic mechanisms are frequently deranged in ALF resulting in metabolic abnormalities ranging from severe hypoglycaemia to metabolic acidosis or alkalosis. Impaired gluconeogenesis, glycogen store depletion, insulin resistance (hepatic and peripheral), and poor oral intake are likely mechanisms of hypoglycaemia. A recent study demonstrated an increase in morbidity and mortality associated with hypoglycaemia as a result of tight glycaemic control [17]. If extrapolated to the ALF population, it is evident that close surveillance of blood sugar levels and appropriate correction is mandatory. Metabolic derangement can arise from lactic acidosis, (tissue hypoperfusion/decreased tissue oxygen delivery, or decreased hepatic metabolism of lactate), and secondary to renal failure and uraemia. Other metabolic abnormalities include hyponatraemia, (potentiates encephalopathy), hypokalaemia, and hypophosphataemia (requiring treatment and representing an improved outcome) [18].

References

1. O'Grady JG, Schalm SW, and Williams R. (1993). Acute liver failure: redefining the syndromes. *Lancet*, **34**, 273–5.
2. Bernuau J and Benhamou JP. (1993). Classifying acute liver failure. *Lancet*, **342**, 252–3.
3. Fujiwara K, Mochida S. Indications and criteria for liver transplantation for fulminant hepatic failure. J Gastroenterol. 2002; 37 Suppl 13:74–7.
4. Bernal W, Ma Y, Smith HM, Portmann B, Wendon J, and Vergani D. (2007). The significance of autoantibodies and immunoglobulins in acute liver failure: a cohort study. *Journal of Hepatology*, **47**, 664–70.
5. Bernal W, Auzinger G, Dhawan A, and Wendon J. (2010). Acute liver failure. *Lancet*, **376**, 190–201.
6. Bhatia V, Singhal A, Panda SK, and Acharya SK. (2008). A 20-year single-center experience with acute liver failure during pregnancy: is the prognosis really worse? *Hepatology*, **48**, 1577–85.
7. Lok AS and McMahon BJ. (2009). Chronic hepatitis B: update 2009. *Hepatology*, **50**, 661–2.
8. Rahman TM and Wendon J. (2002). Severe hepatic dysfunction in pregnancy. *Quarterly Journal of Medicine*, **95**, 343–57.
9. Lee WM, Stravitz RT, and Larson AM. (2012). Introduction to the revised American Association for the Study of Liver Diseases position paper on acute liver failure 2011. *Hepatology*, **55**, 965–7.
10. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, and Ott P. (1999) Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology*, **29**, 648–53.
11. Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, and Wendon J. (2007) Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. *Hepatology*, **46**, 1844–52.
12. Lisman T, Caldwell SH, Burroughs AK, Northup PG, Senzolo M, Stravitz RT, et al. (2010). Hemostasis and thrombosis in patients with liver disease: the ups and downs. *Journal of Hepatology*, **53**, 362–71.
13. Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, and Williams R. (2000). The systemic inflammatory response syndrome in acute liver failure. *Hepatology*, **32**(4 Pt 1), 734–9.
14. Craig DG, Reid TW, Martin KG, Davidson JS, Hayes PC, and Simpson KJ. (2011). The systemic inflammatory response syndrome and sequential organ failure assessment scores are effective triage markers following paracetamol (acetaminophen) overdose. *Alimentary Pharmacology & Therapeutics*, **34**, 219–28.
15. Harry R, Auzinger G, and Wendon J. (2002). The clinical importance of adrenal insufficiency in acute hepatic dysfunction. *Hepatology*, **36**, 395–402.
16. Bellomo R, Ronco C, Kellum JA, Mehta RL, and Palevsky P. (2004). Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Critical Care*, **8**, R204–12.
17. Nice-Sugar Study Investigators, Finfer S, Liu B, et al. (2012). Hypoglycemia and risk of death in critically ill patients. *New England Journal of Medicine*, **367**, 1108–18.
18. Schmidt LE and Dalhoff K. (2002). Serum phosphate is an early predictor of outcome in severe acetaminophen-induced hepatotoxicity. *Hepatology*, **36**, 659–65.

CHAPTER 195

Diagnosis and assessment of acute hepatic failure in the critically ill

Sameer Patel and Julia Wendon

Key points

- A thorough history and examination to determine the aetiology of ALF is essential for initiating appropriate and timely interventions.
- Clinical assessment forms the basis of risk stratification for identifying those patients who can be managed locally from those who need referral to tertiary specialist centres.
- Although the International Normalized Ratio (INR) is prolonged, more extensive assessment of coagulation shows a balanced loss of both pro- and anti-coagulant factors, explaining the low risk of bleeding.
- Prognostication is an essential part of assessment as accurate prediction of outcome is fundamental for the judicious application of donor liver organs, a resource-limited commodity.
- The King's College Hospital criteria are the best known, most widely applied and accepted prognostic tool, incorporating both aetiology and clinical indices.

Introduction

Implementation of correct and timely management is essential in cases of acute hepatic failure. A high index of clinical suspicion derived from an exhaustive history and examination is crucial in targeting investigations and initiating management, sometimes before results are available. Clinical assessment forms the basis of risk stratification, allowing identification of those patients who can continue to be managed locally from those best served in a specialist liver centre, which should have facilities for transplantation. Patient presentation may be hyperacute, acute, or subacute, the former displaying a greater degree of organ failure, but a better chance of spontaneous recovery without the need for liver transplantation. Investigations should encompass the variety of potential causes (Table 195.1), albeit guided by clinical features and presenting history.

History

An accurate history can provide vital clues as to the underlying aetiology. History should focus on the presenting problem, time of onset, and speed of deterioration. Time of onset of jaundice, reversal of sleep cycle and any changes in personality, concentration, or memory are all features inherent to the diagnosis of ALF. Establishing whether the features are consistent with hyperacute, acute, or subacute ALF may then guide subsequent history towards known precipitants and, more importantly, prognostication. A thorough drug history should ascertain current prescribed medication, in particular any new prescriptions in the last few months. Equally important are non-prescribed or over-the-counter medications, such as Chinese or herbal remedies, as these have also been implicated in the pathogenesis of drug-induced ALF. Non-intentional or deliberate drug overdose should be sought in the history. Where deliberate self-harm is considered, a more detailed psychiatric history is necessary. A history of recreational drug use/abuse, in particular ecstasy and cocaine, may provide other potential causes, while a history of foraging mushrooms might suggest amanita phalloides. A travel history may reveal potential hepatitis A (HAV) or hepatitis E (HEV) infection, especially if there has been recent travel to endemic areas, or even exposure to more rare causes of ALF, such as the viral haemorrhagic fevers (e.g. parts of central Africa). Risk factors for potential exposure to HBV should be elicited—intravenous drug use, sexual history, and use of potentially contaminated blood products from abroad. Patients with a history of sepsis, hypovolaemia or hypotension, or the presence of pre-existing cardiorespiratory disease, might suggest an ischaemic hepatopathy, whereas a history of weight loss, night sweats, and fevers may suggest an infiltrative process such as lymphoma. Unfortunately, in a number of cases eliciting a history is impossible as patients may present confused or encephalopathic. In such circumstances a collateral history from relatives, friends, or the patient's family doctor should be obtained.

Examination

Examination should initially focus on a rapid assessment of airway, breathing, circulation and disability (ABCD) with any necessary resuscitation before searching for signs leading to more specific differential diagnoses. Airway compromise is a frequent occurrence in reduced conscious levels, as commonly seen in patients with grade III or IV hepatic encephalopathy (HE). Progression of HE can be rapid, especially in hyperacute presentations. Prompt referral to intensive

Table 195.1 Investigations for ALF

Aetiology	Investigation
General	Full blood count
	Urea & electrolytes
	Liver function tests (AST/ALT/ALP/bilirubin/albumin/GGT)
	Clotting profile
	Glucose
	Arterial blood gas
	Arterial lactate
	Arterial ammonia*
	Liver USS ± CT abdomen (for liver volume/ascites/blood supply/portal hypertension/splenomegaly)
	Liver biopsy
Viral screen	
HAV	Anti-HAV IgM Antibody (Ab)
HBV	HBsAg (may be absent at presentation), anti-HBc IgM, HBeAg, hepatitis B DNA
HDV	Delta Ab
HEV	Anti-HEV IgM Ab
Others	PCR HSV, EBV, CMV, adenovirus, viral haemorrhagic fevers, anti VZV IgM, VZV DNA, Parvovirus B19 DNA
Overdose or toxins	Paracetamol level
	Salicylate level
	Toxicology screen (BDZs/TCAs/ecstasy/cocaine)
Autoimmune	ANA, anti-smooth muscle Ab, anti-liver/kidney/microsome Ab
	Immunoglobulin profile
Pregnancy-related	
HELLP	**Haemolysis:** raised LDH/reticulocyte count/Coombs' test positive, Elevated liver enzymes, low platelets, DIC—low fibrinogen
Pre-eclampsia	Elevated urate, proteinuria, hypertension, low platelets, DIC, reduced GFR, possible liver rupture
AFLP	Elevated urate, bilirubin, prolonged PT, neutrophilia, low glucose
Wilson's disease	Serum ceruloplasmin, urinary copper, Kayser–Fleischer rings: cirrhotic liver, splenomegaly, low alkaline phosphatase, Coombs-negative haemolysis
Malignancy	CT scan
	Leukopenia, pancytopenia
	Bone marrow biopsy
	Raised LDH (lymphoma)
Other	
Heatstroke	CK, myoglobinuria
Hypoxic Hepatitis	**ECG:** arrhythmia, Echocardiogram (low cardiac output syndrome/congestive cardiac failure)

*If patient has grade III or IV encephalopathy, or suspected raised intracranial pressure.

AST, aspartate aminotransaminase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; USS, ultrasound scan; HBsAg, hepatitis B surface antigen; HBeAb, hepatitis B envelope antibody; anti-HBc, hepatitis B core antigen antibody; IgM, immunoglobulin M; HBeAg, hepatitis B envelope antigen; HSV, herpes simplex virus; EBV, Epstein–Barr virus; CMV, cytomegalovirus; VZV, varicella zoster virus; BDZ, benzodiazepine; TCA, tricyclic antidepressant; ANA, antinuclear antibody; DIC, disseminated intravascular coagulation; GFR, glomerular filtration rate; CK, creatine kinase.

care is critical to secure the non-protected airway with intubation and mechanical ventilation [1–4]. Assessment of breathing should focus on eliciting signs consistent with respiratory embarrassment/failure secondary to atelectasis, pneumonia, ventilation–perfusion (V/Q) mismatch, shunting, or diaphragmatic splinting from abdominal distension. Tachypnoea may also reflect compensatory mechanisms secondary to metabolic acidosis, as occurs in Kussmaul breathing, and can also be seen in patients with significantly elevated ammonia as HE progresses. With regards to the circulation, examination should look for evidence of intravascular volume depletion. Such patients are normally hyperdynamic with warm bounding peripheries, but may present with hypotension that is volume-responsive. Hypotension refractory to fluid resuscitation warrants invasive haemodynamic monitoring providing dynamic volume status and cardiac output monitoring [3]. HE may present as overt and rapid falls in the Glasgow Coma Score (GCS), which should always be considered if such patients require transfer. Confusion, reversal of sleep cycle, agitation, and aggression are all signs of HE. Progression

to grade III or IV encephalopathy (GCS <7–9) can be associated with development of clinically significant cerebral oedema and, in rare instances, intracranial hypertension [5]. Abnormal posturing (decorticate or decerebrate) and fixed dilated pupils are late signs of cerebral oedema. Blood glucose measurement forms a vital part of the disability assessment. Hypoglycaemia, in particular, has been found to increase morbidity and mortality. Hyponatraemia is also common, usually due to vomiting and sodium losses, and should be treated appropriately, since it may precipitate and/or worsen HE.

Clinical examination may reveal either hepatomegaly or evidence of a shrinking liver. Lymphadenopathy occurs in lymphoma and malignancy. Ascites is more likely to occur in subacute ALF, which has a more gradual onset than hyperacute forms. A liver flap (asterixis), clonus, hyperreflexia, and positive Babinski's sign are sensitive markers of encephalopathy. Stigmata of chronic liver disease should typically not be present, although can be seen in subacute cases. Where Wilson's disease is suspected, a full neurological examination is warranted. Ataxia, cogwheel rigidity, bradykinesia (Parkinsonian symptoms), tremor and slurred speech are not uncommon features. Kayser–Fleischer rings may be seen on slit-lamp ophthalmic examination, and blood tests characteristically reveal a low alkaline phosphatase and haemolysis. The diagnosis of hypoxic hepatitis should always be considered and echocardiography performed. Subconjunctival haemorrhages are a typical and unique feature of hyperacute aetiologies and severe coagulopathy (commonly due to acetaminophen/paracetamol), and should be suspected in anyone presenting with ALF who has this sign.

Investigations

Investigations for determining the cause of ALF are manifold (Table 195.1) and should be used in conjunction with the history and examination. Although the International Normalized Ratio (INR) is prolonged, more extensive assessment of coagulation shows a balanced loss of both pro- and anti-coagulant factors, explaining the low risk of bleeding in these patients [6]. Paracetamol and salicylate levels should be sent, and treatment initiated while awaiting results if there is a high index of suspicion. A rare and transient cause of profound metabolic acidosis may result from transitory mitochondrial standstill in patients with very high levels of paracetamol without associated liver injury. In severe cases arterial ammonia levels are predictive of outcome and useful for risk stratification for development of intracranial hypertension [7,8]. High serum arterial ammonia concentrations (>150–200 μmol/L) increase the risk of developing cerebral oedema and raised intracranial pressure [5,8] if persistent and associated with grade III/IV coma. Liver imaging with ultrasound is mandatory to assess liver architecture, volume, and integrity of blood supply and drainage to exclude Budd–Chiari syndrome. Transjugular liver biopsy can be helpful in some cases where decisions regarding transplantation may depend upon aetiological features. Infiltrative, malignant or cirrhotic processes exclude the use of emergent transplantation. However, in most cases biopsy does not establish a cause [9], confirming only that necrosis is present.

Functional assessment

As well as the standard investigations outlined previously, specialist centres are able to perform more dynamic assessments of liver function (Box 195.1). These assess the metabolic function and

Box 195.1 Dynamic liver function tests

Test

ICG clearance

- Infrared absorbing, iodine containing dye.
- Inject 0.25–0.5 mg/kg iv.
- Bedside transcutaneous test.
- Measure plasma disappearance rate (PDR):
  - Normal PDR 18–25%.
  - PDR<16% poor prognostic sign.
  - PDR<8% extremely high mortality.

MEG-X

- Hepatic conversion of lidocaine to MEG-X by CYP450.
- Inject 1mg/kg iv.
- Laboratory test.
- Measure MEG-X pre and 15 minutes post-injection:
  - >50 ng/mL normal.
  - <25 ng/mL poor outcome.
  - <10 ng/mL very poor prognosis.

Bromosulfophthalein

- Inject 5 mg/kg iv.
- Measure serum levels at 30 and 45 minutes.
- At 30 minutes <10% normal, at 45 minutes <5% normal.
- Laboratory test only—largely abandoned now.

Amino acid clearance

- Tests liver's ability to clear amino acids.
- Patients fasted overnight.
- Amino acid infusion over 18 hours.
- Amino acid concentration and plasma clearance rate calculated.
- Largely obsolete test.

Galactose elimination capacity (GEC)

- Plot galactose serum concentrations over time.
- GEC calculated using decay of concentration curve (mg/kg/min).
- GEC reduced in liver injury.

Aminopyrine test

- Oral intake of radioactively-labelled aminopyrine.
- Exhaled $^{14}CO_2$ measured—marker of liver function.
- Established in chronic liver disease.

Caffeine test

- Caffeine 300 mg po.
- Metabolite/caffeine ratio measured at 4, 8, and 12 hours.
- Ratio lower in disease.
- Limited use in the critically ill.

Table 195.2 Comparison of King's College Hospital and Clichy Poor Prognostic Criteria for ALF*

Criteria	Parameters
King's College Hospital	
Paracetamol	pH < 7.30 **or**
Non-paracetamol	INR > 6.5/PT > 100s **and** Serum creatinine >300 µmol/L **and** Grade III or IV encephalopathy INR > 6.5/PT > 100s **or** Any three of the following: ◆ Age <10 years or > 40 years ◆ Unfavourable aetiology (seronegative hepatitis, non-paracetamol drug reaction) ◆ Serum bilirubin >300µmol/L ◆ INR > 3.5/PT > 50s ◆ Duration of jaundice before onset of encephalopathy > 7 days
Clichy	Grade III or IV encephalopathy **and** Age < 20 years with factor V level <20% **or** Age > 30 years with factor V levels <30%

*Fulfilment of criteria indicates poor prognosis with high risk of mortality, necessitating referral for consideration of urgent liver transplantation.

King's College Hospital Criteria: this information was published in *Gastroenterology*, **97**(2), O'Grady J et al., 'Early indicators of prognosis in fulminant hepatic failure', pp. 439–445, copyright Elsevier and AGA Institute 1989. Clichy Criteria: reproduced from Bernuau J et al., 'Criteria for emergency liver transplantation in patients with acute viral hepatitis and factor V below 50% of normal: a prospective study', *Hepatology*, **14**(S4), pp. S48–290, with permission from John Wiley and Sons. Copyright © 1991 American Association for the Study of Liver Diseases.

blood flow of the liver, and its ability to eliminate substrates over a fixed period of time. They are especially useful in critically ill patients with multi-organ failure, and are additive to the traditional static tests of liver function [10].

Indocyanine green (ICG) clearance measures the plasma disappearance rate (PDR) of ICG per unit time. It is almost exclusively eliminated in bile without undergoing enterohepatic recirculation. The plasma disappearance rate reflects hepatic function and liver perfusion. Non-invasive transcutaneous systems have been developed [11] (e.g. LiMON) for point of care utilization. Low clearance has been associated with high mortality, and ICG can also be used to predict complications following hepatectomy. In sepsis, ICG clearance can differentiate between survivors and non-survivors after initial resuscitation, with a low PDR being an independent risk factor for mortality [12]. Other potential functional assays are presented in Box 195.1.

Prognostication

Prognostication forms a critical part of assessment. It helps stratify patients who can remain in their local institution from those who would benefit from transfer to a specialist centre for a potentially life-saving transplantation. Accurate prediction of outcome is also essential for judicious application of a resource-limited commodity. Several risk stratification and predictive tools can differentiate those patients likely to recover, those unlikely to survive despite maximal intervention, and those who would potentially benefit from transplantation. Equally important is the prevention of inappropriate transplantation, subjecting patients to unnecessary surgery and a lifetime of immunosuppression with the potential complications that can ensue.

Table 195.3 Referral to specialist unit after paracetamol overdose

Day 2	Day 3	Day 4
Arterial pH < 7.30§. INR > 3 or PT > 50 seconds. Oliguria. Creatinine > 200 µmol/L. Hypoglycaemia	Arterial pH < 7.30§. INR > 4.5 or PT > 75 seconds. Oliguria. Creatinine > 200 µmol/L. Encephalopathy. Severe thrombocytopenia.	INR > 6.0 or PT > 100 seconds. Progressive rise in PT to any level. Oliguria. Creatinine > 300 µmol/L. Encephalopathy. Severe thrombocytopenia.

§After appropriate fluid resuscitation.

Reproduced from *Postgraduate Medical Journal*, O'Grady JG, 'Acute liver failure', **81**(953), pp. 148–54, copyright 2005, with permission from BMJ Publishing Group Ltd.

The King's College Hospital criteria [13] are the best known, and most widely applied and accepted prognostic tool (Table 195.2). This tool incorporates both aetiology and clinical indices into the scoring system. Fulfilment of the criteria is a strong predictor of mortality without transplantation, but lack of fulfilment does not guarantee survival. Additional criteria have been described to expedite referral to a specialist centre for both paracetamol and non-paracetamol induced ALF (Tables 195.3 and 195.4) [14].

The model for end-stage liver disease (MELD) [15] incorporates bilirubin, creatinine, and the INR into a mathematical formula. However, several variables considered to be of prognostic value are not incorporated into the score, namely age, aetiology, encephalopathy, and various other indices listed. The use of MELD is therefore not widely accepted.

Lactate levels have a strong correlation with survival in ALF due to paracetamol overdose [16]. Impaired metabolism and clearance, together with increased production are thought to correlate with hepatic injury. Its addition to the King's College Hospital Criteria has improved the score's sensitivity. Hyperphosphataemia has also been reported to be an accurate early marker of poor

Table 195.4 Referral to specialist unit for non-paracetamol aetiologies

Hyperacute	Acute	Subacute
INR > 2.0 or PT > 30 seconds. Oliguria/renal failure. Hypoglycaemia. Encephalopathy. Hyperpyrexia	INR > 2.0 or PT > 30 seconds. Oliguria/renal failure. Hypoglycaemia. Encephalopathy.	INR > 1.5 or PT > 20 seconds. Oliguria/renal failure. Hypoglycaemia. Encephalopathy. Serum Na < 130 mmol/L. Shrinking liver volume.

Reproduced from *Postgraduate Medical Journal*, O'Grady JG, 'Acute liver failure', **81**(953), pp. 148–54, copyright 2005, with permission from BMJ Publishing Group Ltd.

prognosis in paracetamol-related injury [17]. Other prognostic markers that have been used include the bilirubin, lactate, and aetiology (BiLE) score [18], alpha-foetoprotein, factor VIII/factor V ratio, galactose elimination capacity, Gc globulin concentration and arterial ketone body ratio [4]. Unfortunately, none have been validated in large prospective trials and their validity is, therefore, questionable.

References

1. Auzinger G and Wendon J. (2008). Intensive care management of acute liver failure. *Current Opinions in Critical Care*, **14**, 179–88.
2. Bernal W, Auzinger G, Dhawan A, and Wendon J. (2010). Acute liver failure. *Lancet*, **376**, 190–201.
3. Stravitz RT and Kramer DJ. (2009). Management of acute liver failure. *Nature Reviews Gastroenterology & Hepatology*, **6**, 542–53.
4. Lee WM, Stravitz RT, and Larson AM. (2012). Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. *Hepatology*, **55**, 965–7.
5. Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, and Wendon J. (2007). Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. *Hepatology*, **46**, 1844–52.
6. Stravitz RT, Lisman T, Luketic VA, et al. (2012). Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. *Journal of Hepatology*, **56**, 129–36.
7. Bhatia V, Singh R, and Acharya SK. (2006). Predictive value of arterial ammonia for complications and outcome in acute liver failure. *Gut*, **55**, 98–104.
8. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, and Ott P. (1999). Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology*, **29**, 648–53.
9. Larson AM. (2010). Diagnosis and management of acute liver failure. *Current Opinions in Gastroenterology*, **26**, 214–21.
10. Sakka SG. (2007). Assessing liver function. *Current Opinions in Critical Care*, **13**, 207–14.
11. Sakka SG, Reinhart K, and Meier-Hellmann A. (2000). Comparison of invasive and noninvasive measurements of indocyanine green plasma disappearance rate in critically ill patients with mechanical ventilation and stable hemodynamics. *Intensive Care Medicine*, **26k**, 1553–6.
12. Kimura S, Yoshioka T, Shibuya M, Sakano T, Tanaka R, and Matsuyama S. (2001). Indocyanine green elimination rate detects hepatocellular dysfunction early in septic shock and correlates with survival. *Critical Care Medicine*, **29**, 1159–63.
13. O'Grady JG, Alexander GJ, Hayllar KM, and Williams R. (1989). Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology*, **97**, 439–45.
14. O'Grady JG. (2005). Acute liver failure. *Postgraduate Medical Journal*, **81**(953), 148–54.
15. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, and ter Borg PC. (2000). A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*, **31**, 864–71.
16. Bernal W, Donaldson N, Wyncoll D, and Wendon J. (2002). Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. *Lancet*, **359**, 558–63.
17. Schmidt LE and Dalhoff K. (2002). Serum phosphate is an early predictor of outcome in severe acetaminophen-induced hepatotoxicity. *Hepatology*, **36**, 659–65.
18. Hadem J, Stiefel P, Bahr MJ, et al. (2008). Prognostic implications of lactate, bilirubin, and etiology in German patients with acute liver failure. *Clinical Gastroenterology and Hepatology*, **6**, 339–45.

CHAPTER 196

Management of acute hepatic failure in the critically ill

Deepak Joshi and Georg Auzinger

Key points

- Acute liver failure (ALF) occurs in patients with acute hepatic necrosis resulting in hepatic encephalopathy, jaundice, and coagulopathy.
- Acute liver failure is a multisystem disorder.
- The management is initially supportive. Intravenous N-acetylcysteine is recommended for all patients.
- Brain dysfunction is common. Elective intubation is recommended for all patients who develop Grade III hepatic encephalopathy.
- Liver transplantation is an appropriate and viable treatment for ALF. Early and safe transfer to a transplant centre for transplant assessment is advised.

Introduction

Acute liver failure (ALF) is characterized by the sudden loss of hepatic function due to acute hepatocyte necrosis resulting in hepatic encephalopathy (HE), jaundice, and coagulopathy. ALF is a multisystem disorder, leading to renal failure, sepsis, cardiovascular instability, and eventually multi-organ failure (MOF). Common causes of ALF include paracetamol (acetaminophen) overdose, viral infections including hepatitis B virus (HBV), hepatitis A virus (HAV), hepatitis E virus (HEV), and idiosyncratic drug reactions. Rarer causes include MDMA toxicity, mushroom poisoning (Amanita species), Wilson's disease, Budd–Chiari syndrome, acute fatty liver of pregnancy, and metastatic cancer. In some patients, a clear aetiology cannot be defined—these cases are termed seronegative ALF.

Although ALF is rare, with an incidence in the Western World of 1–6 cases per million per year, it is associated with a high mortality. ALF can be subdivided into three groups according to the onset of jaundice to the development of encephalopathy: 'hyper-acute' (0–7 days), 'acute' (1–4 weeks) and 'sub-acute' (4–12 weeks). Although most patients develop severe coagulopathy and cerebral oedema in 'hyper-acute' liver failure, most will survive without the need for liver transplantation. In stark comparison, although the coagulopathy is less severe and the incidence of cerebral oedema markedly lower, patients with 'sub-acute' liver failure develop more severe hyperbilirubinaemia and are more likely to require transplantation as any regenerative capacity of the organ is often exhausted.

Investigations

All patients with ALF require a comprehensive liver screen to establish the underlying cause (Table 196.1), as prognosis and transplant listing criteria both depend on aetiology. Certain caveats should be taken into account when interpreting blood results, e.g. the acute phase protein, ferritin is elevated in ALF in the absence of hemochromatosis. Conversely, serum ceruloplasmin and alpha-1 antitrypsin levels are low in ALF, independent of any underlying genetic deficiency, as they are liver-synthesized.

Imaging, Doppler ultrasound or cross-sectional imaging is required in all patients. Key questions are patency of the hepatic veins, evidence of chronic liver disease (signs of portal hypertension, nodular liver), and evidence of malignancy. Findings of a small liver or, in particular, a liver that is decreasing in size over time are poor prognosticators. Liver biopsy needs to be considered on an individual basis; in most cases, data provided by biopsy will not change management, are subject to sampling error and may be too high-risk in severely coagulopathic patients. Biopsy can prove useful in patients with a 'sub-acute presentation' by providing information that may exclude chronic liver disease or an underlying malignancy. In view of the bleeding risk, a transjugular approach is strongly advised.

Management

Over the last decade, survival of ALF patients not undergoing transplantation has improved considerably. Although reasons are not entirely clear, general improvements in the level of care including timely admission to level 3 care facilities and referral to tertiary referral centres appear important. To improve outcomes further, certain key principles must be adopted. The underlying aetiology should be sought and disease-specific treatment instigated as early as possible. Extra vigilance is required to prevent infectious complications in conjunction with aggressive treatment of organ dysfunction, including early extracorporeal device therapy to maintain metabolic stability, even in the absence of established renal failure. Finally, early identification of patients that are unlikely to survive without transplantation and transfer to a transplant centre is paramount.

Specific therapies

Few are available for ALF. Nucleoside analogues should be considered for ALF secondary to acute HBV or reactivation/flare of

Table 196.1 Investigation of acute liver failure

	Investigation	Notes
Haematology	◆ Full blood count and blood film	
	◆ Haemolysis screen	◆ Perform in patients with unconjugated hyper-bilirubinaemia
	◆ INR and clotting studies	
	◆ Pro-thrombotic screen	◆ Perform in patients with Budd–Chiari syndrome or veno-occlusive disease
	◆ Bone marrow aspirate and trephine	◆ Perform in patients where lymphoma or haemophagocytosis is being considered
Biochemistry	◆ Electrolytes, urea and creatinine	
	◆ Liver biochemistry	
	◆ Arterial blood gas and lactate	
	◆ Amylase	
	◆ Toxicology screen including paracetamol and salicylate levels	
	◆ Copper studies (serum copper, ceruloplasmin, urinary copper +/– pencillamine challenge)	◆ Perform in patients where Wilson's disease is being considered
	◆ Serum urate	◆ Perform in acute fatty liver of pregnancy
Immunology	◆ Auto-antibodies	
	◆ Immunoglobulin profile	
Virology	◆ Hepatitis A IgM	
	◆ Hepatitis B (surface Ag and Ab, IgM core Ab. If positive then test HBV DNA viral load, e Ag and Ab)	
	◆ Hepatitis C Ab	◆ HCV is a rare cause of ALF in the Western World: perform in pregnant women
	◆ Hepatitis E IgM. If positive then test HEV RNA viral load	
	◆ HIV Ab	◆ HIV co-infection is not an absolute contra-indication to LT:
	◆ CMV IgM and PCR	◆ Perform in immunocompromised patients i.e. solid-organ transplant recipients
	◆ HSV IgM and DNA	◆ Perform in immunocompromised patients or pregnancy
Imaging	◆ Doppler liver ultrasound	
	Or	
	◆ Computed tomography with contrast	

Ab, antibody; Ag, antigen; CMV; cytomegalovirus; HSV, herpes simplex virus; INR, international normalized ratio.

chronic HBV following chemotherapy or immunosuppression. acetylcysteine (N-acetylcysteine, NAC) is an effective treatment for paracetamol (acetaminophen)-induced hepatotoxicity [1]. Use of NAC is associated with improvements in circulatory dysfunction and oxygen delivery. As it is readily available, cheap, and generally tolerated well, we routinely use NAC for non-paracetamol-induced ALF. Although the evidence base is less established compared with paracetamol-induced ALF, benefit in transplant-free survival was seen in a subset of patients with low-grade HE, but no overall survival benefit was found [2]. Use of NAC is also associated with a decreased incidence of cerebral oedema and improved cerebral blood flow. Lymphomatous infiltration as the cause of liver failure may respond to chemotherapy, whereas acute presentations of the Budd–Chiari syndrome can, in some selected cases, be successfully managed with shunt procedures, such as emergency TIPS or surgical portocaval shunt.

Respiratory system

Airway protection and controlled mechanical ventilation are required in patients with ALF and high-grade HE (>grade III). Although hypoxaemia is not usually the primary indication for airway support, secondary respiratory complications are common. These include acute respiratory distress syndrome (ARDS), pleural effusions, atelectasis, and reduced compliance of the respiratory system due to raised intra-abdominal pressure or chest wall oedema. Intrapulmonary shunting and the hepatopulmonary syndrome are described in ALF secondary to hypoxic hepatitis.

ARDS was previously considered a relatively common sequelum of ALF, impacting significantly on morbidity and mortality. Current management guidelines for ARDS, such as low tidal volume ventilation and fluid restriction compete against the brain-protective and fluid requirement needs of the ALF patient. ARDS-induced increases in right ventricular afterload can be further exacerbated during liver transplantation by reperfusion injury, with ensuing risks of right ventricular failure and subsequent graft loss.

Recent data suggest that acute liver injury affects only 10% of patients with ALF [3] and, more importantly, does not affect overall mortality or length-of-stay. Early recognition of the disease process, adoption of 'pulmonary-protective' ventilation strategies in the initial stages, and improved intensive care unit (ICU) management all

seem to be contributory. The anti-oxidant effects of NAC may also protect against acute liver injury development.

Cardiovascular system

ALF shares many clinical characteristics with septic shock, i.e. hypotension, low systemic vascular resistance, and increased cardiac output. Assessment of fluid status is important, as intravascular volume depletion is common. As with general ICU patients, crystalloid, and colloid solutions can be used to augment preload; however, some particular points are worth considering in relation to ALF. Hartmann's solution is generally poorly tolerated as the failing liver cannot clear the additional lactate load. The use of N-saline can lead to hyperchloraemic metabolic acidosis, adding a non-anion gap component to the frequently present anion gap, while 5% glucose lacks any volume effect and can lead to hyponatraemia and risk of worsening cerebral oedema.

Starch solutions including newer low-molecular-weight preparations with high degrees of substitution have been associated with an increased incidence of renal failure and mortality in septic shock patients [4]. Gelatin-based colloids can interfere with von Willebrand Factor (vWF) activity and have been linked with increased transfusion needs. Human albumin solutions have experienced a renaissance since the SAFE trial [5] with trends to improved outcome over crystalloid resuscitation during shock treatment. As subgroup analysis showed worse outcomes in patients with traumatic brain injury, its role in ALF, where there is a high incidence of intracranial hypertension, is unclear.

Invasive haemodynamic monitoring is recommended in all ALF patients. Central venous oxygen saturations are invariably high and, in general, a sign of inadequate oxygen extraction. Its role as a marker of preload is limited. As with other disease processes, dynamic markers of preload dependence are preferred. Pulse pressure variation (PPV) may be superior to stroke volume variation (SVV) in the assessment of fluid responsiveness, dependent on the algorithm used, as the former is less dependent upon the influence of increased pleural pressure. This is especially true if pulse contour methods for stroke volume estimation are used.

Transpulmonary thermodilution monitoring devices may offer extravascular lung water measurement, which can be helpful in the early diagnosis of increased pulmonary vascular permeability. Understandably, concerns are raised regarding the insertion of these devices in the setting of a severe coagulopathy. In our experience, bleeding complications are rare when performed by experienced physicians. Ultrasound guidance can also help avoid complications. Fresh frozen plasma (FFP) cover for the insertion of central venous or arterial lines is not recommended, although administration of platelets in case of significant thrombocytopenia is appropriate. In general, the risk of bleeding in ALF is probably overestimated, as recently shown during functional assessment with thrombo-elastography; causative factors include a concomitant decrease in both pro- as well as anticoagulant proteins [6].

For refractory hypotension, norepinephrine is the recommended first-line vasopressor. Adrenal insufficiency is common in ALF, leading to haemodynamic compromise; it occurs most often in those with the most severe liver disease [7]. A short adrenocorticotrophin test should be performed on patients requiring vasopressors. Those with a subnormal response receive 'stress doses' of hydrocortisone (200–300 mg/day) for 5 days before gradual withdrawal. As in septic shock, vasopressin has significant pressor effects in ALF. We routinely use vasopressin plus hydrocortisone in the context of increasing norepinephrine requirements. Although the use of vasopressin, or its analogue terlipressin, has been associated with worsening intracranial pressure, a more recent trial using cerebral microdialysis did show improvements in cerebral perfusion pressure and a favourable lactate:pyruvate ratio suggesting improved cerebral oxygen consumption [8,9].

Gastro-intestinal system

ALF is a hypercatabolic state associated with muscle wasting and vitamin deficiency. Hypoglycemia is common and intravenous glucose infusion is recommended until feeding is established. Moderate glucose control (targeting 6–10 mmol/L) is recommended as hyperglycaemia can contribute to poor intracranial pressure control; tight glucose control can be detrimental as the injured brain is exquisitely sensitive to hypoglycaemia. Hypophosphataemia is common in patients receiving high-volume continuous haemofiltration, but may also occur during liver regeneration due to increased hepatic ATP production. Prompt intravenous phosphate replacement is required. Enteral feeding is the preferred route, although the parenteral route is an acceptable alternative. Glutamine supplementation in parenteral feeds should be avoided due to the integral role of glutamine in the pathogenesis of ALF-induced cerebral oedema. We have abandoned early, aggressive caloric provision, and advocate against hypercaloric alimentation during the acute phase of the illness. Pancreatitis not infrequently complicates ALF, especially when paracetamol-induced—this needs to be excluded, particularly if the patient is listed for emergency transplantation.

Intra-abdominal hypertension secondary to ileus or bleeding can complicate ALF. Development of portal hypertension and ascites, more common in subacute liver failure, may also contribute.

Systemic inflammatory response syndrome and sepsis

Systemic inflammatory response syndrome (SIRS) is associated with the progression of HE and confers a poor prognosis in ALF [10]. Complement deficiency, impaired Kupffer cell function, and increases in both pro- and anti-inflammatory cytokines lead to a state of immunoparalysis, thereby increasing susceptibility to both bacterial and fungal infections [11]. It is therefore unsurprising that sepsis is the leading cause of death in ALF patients. Prophylactic antibiotics and antifungal agents are recommended. Initial choice of antibiotic should be dictated by local policy and then guided by sensitivities. Meticulous attention should be given to universal precautions for preventing nosocomial infection.

Neurological system

Disturbance of brain function is common in ALF, and normal compensatory mechanisms of cerebral auto-regulation are impaired. Evidence of HE can be very subtle; mild confusion may be the only clinical manifestation. Sedative agents are not recommended as they can mask development of HE. However, progression from grade I HE (mild confusion and disorientation) to grade IV HE (coma, GCS <8) can be rapid. Patients with ALF and high-grade HE are at risk of cerebral oedema, a common cause of death in these patients. Risk factors for development of cerebral oedema include high-grade HE (grade III or IV), hyperammonaemia (> 150 μmol/L), hyponatremia, seizure activity, and young age (<35 years).

The pathogenesis of cerebral oedema in ALF appears to be primarily cytotoxic involving astrocyte swelling. Ammonia, produced by degradation of nitrogenous compounds or by mitochondrial metabolism of glutamine, causes astrocyte swelling and dysfunction. Cerebral glutamine metabolism is also impaired, resulting in increased nitric oxide production and subsequent vasodilatation. Hyponatraemia may further exacerbate astrocyte swelling due to differences in osmolality between intracellular and extracellular compartments. A vasogenic component may exist due to disruption of tight junction proteins in endothelial cells by inflammatory mediators resulting in an increase in blood–brain barrier permeability.

Patients with grade III HE should be electively intubated and ventilated. There is no role for lactulose or non-absorbable antibacterials. Patients should be nursed at 20–30° head-up tilt to optimize cerebral perfusion pressure. The endotracheal tube should not be tied too tightly to maintain adequate jugular venous return. Clinical signs of intracranial hypertension (ICH) may be subtle, e.g. systolic hypertension, bradycardia and pupillary abnormalities. As with traumatic brain injury and ICH, one should be meticulous about avoidance of secondary insults such as uncontrolled hyperpyrexia, arterial hypotension, hypoxaemia, and hypercapnoea.

Moderate hypothermia (32–33°C) prevented ICH in a small pilot trial [12]. We generally control body temperature at 35–36°C and avoid hyperthermia. Lower temperature targets are only used in patients with difficult-to-control intracranial pressures. Adequate sedation and analgesia (propofol, fentanyl) should be administered to avoid surges in intracranial pressure. For refractory hypertension, barbiturate coma may be induced although its routine use has been abandoned due to cardiovascular and immunological side effects.

Any patient with ALF and an acute deterioration in Glasgow Coma Score should undergo a non-contrast head CT to exclude intracranial haemorrhage. CT is not a reliable modality to exclude the presence of cerebral oedema. MRI provides greater sensitivity and specificity, but is generally not practicable in this population. We routinely use transcranial Doppler ultrasonography to screen for evidence of increased vascular resistance as a surrogate marker for raised intracranial pressure. Electroencephalography is not routinely performed, but may be helpful in patients where subclinical seizure activity is suspected.

Although intracranial monitoring is controversial, we recommend its use in all patients with pupillary abnormalities, unexplained systolic hypertension, bradycardia, and grade III/IV HE who are potential transplant candidates. High-resistance flows on transcranial Doppler provide further guidance. Ammonia levels >200 μmol/L may sometimes be used as a trigger. Prior to catheter insertion, the INR should be corrected below 2.0 with fresh frozen plasma and the plalelet count augmented (>50 × 10^9/L). Cryoprecipitate should be administered if fibrinogen levels are low (<1.5). We do not routinely use factor VII concentrate. In our experience, if sited in the extra- or subdural space, catheter-related bleeding complications are rare. A catheter positioned in the jugular venous bulb may provide further, albeit indirect, data of cerebral oxygen consumption and extraction, and therefore the adequacy of cerebral oxygenation.

Medical management of ICH includes adequate sedation, maintenance of CPP >50 mmHg, routine use of hypertonic saline to achieve target serum sodium levels of 145–150 mmol/L, plus moderate temperature and glucose control. Mannitol (0.25–0.5 mg/kg bolus) can be used in patients with persistently elevated intracranial pressures as a flow- and perfusion-enhancing strategy over and above its osmotic activity. If renal function is preserved adequate volume replacement must accompany any fluid losses through osmotic diuresis. Repeated mannitol boluses are only recommended provided serum osmolarity remains <320 Osm/L. The role of inducing hypocapnoea to control intracranial pressure is poorly understood, and should only be performed in individuals with some form of direct or indirect brain oxygen monitoring in place. The same holds true for treatment with pre-capillary vasoconstrictor agents such as indomethacin that has been used with anecdotal success.

Renal system and extracorporeal support

Renal failure is commonplace in ALF. Hypovolaemia and hypotension are the commonest causes, but other aetiologies include direct drug-induced nephrotoxicity and the hepatorenal syndrome.

Initial management should concentrate primarily on adequate volume resuscitation. Renal replacement therapy is generally commenced early, before significant metabolic disarray is evident. Continuous forms of extracorporeal support are the preferred mode as they reduce episodes of hemodynamic instability. Ultrafiltration rates of 35 ml/kg/hour are commonly used. Ultra-high-volume haemofiltration (90 mL/kg/hour) should be considered in ALF patients with severe metabolic failure and haemodynamic instability who are being considered for transplantation. Increasing ultrafiltration rates may also have a beneficial effect on ammonia production and clearance, and hence are sometimes used as an adjunct treatment for intracranial hypertension. Heparin anticoagulation is rarely used in view of the significant coagulopathy accompanying most cases of ALF. No anticoagulation or the use of epoprostenol (2.5–5 ng/kg/min) is our local standard. The use and safety of citrate anticoagulation in the context of ALF is subject to ongoing trials.

Other forms of liver-specific extracorporeal device therapy has been disappointing, with no device studied over the last three decades having shown a significant outcome benefit. High volume plasmapheresis has shown a small, but significant mortality reduction in patients fulfilling transplant criteria who did not undergo emergency liver transplantation [13].

Role of liver transplantation

Potential patients should be discussed early and transferred to a transplant centre where an ongoing assessment of the disease kinetic can be made. Transplantation remains the only definitive treatment for ALF patients who fail to recover spontaneously as other therapeutic modalities are essentially supportive. Prognostic models are widely used to identify adult patients with ALF that will benefit. The King's College criteria introduced in 1989, and subsequently modified to include serum lactate, differentiate between paracetamol-induced and non-paracetamol induced ALF. Other adopted criteria include the Clichy criteria that incorporate factor V levels, and the MELD (model for end-stage liver disease) score. The MELD score may disadvantage patients with subacute liver failure due to the relative late occurrence of renal dysfunction and sometimes only mild derangement of coagulation. Although transplantation is limited by the availability of blood-type specific organs, 1-year survival rates exceed 80% and have increased considerably over the last decade.

References

1. Keays R, Harrison PM, Wendon JA, et al. (1991). Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *British Medical Journal*, **303**, 1026–9.
2. Lee WM, Hynan LS, Rossaro L, et al. (2009). Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology*, **137**, 856–64.
3. Audimoolam V, McPhail MJ, Wendon JA et al. (2014). Lung injury and its prognostic significance in acute liver failure. *Critical Care Medicine*, **42**, 592–600.
4. Perner A, Haase N, Guttormsen AB, et al. (2012). Hydroxyethyl starch 130/0.42 versus Ringers acetate in severe sepsis. *New England Journal of Medicine*, **367**, 124–34.
5. Finfer S, Bellomo R, Boyce N, et al. (2004). A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *New England Journal of Medicine*, **350**, 2247–56.
6. Stravitz RT, Lisman T, Luketic VA, et al. (2012). Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. *Journal of Hepatology*, **56**, 129–36.
7. Harry RA, Auzinger G, and Wendon JA. (2002). The clinical importance of adrenal insufficiency in acute hepatic dysfunction. *Hepatology*, **36**, 395–402.
8. Shawcross D, Davies N, Mookerjee R, et al. (2004). Worsening of cerebral hyperemia by the administration of terlipressin in acute liver failure with severe encephalopathy. *Hepatology*, **39**, 471–5.
9. Eefsen M, Dethloff T, Frederiksen HJ, et al. (2007). Comparison of terlipressin and noradrenalin on cerebral perfusion, intracranial pressure and cerebral extracellular concentrations of lactate and pyruvate in patients with acute liver failure in need of inotropic support. *Journal of Hepatology*, **47**, 381–6.
10. Rolando N, Wade J, Davalos M, et al. (2000). The systemic inflammatory response syndrome in acute liver failure. *Hepatology*, **32**, 734–9.
11. Antoniades C, Berry P, Wendon J, and Vergani D. (2008). The importance of immune dysfunction in determining outcome in acute liver failure. *Journal of Hepatology*, **49**, 845–61.
12. Jalan R, O Damink SW, Deutz NE, et al. (1999). Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. *Lancet*, **354**, 1164–8.
13. Larsen F, Schimdt L, Wendon J, et al. (2010). Liver assisting with high-volume plasma exchange in patients with acute liver failure. *Hepatology*, **52**, 376A.

CHAPTER 197

The effect of acute hepatic failure on drug handling in the critically ill

Andreas Kortgen and Michael Bauer

Key points

- Liver failure may lead to profound and sometimes unpredictable changes in pharmacokinetics and pharmacodynamics.
- Changes in liver blood flow, enzyme function, excretory function, and/or further remote organ dysfunction are the most likely causes of pharmacokinetic and pharmacodynamic changes.
- Decrealsed levels of albumin and other transport proteins, and impaired binding capacity results in an increased free fraction of the drug and an increased volume of distribution.
- Clinicians must carefully evaluate drug therapy in this patient group.
- Knowledge of basic principles backed up by therapeutic drug monitoring represents an important tool to govern therapy.

Introduction

Impaired hepatic function is a common event in intensive care unit (ICU) patients. It may be due to the underlying reason for admission (e.g. acetaminophen-induced liver failure), to a pre-existing co-morbidity (e.g. patients with cirrhosis undergoing major surgery), to a complication of critical illness (e.g. sepsis) or critical care (e.g. drug-induced alterations), or combinations of any of these factors. The liver is a major site of metabolism. As many drugs used in critical care are metabolized and/or excreted by the liver, hepatic dysfunction may lead to profound changes in pharmacology. Patients with liver disease have an increased incidence of adverse drug effects.

Altered enzyme function

The liver plays a key role in biotransformation of xenobiotics. Lipophilic substances are usually metabolized to water-soluble products in a two-step process:

- Phase-I metabolism comprises intramolecular modifications via oxidation, reduction, or hydrolysis. Oxidative reactions are by far the most important and usually involve enzymes of the cytochrome-P450 superfamily (CYP). More than 20 of these enzymes exist in the liver, each named by a number, a letter and a further number, identifying the family, the subfamily and the gene product, respectively. Each enzyme can metabolize multiple substrates (Table 197.1). Products of phase-I metabolism can be highly active.
- Phase-II metabolism usually involves conjugation of intermediate products of phase-I metabolism as well as other substances, e.g. with glucuronic acid, glutathione, or amino acids.

While increased water-solubility and detoxification usually result from these phase-I and phase-II reactions, formation of toxic products is also possible. For example, oxidation of acetaminophen by CYP1A2, 2E1, and 3A4 forms N-acetyl-p-benzoquinonimine (NAPQI), a hepatotoxic product responsible for acute liver failure in acetaminophen overdose. Detoxification of NAPQI relies on glutathione conjugation.

Activity of enzymes of the cytochrome-P450 superfamily can be induced or inhibited by several xenobiotics, leading to marked changes in drug levels resulting in over- or underdosing. For example, macrolides such as erythromycin, and antifungal azoles are potent inhibitors of CYP3A4 (Table 197.1). Accordingly, in patients treated with statins that are metabolized by CYP3A4 risk of rhabdomyolysis is increased when they are concomitantly treated with CYP3A4-inhibitors due to resulting higher plasma statin levels. In addition, inflammatory reactions lead to alterations in gene expression and cytochrome activity, usually resulting in a decreased capacity for biotransformation. For example, CYP1A2 activity is decreased, leading to reduced theophylline clearance. Activity of the various CYP450 enzymes may be differentially affected in inflammation, and acute or chronic liver dysfunction. Phase-II metabolism appears less affected in mild liver disease, while substantial impairments are reported in advanced liver disease.

Esterases, another group of enzymes of phase-I metabolism, hydrolyse substances containing ester, amide, or thioester bonds. They have broad and overlapping substrate specificities, can be expressed in the liver and many other tissues, and are also present in plasma. Esterases such as butyrylcholinesterase may be involved in drug metabolism and prodrug activation. When a drug such as remifentanil can be metabolized by different enzymes, impaired elimination due to illness is unlikely. However, reduced activity of esterases has been described in acute inflammation.

Table 197.1 Examples of drugs that are substrates, inhibitors or inducers of enzymes of the cytochrome-P450 superfamily

Cytochrome P450 iso-enzyme	Substrates	Inhibitors	Inducers
1A2	Theophylline	Ciprofloxacin, verapamil	Tobacco
2C9	Fluvastatin, phenytoin	Fluconazole, amiodarone	Rifampicin
2C19	Omeprazole, pantoprazole, diazepam	Omeprazole	Rifampicin
2E1	Acetaminophen, volatile anaesthetics		Ethanol
3A4/5	Midazolam, cyclosporin, tacrolimus, atorvastatin	Antifungal azoles, macrolides, grapefruit juice	Rifampicin, phenytoin

Where groups of drugs are given, not necessarily all drugs of the group must be metabolized by the given enzyme.

Altered transporter protein function and cholestasis

Transport proteins located at the sinusoidal/basolateral and canalicular membranes of hepatocytes are needed for uptake of endogenous and exogenous substances from blood and their excretion into bile (Table 197.2). In addition, transport proteins mediate efflux of substances from hepatocytes into blood. While uptake into hepatocytes by solute carriers at the basolateral membrane is usually an energy-independent process, many efflux pumps located at the canalicular and basolateral membranes, such as multidrug resistance proteins (MDR) or multidrug resistance associated proteins (MRP), are ATP-dependent. Like cytochromes, transporter proteins are not substrate-specific but shuttle many different substances. Transporters may be inhibited or induced by several drugs while inflammatory diseases may lead to profound alterations in gene expression and protein amount and distribution. For example, macrolides can inhibit solute carriers such as OATP1B1 and OATP1B3 which are responsible for pravastatin uptake, leading to increased plasma levels of the drug.

In cholestatic liver disease, biliary excretion of drugs and their metabolites may be impaired, necessitating dosage adjustments. However, transporter proteins may be differentially affected in inflammatory diseases and liver failure.

Perfusion disorders

The liver is a highly perfused organ and there are complex mechanisms to regulate liver blood flow. Under pathophysiological conditions these regulatory mechanisms may be ineffective and impaired. Together with the macrocirculatory changes frequently seen in critically-ill patients, this can lead to reductions in effective sinusoidal blood flow. There may be overall reductions in blood flow (e.g. in haemorrhagic shock, right heart failure), or distribution disorders and shunting. Shunts can be both intra- and extrahepatic. Particularly in chronic liver disease with portal hypertension a large amount of portal blood can be redirected to extrahepatic shunts. On the other hand, increased liver blood flow is also described in acute hepatitis.

Plasma protein binding and volume of distribution

Critical illness, and acute or chronic liver failure lead to decreased levels of albumin and other transport proteins, and to altered proteins [2]. In addition, binding capacity (e.g. of albumin) may be impaired due to reduced hepatocellular clearance of endogenous and exogenous compounds, such as bilirubin or bile acids. Together this results in reduced binding and an increased free fraction of the drug. Reduced plasma protein binding leads to an increased volume of distribution; these alterations are more pronounced in drugs with high protein binding. A higher free fraction generally results in increased elimination and distribution of the drug and, therefore, a new equilibrium. However, elimination may be impaired due to organ dysfunction, especially in capacity-limited drugs, thus resulting in a truly increased free fraction. In drug monitoring of highly protein-bound substances, while overall drug levels may be reduced, free drug concentrations may be relatively higher.

Table 197.2 Examples of drugs that are substrates, inhibitors or inducers of hepatic membrane transporters

Transporter	Hepatic localization	Substrates	Inhibitors	Inducers
OATP2 (1B1) SLCO1B1	Basolateral	Rifampicin, statins, benzylpenicillin	Cyclosporin	
MDR1 (ABCB1)	Canalicular	Cyclosporin, tacrolimus, macrolides, statins	Antifungal azoles, cyclosporin	Rifampicin
MRP2 (ABCC2)	Canalicular	Ampicillin, ceftriaxone, cisplatin, pravastatin	Cyclosporin	

Where groups of drugs are given, not necessarily all drugs of the group must be transported by the given transport protein. OATP, organic anion transporting polypeptide; MDR, multidrug resistance protein; MRP, multidrug resistance associated protein.

In patients with ascites, water-soluble drugs have a higher volume of distribution [1,2]. Fat- soluble drugs may have a reduced volume of distribution in patients with malnutrition, or chronic liver disease due to reduced fat and muscle mass. Drug dosages may need to be adjusted.

Pharmacokinetic alterations

The amount of a drug removed from blood during liver passage is influenced by hepatic blood flow, the extent of binding to blood components such as proteins, and hepatocellular uptake [2]. Hepatic drug clearance (Cl_H), i.e. the volume of blood from which a drug is removed completely by the liver during a time period, depends on effective hepatic blood flow (Q_H) and the hepatic extraction ratio (E_H (= the difference between venous (C_V) and arterial (C_A) concentrations in relation to the arterial concentration ($E_H = (C_A - C_V) / C_A$)). Thus:

$$CL_H = Q_H \times E_H \quad \text{[eqn 1]}$$

The extraction ratio depends on hepatic blood flow, the unbound fraction of the drug (fu) and the intrinsic clearance of unbound drug (Cl_{int}):

$$E_H = (fu \times Cl_{int}) / (Q_H \times fu \times CL_{int}) \quad \text{[eqn 2]}$$

$$Cl_H = Q_H \times (fu \times Cl_{int}) / (Q_H \times fu \times CL_{int}) \quad \text{[eqn 3]}$$

For drugs with a high extraction (>0.6), e.g. lidocaine, verapamil, fluvastatin, morphine, hepatic clearance depends on liver blood flow (i.e. blood flow-limited), while for drugs with a low extraction ratio (<0.3), e.g. acetaminophen, rifampicin, levetiracetam), clearance is capacity-limited, i.e. depends on transporter and enzyme functionality [3].

Pharmacodynamic alterations

Clinically relevant alterations in pharmacodynamics have been reported for some drugs [1,3]. These include an attenuated response to a variety of vasoconstrictor agents, such as catecholamines, especially in cirrhosis. This may be due to various alterations associated with portal hypertension. For sedative drugs, pharmacokinetic and pharmacodynamic changes are also recognized with an increased susceptibility of the central nervous system to benzodiazepines and opioids. Vasoconstrictors, sedatives, and analgesics should be titrated carefully to clinical effect. Other drugs for which altered pharmacodynamics have been reported are ß-adrenoceptor antagonists and diuretics, such as furosemide or torasemide. Both groups of drugs exhibit reduced therapeutic effects in patients with liver cirrhosis.

Renal dysfunction in patients with liver failure

Patients with liver failure, whether acute or acute-on-chronic, usually present with multi-organ dysfunction. With respect to the pharmacology of xenobiotics, renal impairment is of utmost importance. Patients with chronic liver disease often present with concomitant renal impairment, though serum creatinine levels may be within the normal range. Creatinine clearance should thus be measured, acknowledging that the glomerular filtration rate may be overestimated by a factor of two in calculating creatinine clearance, even when this is actually measured, rather than estimated [2,3].

While many dosing recommendations exist for patients with renal impairment, e.g. based on creatinine clearance, concurrent liver and renal dysfunction makes the pharmacokinetics difficult to predict. This is particularly valid for those drugs that are metabolized/excreted by both kidney and liver. In addition, pathophysiological conditions accompanying renal dysfunction, e.g. disturbed acid-base balance, altered fluid balance or blocked protein-binding sites, can also change pharmacokinetics and pharmacodynamics.

Prescribing in liver failure

Patients with liver disease present with complex functional alterations leading to considerable pharmacological changes that may sometimes be virtually unpredictable. The clinician must therefore carefully evaluate medications given to such patients. Especially for those drugs with a narrow therapeutic index, the additional risk of (hepatotoxic) side-effects must be taken into account due to altered pharmacokinetics. Extreme caution is advised when using such drugs.

The optimal way to adjust drug dosages, especially in the ICU patient, is to perform therapeutic drug monitoring wherever possible. For some drugs, titrating dosage according to clinical effect may be sufficient, e.g. for sedatives or analgesics. Nevertheless, for some essential therapies, clinicians must avoid (initial) underdosing, e.g. in antibiotics early and effective drug levels are essential for survival in septic patients.

Some general recommendations for drug dosing in patients with liver dysfunction should be observed, assuming that the drug is eliminated by hepatic metabolism and excretion. In drugs with a high extraction ratio (>0.6), oral/enteral application leads to a high first-pass metabolism and, therefore, to low bioavailability. Patients with a reduced hepatic blood flow, e.g. due to shunting (intra-, extrahepatic, or artificial after, e.g. transjugular intrahepatic portosystemic shunt (TIPS) placement), as seen in patients with cirrhosis, may present with a substantial increase in bioavailability of such drugs [3]. Reduced initial doses and titration of maintenance doses should be considered for drugs with a high hepatic extraction ratio. Intravenous administration of drugs is usually more reliable and predictable. If liver blood flow is reduced, the maintenance dose should be reduced [2]. On the other hand, administration of prodrugs that require hepatic metabolism to their active forms can lead to reduced levels of active drug (e.g. clopidogrel, enalapril).

For drugs with a low hepatic extraction ratio (<0.3), clearance depends on the intrinsic capacity of the elimination mechanism and the fraction of unbound drug. Impairment of these specific elimination mechanisms should be considered. For drugs with protein binding <90%, initial dosing does not need to be modified, however, the maintenance dosage should be reduced. This can be estimated according to the severity of liver dysfunction. For example, a 50% reduction should be considered in Child–Turcotte–Pugh (CTP) Class A liver dysfunction, and to 25% in Class B cases; for Class C the use of drug monitoring is recommended [3]. These recommendations have limitations due to the rough classification of the CTP score and the variable impairment of the elimination

mechanisms. As phase-II metabolism is often less impaired, drugs solely metabolized via this pathway may be preferable.

For drugs with a low hepatic extraction ratio and high protein binding, changes in pharmacokinetics are unpredictable. Therefore, drug monitoring is recommended wherever possible and the unbound fraction ideally measured.

For hydrophilic drugs, such as ß-lactam antibiotics, an increased initial dosage should be considered in patients with ascites and oedema as the volume of distribution may be substantially increased. However, for maintenance dosage of these drugs, any potential renal dysfunction should be considered [2].

Recently, there have been reports of using liver function tests to predict the required drug dosage, i.e. the plasma disappearance rate of indocyanine green for calculating the argatroban maintenance dose in critically-ill patients with type II heparin-induced thrombocytopenia, and the methacetin breath test for assessing tacrolimus trough levels after liver transplantation [4,5]. This may be a future option to direct therapy where drug monitoring is not available in a clinical setting, or where initial correct dosing is crucial with respect to toxicity/side-effects or therapeutic effect.

References

1. Nguyen HM, Cutie AJ, and Pham DQ. (2010). How to manage medications in the setting of liver disease with the application of six questions. *International Journal of Clinical Practice*, **64**, 858–67.
2. Verbeeck RK. (2008). Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *European Journal of Clinical Pharmacology*, **64**, 1147–61.
3. Delco F, Tchambaz L, Schlienger R, Drewe J, and Krähenbühl S. (2005). Dose adjustments in patients with liver disease. *Drug Safety*, **28**, 529–45.
4. Link A, Girndt M, Selejan S, Mathes A, Böhm M, and Rensing H. (2009). Argatroban for anticoagulation in continuous renal replacement therapy. *Critical Care Medicine*, **37**, 105–10.
5. Lock JF, Malinowski M, Schwabauer E. et al. (2011). Initial graft function is a reliable predictor of tacrolimus trough levels during the first post-transplant week. *Clinical Transplantation*, **25**, 436–43.

CHAPTER 198

Extracorporeal liver support devices in the ICU

Rajiv Jalan and Banwari Agarwal

Key points

- There is an unmet need for a liver support system because of the increasing shortage of organs for transplantation and the complications associated with the procedure.
- In theory, acute liver failure and acute decompensation of chronic liver disease secondary to a precipitating event are potentially reversible. In this context, an extracorporeal liver support can temporarily substitute liver functionality to allow natural recovery through regeneration of hepatocytes and elimination of the precipitating event.
- Goals of liver support system are to provide all functions of the liver, including synthetic and metabolic functions, and to remove as well as reduce the production of pro-inflammatory mediators to attenuate the inflammatory process.
- Currently existing devices are either purely mechanical and/or cell-based. Detoxification is provided by both systems, but biological activities are limited only to the cell-based systems. Albumin dialysis is the major component of mechanical devices because albumin is irreversibly destroyed in liver failure.
- Cell-based or bio-artificial systems are essentially 'mini-livers', but their success is limited by the lack of a continuous and abundant supply of high-quality hepatocytes.

Introduction

The burden of liver disease continues to rise, with 10% of the current world population estimated to suffer from chronic liver disease. Annually, over a million people die from liver-related illnesses; severe acute liver failure is associated with 50–60% mortality, while deaths from cirrhosis-related complications are projected to be the ninth most common in the developed world by 2015 [1].

Liver transplantation (LT) remains the only optimal treatment for the majority of patients, but the expanding gap between organ availability and increasing waiting lists results in a significant mortality for patients awaiting transplantation. In the UK the average waiting time for chronic liver disease patients is between 3 and 18 months; >500 patients are on the waiting list at any one time with 15–20% dying without LT becoming available [2].

There is an urgent need for an extracorporeal liver assist device with the capacity to support liver function and provide a temporary holding measure as a bridge to transplantation, or ideally, facilitate natural recovery of native liver function. The quest for such devices dates back to the 1960s, but the realization of developing an ideal liver device has only been partially achieved.

Liver failure syndromes

Liver failure can be broadly viewed as a spectrum of disease ranging from acute to acute-on chronic and end-stage liver failure. This classification captures different clinical phenotypes of liver illness and allows formulation of appropriate treatment plans.

Acute liver failure

Acute liver failure (ALF) is characterized by a rapid decline in liver function (within days to weeks) secondary to massive necrosis of hepatocytes following an acute insult (infective, metabolic, vascular, or drug-induced). This occurs in patients with previously normal liver function, and results in varying degrees of coagulopathy and hepatic encephalopathy (HE), eventually progressing to extrahepatic organ involvement and failure. Cerebral complications, superimposed sepsis and the multiple organ dysfunction syndrome account for most deaths in these patients. ALF stratification, based upon the length of time elapsed between the appearance of first symptoms and the development of HE, into the hyperacute (1–7 days), acute (8–28 days), and subacute (28 days–24 weeks) subvarieties, in conjunction with markers of acute physiological derangement (blood pH and lactate levels), patient age, and the aetiology of ALF, informs prognosis and identifies patients unlikely to survive without emergency or super-urgent LT [3]. LT is a life-saving procedure, but is a major intervention with attendant morbidity and mortality, requires life-long immunosuppression, is expensive and limited by organ availability.

Acute on chronic liver failure

Acute on chronic liver failure (ACLF) is an increasingly recognized clinical entity referring to the coincidence of either an identified or unidentified acute precipitating event (either superimposed liver injury or extra hepatic factors, such as infection) in patients with existing compensated or decompensated cirrhosis, culminating in further deterioration of liver function, and development of end-organ damage leading to high short term mortality [4]. The final common pathway of a precipitating event—infection, variceal bleed, or additional liver injury—seems to be the development of an unquenched dysregulated systemic and hepatic inflammation resulting in worsening encephalopathy, aggravation of portal

hypertension, development of renal dysfunction and haemodynamic embarrassment, and retardation of liver regeneration.

End-stage liver disease

End-stage liver disease is an irreversible condition representing the terminal phase of liver failure, with little capacity for regeneration by the native liver. The only treatment known to improve survival in this situation is LT.

Liver support systems: types, technical issues, operational and functional characteristics, and current clinical evidence

The liver is a complex organ, central to the body's metabolic processes. It has an unparalleled ability to handle multiple tasks required to maintain metabolic homeostasis and to act as the major regulatory player in the organ cross-talk framework. Hepatocytes perform a range of functions including:

- Detoxification (of drugs, toxins and chemicals such as ammonia and lactate).
- Metabolic and biotransformation activities (e.g. drug metabolism, maintenance of glucose homeostasis and thermogenesis).
- Synthesis (of coagulation proteins, albumin, globulins, acute phase and transporter proteins.
- Immune modulation functions.

Hepatocellular failure results in toxin (ammonia, bilirubin, lactate, mercaptans, and bile acids) accumulation, an imbalance of metabolic substrates, and increased levels of inflammatory mediators.

The premise and concept behind an ideal extracorporeal liver support device therefore hinges on its ability to detoxify blood, perform synthetic, metabolic and immune functions, and to remove and/or inhibit production of inflammatory signalling molecules (e.g. cytokines). This breaks the vicious circle of liver injury characterized by production of inflammatory mediators and propagation of further liver injury, the ultimate aim being stimulation and promotion of liver regeneration. Because of the temporary nature of the support offered by the currently available devices, their clinical application is targeted largely to situations where liver injury is acute, as in ALF and ACLF. In addition, these devices can be used to improve and alleviate symptoms arising from cholestasis such as pruritus (Box 198.1).

There are two types of liver support systems, namely artificial (non-biological) systems, which are purely mechanical dialysis devices based on blood detoxification, and bio-artificial devices, which are cell-based devices incorporating hepatocyte-derived cells that can potentially substitute liver metabolic function. Blood purification devices are also added to some of these systems. For a summary of this section, see Tables 198.1 and 198.2.

Artificial devices

Conventional blood purification methods, such as continuous haemofiltration or haemodiafiltration, although highly effective in removing small, water-soluble toxins, are no longer used as the sole means of detoxification in liver failure patients. This is due to their inability to remove protein-bound substances and their ineffectiveness in liver failure. They are still used in conjunction with liver support devices to augment elimination of water-soluble toxins. The first generation of liver devices utilized activated charcoal haemoperfusion as the basis for toxin adsorption, but failed to demonstrate significant benefit and is now largely superseded by albumin-based systems. Albumin is the most abundant circulating plasma protein and maintains plasma oncotic pressure. In addition, current literature consistently points towards a number of other biological functions such as fatty acid transport, drug binding, metal chelation, and antioxidant activity performed by albumin, rendering it an important detoxification molecule and a candidate protein to be targeted in liver dialysis systems [5]. In addition to quantitative hypoalbuminaemia in liver failure, there is a severe functional impairment of the available albumin rendering it an inefficient transporter protein [6].

The two most commonly used artificial systems are the molecular adsorbent recirculating system (MARS) and the fractional separation of plasma and albumin dialysis (Prometheus). Both forms of treatment are relatively new; MARS was used clinically for the first time in 1993 and Prometheus in 2003.

Box 198.1 Potential indications for liver supportive therapy

ALF patients

- Failure to reach criteria for emergency LT, but remain at high risk of dying (10–15% of non-survivors do not fulfil King's College Criteria for emergency transplantation).
- Patients either precluded from LT due to medical, surgical, or psychological reasons, or those who continue to deteriorate rapidly, while on the emergency transplant list.

ACLF patients

- These patients are currently not considered for emergency LT in the UK, so a device can provide support until spontaneous recovery to pre-injury levels of liver function.
- As a bridge to LT, especially for those patients who are high up on the waiting list and would receive LT within the next few weeks.

End stage liver disease

Patients with ESLD lack reversibility. Since currently available liver assist devices are unable to sustain liver support for longer than a few weeks, the only role of liver devices pertains to symptom reduction and quality of life improvement as in:

- Intractable pruritus.
- Hepatic encephalopathy.
- Severe chronic fatigue.

Other indications

- Primary graft non-function after transplantation, and waiting for super-urgent re-transplant.
- Small-for-size syndrome:
  - Development of liver failure following extensive resection for malignancy.
  - Following donor hepatectomy in living donation liver transplantation.

Table 198.1 Artificial devices

Device	Principles of therapy	Clinical studies
SPAD (single-pass albumin dialysis)	Albumin dialysis against 2–5% albumin	Improvement in biochemical parameters, comparable with MARS. Only single case studies available [13], no RCTs
MARS (molecular adsorbent recirculating system)	Albumin dialysis against 20% albumin	Improved hepatic encephalopathy [14], improved quality of life, no significant survival benefit [9]
Prometheus (fractionated plasma separation and adsorption—Prometheus)	Plasma separation, adsorption using neutral resin, and anion adsorbers	Improvement in biochemical parameters. No significant benefit at 28 days [10]
SEPET (selective plasma filtration technology)	100 kDa hollow fibre membrane, albumin, and fresh-frozen plasma mixture as replacement fluid	No human RCTs. Animal models show improved survival [15]
HVPE (high volume plasma exchange)	Patient's plasma removed and replaced with fresh frozen plasma	Improved transplant-free survival in ALF [7]

Data from various studies (see references).

MARS (Gambro, Sweden) combines albumin dialysis with conventional haemodialysis to remove both water-soluble and protein-bound toxins. The patient's blood is detoxified of protein-bound substances via an albumin-impregnated polysulfone dialysis membrane (50 kDa) against a concentration gradient exchange mechanism by the albumin solution stored in the adjacent chamber (600 mL 20% human albumin). The selective pore size stops the patient's own toxin-laden albumin from crossing the membrane. The albumin dialysate is passed through an activated charcoal and anion exchange resin to regenerate the protein to allow its continued use as a detoxification medium (Fig 198.1a). The haemodialysis circuit in the system removes water-soluble substances.

Prometheus (Fresenius, Germany) combines plasma separation and adsorption in a double circuit design. A high cut-off membrane of 250 kDa filters the patient's albumin into a secondary plasma circuit. The albumin-rich plasma then passes through two columns of adsorbent resins (neutral and anion exchange, see Fig 198.1b), to remove bound toxins before recombining with the cell fraction prior to return to the patient. A high-flux dialysis system is applied to the blood circuit to enhance elimination of water-soluble toxins.

Single-pass albumin dialysis (SPAD) is a non-commercial simplified system of albumin dialysis designed to remove protein-bound toxins using an albumin solution (typically 5%) as the dialysate separated from the patient's blood by a high-flux albumin-impermeable membrane. Unlike MARS where the albumin dialysate is re-circulated, it is discarded after a single pass (Fig. 198.1c). Continuous veno-venous haemodiafiltration can be added to augment removal of water-soluble substances. The SPAD system is simple, safe, and has similar efficiency to MARS in removing bilirubin, ammonia, bile acids, and creatinine.

Plasmapheresis (plasma exchange) separates the patient's plasma from cellular blood components to be then replaced by donor fresh-frozen plasma and/or albumin. It is effective in removing circulating antibodies, inflammatory cytokines, and other toxic substances, as well as toxins bound to tissue sites, and is used for a number of autoimmune conditions. In liver failure, enhanced or high volume plasmapheresis (>10 L of plasma removed and replaced per day) has demonstrated clinical improvement in hepatic encephalopathy, hepatic and cerebral blood flow, and even a survival benefit in patients with ALF [7].

SEPET (selective plasma filtration technology) incorporates a 100 kDa hollow-fibre membrane where the ultrafiltrate is replaced by a mixture of electrolyte, albumin, and fresh-frozen plasma solutions.

Table 198.2 Bio-artificial devices

Device	Principle and cell type	Main concern	Clinical studies
Hepat Assist	Plasma separation, charcoal adsorption, porcine hepatocytes	Zoonoses	176 patients, no survival advantage in fulminant and sub-fulminant [16]
MELS (modular extracorporeal liver system)	Plasma separation, then plasma passed through human hepatocytes	Supplies low, function difficult to maintain	Eight patients, successfully bridged to transplant [17]
ELAD (extracorporeal liver assist device)	Human hepatoblastoma cell (C3A cells)	Tumourogenicity	Six human studies, 150 patients treated. Survival benefit in ACLF study in 49 patients [18]
BLSS (bio artificial liver support system)	Porcine hepatocytes	Zoonoses	Phase I study in four patients, no serious adverse events [19]
AMC-BAL	Porcine hepatocytes	Zoonoses	12 patients treated, 11 bridged to transplant [20]

Data from various studies (see references).

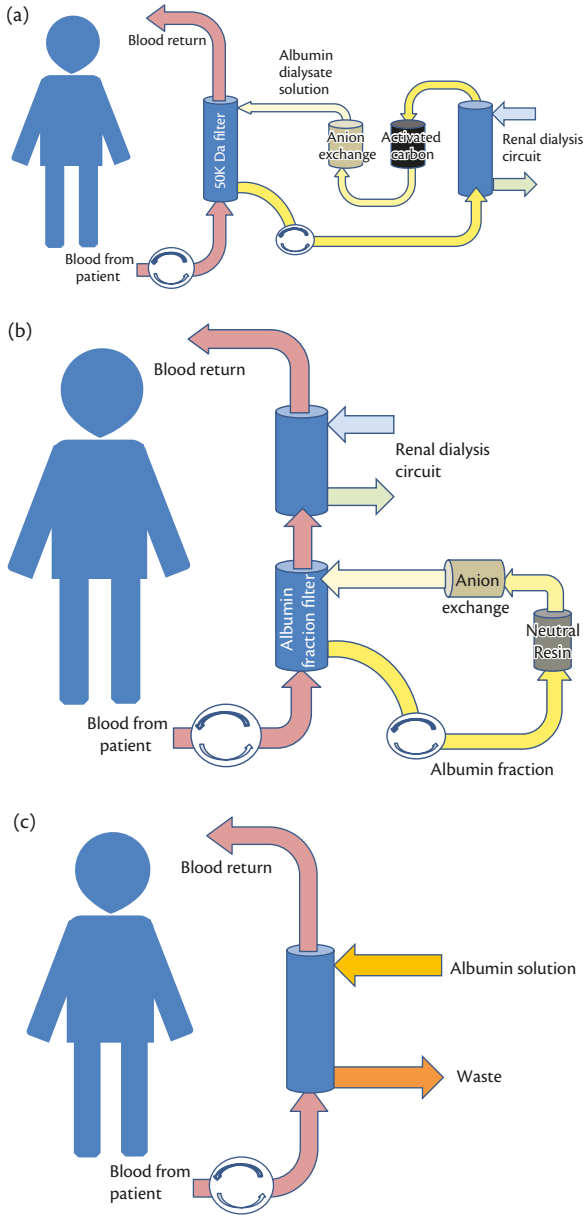


Fig. 198.1 Schematic representations of (a) molecular adsorbent recirculating system (MARS). (b) Fractional separation of plasma and albumin dialysis (Prometheus). (c) Single pass albumin dialysis (SPAD) artificial systems.

Safety profile and clinical efficacy of artificial devices

MARS is the most studied device with over 5000 patients having been treated for more than 20,000 therapy sessions, followed by Prometheus that has also been used extensively. These are largely safe procedures, with no serious side effects reported for either treatment. Reported complications have included modest thrombocytopenia, bleeding episodes, transient haemodynamic instability, a need for more anticoagulation treatment, and reversible leukocytosis unrelated to sepsis.

Both MARS and Prometheus effectively remove water-soluble and albumin-bound toxins, as well as cytokines, but without significant reduction in plasma cytokine levels, reflecting an imbalance between the modest cytokine elimination ability of these systems, and their continuous production during liver failure [8]. Both systems lose detoxification capability significantly after 6 hours' use.

Most of the published evidence relates to these two main artificial devices. The MARS system has received US FDA approval as a therapy for use in hepatic encephalopathy, in addition to previous approval for the management of drug toxicity. Both MARS and Prometheus are effective in supporting patients with severe liver dysfunction either following surgery or as a bridge to transplantation. Crucially, neither system could show an independent survival benefit (in the absence of transplantation) in phase III multicentre trials [9,10]. Albumin dialysis/detoxification has been shown to be very effective for intractable pruritus and provides symptom relief for prolonged periods (3–4 months) [11]. As these patients often will not qualify for LT based on their liver function, this treatment option can play a vital role in improving their quality of life (Table 198.1).

Biological or bio-artificial liver system

A bio-artificial liver system (BAL) system employs biochemically active cells contained in a bioreactor. In theory, it is capable of carrying out a proportion of the metabolic, synthetic, and immune function provided by the liver. A blood purification device is often added to improve efficacy. The essential pre-requisites for a functioning BAL system are:

- High quality, well-differentiated cells retaining a high degree of hepatocyte function, which are stable in vitro.
- Sufficient quantities of these cells equating to up to one-third of normal liver mass as extrapolated from data on large liver resections.
- Ready and unlimited availability of these cells at any time.

Cell sources most commonly studied have been derived from primary human and porcine sources, immortalized human cells, and cells derived from hepatic tumours such as hepatoblastoma. The cells are used as either tissue slices, homogenates or as single cell layer columns supported on matrices similar in appearance to dialysis filters.

The disadvantages of human cells are limited availability, while porcine hepatocytes tend to be less stable and carry a theoretical risk of xenozoonosis, which although not yet reported, will prevent their use in Europe and the USA. On the other hand, cell lines such as C3A derived from human hepatoblastomas lose functionality following transformation, e.g. their ureagenesis capacity is limited only to the arginine aspect of the urea cycle and thus cannot completely detoxify ammonia.

Currently available BAL systems

The ELAD C3A-based BAL system is currently under development and undergoing clinical trials (Vital Therapies, San Diego, USA). Small-scale studies have shown survival benefit or use as a bridge to transplantation, although a large-scale pivotal survival study has not yet been undertaken. Other systems are in varying stages of development, seeking to optimize the bioreactor design or the cell type contained within them. It is not yet clear as to how successful these technologies will be. A major limiting factor in whether BAL systems will be adopted widely would be the considerable cost of therapy associated with generating, shipping, and

maintaining bioreactors. Clinical studies therefore need to demonstrate clear, unequivocal survival benefit of ELAD over other treatment options before acceptance into the majority of healthcare systems (Table 198.2).

Conclusion

Specific therapies aimed at targeting factors identified in relation to the progression of liver injury are being developed for the next generation of liver dialysis systems. Proof-of-principle systems have shown clinical benefit by combining endotoxin removal filters with albumin dialysis [12]. These endotoxin filters, developed as therapies for sepsis, are used to reduce the ongoing inflammatory stimulus associated with end-stage liver disease. Another approach is to improve the quality and functional capacity of the patient's albumin during therapy. The disease process damages albumin binding and transport capability, so methods to replace the damaged protein to restore function rather than just to dialyse the bound toxins is the next logical step in system design. Improved BAL systems may be able to demonstrate a large functioning cell mass that can effectively replace liver function for a prolonged period, though this would still appear to be some way from the clinic. Current artificial liver dialysis systems offer effective support for a number of applications. Though they are not able to replace the failing liver, they do offer detoxification functions and can act as a bridge to transplantation.

References

1. Mathers C, Fat DM, Boerma JT, and the World Health Organization. (2008). *The Global Burden of Disease: 2004 Update*. Geneva: World Health Organization.
2. NHS Blood and Transplant (2011). *Transplant Activity in the UK. Report 2010/2011: Statistics and Clinical Audit*. London: NHS Blood and Transplant.
3. Lee WM, Stravitz RT, and Larson AM. (2012). Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. *Hepatology*, **55**, 965–7.
4. Moreau R, Jalan R, Gines P, et al. (2013). Acute-on-chronic liver failure is a distinct syndrome developing in patients with acute decompensation of cirrhosis. *Gastroenterology*, **144**, 1426–37.
5. Quinlan GJ, Martin GS, and Evans TW. (2005). Albumin: biochemical properties and therapeutic potential. *Hepatology*, **41**, 1211–19.
6. Jalan R, Schnurr K, Mookerjee RP, et al. (2009). Alterations in the functional capacity of albumin in patients with decompensated cirrhosis is associated with increased mortality. *Hepatology*, **50**, 555–64.
7. Larsen FS, Schmidt LE, Bernsmeier C et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. *J Hepatol*, 2015 Aug 29. pii: S0168-8278(15)00590-5. doi: 10.1016/j.jhep.2015.08.018. [Epub ahead of print]
8. Stadlbauer V, Krisper P, Aigner R et al. (2006). Effect of extracorporeal liver support by MARS and Prometheus on serum cytokines in acute-on-chronic liver failure. *Critical Care*, **10**, R169.
9. Banares R, Nevens F, Larsen FS, et al. (2013). Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: The RELIEF trial. *Hepatology*, **57**, 1153–62.
10. Kribben A, Gerken G, Haag S, et al. (2012). Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. *Gastroenterology*, **142**, 782–9.
11. Leckie P, Tritto G, Mookerjee R, Davies N, Jones D, and Jalan R. (2012). 'Out-patient' albumin dialysis for cholestatic patients with intractable pruritus. *Alimentary Pharmacology & Therapeutics*, **35**, 696–704.
12. Novelli G, Morabito V, Pugliese F, et al. (2011). Management of sepsis during MARS treatment in acute on chronic liver failure. *Transplantation Proceedings*, **43**, 1085–90.
13. Kortgen A, Rauchfuss F, Gotz M, et al. (2009). Albumin dialysis in liver failure: comparison of molecular adsorbent recirculating system and single pass albumin dialysis—a retrospective analysis. *Therapeutic Apheresis and Dialysis*, **13**, 419–25.
14. Hassanein T, Blei AT, Perry W, et al. Performance of the hepatic encephalopathy scoring algorithm in a clinical trial of patients with cirrhosis and severe hepatic encephalopathy. *American Journal of Gastroenterology*, **104**, 1392–400.
15. Rozga J, Umehara Y, Trofimenko A, et al. (2006). A novel plasma filtration therapy for hepatic failure: preclinical studies. *Therapeutic Apheresis and Dialysis*, **10**, 138–44.
16. Demetriou AA, Brown RS Jr, Hewitt RW, et al. (2004). Prospective, randomised, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. *Annals of Surgery*, **239**, 660–7.
17. Sauer IM, Kardassis D, Zeillinger K, et al. (2003). Clinical extracorporeal hybrid liver support—phase I study with primary porcine liver cells. *Xenotransplantation*, **10**, 460–9.
18. Zhong-Ping Duan JZ, Xin X, Chen JM, et al. (2007). Interim results of randomised controlled trial of ELAD in acute on chronic liver disease. *Hepatology*, **46**, 274A.
19. Mazariegos GV, Patzer JF II, Lopez RC et al. (2002). First clinical use of a novel bioartificial liver support system (BLSS). *American Journal of Transplantation*, **2**, 260–6.
20. Van de Kerkhove MP, Di Florio E, Scuderi V, et al. (2002). Phase I clinical trial with the AMC-bioartificial liver. *International Journal of Artificial Organs*, **25**, 950–9.

PART 6.9

Acute on chronic hepatic failure

CHAPTER 199

Pathophysiology, diagnosis, and assessment of acute or chronic hepatic failure

Alastair O'Brien

Key points

- Cirrhosis is an increasing problem and prognosis following ICU admission is poor.
- Acute on chronic liver failure (ACLF) is a separate entity to cirrhosis with organ failure at the core of this syndrome.
- ACLF results from an acute 'new' insult that may/may not be related to the original cause of chronic liver disease.
- Infection and the associated SIRS response are the most important precipitants of ACLF.
- Clinical assessment should follow the standard ABCDE approach to the critically-ill patient.

Introduction

Cirrhosis is the end result of liver damage caused by a wide variety of insults including alcohol, chronic viral infection, non-alcoholic fatty liver disease, autoimmune disease, certain genetic conditions, and other less common conditions. It represents a leading cause of death worldwide. In the UK it is currently the fifth leading cause of death and, unlike many other common diseases, there is an upward trend in mortality. The average age of death from liver disease is only 59 years, compared with 82–84 years for cardiovascular and lung diseases.

Cirrhosis and intensive care unit admission

Cirrhosis is rarely reversible and the natural progression from compensated to decompensated disease results in a significant increase in morbidity and mortality, and a much decreased quality of life. This is a direct consequence of the impairment in liver function secondary to decreased functional hepatocytes and the architectural disruption that impairs a normal hepatic and enteric circulation. Management of the complications of cirrhosis, such as gastrointestinal bleeding, sepsis, and renal failure, frequently involves ICU admission. All studies in ICU patients report a poor prognosis with an overall hospital mortality of 44–71%, although a small improvement in mortality has been described over time. Patients admitted for airway protection following an upper gastrointestinal bleed fare well with a mortality of 20%. However, mortality in those with organ failure, septic shock, or hepatorenal syndrome may approach 85–100%. Liver transplantation is the only curative therapy for established cirrhosis, giving excellent 5-year survival rates of 75%. However, the limited number of available organs dictates that the vast majority of patients will not be considered. For example, approximately 600-800 transplants are performed annually in the UK, while over 550,000 patients were admitted with complications of cirrhosis during 2012. This mismatch results in a large number of intensive care unit (ICU) admissions of patients that will never be considered suitable for transplantation. The estimated number of ICU admissions related to cirrhosis in the United States is in excess of 26,000 per year with an estimated cost of $3 billion. In the UK this represents approximately 2.6% of total admissions per year (approximately 1250 patients).

Acute on chronic liver failure: definition

Acute on chronic liver failure (ACLF) refers to an acute deterioration in liver function in cirrhotic patients secondary to superimposed hepatic or extrahepatic injury, such as infection [1]. The most recent definition by the EASL-CLIFF consortium refers to an acute decompensation (ascites, encephalopathy, gastrointestinal bleeding, bacterial infection) associated with organ failure (worsening of liver function, and/or kidney failure or other organs). The previous definition proposed by a working group from the American Association for the Study of Liver Disease (AASLD) and the European Association for Study of the Liver (EASL) is 'acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure'. Ongoing studies are aimed at further refinements, however the most important message from studies published thus far is that in ACLF it is the degree of organ failure that determines outcome, rather than the severity of liver disease.

ACLF must be contrasted with acute or 'fulminant' liver failure that develops in patients without pre-existing liver disease and is described elsewhere. Distinction between the two is important as the treatment and prognosis is, in most cases, dissimilar.

Precipitating event

ACLF results from an acute 'new' insult that may/may not be related to the original cause of chronic liver disease [1,2]. This separates it

from cases of cirrhosis in which continued hepatocellular damage leads to progression and worsening of disease. Although this distinction has been made between ACLF and advanced cirrhosis for the purposes of this chapter and the ACLF management chapter, the recommendations made for assessment and management can be applied to any critically-ill patient with cirrhosis. Precipitants include bacterial infections, alcoholic hepatitis, superimposed viral hepatitis, drug (or hepatotoxin)-induced liver injury, variceal bleeding, ischaemia, and surgery. There is global variation, for example, viral infections are more common in Asia, while alcoholic and non-alcoholic fatty liver disease (NAFLD) are more common in Europe and the United States.

Reversibility

In contrast to the natural progression of cirrhosis, a key defining principle of ACLF is the element of reversibility if the patient is identified early and aggressive intensive care support given [1]. However, full recovery to the previous baseline is not likely. Indeed, in patients who survive to hospital discharge, there is a median survival of only 4 months if their admission APACHE III (Acute Physiology and Chronic Health Evaluation) score exceeded 90, and 17 months if <90. In addition, 72% of survivors reported a poor quality of life.

To ensure improved outcomes in cirrhosis, early identification and management of these events is essential. This is best achieved if the physician has a good understanding of the pathophysiology underlying ACLF.

Multi-organ failure and prognosis

Multi-system organ failure is the primary cause of death in ACLF. Studies demonstrate higher mortality rates for ACLF than expected in a population of similar patients awaiting liver transplant, i.e. cirrhotic patients without ACLF. The natural history of ACLF is varied, reflecting the heterogeneity of patients; it remains to be determined whether distinct subgroups exist. Methods of assessment include the Child–Turcott–Pugh or MELD scores and, possibly, biomarkers in development or new imaging modalities [1,2]. Recent hospitalization carries a grave prognosis. The precipitating insult will also have prognostic significance and infection, in particular, carries a poor prognosis. Increasing organ failure and increasing markers of systemic inflammatory response are associated with a poor prognosis [1,2]. The Sequential Organ Failure Assessment (SOFA) score is reflective, but not predictive of organ failure; as yet there is no system for early identification of patients likely to develop ACLF.

Pathophysiology

Infection and inflammation

Infection (bacterial, viral, or fungal) and the associated systemic inflammatory response (SIRS) is the most important precipitant. Many regard this as the central feature [1,2]. Patients with cirrhosis are highly susceptible to infection. In 50% of cirrhotic inpatients, infection was the precipitant for hospital admission, while a further 15–35% develop nosocomial infections compared with 5–7% of general ward patients. Of those cirrhotic patients who develop sepsis and organ dysfunction, up to 80–90% die. Portosystemic shunting of blood bypassing the liver coupled with impaired Kupffer cell activity probably increases the burden on innate immune cells within the peripheral circulation. Elevated endotoxin secondary to bacterial translocation, altered Toll-like receptor expression and endotoxin tolerance have also been proposed as causes of immunosuppression. In addition, elevated IL-10 and ammonia inhibit neutrophil function and this may be reversed by treatment with albumin. While this may appear important in the aetiology of cirrhosis-associated immune-suppression, a unifying mechanism remains elusive. Notwithstanding this, there is generalized acceptance of a defect in leukocyte mobilization to sites of infection and, once there, leukocytes have a decreased ability to secrete cytokines, phagocytose, and kill bacteria. While this defective innate immune response was first observed over 30 years ago, and is considered to underlie the predisposition to and poor outcome from, infection, precise factors that cause it are unknown. Infection precipitates hepatic encephalopathy, renal dysfunction, and variceal bleeding. The robust association between infection and deleterious outcomes in cirrhosis mandates aggressive surveillance and early treatment of suspected infection. A recent Cochrane meta-analysis, however, concluded that antibiotic prophylaxis is still far from being a substantiated prevention strategy. Nevertheless, a mortality benefit has been demonstrated with prophylactic antibiotics following an oesophageal variceal bleed.

Superimposed hepatotrophic viral infections in cirrhosis patients can have devastating consequences and must be considered, e.g. hepatitis E virus superinfection and reactivation of hepatitis B virus (HBV) in patients on immunosuppression.

Drugs and hepatotoxins may cause direct hepatocellular damage and precipitate ACLF. It is a common misconception that patients with chronic liver disease are at higher risk of hepatic damage from certain medications such as statins. Exceptions to this include methotrexate, anti-TB medication, anti-HIV treatment, and ibuprofen.

SIRS is closely linked to outcome in ACLF. Regardless of the precipitating factor, the final common pathway to multi-organ failure is an exaggerated activation of systemic inflammation followed by a period of immunoparalysis. The initial cytokine storm is responsible for profound macro/microcirculatory changes and subsequent multi-organ injury. Following this 'storm', an excessive compensatory anti-inflammatory response system can lead to immune dysfunction with possible episodes of nosocomial infection, sepsis, and further clinical deterioration.

Clinical features

Liver

Hyperbilirubinaemia is the central feature of hepatic ACLF [2]; although the pathophysiology is currently uncertain, it is likely to differ among patients according to the cause of their cirrhosis and precipitating insult. Bilirubin stasis represents a risk factor for subsequent infection and sepsis, while systemic inflammation generates increased tumour necrosis factor-α and interleukin-6 causing hepatic microcirculatory endothelial dysfunction, elevated portal pressures and decreased hepatic blood flow, further worsening liver function. Bacterial translocation and gut-derived endotoxaemia are considered to drive this process. Anti-TNFα therapy reduced portal pressures in severe alcoholic hepatitis. Furthermore, an upregulation of sympathetic tone in sepsis and ACLF is also associated with increased portal pressure.

Renal

Renal failure is the most common organ dysfunction associated with ACLF and carries a poor prognosis [2]. By common consensus,

the best definition of renal failure in cirrhosis is an increase in serum creatinine to 1.5 mg/dL (133 μmol/L), which represents a glomerular filtration rate of 30 mL/min. Unfortunately, this often represents an overestimate of glomerular filtration rate because of decreased creatinine production or reduced muscle mass. Hence, several biomarkers of renal dysfunction in cirrhosis are under investigation including neutrophil gelatinase-associated lipocalin (NGAL), kidney-injury molecule-1 (KIM-1) and serum cystatin C (CyC). However, as yet none are routinely used in current clinical practice. Hyponatraemia (<130 mmol/L) occurs commonly due to an impairment in renal capacity to eliminate solute-free water. This results in retention of water disproportionate to that of sodium, leading to a decrease in serum sodium concentration and hypo-osmolality. It is associated with a poor prognosis, the presence of ascites, hepatorenal syndrome (HRS), spontaneous bacterial peritonitis, and hepatic encephalopathy. Renal failure can be divided into four main categories: HRS, hypovolaemia-induced, parenchymal disease, and drug-induced. Bacterial infection is a major precipitant of all these categories. Patients with ACLF may present with any cause and outcome will vary accordingly. HRS is considered a functional disorder secondary to splanchnic vasodilatation and renal vasoconstriction, which is reversible following liver transplantation, but otherwise carries an extremely poor prognosis. In patients with cirrhosis and ascites the 1-year probability of developing HRS is 20% and, at 3–5 years, 50%. Hypovolaemia is most commonly due to gastrointestinal bleeding or excessive diuretic treatment. Any potentially nephrotoxic drug, such as NSAIDs or gentamicin should be avoided in cirrhotics. Interestingly, it was recently shown that cirrhotic patients with acute kidney injury (e.g. secondary to sepsis, nephrotoxic drugs, or intravenous contrast) who underwent liver transplantation had a higher 5-year mortality and incidence of renal dysfunction compared with those with HRS.

Brain

ACLF patients may present with an acute confusional state superimposed on varying degrees of cognitive impairment that can evolve to coma. This is considered a form of hepatic encephalopathy (HE) [2,3]. Once again, the difference between cirrhosis and ACLF-induced is a precipitating inflammatory factor. This enhances the disturbances attributable to liver failure (secondary to hyperammonaemia) or can exert a direct neuro-inflammatory effect on the brain. Precipitants include infection, SIRS, and circulatory dysfunction. Neurotoxins such as ammonia may have their effects exacerbated by inflammatory cytokines [3]. Equally, SIRS may increase blood–brain barrier permeability and cause nitric oxide (NO)-mediated astrocyte swelling. Other described defects include neurotransmission disruption, astrocyte injury, loss of autoregulation, and cerebral atrophy.

Cerebral oedema was considered a very uncommon finding in cirrhotics but has been reported in ACLF, although to a much lesser extent than in acute liver failure. Computed tomographic imaging or invasive measurement of intracranial pressure are not routinely performed in ACLF patients, so the true prevalence is unknown.

Cardiovascular system

A hyperdynamic, vasodilated cardiovascular state is well described in cirrhosis. Therefore, only small decreases in arterial tone may be required to reduce circulating blood volume and cause hypotension [2]. The subset of ACLF patients with reduced cardiac output is associated with a poorer outlook. Putative mechanisms are similar to those in sepsis, e.g. elevated levels of TNFα and NO.

Pulmonary system

An increased risk of bacterial pneumonia and aspiration pneumonia due to altered consciousness is recognized in cirrhosis patients. Ascites may lead to decreased chest wall compliance or pleural effusion (hepatic hydrothorax). Portopulmonary hypertension and hepatopulmonary syndrome are notoriously underdiagnosed. The former is a predominantly haemodynamic problem, while the latter is one of intrapulmonary shunting. Chest X-ray (CXR) and arterial blood gases are mandatory in any patient complaining of breathlessness or cough.

Coagulation

Prolongation of the prothrombin time consequent to impaired synthesis and increased consumption of coagulation factors is common [2]. However, spontaneous bleeding is rare and often occurs as a result of the short half-life of factor VII. Bleeding associated with trauma or acute variceal haemorrhage may be more dramatic. Infection is again a key precipitant in cirrhosis-induced coagulopathy with development of endogenous low-molecular-weight heparinoids and elevated portal pressure. This is likely to be a key reason underlying the reduction in early variceal rebleeding rates seen with prophylactic antibiotics.

Hepato-adrenal axis

Adrenal insufficiency (insufficient rise in cortisol following corticotrophin administration) is described in >50% of patients with cirrhosis and severe infection, especially those with advanced liver disease, and is associated with increased mortality [2]. Primary and secondary adrenal insufficiency with an inadequate pituitary response and low adrenocorticotropic hormone levels may co-exist.

Thrombosis

Extrahepatic portal venous thrombosis secondary to sluggish portal flow or underlying thrombophilia is common. The development is often insidious and recognized only on radiological imaging. However, an acute portal vein thrombosis in cirrhotic patients may precipitate ACLF. Finally, counter to widespread opinion, patients with a prolonged international normalized ratio can develop deep vein thrombosis and pulmonary emboli.

Assessment

Clinical assessment should follow the standard ABCDE approach to the critically-ill patient

A—airway

Does the patient have HE with a Glasgow Coma Scale <8? Intubation should then be considered. CT scanning is mandatory if localizing neurological signs are present.

B—breathing

Is the patient hypoxic? Oxygen (O_2) saturations and arterial blood gases should be checked though coagulopathy may worsen bleeding at the puncture site. The inspired O_2 (FiO_2) concentration should be increased and non-invasive or invasive ventilation

considered. An underlying aetiology should be sought with CXR, electrocardiogram (ECG), and CT scan of the thorax. Significant hepatopulmonary syndrome can be excluded by contrast echocardiography.

C—circulation

Peripheral venous access should be obtained, blood tests and cultures sent, and cross-matching performed as needed. Central venous and arterial access should be obtained if hypotension persists despite volume challenges guided by the right atrial pressure (RAP) response to fluid. A high RAP value may occur due to raised intra-abdominal pressure secondary to large-volume ascites, in which case paracentesis should be considered. If the central venous oxygen saturation is <70%, causes of hypovolaemia such as sepsis, gastrointestinal blood/fluid loss, or excessive diuresis should be sought. Values >70% may still be associated with fluid depletion. If the patient remains hypotensive despite volume replacement, then cardiac index/volume status should be assessed and an inotrope/pressor agent given as appropriate.

D and E—disability/exposure: metabolic

A haemoglobin value >8 g/dL should be targeted and clotting corrected only if active bleeding is present. Saline-containing fluid should be avoided if the patient is hyperchloraemic. A metabolic acidosis may be secondary to liver or renal dysfunction, or to tissue hypoperfusion. If severe, early renal replacement with bicarbonate buffer may be needed. Serum glucose, magnesium, and phosphate should be checked and corrected, if necessary.

Conclusion

ACLF is a distinct clinical syndrome within the natural history of advanced cirrhosis, which carries a poor prognosis. There are multiple causes, with infection the most common and sepsis/inflammation the central pathophysiological feature. Very few patients will be candidates for liver transplantation and ICU mortality rates have improved little over 20 years [4]. Therefore novel treatments are desperately needed.

References

1. Graziadei IW. (2011). The clinical challenges of acute on chronic liver failure. *Liver International*, Suppl. 3, 24–6.
2. Jalan R, Gines P, Olson JC, et al. Acute on chronic liver failure. *Journal of Hepatology*, **57**, 1336–48.
3. García-Martínez R and Córdoba J. (2011). Acute-on-chronic liver failure: the brain. *Current Opinions in Critical Care*, **17**, 177–83.
4. Olson JC and Kamath PS. (2011). Acute-on-chronic liver failure: concept, natural history, and prognosis. *Current Opinions in Critical Care*, **17**, 165–9.

CHAPTER 200

Management of acute or chronic hepatic failure in the critically ill

Alastair O'Brien

Key points

- Acute on chronic liver failure is associated with a very poor prognosis and early identification of the precipitating cause is essential to successfully attempt to reverse decompensation.
- The most common precipitant is infection and therefore a high index of suspicion is required.
- Other management is largely supportive with close attention to renal dysfunction particularly important.
- Regular, effective, and compassionate communication with the patient and family members is extremely important to update any changes in condition and provide a realistic prognosis.
- All patients admitted to ICU with complications of cirrhosis warrant consultation with a transplant centre to determine whether they fulfil criteria for transplantation, and for expert advice.

Introduction

Acute on chronic liver failure (ACLF) is characterized by an acute deterioration of liver function in a patient with previously compensated cirrhosis secondary to a precipitating event, most commonly infection. However, most of the management approach to ACLF described herein relates to studies performed in patients with advanced liver cirrhosis, rather than ACLF *per se* and may therefore be equally applied to any critically-ill cirrhosis patient.

The mortality of patients with decompensated cirrhosis has changed little in the last 20 years. Organ failure is the key determinant of mortality, approaching 95% in patients with ≥3 organ failures. Liver transplantation is an extremely successful treatment for end-stage liver failure, but lack of donor organ availability limits this option to a minority of patients with advanced liver disease. Early detection and aggressive treatment of precipitant factors or complications of ACLF by a team with expertise in both hepatology and critical care will improve the severe associated mortality. Such an approach is described here. Treatment goals are to reverse precipitating factors of ALCF and support failing organs, thereby preventing further deterioration and allowing time for liver function to recover.

Infection

Clinical signs of infection, such as pyrexia or tachycardia, are often absent, so a high level of suspicion is required. In those with suspected infection, a broad-spectrum antibiotic, preferably given within 1 hour of assessment, is recommended. Piperacillin–tazobactam (Tazocin) is often used empirically, but choice should be guided by local knowledge of prevalent organisms and resistance patterns. Further treatment changes should be guided by culture results/sensitivities; early communication with the microbiology team is recommended. Strict attention to hand hygiene and local 'bundles' of care (e.g. for arterial and venous catheters) minimizes the risk of hospital-acquired infections.

Spontaneous bacterial peritonitis is usually treated with cefotaxime (2 g iv, tds) in addition to albumin boluses, although some units may have different policies. In selected high-risk patients, prophylactic norfloxacin to prevent spontaneous bacterial peritonitis delays the development of hepatorenal syndrome (HRS) and improves survival rates. However, widespread antibiotic prophylaxis is not recommended in view of an increased incidence of multidrug-resistant bacterial infections, which carry a high mortality.

For prolonged intensive care unit (ICU) admissions, weekly swabs to test for the development of resistant organisms are recommended. Testing for *Clostridium difficile* infection should be routinely performed, especially in patients with diarrhoea, which may be overlooked in patients receiving lactulose [1].

Renal failure

Renal dysfunction in ACLF patients is characterized by increased renal sodium and solute-free water retention, leading to ascites and hyponatraemia, as well as renal vasoconstriction causing a decreased glomerular filtration rate [2]. The development of renal failure in ACLF portends a grim outcome so precipitants such as nephrotoxic drugs, e.g. non-steroidal anti-inflammatory drugs or gentamicin, intravascular volume depletion, or large-volume paracentesis without albumin replacement must be avoided [1]. Despite being the key marker of renal dysfunction in cirrhosis, serum blood creatinine commonly underestimates renal dysfunction in ACLF because of decreased creatinine production or reduced muscle mass [2]. Iothalamate clearance measurement of glomerular filtration is usually not feasible in critically-ill patients. Volume expansion with albumin (1 g/kg/day initial dose to a maximum 100 g, followed by 20–40 g/day) combined with administration of vasopressors to reduce serum creatinine to <1.2 mg/dL is recommended [1]. Vasoconstrictor choice depends on availability, with terlipressin most commonly used in the UK and Europe at 0.5–1 mg every 4–6 hours, increasing to 2 mg every 4–6 hours for up to 14 days.

Alternative regimens include norepinephrine infusion (0.5–3 mg/hour) or midodrine 7.5–12 mg orally with octreotide 100–200 μg given sc tds. In approximately 50% of patients, renal function worsens despite these measures [1]. Even in those patients whose renal function improves, this benefit may only be short-term. Good predictors of response to therapy include less severe renal impairment, an early drop in serum creatinine and an early increase in mean arterial pressure following terlipressin. Renal replacement therapy is recommended to manage severe volume overload, electrolyte abnormalities, and metabolic acidosis. Unfortunately, many patients develop adverse effects, such as hypotension, bleeding, or infection during haemodialysis, and it has not been associated with improved outcomes in HRS.

Cardiovascular dysfunction

Patients are frequently hypotensive and a hyperdynamic circulation, and cirrhotic cardiomyopathy commonly co-exists [1]. Ventricular compliance is decreased; this can be assessed by observing the change in central venous pressure (CVP) after a 200-mL colloid fluid challenge, which is more instructive than a single CVP measurement. The optimum colloid for fluid resuscitation is uncertain with hepatologists and intensivists often disagreeing over the merits of albumin in particular. Albumin is safe, but is five times more expensive than many other colloids. This author's opinion is that targeted fluid resuscitation, i.e. aimed at objectively improving cardiovascular parameters and therefore organ perfusion, is more important than the type of colloid used. Moderate–large volume ascites raises intra-abdominal pressure and results in reduced thoracic compliance which further increases the measured CVP but without an accompanying increase in ventricular preload. Echocardiography is non-invasive, and offers a more detailed and accurate assessment of ventricular function and response to volume loading. Transoesophageal echo-Doppler is not considered appropriate for most critically-ill cirrhosis patients because of the presumed increased risk of variceal bleeding following insertion (although this has never been reported). In the non-spontaneously breathing ventilated patient, the impact of phasic increases in intrathoracic pressure on venous return and cardiac output can be assessed by analysis of stroke volume or pulse pressure variation from an arterial catheter; the more volume deplete the patient is the greater the degree of variation, provided no arrhythmias are present and tidal volumes are >8 mL/kg. For patients with suspected portopulmonary hypertension, pulmonary artery catheterization should be considered to guide therapy, for example, with endothelin antagonists or sildenafil.

Raised intra-abdominal pressure with large volume ascites can cause an abdominal compartment syndrome, which is associated with renal, cardiovascular, and respiratory dysfunction. Measurement of bladder pressure via a urinary catheter is a good surrogate for intra-abdominal hypertension and should be kept <20 mmHg by large-volume paracentesis with albumin replacement (6–8 g albumin/L of ascites drained) [1].

The optimal blood pressure for ACLF is unknown. Hepatorenal syndrome (HRS) does respond to terlipressin, which acts by increasing perfusion pressure. A pragmatic approach is to give fluid challenges to restore circulating intravascular volume and, if still hypotensive, to use vasopressors such as norepinephrine to achieve mean arterial pressures of 65–70 mm Hg. Vasopressin (or terlipressin) has been used as a norepinephrine-sparing agent in sepsis and has a similar effect in cirrhosis patients [1].

Prevention and control of bleeding

Although the INR may be significantly prolonged in ACLF, routine correction of coagulation abnormalities in the absence of active bleeding is rarely necessary. Furthermore, correction prior to central venous or arterial catheter placement, paracentesis, thoracentesis, bronchoscopy, or endoscopy without biopsy is not usually required. Correction may be associated with significant complications including transfusion-associated lung injury or circulatory overload, and therefore should be performed only when there is a clear indication. Correction is recommended in the presence of active bleeding with thromboelastography (TEG), prothrombin time, complete blood count, and activated partial thromboplastin time used to guide therapy [1]. Vitamin K, 2 mg daily for 3–5 days, should be given to eliminate deficiency as a cause of coagulopathy. Massive acute haemorrhage should be managed with transfusion of red blood cells (RBCs) and fresh frozen plasma (FFP) in a 1:1 or 2:1 ratio, with transfusion of platelets and cryoprecipitate to treat consumption; early liaison with haematology is recommended. For less severe bleeding, a 4:1 RBC-to-FFP ratio may be used. Maintaining platelets with transfusion to a level of ≥50 $\times 10^9$/L is recommended; platelet dysfunction may be improved with desmopressin (DDAVP). Fibrinolysis is common and easily assessed by TEG or euglobulin lysis time. Treatment of fibrinolysis with epsilon-aminocaproic acid or tranexamic acid is indicated if bleeding persists despite thrombocytopenia and clotting factor correction, in the absence of disseminated coagulopathy. When the partial thromboplastin time is excessively prolonged, use of protamine, even without previous heparin administration, may help counteract endogenous heparin-like compounds.

For gastrointestinal bleeding, correction of coagulation abnormalities must be accompanied by antibiotic therapy, usually iv ceftriaxone or po norfloxacin, and vasoactive medications for up to 5 days. Terlipressin 2 mg 4-hourly, somatostatin 250–500 μg/hour, or octreotide 50–100 μg/hour may be used according to local protocols. Early transjugular intrahepatic portosystemic shunt (TIPSS) may be beneficial in Child–Turcotte–Pugh class C patients (>13 points) or class B with active variceal bleeding [1].

Cirrhosis patients carry a risk of venous thromboembolism, even in the presence of coagulopathy. In the absence of contraindications, cirrhosis patients in intensive care should have mechanical DVT prophylaxis, but routine pharmacological prophylaxis is not currently recommended [1].

Neurological system

Hepatic encephalopathy (HE) is treated with lactulose and non-absorbable antibiotics [1]. Titrating the lactulose dose to two or three semi-formed stools per day, while avoiding diarrhoea (and potential electrolyte abnormalities) is current practice. When advanced encephalopathy or mechanical ventilation precludes oral administration, administration should be via nasogastric tube or retention enema. The non-absorbable antibiotic rifaximin improves recurrent HE in outpatients by reducing ammonia-producing enteric bacteria, but it is unclear whether this applies to ICU patients. Furthermore, most ACLF patients will receive broad-spectrum antibiotics and rifaximin may not offer added benefit. Equally, probiotics improve minimal HE in outpatients, but are

untested in the ICU. Avoidance of sedative agents is strongly recommended. Cerebral oedema is described in ACLF; if suspected, mannitol is administered with possible invasive intracranial pressure monitoring [1]. Suggested future directions of therapy for HE include examining the effect of improving circulatory dysfunction with vasoconstrictors and albumin, or vaptans to improve hyponatremia.

Respiratory failure

Endotracheal intubation for airway control is mandatory in patients with a Glasgow coma score ≤8 and/or during active upper gastrointestinal bleeding (for safe endoscopic therapy) [1]. Lung protective ventilation strategies are recommended for respiratory failure and acute lung injury, with low tidal volumes (~6 mL/kg body weight), positive end-expiratory pressure to maintain oxygenation, and plateau pressures <30 cmH_2O to prevent further lung injury. Many patients can be managed with intermittent opiates with prompt extubation when able to protect their airway; sedatives being liver-metabolized often prolong altered consciousness or may precipitate HE. Prolonged translaryngeal intubation should be avoided, while percutaneous tracheostomy can be performed with low risk, even with coagulopathy. All patients should undergo early mobilization to prevent critical care weakness [1].

Hepatic hydrothorax may cause pulmonary or haemodynamic compromise and may therefore necessitate thoracocentesis. If the patient is not compromised, sodium restriction and diuretics may be sufficient. If refractory, TIPSS insertion should be considered. Long-duration chest drain placement carries a risk of hypovolaemia or infection and is best avoided [1].

Nutritional support

This is necessary for patients unable to maintain an adequate intake, a commonplace occurrence in ACLF. A low-protein diet neither improves outcome of HE nor the rate of recurrence so a normal intake (0.8–1.2 g/kg/day) is recommended [1]. Protein requirements may be modified on the basis of the degree of catabolism and presence of renal failure. In patients receiving continuous renal replacement therapy, the goal of protein supplementation is to prevent a negative nitrogen balance. The enteral route is preferred, but aggressive enteral feeding in patients with ileus may worsen bacterial translocation and sepsis; mixed enteral and parenteral nutrition is probably a better option. Parenteral nutrition must be administered via a dedicated line to reduce the incidence of infection.

A functioning liver is critical for glucose homeostasis. In advanced liver disease, glycogen storage may become impaired, predisposing the patient to hypoglycaemia. Nutritional support may require modification to maintain normoglycaemia [1].

Deficiencies in water-soluble vitamins (vitamin B complex and C) are common in alcoholic cirrhosis in particular, but also occur in non-alcoholic liver disease. The risks of Wernicke's encephalopathy and Korsakoff's dementia are well described in thiamine-deficient alcoholic patients, but are also seen in hepatitis C-related cirrhosis. Therefore, iv thiamine administration (100 mg daily for 3–5 days) is recommended for all cirrhotics as gut absorption may be unreliable [1].

Low levels of trace elements such as selenium and zinc are described in cirrhosis. Supplementation with zinc improves glucose disposal in cirrhotics and although deficiency is considered to precipitate HE, trials of supplementation have shown conflicting results. Nevertheless, zinc replacement at a dose of 25–50 mg elemental zinc tds is recommended, but insufficient evidence exists to recommend routine replacement of selenium.

Metabolic abnormalities

As mortality is increased in cirrhosis patients when blood glucose rose above a threshold of 146 mg/dL (8.1 mmol/L), it is recommended that blood glucose be maintained at or below this value. However, cirrhosis patients are more likely to develop hypoglycaemia and so great care must be taken with glycaemic control.

Relative adrenal insufficiency occurs in 60–80% of critically-ill cirrhosis patients. These patients may have improved cardiovascular parameters and even improved mortality following steroid therapy. However, routine administration of steroids to cirrhosis patients admitted to ICU was not beneficial in a recent controlled trial. Therefore, in the absence of adrenal insufficiency, steroid therapy is not recommended [1].

Communication

Regular, effective, and compassionate communication with the patient and family members is extremely important to update any changes in condition and provide a realistic prognosis. When multiple referring and consulting services are involved, a cohesive plan of care must be provided to avoid confusion and facilitate informed decision-making. To minimize futile care, daily reassessment of the patient's response to intensive care is needed. Given the extremely poor prognosis, if multisystem organ failure persists after several days' treatment, and especially when there is no option for liver transplantation, a change of emphasis to palliative care should be strongly considered.

Referral to a liver transplant centre

The determination of suitability for liver transplantation is beyond the scope of this chapter. All patients admitted to ICU with complications of cirrhosis warrant consultation with a transplant centre to determine whether they fulfil criteria and for expert advice. Two recent retrospective analyses of patients undergoing transplantation demonstrated that ACLF pre-transplant did not lead to worse post-transplant outcomes [1].

Liver support devices

Liver support devices based on detoxification of the patient's blood are intended to support liver function until the native liver recovers, or as a bridge to transplantation. There are two main types of liver support devices—artificial livers (acellular devices, e.g. albumin dialysis) and bioartificial devices (containing human, animal, or transformed cells) [3]. Studies have demonstrated attenuation of the systemic inflammatory response, improved cholestasis, and HE suggesting that liver support devices may improve quality of life and perhaps reduce hospital stay. However, a recent meta-analysis demonstrated no survival benefit in ACLF [4]. Liver support devices have, at this time, failed to gain US Food and Drug Administration approval. Further clinical trials are required to determine whether subsets of patients might benefit from these devices.

Conclusion

The predicted increases in the global health burden of cirrhosis due to chronic viral hepatitis, alcohol and non-alcoholic fatty liver disease will inevitably lead to increased demands for ICU admission to support organ failure. Management of these patients represents a substantial challenge in an era of liver transplantation severely limited by donor organ shortage. ACLF is associated with a very poor prognosis and early identification of the precipitating cause is essential to successfully attempt to reverse decompensation. Other management is largely supportive with close attention to renal dysfunction particularly important. Liver support devices may play a role in certain subgroups of patients in the future, but are not recommended at present. An improved understanding of pathophysiology and precipitating factors to identify who may develop ACLF, associated with aggressive early management may possibly improve outcome.

References

1. Olson JC, Wendon JA, Kramer DJ, et al. (2011). Intensive care of the patient with cirrhosis. *Hepatology*, **54**, 1864–72.
2. Cárdenas A and Ginès P. (2011). Acute-on-chronic liver failure: the kidneys. *Current Opinions in Critical Care*, **17**, 184–9.
3. Tritto G, Davies NA, and Jalan R. (2012). Liver replacement therapy. *Seminars in Respiratory and Critical Care Medicine*, **33**, 70–9.
4. Stutchfield BM, Simpson K, and Wigmore SJ. (2011). Systematic review and meta-analysis of survival following extracorporeal liver support. *British Journal of Surgery*, **98**, 623–31.

SECTION 7

Nutrition

PART 7.1

Physiology

CHAPTER 201

Normal physiology of nutrition

Annika Reintam Blaser and Adam M. Deane

Key points

- Ingested carbohydrate, glycogenolysis, and gluconeogenesis are essential for function of brain and anaerobic tissues that depend on glucose as their main energy source.
- Fat is the most energy-rich nutrient, but most of ingested lipids will be stored in adipose tissue because the oxidative capacity for lipids is low.
- During periods of inadequate energy delivery, ingested or endogenous proteins are diverted into glucose metabolism, and this provides a rationale to deliver more protein during these periods.
- Basic metabolic rate (BMR) is the largest component of total daily energy requirements, even in the case of very high physical activity or acute illness.
- Daily energy requirements range from 1800 to 2800 kcal/day or 25 to 30 kcal/kg body weight (BW)/day roughly—carbohydrates should provide 55–60%, lipids 25–30%, and proteins 10–15%.

Body composition

Water (approximately 60% in adult males and 50% in females [1]), protein, minerals, and fat are the main components of human body. Essential fat is contained in bone marrow, the heart, lungs, liver, spleen, kidneys, intestines, muscles, and central nervous system. Fat located in adipose tissue is called storage fat. The two-component model distinguishes between fat and fat-free mass (FFM), while the three-component model further divides FFM into body cell mass and extracellular mass [2]. **Lean body mass** is an indirect estimation of the weight of bones, muscles, ligaments, and internal organs, which can be calculated using various equations [3].

Direct methods of assessing body composition, such as skinfolds, bioelectrical impedance analysis, and hydrostatic weighing are not routinely used in the critically ill.

Estimation of nutritional status

Body mass index (BMI) = weight (kg)/height (m) and provides a rough estimation of nutritional status [2]. A limitation of BMI is that the calculation does not distinguish between muscle and fat mass. A BMI of 18.5–24.9 kg/m^2 is considered 'normal' regardless of age or population [1]. BMI has a U-shape relation to morbidity and mortality [2]. In persons >60 years old being slightly heavier (BMI 26–27) is associated with the longer life expectancy [2]. While being underweight is associated with poorer outcomes in the critically ill, obesity does not appear to be harmful (and may be beneficial) [4].

Estimation of the **ideal body weight** [5] is often inaccurate, but the range may be useful and can be calculated (Broca's index):

$$\left(\text{Height}\,(\text{cm}) - 100\right) \pm 15\% \text{ for women or } 10\% \text{ for men} \qquad \text{[eqn 1]}$$

Clinical examination and laboratory tests

General **clinical examination** of skin, hair, eyes, gums, tongue, bones, muscles, and thyroid gland tends only to reveal signs in cases of marked malnutrition or vitamin/mineral deficiencies.

Laboratory tests such as blood haemoglobin, total lymphocyte count, glucose, serum albumin, prealbumin, transferrin, total protein measurements, and calculation of nitrogen balance have limitations, but have been used. Nitrogen balance is considered the most dynamic nutritional indicator.

Essential nutrients: substrate and energy metabolism

Essential nutrients are substances that are not synthesized (or are synthesized in too small amounts) within the body and must, therefore, be ingested or administered. They include essential fatty acids, essential amino acids, vitamins, and dietary minerals.

Energy

Energy is derived from three major categories of macronutrient—protein, carbohydrate, and lipids—and is released by breaking down carbon–carbon bonds created in plants via photosynthesis. Energy requirements to maintain stable weight can be estimated, using calculations or measured using calorimetry.

Oxidative (burning for energy) and **non-oxidative** (storage, synthesis) substrate metabolism occur to a different extent according to the type of macronutrient and state of energy stores [2]. **Respiratory quotient (RQ)** is used to describe oxidative substrate metabolism.

Carbohydrates

Carbohydrates are compounds comprised of carbon, hydrogen, and oxygen. Depending on the composition of these molecules, carbohydrates are divided into mono-, di-, oligo-, and polysaccharides. While carbohydrates are non-essential nutrients, they comprise a substantial proportion of calories (4.1 kcal/g) in a normal diet [1]. In plants, carbohydrate is stored as starch, whereas in animals it is stored as glycogen.

Table 201.1 Nutritional requirements in adults

Nutrient	Role	Daily needs	Deficiency	Abnormalities in ICU
Macronutrients	Energy, structure, all functions	No absolute daily requirements exist	Starvation	
Carbohydrates	Major energy source, energy storage and transport, structure	55–60% of calories, max. 4 g/kg BW at rest	Hypoglycaemia, ketoacidosis	Hyperglycaemia (insulin resistance, counter-regulatory hormones)
Lipids	Energy storage, cell membrane structure, signalling molecules	25–30% of calories	Malabsorption of fat-soluble vitamins	Hyperlipidaemia with excessive parenteral nutrition and propofol
Proteins	Enzymes, structure, signalling, immune response	10–15% of calories 0.8 g/kg BW	Kwashiorkor, cachexia	Protein energy wasting occurs frequently
Vitamin	**Role**	**RDA**	**Deficiency**	**In ICU**
A (retinol)	Retinal pigment	Male 1000 µg female 800 µg	Night blindness, follicular hyperkeratosis	
B1 (thiamine)	Coenzyme in decarboxylation of pyruvate and alpha-keto acids	Male 1.5 mg, female 1.1 mg	Beriberi, Wernicke's encephalopathy	Threshold for thiamine administration should be low
B2 (riboflavin)	Coenzyme for oxidative enzymes	Male 1.7 mg, female 1.3 mg	Mouth ulcers, normocytic anaemia	
B3 (niacin) also vitamin PP or nicotinic acid	Coenzyme, precursor for NAD and NADP	Male 19 mg, female 15 mg	Pellagra, neurological symptoms	
B6 (pyridoxine)	Coenzyme in synthesis of amino acids, haeme, neurotransmitters	Male 2.0 mg, female 1.6 mg	Muscle weakness, depression, anaemia	
B12 (cobalamin)	coenzyme (deoxyribonucleotids), formation of erythrocytes, myelin	2 µg	Neurological symptoms	With pernicious anaemia (lack of intrinsic factor)
C (ascorbic acid)	Cofactor in collagen synthesis	60 mg	Scurvy	Antioxidant effect, cave oxalosis
D (1,25-cholecalciferol)	Ca^{2+} absorption and metabolism	5–10 µg	Rickets	
E (alpha-tocopherol)	Antioxidant	Male 10 mg, female 8 mg	Peripheral neuropathy	Antioxidant effect
K	Clotting, synthesis of prothrombin, factors VII,IX,X	Male 70–80 µg female 60–65 µg	Coagulopathy	
Biotin (also vitamin B7 or H, or coenzyme R)	Cofactor for several carboxylase enzymes; cell growth	30–100 µg	Neurological symptoms, alopecia, conjunctivitis, dermatitis	
Folate (vitamin B9)	Necessary for synthesis of DNA, haemopoesis	Male 200 µg female 180 µg (pregnancy 400)	Megaloblastic anaemia, peripheral neuropathy, neural tube defects	
Panthothenic acid (vitamin B5)	Synthesis of CoA. Carbohydrate, and fat metabolism	4–7 mg	Gastrointestinal and neurological symptoms	
Mineral	**Role**	**RDA**	**Deficiency**	**In ICU**
Calcium	Bone, intracellular signalling	800–1200 mg	Osteoporosis, arrhythmia hypertension	
Chromium	Cofactor	50–200 µg	Impaired glucose tolerance, peripheral neuropathy	Deficiency reported during long-term parenteral nutrition
Copper	Cofactor (oxidative phosphorylation, neurotransmitter synthesis etc.)	1.5–3 mg	Myelodysplasia, anaemia, leucopenia, neurological symptoms	Deficiency after gastric bypass. Reduce replacement in liver failure
Iron	Haemoglobin and cytochromes	Male 10 mg, female 15 mg	Microcytic anaemia, mucosal atrophy	

(*continued*)

Table 201.1 Continued

Nutrient	Role	Daily needs	Deficiency	Abnormalities in ICU
Iodine	Thyroid hormones	150 µg	Goitre, hypothyroidism	
Magnesium	Complex with ATP	Male 350 mg, female 280 mg	Muscle weakness, GI, and cardiac symptoms	Deficiency common and associated with major adverse outcomes
Manganese	Antioxidant	2–5 mg		Reduces replacement in liver failure
Molybdenum	Cofactor	75–250 µg	Liver dysfunction	
Phosphorus	Major component of the skeleton, nucleic acids, and ATP	800–1000 mg		Potentially catastrophic reduction during refeeding syndrome
Potassium	Membrane potential	At least 3510 mg (conditional recommendation by WHO)	Arrhythmias	Often life-threatening hyper- or hypo-K, narrow therapeutic/normal range
Selenium	Antioxidant	Male 70 µg, female 55 µg	Cardiomyopathy	Antioxidant effect
Zinc	Antioxidant, cofactor	Male 15 mg, female 12 mg	Skin lesions, loss of appetite	Antioxidant effect

RDA, Recommended daily allowance.

Adapted from a table published in *Medical Physiology*, Second Edition, Boron WF and Boulpaep EL, Copyright Elsevier 2012.

As an energy source, glucose is oxidized to CO_2 and water:

$$C_6H_{12}O_6 + 6O_2 + 32ADP + 32P -> 6\,CO_2 + 6H_2O + 32ATP + \text{heat} \quad (RQ = 6CO_2 / 6O_2 = 1.0) \qquad \text{[eqn 2]}$$

At rest, the maximum oxidative capacity is approximately 4 g glucose/kg BW/day [2]. If the glucose intake is greater non-oxidative metabolism occurs, resulting in glycogenesis (glycogen store is limited to 200–500 g; storing consumes about 6% of energy stored in glucose) and, after reaching the limit, in lipogenesis (storing costs 23% of energy) [6]. As an isolated energy source blood glucose covers energy needs for about 30 minutes, whereas glycogen would last for approximately one day [2]. Glycogen is stored in hydrated form, making it less energy-efficient, but easily available. Hepatic or muscle glycogenolysis occurs rapidly in response to hypoglycaemia or anaerobic demands.

Gluconeogenesis is the synthesis of glucose from non-hexose precursors (lactate, pyruvate, intermediates of the citric acid cycle, 18 of 20 amino acids and glycerol) [1]. Leucin and lysine together with fatty acids are not gluconeogenic, but ketogenic. Their breakdown-product is acetyl coenzyme A (CoA), which cannot generate pyruvate or oxalo-acetate. Gluconeogenesis is essential for the brain and anaerobic tissues (blood cells, bone marrow, renal medulla) that depend on glucose as their main energy source [1], but is energy-expensive, consuming 24% of energy contained in amino acids (AA) [6].

Lipids

Lipids are hydrophobic compounds that are soluble in organic solvents such as acetone.

Lipids contain 9.4 kcal/g of energy and can be ingested as triglycerides, sterol esters or phospholipids [1]. To generate energy, fatty acids are oxidized to CO_2 and water.

$$C_{15}H_{31}COOH\,(\text{palmitic acid}) + 23O_2 + 106ADP + 106P -> 16CO_2 + 16H_2O + 106ATP + \text{heat} \quad (RQ = 16CO_2/23O_2 = 0.70) \qquad \text{[eqn 3]}$$

In resting humans the oxidative capacity for lipids is 0.7 g/kg BW/day [2]. Greater amounts of ingested lipid will be stored as triglycerides in fat tissue. Fat constitutes approximately 20% of body weight, and the standard triglyceride store has the capacity to cover the body's energy requirements for about 2 months.

Ketone bodies are produced when accelerated oxidation of fatty acids leads to incomplete breakdown, producing acetyl CoA faster than the citric acid cycle can utilize it [1]. Ketone bodies (acetoacetate, β-hydroxybutyrate, and acetone) may serve as an alternative energy resource, e.g. during starvation up to 50% of brain energy demands might be met via ketone bodies [2].

Protein

Nitrogen differentiates protein from carbohydrates and fats. The major source of endogenous protein is muscle, which is converted into energy via complex metabolic pathways. When AA, either endogenous proteins or ingested, are metabolized to CO_2 and water, 4.3 kcal/g of energy can be released [1]. Protein metabolism in cells additionally results in the production of energy-containing metabolites (urea, ureic acid, and creatinine). The RQ for protein oxidation is 0.80–0.85 [1]. Protein stores are about 14% of body weight, but only half of it is available as an energy source, lasting for 10 days approximately. In health, protein catabolism contributes less than 5% of energy requirements, but this increases to 15% during starvation. The body constantly breaks down proteins to AAs and synthesizes other proteins according to the current needs of the body (protein turnover). Nine out of 20 AAs are essential—the body cannot synthesize them at sufficient rates for long-term survival and they must be ingested to replace the proteins oxidized during daily turnover. Excess protein is converted to glycogen or triacylglycerols [1].

To maintain nitrogen balance in an average adult individual, ingestion of 0.6–0.8 g/kg BW/day of protein is needed [2]. However, during periods of inadequate energy delivery greater amounts of protein are diverted into glucose metabolism and, in catabolic states, there is a marked increase in endogenous protein breakdown. Accordingly, more protein either ingested or administered may be beneficial during these periods [7].

Nitrogen (N) balance is the sum of protein degradation and protein synthesis, reflecting the changes in protein stores where:

$$\text{N Balance} = \text{N intake} - \text{N losses},$$

$$\text{N intake} = \text{protein intake}\ (\text{g/day})/6.25,\ \text{and}$$

$$\text{N losses} = \text{urinary urea N}\ (\text{UUN}),\ \text{g/day, determined from a 24-hour urine collection)} + 4\ \text{g miscellaneous other N losses from skin, mucosa and with faeces.} \quad \text{[eqn 4]}$$

N balance is used to estimate current protein requirements. Positive or negative N balances indicate anabolic or catabolic states respectively.

As in patients with renal replacement therapy (RRT) measurement of UUN is not applicable; the **total nitrogen appearance (TNA)** is used to express nitrogen losses [8]:

$$\text{TNA in a patient with RRT} = \left[\begin{array}{l}\text{urea nitrogen loss +}\\ \text{AA nitrogen loss during RRT}\ (\text{g})\end{array}\right] + \left[\begin{array}{l}\text{change in interdialytic blood urea}\\ \text{nitrogen}\ (\text{BUN})\ (\text{g/L}) \times \text{total body water}\ (\text{L})\end{array}\right] \quad \text{[eqn 5]}$$

Protein energy wasting [9] due to inadequate protein intake and high catabolism is thought to occur frequently in the critically ill. While preventing or limiting protein deficiency in this group is often proposed as beneficial, it is not yet established that such an approach improves outcomes.

Other

Other essential nutrients include inorganic elements like calcium, potassium, iodine, iron, trace elements (dietary minerals that are needed in very small quantities) and vitamins, which are necessary for normal functioning of the body. The role, recommended daily allowances and signs of deficiency of these essential vitamins and minerals are presented in Table 201.1.

Vitamins

Vitamins are divided into water-soluble (B,C) and fat-soluble (A, D, E and K) groups. Bonds between fat-soluble vitamins with proteins are broken by the acidity of gastric juice and proteolysis. Assimilation of fat-soluble vitamins relies on lipid absorption and their deficiency occurs in various fat malabsorption states.

Thiamine (B_1) with its phosphorylated derivatives plays a fundamental role in energy metabolism and is used in the biosynthesis of the neurotransmitters. Its best-characterized derivate thiamine pyrophosphate is a coenzyme in the catabolism of sugars and amino acids. Thiamine derivatives and thiamine-dependent enzymes are present in all cells of the body, but the nervous system and the heart are particularly sensitive to its deficiency. Thiamine deficiency may occur because of concomitant chronic disease or alcoholism and can lead to severe neurological impairment and contribute to increased mortality [10].

Vitamin K is pivotal for synthesis of coagulation factors VII, IX, X, protein C and protein S in liver, acting as a co-factor for carboxylation. Its deficiency occurs with fat malabsorption, but also during severe bleeding (disseminated intravascular coagulation). Previous treatment with vitamin K antagonists, blocking carboxylation of prothrombin (factor II), factors VII, IX and X, and making their complexes with Ca^{2+} and therefore usage for coagulation impossible, is common in hospitalized patients.

Supplementation of **vitamins E and C** has been proposed as having beneficial antioxidant effects in the critically ill [11]. This has yet to be established and particularly in patients with renal failure excessive vitamin C may lead to oxalosis.

Minerals

Calcium is necessary for the structure (calcium phosphate in bones), signalling, and enzymatic processes (co-enzyme for clotting factors, pre-synaptic release of acetylcholine) in the body.

Magnesium is essential for energy in every cell type in organism, as ATP, the main source of energy in cells, must be bound to a magnesium ion in order to be biologically active.

Supplementation of minerals such as **selenium** and **zinc** has been described in the critically ill and warrants further study [12].

Next to the essential nutrients food includes fibres and other ballast substances, carotinoides, bioflavonoids etc. considered important for health, but their functions are clarified incompletely.

Energy consumption

Estimation of energy consumption

Basal metabolic rate (BMR) is an estimation of metabolism, measured under standardized conditions in the absence of stimulation. **Resting metabolic rate (RMR)** is measured during less strict conditions and is therefore higher than BMR [1]. BMR and RMR are measured by gas analysis through either **direct** (the body is positioned in a chamber to measure the body's heat production) or **indirect** (CO_2 production is measured) **calorimetry** [13].

BMR can be estimated by a number of calculations of **Basal Energy Expenditure (BEE)** with Harris-Benedict equation being the most frequently used in critical care:

Adult males:

$$\text{BEE}\ (\text{kcal/day}) = (13.8 \times \text{weight in kg}) + (5 \times \text{height in cm}) - (6.8 \times \text{age}) + 66.5. \quad \text{[eqn 6]}$$

Adult females:

$$\text{BEE}\ (\text{kcal/day}) = (9.6 \times \text{weight in kg}) + (1.8 \times \text{height in cm}) - (4.7 \times \text{age}) + 655. \quad \text{[eqn 7]}$$

As body weight is the major factor that determines BEE, a simplified estimate of 25 kcal/kg BW/day is often used and our experience is that the latter approach is adequate for clinical purposes. The BMR is the largest component of total daily energy requirements, even in case of very high physical activity, as well as in the most hypermetabolic patients. The various estimations of stress/activity factors available to calculate the total energy expenditure (TEnE = BEE × stress/activity factor) tend to overestimate the TEnE in ICU patients, as measured TEnE is often close to calculated BEE [6].

References

1. Boron WF and Boulpaep EL. (2012). *Medical Physiology*, 2nd edn. Philadelphia: Saunders.
2. Speckmann EJ, Hescheler J, Köhling R. (2008). *Physiologie*, 5th edn. Munich: Elsevier.
3. R. Hume. (1966). Prediction of lean body mass from height and weight. *Journal of Clinical Pathology*, **19**, 389–91.
4. Heyland DK, Dhaliwal R, Jiang X, and Day AG. (2011). Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Critical Care*, **15**, R268.
5. Pai MP and Paloucek FP. (2000). The origin of the 'ideal' body weight equations. *Annals of Pharmacotherapy*, **34**, 1066–9.
6. Fontaine E and Müller MJ. (2011). Adaptive alterations in metabolism: practical consequences on energy requirements in the severely ill patient. *Current Opinion in Clinical Nutrition and Metabolic Care*, **14**, 171–5.
7. Shils ME, Shike M, Ross AC, Caballer B, and Cousins RJ. (2006). *Modern Nutrition in Health and Disease*, 10th edn. London: Lippincott Williams & Wilkins.
8. Chua HR, Baldwin I, Fealy N, Naka T, and Bellomo R. (2012). Amino acid balance with extended daily diafiltration in acute kidney injury. *Blood Purification*, **33**, 292–9.
9. Kopple JD. (1999). Pathophysiology of protein-energy wasting in chronic renal failure. *Journal of Nutrition*, **129**(1 Suppl.), 247S–51S.
10. Berger MM, Shenkin A, Revelly JP, et al. (2004). Copper, selenium, zinc, and thiamine balances during continuous venovenous hemodiafiltration in critically ill patients. American Journal of Clinical Nutrition, **80**, 410–16.
11. Casaer MP, Mesotten D, and Schetz MRC. (2008). Bench-to-bedside review: Metabolism and nutrition. *Critical Care*, **12**, 222.
12. Andrews PJ, Avenell A, Noble DW, et al. (2011). Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients; Scottish Intensive care Glutamine or selenium Evaluative Trial Trials Group. *British Medical Journal*, **342**, d1542.
13. Singer P, Anbar R, Cohen J, et al. (2011). The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Medicine*, **37**, 601–9.

CHAPTER 202

The metabolic and nutritional response to critical illness

Linda-Jayne Mottram and Gavin G. Lavery

Key points

- The metabolic response to critical illness is biphasic, the acute stage being accompanied by increased hypothalamic pituitary function and peripheral resistance to effector hormones.
- The acute phase has been considered adaptive, increasing the availability of glucose, free fatty acids, and amino acids as substrates for vital organs.
- Prolonged critical illness results in damped hypothalamic responses that are implicated in the critical illness wasting syndrome.
- Cytokines can stimulate the hypothalamic pituitary axis directly as part of the stress response in critical illness.
- Gastrointestinal failure may in part be a neuroendocrine phenomenon, with disordered hormonal and enteric nervous system responses.

Introduction

The metabolic response to critical illness is complex and affects every body system. The response to acute critical illness differs from the response to more prolonged states. These differences or the dynamic complexity of the neuroendocrine changes themselves, may explain the failure of pharmacological manipulation to date. The gut response to critical illness is also an example of neuroendocrine derangement. The interaction between body systems becomes apparent when gastrointestinal failure and inadequate nutrition combine to exacerbate the catabolic state. Ultimately, the consequence is to lengthen the illness, prolong intensive care stay, and hamper the recovery process.

The somatotrophic axis

Normal physiology

Human growth hormone (GH) is produced in the somatotrophic cells of the anterior pituitary in response to hypoglycaemia, exercise, sleep, high protein intake, and acute stress. This process is regulated by the stimulatory effect of growth hormone releasing hormone (GHRH) from the hypothalamus and also by the hunger-stimulating hormone, ghrelin. Inhibitory effects on GH release occur via somatostatin secretion from the hypothalamus. GH acts directly on the tissues causing lipolysis, anti-insulin effects, sodium and water retention, and immunomodulation. It also acts indirectly via hepatic production of insulin-like growth factor 1 (IGF-1) to bring about protein synthesis and thus protect lean body mass.

Acute critical illness

Serum GH levels are elevated overall and demonstrate increased pulsatility. However, IGF-1 levels are lower and GH receptor expression is reduced, which together produce a state of peripheral GH resistance. Energy-consuming anabolic processes are halted, permitting the release of amino acids for use as an energy substrate. The direct effects of lipid breakdown and antagonism of insulin are permitted, which again favourably releases energy reserves in the acute phase of critical illness [1].

Prolonged critical illness

Levels of GH are reduced with a more erratic and less pulsatile pattern of secretion, a process that is compounded by low ghrelin levels. Despite less peripheral resistance to GH, a state of relative deficiency persists and contributes to critical illness wasting [2]. The return of peripheral responsiveness to GH was thought to provide a therapeutic target for exogenous GH administration, but actually results in higher morbidity and mortality. These findings may be a function of timing of GH administration and remain under investigation. Greater abnormalities are seen in the male GH axis, which has been theorized to account for some gender differences in ICU outcome.

The thyrotropic axis

Normal physiology

In health, thyrotropin-releasing hormone (TRH) is released from the hypothalamus and in turn the anterior pituitary secretes thyroid-stimulating hormone (TSH), with negative feedback via the thyroid hormones triiodothyronine (T3) and thyroxine (T4).

Acute critical illness

The adaptive response of the thyroid to critical illness is an energy conservation strategy, reducing expenditure on metabolic processes. It is often called 'non-thyroidal illness syndrome', but may also be known as 'low T3 syndrome' or 'sick euthyroid syndrome'. Laboratory parameters include low serum T3 levels, increased reverse T, while TSH and free T4 remain largely normal [3].

Low T3 levels are partly due to reduced peripheral conversion from T4. The enzyme 5'-monodeiodinase catalyses this peripheral

conversion and accounts for 80% of free T3 in the circulation. This enzyme is inhibited during the stress response and in particular by glucocorticoids. It contains the novel amino acid selenocysteine and so may be affected by selenium deficiency.

Prolonged critical illness

As the illness progresses, free T4 decreases and is a reflection of illness severity. Those with the lowest T3 and T4 levels in critical care have the highest mortality [4]. There is dampening of the normal negative feedback loop. TSH fails to increase and loses its pulsatile secretion pattern, only doing so as the patient starts to recover.

Non-thyroidal illness syndrome is associated with prolongation of mechanical ventilation in the ICU population [5]. Despite the biological rationale for treating such a state of continued relative hypothyroidism, there is little convincing proof of efficacy. Others [6] have argued for treatment with hypothalamic releasing peptides, rather than thyroid hormone per se, but again definitive evidence to support this strategy is lacking.

The adrenocortictrophic axis

In health, corticotrophin-releasing hormone (CRH) from the paraventricular nucleus is carried in the hypophyseal-portal tract and stimulates release of adrenocorticotrophic hormone (ATCH). Cortisol is produced in the zona fasiculata of the adrenal cortex and a negative feedback loop exists to regulate secretion and synthesis.

Acute critical illness

Plasma ACTH and cortisol levels increase with loss of the normal circadian rhythm. The hypothalamus is stimulated by a direct effect of cytokines. The typical effects of glucocorticoids are manifest in order to maintain homeostasis after the stressful insult. These include use of alternative energy strategies, such as mobilization of amino acids from extrahepatic tissues, lipolysis, and subsequent utilization of glycerol, and gluconeogenesis in the liver. They have a regulatory role in the acute inflammatory response, by blocking cytokine gene expression and up-regulating specific anti-inflammatory processes. The cardiovascular effects of glucocorticoids include the maintenance of vascular responsiveness to catecholamines, endothelial integrity, and intravascular volume via their mineralocorticoid actions [7]. These anti-inflammatory and vascular effects explain the biological rationale for the use of low-dose corticosteroids in septic shock [8].

Prolonged critical illness

When critical illness is protracted, plasma cortisol levels remain high, but ACTH decreases. It is likely that this effect is mediated via peripheral mechanisms, such as substance P, atrial natriuretic peptide, endothelin, and cytokines. The adverse effects of sustained hypercortisolism, such as muscle wasting, hyperglycaemia, hypokalaemia, poor wound healing, and psychiatric sequelae become apparent and can be seen as a maladaptive response [9,10].

Sex hormones and prolactin

In health gonadotrophin-releasing hormone (GNRH) is secreted in a pulsatile pattern and stimulates the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the gonadotroph cells. In males, LH drives testosterone production in the Leydig cells of the testes

In the acute phase of critical illness, serum testosterone levels are low (in spite of elevated LH levels) and prolactin is high. Low testosterone switches off the anabolic processes that maintain skeletal muscle mass. High oestradiol levels are found—an adaptation that was originally thought to be beneficial as oestrogens inhibit pro-inflammatory cytokine production. Recent findings appear to contradict this and there is an association with increased mortality [11].

In prolonged critical illness there is a state of hypogonadal hypogonadism and prolactin deficiency. T- and B-lymphocytes possess prolactin receptors, requiring it for their function. Hypoprolactinaemia may play a role in the immune paralysis seen in illnesses of longer duration. The use of exogenous dopamine could theoretically suppress prolactin secretion and negatively impact immune function. Despite these concerns and a higher incidence of adverse events in shocked patients treated with dopamine, the evidence falls short of it having an adverse impact on mortality [12].

The role of the autonomic nervous system

The classical 'fight or flight' response is mediated via adrenaline and noradrenaline. A variety of physiological insults, such as pain, hypotension, hypoxia, acidosis, and hypercarbia can stimulate the sympathetic nervous system. Pre-ganglionic sympathetic fibres terminate in the adrenal medulla and cathecholamines are released rapidly from synaptic vesicles. The leukocyte itself can be an additional source of cathecholamines.

Cardiovascular responses occur via B1 receptors and include positive inotropy and chronotropy. Stimulation of the renin-angiotensoin system at the juxta-glomerular cells acts to maintain intravascular volume and tone. B2 receptor activation results in gluconeogensesis and glycongenolysis. B2 stimulation dampens the pro-inflammatory cytokine response and in sepsis it alters the balance of T helper cells from THC1 to THC2. Some regulation also occurs via α-receptors. Alpha-1-mediated vasconstriction acts to maintain blood pressure, but reduced gut perfusion and motility are adverse consequences discussed in 'Loss of Barrier Function'. The parasympathetic response to traumatic and infectious insults is largely anti-inflammatory and occurs through the activation of α7 nicotinic acetylcholine receptors. This acetylcholine-mediated reduction in cytokine production occurs, not only from a direct effect on macrophages, but also indirectly via vagal splenic innervation.

Vitamin D metabolism

Vitamin D deficiency is common in critical illness for two reasons:

- Vitamin D is lost through lack of serum binding proteins in acute illness.
- Many chronic conditions predisposing to critical illness will reduce sunlight exposure and thus synthesis of Vitamin D in the skin.

The clinical consequences of Vitamin D deficiency are bone resorption, hypercalcaemic immune dysfunction, namely reduced innate responses and heightened adaptive responses, such as prolonged hypercytokinaemia [13].

The role of cytokines

Cytokines are intercellular messenger proteins that act on various cell types to bring about pro- and anti-inflammatory responses

during critical illness. They can have local (autocrine or paracrine) or widespread (endocrine) effects.

Cytokines are produced via stimulation of Toll-like receptors (TLRs), which may be a future pharmacological target. At the cellular level, TLRs are activated not only by the presence of microbial proteins as part of the innate immune response, but also by non-infectious insults, such as tissue injury. Here, endogenous intracellular proteins released from dying cells are the trigger, and are known as 'alarmins'. The cell surface TLRs initiate the nuclear factor kappa-beta (NF-κβ) transcription pathway, which ultimately generates cytokine proteins. Note that some cytokines can be released more readily in response to catecholamines with no requirement for gene transcription. Tumour necrosis factor α (TNFα) has a positive effect on NF-κβ and is responsible for triggering further cytokine release, in what is described clinically as the 'cytokine storm'.

There are several cytokine families (Table 202.1) including the interleukins, interferons, tumour necrosis factors, chemokines, and colony-stimulating factors. Burns, tissue trauma, or infection results in a cascade of pro-inflammatory cytokines, of which the key players are TNFα, IL-1, IL-6, and IL-8. Levels of these cytokines correlate with illness severity and outcome. Cytokine gene polymorphisms and aberrant responses to TLR ligands are partly accountable for the individual response to sepsis and other insults. However, despite the wealth of research in this area, modulation of interleukins and TNFα with recombinant pharmacological agents has not been widely successful.

Table 202.1 Effects of cytokines in the inflammatory process

Cytokine	Effects
TNFα	◆ Rises early in response to sepsis and trauma ◆ Activates HPA axis ◆ Induces fever and increases insulin resistance ◆ Major trigger for other cytokine release (IL-1 and IL-6) ◆ Promotes phagocytosis and neutrophil chemotaxis
IL-1	◆ Fever ◆ T cell activation and B cell proliferation ◆ Activates HPA axis and suppresses anabolic activity
IL-6	◆ Major activator of acute phase protein synthesis ◆ B and T cell differentiation
IL-8	Neutrophil chemotaxis and activation
HMGB1	◆ Multiple effects including acting as an alarmin and cytokine ◆ Can be induced via NF-κβ and cell death ◆ Therefore, an initiator and effector of the inflammatory response ◆ Role in vascular endothelium and enterocyte permeability
Macrophage migration inhibitory factor (MIF)	◆ Key link between immune and endocrine system ◆ Expressed by leucocytes and stored intracellularly unlike other cytokines ◆ Secreted by HPA axis in response to stress or infection ◆ Antagonizes the immunosuppressive actions of endogenous steroids

Pathophysiology of the gastrointestinal tract in critical illness

The normal functions of the gastrointestinal (GI) tract extend beyond digestion, absorption, and elimination. Important immune and metabolic functions are performed by the gut, and crucially it forms a barrier between bacteria in the intestinal lumen and the sterile internal milieu.

The GI dysfunction associated with critical illness has been poorly defined and lacked universal terminology until recently [14]. A number of clinical manifestations of GI dysfunction are recognized, including stress ulceration, gastro-oesophageal reflux, intolerance of enteral nutrition, ileus, acalculous cholecystitis, abdominal compartment syndrome, intestinal ischaemia, and gastrointestinal hypermotility.

The pathophysiology of these well recognized clinical phenomena can be explained by the complex interplay between the epithelium, commensal bacteria, and the mucosal immune system [15]. The gut has been described as the 'motor' of multi-organ dysfunction syndrome and a number of key factors in its response to critical illness reinforce that status as a driver of systemic inflammation.

Loss of barrier function

Although perfusion of the gut is autoregulated, the gastrointestinal epithelium is predisposed to ischaemia for anatomical reasons. Macroscopically, endogenous cathecholamines acting on alpha-receptors constrict the splanchic circulation. Arginine vasopressin and angiotensin also contribute to this non-occlusive ischaemia. The small bowel is particularly prone to this.

Microscopically, the mucosa at the tips of the villi are most at risk of hypoxia. A countercurrent blood supply to the metabolically active villus via a central arteriole and network of venules renders it extremely supply dependent. The damaged enterocytes slough off and permit translocation of endotoxins and bacteria. In addition, ischaemia-reperfusion injury and oxidant stress are likely to further exacerbate mucosal injury.

Even in the absence of epithelial cell death, the barrier function of the intestine can be lost through disruption of cellular tight junctions. This paracellular route is another way in which endotoxin and bacteria may enter the circulation or lymphactics, resulting in sepsis or the systemic inflammatory response syndrome. Cytokines are likely to be responsible, with IL-4, interferon-gamma and HMGB-1 being implicated.

Alteration of gut microflora in critical illness can also compromise intestinal barrier function [16]. This shift from commensal bacteria to pathogenic strains can occur as a result of antibiotic use, acid suppression or the illness itself. It is likely that commensal Gram-negative anaerobes provide protection to the mucosa through promotion of mucosal repair, increased mucus production and the induction of selective bactericidal proteins, which preferentially target Gram-positive pathogens.

In the stomach, stress ulceration may be regarded as loss of barrier function and classically affects the gastric fundus. Reduced mucosal prostaglandin synthesis and lower secretion of bicarbonate-rich

mucus by goblet cells is implicated. In fact, gastric acid secretion may not be increased at all in critical illness [17].

Motility disturbances

Up to 50% of critically-ill patients suffer from gastrointestinal motility disorders, the adverse consequences of which include inadequate nutrition and aspiration of gastric contents. Common factors contribute to this problem, including electrolyte imbalance, gut oedema and drugs used in intensive care such as opioids, synthetic cathecholamines and alpha-2 agonists [18]. Although, the contribution of deranged physiology is significant.

Gastrointestinal motility in health is regulated via neural and hormonal mechanisms. Cholecystokinin (CCK), a peptide hormone that normally inhibits gastric emptying, is found at higher levels in critical illness. Peptide YY may also have a role in slowing gastric emptying and small intestine transit in these patients. Neither of these hormones has been exploited pharmacologically in clinical settings, although a CCK anatagonist does exist.

In contrast, motilin and ghrelin act to accelerate gastric emptying, but ghrelin levels are reduced in early critical illness by up to 50%. Erythromycin is a drug with agonist activity at the motilin receptor, hence the rationale for using it to treat feed intolerance. Ghrelin agonists have potential use in the treatment of gastroparesis and appetite stimulation. They may also have a wider role as ghrelin is an endogenous ligand of the GH secretagogue receptor and theoretically could reverse the catabolic state and negative nitrogen balance described previously. In summary, the gut hormone response can be considered like any other endocrine organ dysfunction in the critically ill [19].

The enteric nervous system of the gut contains the largest amount of neuronal cells outside the central nervous system. The myenteric plexus regulates motility while the submucous plexus controls secretory functions and blood flow. The migrating motility complex (MMC) is the collective term for the three phases of motility seen in the small bowel *between* meals, also known as the 'interdigestive' pattern. It has a cleansing effect, sweeping gastrointestinal debris into the colon, but is rendered defective during acute illness and contributes to ileus. The usual 'digestive' motility pattern occurs **after** a meal producing segmentation of the bowel and peristalsis. In critical illness it can be abnormally increased and promotes diarrhoea. Local and systemic factors essentially produce an imbalance between sympathetic and parasympathetic motor inputs as the single common pathway for these clinical manifestations.

References

1. Elijah I, Branski L, Finnerty C, and Herndon D. (2011). The GH/IGF-1 system in critical illness. *Best Practice & Research Clinical Endocrinology & Metabolism*, **25**,759–67.
2. Van den Berghe G. (2002). Dynamic neuroendocrine responses to critical illness. *Frontiers in Neuroendocrinology*, **23**, 370–91.
3. Economidou F, Douka E, Tzanela M, et al. (2011). Thyroid function during critical illness. *Hormones*, **10**, 117–24.
4. Mebis L and Van den Berghe G. (2011). Thyroid axis function and dysfunction in critical illness. *Best Practice & Research Clinical Endocrinology & Metabolism*, **25**, 745–57.
5. Bello G, Pennisi M, Montini L, et al. (2009). Nonthyroidal illness syndrome and prolonged mechanical ventilation in patients admitted to the ICU. *CHEST Journal*, **135**, 1448–54.
6. Mebis L and Van den Berghe G. (2009). The hypothalamus-pituitary-thyroid axis in critical illness. *Netherlands Journal of Medicine*, **67**, 332–40.
7. Venkatesh B and Cohen J. (2011). Adrenocortical (dys) function in septic shock-A sick euadrenal state. *Best Practice & Research Clinical Endocrinology & Metabolism*, **25**, 719–33.
8. Annane D. (2011). Corticosteroids for severe sepsis: an evidence-based guide for physicians. *Annals of Intensive Care*, **1**, 1–7.
9. Vanhorebeek I and Van den Berghe G. (2006). The neuroendocrine response to critical illness is a dynamic process. *Critical Care Clinics*, **22**, 1.
10. Gibson S, Hartman D, and Schenck J. (2005). The endocrine response to critical illness: update and implications for emergency medicine. *Emergency Medicine Clinics of North America*, **23**, 909–30.
11. Kauffmann R, Norris P, Jenkins J, et al. (2011). Trends in estradiol during critical illness are associated with mortality independent of admission estradiol. *Journal of the American College of Surgeons*, **212**, 703–12.
12. De Backer D, Biston P, Devriendt J, et al. (2010). Comparison of dopamine and norepinephrine in the treatment of shock. *New England Journal of Medicine*, **362**, 779–89.
13. Lee P. (2011). Vitamin D metabolism and deficiency in critical illness. *Best Practice & Research Clinical Endocrinology & Metabolism*, **25**, 769–81.
14. Reintam Blaser A, Malbrain MN, Starkopf J, et al. (2012). Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. *Intensive Care Medicine*, 1–11.
15. Clark J and Coopersmith C. (2007). Intestinal crosstalk-a new paradigm for understanding the gut as the 'motor' of critical illness. *Shock*, **28**, 384.
16. Balzan S, De Almeida Quadros C, De Cleva R, Zilberstein B, and Cecconello I. (2007). Bacterial translocation: overview of mechanisms and clinical impact. *Journal of Gastroenterology and Hepatology*, **22**, 464–71.
17. Stannard V, Hutchinson A, Morris D, and Byrne A. (1988). Gastric exocrine 'failure' in critically ill patients: incidence and associated features. *British Medical Journal*, **296**, 155.
18. Fruhwald S, Holzer P, and Metzler H. (2007). Intestinal motility disturbances in intensive care patients pathogenesis and clinical impact. *Intensive Care Medicine*, **33**, 36–44.
19. Deane A, Chapman M, Fraser R, and Horowitz M. (2010). Bench-to-bedside review: The gut as an endocrine organ in the critically ill. *Critical Care*, **14**, 228.

PART 7.2

Nutritional failure

CHAPTER 203

Pathophysiology of nutritional failure in the critically ill

Jan Wernerman

Key points

- There is no evidence supporting nutritional supply of calories in excess of energy expenditure in critical illness.
- Early enteral nutrition in critical illness is associated with more favourable outcomes.
- In the acute phase of critical illness parenteral nutritional supplementation is not evidence based.
- The exact time-point when full nutrition should be provided in critical illness is based on individual factors, and not well defined.
- The optimal protein nutrition in critical illness remains to be established.

Background

Nutritional failure in critical illness is poorly defined. The term nutritional failure implies there is a definition of correct nutrition. This is not the case. At best, we know the energy expenditure of the patient together with whole body balance of a number of substances and nutrients. Nevertheless, optimal nutrition should be a part of optimal medical care of the critically-ill patient. There is considerable evidence that nutritional care and metabolic care makes a difference [1]. This is particularly true for overweight and underweight patients, while normally-fed patients have a larger safety margin [2].

There is a dogma that critically-ill patients should be in a positive energy balance. In current guidelines this results in recommendations of 20–25–30 kcal/kg/day [3–5]. The background is not survival advantage demonstrated by randomized controlled trials, but rather studies of nitrogen balances, where whole-body nitrogen economy is more favourable when patients are in a positive energy balance [6]. This concept has historically led to massive overfeeding, which has repeatedly been demonstrated to be harmful for critically-ill patients [1,7,8].

Overall, two extrapolations that are not validated to be true, are commonly used in guidelines for critically-ill patients:

- Findings from post-operative patients have been thought to be valid for all critically-ill patients.
- Measurements and observations made at times not related to the admission to the ICU.

This is particularly troublesome as most post-operative patients have quite different characteristics compared with patients with septic shock, with multi-organ failure, or with mechanical ventilation. Similarly, the time course for an individual patient may change rather dramatically in terms of energy expenditure during a prolonged period of critical illness.

Optimal energy supply

Measurement of energy expenditure by the use of indirect calorimetry has been used for many years. The technique is not easy to use and the availability of indirect calorimetry for critically-ill patients is often limited. Still the most important question is if actual energy expenditure should be the nutritional target calorie-wise? There is limited literature indicating that feeding in excess of energy expenditure is not a very good idea during critical illness. A pilot study with daily measurements of energy expenditure gave a signal of better outcomes compared with protocolized energy intake [9]. In the classic study by Krishnan et al., 33–67% of an arbitrary energy target of 27 kcal/kg/day (9–18 kcal/kg/day) was associated with a better outcome than 67–100% [8]. Another study demonstrated an advantage in hospital mortality when permissive hypocaloric feeding was employed and 58% of an energy target of 20–25 kcal/kg/day was compared with 71% of the energy target among the controls [10]. None of these studies properly characterized the temporal relation to ICU admission. The EPaNIC study suggests delayed parenteral nutritional supplementation shortens ICU stay and prevents infections [1]. In another classic study, Sandström et al. demonstrated full parenteral nutrition following elective surgery is a disadvantage, while parenteral nutrition may be an advantage for patients developing post-operative complications [11]. Again, in this study, the temporal relationship of extraparenteral nutrition to the course of critical illness was not well defined.

Underfeeding

In epidemiology, malnutrition is strongly associated with an unfavourable outcome. This is true also in critical illness, where the highest mortality is seen in the cohort of patients with a BMI < 20 [2,12]. The possible benefit of nutritional support in this high risk group of patients is not very strong. Observational data indicate an advantage, but again the relation between admission and treatment has been poorly characterized. Within the EPaNIC study patients with BMI < 17 were excluded, although patients with BMI > 17, but with a high nutritional risk score [13], did not benefit from early parenteral nutrition supplementation [1]. This is clearly an

area where more evidence is badly needed, as depleted underweight patients with limited physiological reserve are very vulnerable. Optimal nutrition is therefore particularly important for these patients.

Overfeeding

A caloric surplus above energy expenditure leads to fat accumulation and is well characterized in healthy individuals, as well as in critical illness [7]. The crucial question is if a marginal surplus of calories is a disadvantage as compared with hypocaloric feeding? It is probably important to differentiate between the acute phase of critical illness and the chronic phase. Indirect evidence suggests marginal overfeeding is harmful, particularly in the early phase of critical illness [1,8,10]. The positive results obtained when employing early enteral nutrition [14] may be interpreted as a beneficial effect, directly related to nutrition in the gut at an early time-point. An alternative interpretation of the results is that tolerance of early enteral nutrition selects patients with sufficient reserve to tolerate feeding in the early phase of critical illness. As success rate of enteral feeding will always have a large scatter, these questions of interpretation will always remain.

A mechanistic hypothesis concerning the harmful effects of full feeding in the early phase of critical illness is the inhibited autophagy as a result of feeding. Autophagy represents the necessary turnover of cellular structures and body proteins. Insufficient autophagy is frequently seen in muscle and liver tissue of critically-ill patients and proteins that are normally eliminated by autophagy are accumulated [15]. Early feeding and insulin therapy are potent inhibitors of autophagy [16], while blood sugar control offers a possibility to eliminate the inhibition. More research to clarify the mechanisms behind the negative effects of marginal overfeeding during the early phase of critical illness is needed.

Optimal protein supply

Available evidence concerning the protein or amino acid requirements of ICU patients is sparse and not very recent [6,17]. In summary, an amino acid supply of more than 0.2 g nitrogen/kg/day does not improve nitrogen balance if the energy provided is on the level of energy expenditure. Techniques to estimate whole-body protein content have insufficient precision and proxy measures, such as nitrogen balance or protein turnover, are not always easy to interpret [18]. The obvious increased losses associated with continuous renal replacement therapy have attained special interest [19]. This group of patients in the ICU are at particular risk to be under-fed in terms of proteins and/or amino acids.

Several authors who have reviewed this area recently recommend not less than 1.5 g of protein/kg/day for critically-ill patients [20], which is more than what is usually given today. However, the shortage of solid evidence and the poorly-understood underlying mechanisms regulating protein economy in critical illness are underlined.

Conclusion

Nutritional failure implies there may be a concept of correct or optimal nutrition. Today sufficient knowledge is not at hand to define such optimal nutrition in critical illness. Over time in longstanding critical illness malnutrition develops, which may be attenuated or delayed by nutrition therapy. On the other hand, overfeeding in the very early phase of critical illness may be detrimental for the patient. Knowledge is particularly sparse concerning the optimal protein intake during critical illness.

References

1. Casaer MP, Mesotten D, Hermans G, et al. (2011). Early versus late parenteral nutrition in critically ill adults. *New England Journal of Medicine*, **365**(6), 506–17.
2. Alberda C, Gramlich L, Jones N, et al. (2009). The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Medicine*, **35**(10), 1728–37.
3. Kreymann KG, Berger MM, Deutz NE, et al. (2006). ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clinical Nutrition*, **25**(2), 210–23.
4. McClave SA, Martindale RG, Vanek VW, et al. (2009). Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *Journal of Parenteral and Enteral Nutrition*, **33**(3), 277–316.
5. Singer P, Berger MM, Van den Berghe G, et al. (2009). ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clinical Nutrition*, **28**(4), 387–400.
6. Larsson J, Lennmarken C, Martensson J, Sandstedt S, and Vinnars E. (1990). Nitrogen requirements in severely injured patients. *British Journal of Surgery*, **77**(4), 413–16.
7. (1991). Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. *New England Journal of Medicine*, **325**(8), 525–32.
8. Krishnan JA, Parce PB, Martinez A, Diette GB, and Brower RG. (2003). Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. *Chest*, **124**(1), 297–305.
9. Singer P, Anbar R, Cohen J, et al. (2011). The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Medicine*, **37**(4), 601–9.
10. Arabi YM, Tamim HM, Dhar GS, et al. (2011). Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. *American Journal of Clinical Nutrition*, **93**(3), 569–77.
11. Sandstrom R, Drott C, Hyltander A, et al. (1993). The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. *Annals of Surgery*, **217**(2), 185–95.
12. Gupta R, Knobel D, Gunabushanam V, et al. (2011). The effect of low body mass index on outcome in critically ill surgical patients. *Nutrition in Clinical Practice*, **26**(5), 593–97.
13. Kondrup J, Allison SP, Elia M, Vellas B, and Plauth M. (2003). ESPEN guidelines for nutrition screening 2002. *Clinical Nutrition*, **22**(4), 415–21.
14. Doig GS, Heighes PT, Simpson F, Sweetman EA, and Davies AR. (2009). Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. *Intensive Care Medicine*, **35**(12), 2018–27.
15. Vanhorebeek I, Gunst J, Derde S, et al. (2011). Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. *Journal of Clinical Endocrinology & Metabolism*, **96**(4), E633–45.
16. Klionsky DJ. (2007). Autophagy: from phenomenology to molecular understanding in less than a decade. *Nature Reviews Molecular Cell Biology*, **8**(11), 931–7.
17. Pitkanen O, Takala J, Poyhonen M, and Kari A. (1991). Nitrogen and energy balance in septic and injured intensive care patients: response to parenteral nutrition. *Clinical Nutrition*, **10**(5), 258–65.

18. Ishibashi N, Plank LD, Sando K, and Hill GL. (1998). Optimal protein requirements during the first 2 weeks after the onset of critical illness. *Critical Care Medicine*, **26**(9), 1529–35.
19. Bellomo R, Seacombe J, Daskalakis M, et al. (1997). A prospective comparative study of moderate versus high protein intake for critically ill patients with acute renal failure. *Renal Failure*, **19**(1), 111–20.
20. Sauerwein HP and Serlie MJ. (2010). Optimal nutrition and its potential effect on survival in critically ill patients. *Netherlands Journal of Medicine*, **68**(3), 119–22.

CHAPTER 204

Assessing nutritional status in the ICU

Pierre-Yves Egreteau and Jean-Michel Boles

Key points

- All the traditional markers of malnutrition lose their specificity in the sick adult as each may be affected by a number of non-nutritional factors.
- Nutritional assessment is required for patients presenting with clinical evidence of malnutrition, patients with chronic diseases, patients with acute conditions accompanied by a high catabolic rate, and elderly patients.
- The initial nutritional status and the extent of the disease-related catabolism are the main risk factors for nutrition related complications.
- Muscle function evaluated by hand-grip strength and serum albumin provide an objective risk assessment. Calculating a nutritional index is helpful in subsets of patients to determine complication risk and the need for nutritional support.
- A strong suspicion remains the best way of uncovering potentially harmful nutritional deficiencies.

Introduction

Normal nutritional status is a key element in the ability to overcome critical illness. Normal body composition and function are maintained in adults by a daily diet providing nutrients meeting the needs of the individual.

Why assess nutritional status?

Nutrition and disease interact in several ways. Decreased nutrient intake, increased body requirements, and/or altered nutrient utilization are frequently combined in critically-ill patients. The frequency of malnutrition in hospital in-patients has been estimated to be between 30 and 50% of both medical and surgical patients.

There is an established relationship between initial nutritional status and in-hospital morbidity and mortality [1]. Many complications are related to protein energy malnutrition (PEM): increased nosocomial infection rates due to diminished immune competence, delayed wound healing due to decreased ability to repair tissue, delayed weaning from mechanical ventilation due to altered vital functions, and frequent depression and psychological disturbances.

Assessing nutritional status pursues several goals—determination of nutritional deficiencies and evaluation of risk factors of nutrition-related complications that could affect patient outcome, evaluation of the need and potential value of nutritional support, and monitoring the efficacy of and therapeutic response to nutritional support, including tolerance.

An international committee proposed a nomenclature based on recognition of acute systemic inflammatory response [2]. The aetiology-based malnutrition definitions include 'starvation-associated malnutrition':

- When there is chronic starvation without inflammation.
- 'Chronic disease-associated malnutrition', when inflammation is chronic and of mild to moderate degree.
- 'Acute disease or injury-related malnutrition', when inflammation is acute and of severe degree [3,4].

Which patients should be assessed?

Obviously, patients with apparently normal physical build, normal diet intake, and no reason for significant increased nutrient requirements need no further investigation. Several subsets of patients require a more precise assessment:

- Patients presenting with clinical evidence of malnutrition (marasmus or the hypoalbuminaemic form of protein energy malnutrition or a mixed form).
- Patients with chronic disease, such as malignancy, alcoholism, organ dysfunction, particularly those undergoing treatment, which impairs nutrient absorption and/or utilization.
- Patients with acute conditions accompanied by a high catabolic rate, such as severe sepsis, trauma, or burns, and emergency surgery.
- **Elderly patients**: ageing is associated with a physiological anorexia, and poor dentition, economic problems, and chronic illness affect nutritional status.

How can nutritional status be assessed?

Nutritional assessment should include assessment of body composition, the presence and duration of inadequate nutrient intake, and the degree and duration of metabolic stress. The main markers of nutritional assessment in healthy adults are shown in Table 204.1. All the current criteria for objective evidence of malnutrition are non-specifically affected by many diseases and are subject to wide errors; also, disease and inactivity alone can result in the same effects as malnutrition.

Table 204.1 Markers of nutritional assessment

Anthropometric measurements	Body mass (usual, actual, ideal)	Female	19–25	Male
	BMI = BM/H^2 (kg/m^2)	16.5		12.5
	Mid-arm circumference (mid-AC) (cm)	28.5		29.3
	Triceps skinfold thickness (TSF) (mm)	23.2		25.3
	Mid-arm muscle circumference (MAMC)			
	MAMC = mid-AC – (0.314 × TSF)			
Biological tests	Plasma proteins	Normal values	23 ± 7.10^{-3}	Half-life (days)
	Albumin (g/L)	40 ± 5		21
	Transferrin (g/L)	2.8 ± 0.3		10
	Prealbumin (TTr) (mg/L)	307 ± 36		2
	Retinol-binding protein (mg/L)	62 ± 7		0.5
	IGF1	Female 18		0.08–0.16
	Urinary index			Male 23
	Creatinine height index (mg/kg ideal body weight)			
	Urinary 3 methyl histidine/urinary creatinine			
Muscle function testing	◆ Hand-grip strength			
	◆ Force-frequency curve and relaxation rate of the adductor pollicis muscle			
History	◆ Usual nutritional intake			
	◆ Impossibility of oral intake			
	◆ Physical and mental capacities			
Body composition	◆ Bioelectrical impedance analysis			
	◆ Ultrasound, CT, MRI, X-Ray absorptiometry, isotopic evaluation			

In current practice, a comprehensive assessment of nutritional status relies on a step-by-step clinically based approach and cautious interpretation of measurements and results.

Clinical assessment

Recording the patient's history and physical examination is the first stage of nutritional assessment.

History

The history includes dietary habits, nutrient intake, and interference between nutrition and the disease process itself. The latter may be responsible for either inadequate intake or excessive losses.

Physical examination

Signs of nutritional deficiency, such as muscle wasting, loss of subcutaneous fat, skin rashes, hair thinning, oedema, ascites, fingernail abnormalities, such as koilonychia, glossitis, and other mucosal lesions, should be sought. Particular signs of specific nutrient deficiencies may also be observed.

Estimation of weight loss

A loss of 10% of the usual body weight over a 6-month period or 5% over a 1-month period are indicative of a compromised nutritional status. Weight and weight variations do not reflect nutritional status or nutritional support efficacy when oedema or dehydration are or have been present.

Other anthropometric measurements

Anthropometric measurements must be interpreted with care as they may be affected by non-nutritional factors. Bed-ridden patients will lose muscle mass without malnutrition.

Measurements include weight, height, and body mass index (BMI) and mid-arm circumference (mid-AC) and triceps skinfold thickness (TSF) of the non-dominant side measured with a skin caliper. Mid-arm muscle circumference (MAMC), which is calculated from the preceding two measures, reflects skeletal muscle. TSF reflects fat stores. Mid-AC < 15th percentile defines serious malnutrition and predicts a high mortality and complication rate in critical patients [5]. High coefficients of variation between observers suggest that measurements should always be recorded by the same observer. These measurements are of no value in cases of subcutaneous emphysema or generalized oedema. Because of slow variations, they cannot be used to evaluate nutritional support efficacy.

Functional tests

Functional changes, such as a reduction in muscle power due to reduced nutrient intake, occur long before demonstrable anthropometric changes and are better predictors of complications than other anthropometric measurements (6,7). Muscle function can be considered as a specific measure of the effect of nutrient inadequate intake and refeeding. Two methods can be used in critically-ill patients.

- **Assessment of hand-grip strength** (of the non-dominant side) with a hand-grip dynamometer is reserved for co-operative patients: it has been shown to correlate with MAMC and to be the most sensitive test for predicting postoperative complications [6].
- **Measurement of the contraction of the adductor pollicis muscle** in response to an electrical ulnar nerve stimulation at the wrist can be performed in unconscious patients. The combination of an abnormal force–frequency curve and a slow relaxation rate is the

most specific and sensitive predictor of nutritionally-associated complications in surgical patients [7].

Plasma proteins

Plasma proteins reflect the visceral protein mass. They include albumin, transferrin, thyroxin-binding pre-albumin, and in patients with normal kidney function, retinol-binding protein.

Serum albumin level is the most widely used measure of plasma proteins in nutritional assessment. A fall in albumin level reflects more the severity and duration of the metabolic stress than the nutritional status itself. Sensitivity to predicting complications is better when measurements of serum albumin and transferrin are combined. Although dependent on the iron status, transferrin has a better response than albumin to nutritional repletion.

Transthyretin (TTr, called prealbumin or thyroxin-binding pre-albumin), retinol-binding protein or insulin-like growth factor 1 (IGF1), are particularly useful for following the efficacy of nutritional support [8].

Creatinine height index

The daily urinary creatinine excretion is correlated with the lean body mass. Averaged over three consecutive days, it is matched with normal controls for sex and height. Creatinine Height Index (CHI) is a reliable index of muscle mass in patients without renal failure or rhabdomyolysis.

Urinary 3 methyl-histidine also reflects muscular catabolism. Repeated measurements allow an evaluation of therapeutic response.

Immune competence

Cellular immunity is the most sensitive component of malnutrition, but reduced immune competence is not specific of malnutrition, thus making it a poor predictor of such a state in sick patients.

Subjective global assessment

Subjective global assessment (SGA) is based on history and physical examination of the patient.

- **Weight change**: loss in past 6 months, and change in past 2 weeks (in the case of recent weight gain, previous loss is not considered).
- **Dietary intake**: no change or suboptimal intake, liquid diet, or hypocaloric fluids or starvation.
- **Gastrointestinal symptoms** for more than 2 weeks (none, anorexia and nausea, vomiting, diarrhoea).
- **Functional capacity**: normal, suboptimal work, ambulatory, or bedridden.
- **Stress**: none, minimal, or high.
- **Physical signs**: loss of subcutaneous fat, muscle wasting, fluid retention, or mucosal lesions suggestive of deficiency.

The patient is classified into one of three classes.

- **Well nourished**: no or minimal restriction of food intake and/or absorption with minimal change in function and body weight.
- **Moderate malnutrition**: clear evidence of food restriction with functional changes but little evidence of any changes in body mass.
- **Severe malnutrition**: changes in both food intake and body mass with poor function.

In a critically-ill population, SGA is a reliable, easy to handle and reproducible method of nutrition assessment [9].

Nutritional indices

Several nutritional indices have been developed using mathematical and statistical methods to identify patients at risk of nutritionally-mediated complications. These indices were designed and generally validated in specific groups of patients, usually cancer or surgery.

The most widely studied is the Prognostic Nutritional Index (PNI) calculated from albumin, TSF, transferrin, and evaluation of delayed hypersensitivity reactivity. This equation correctly predicts the percentage risk of post-operative complications. Adequate nutritional support in patients with a high PNI has been shown to improve post-operative outcome [10].

The Nutritional Risk Index (NRI), using serum albumin and weight variation [11], allows identification of patients who can profit from nutrition therapy.

$$\mathrm{NRI} = [1.519 \times \mathrm{albumin(g/L)}] + (0.417 \times \%\ \text{usual body weight}) \quad \text{[eqn 1]}$$

The Pronostic Inflammatory Nutritional Index (PINI) reflects inflammation influence on plasma nutritional protein levels in critically-ill patients and discriminates risk of complications [12].

$$\mathrm{PINI} = [\mathrm{CRP\,(mg/L)} \times \mathrm{orosomucoid\ (mg/L)}] / [\mathrm{albumin\ (g/L)} \times \mathrm{TTr\ (mg/L)}]. \quad \text{[eqn 2]}$$

where CRP is C-reactive protein. Two scores associate clinical assessment and severity of disease: the Malnutrition Universal Screening Tool (MUST) [13] and the Nutritional Risk Screening tool 2002 (NRS-2002) [14]. In a study comparing NRS-2002, MUST, and the NRI to SGA, NRS-2002 was the most reliable [15].

The NUTRIC scores age, severity of disease (APACHE II, SOFA), comorbidities, days from hospital to ICU admission and serum interleukin-6. As the score increases, so does the mortality and the duration of mechanical ventilation [16].

Assessment methods of human body composition

Bioelectric impedence provides a reliable estimate of total body water, fat-free mass, and body fat in healthy individuals and in critically-injured patients. Disturbance of water distribution is frequent in critically-ill patients, making this technique irrelevant in the ICU setting [17].

Sophisticated methods measuring body composition have been developed, such as multiple isotope dilution methods, dual-photon absorption, and g-neutron activation. Because of their technical complexity, scientific limitations, and high cost, none of these methods is of clinical utility in routine critical care [17].

Computed tomography and MRI also allow for estimation of adipose tissue, skeletal muscle.

Guidelines for the assessment of nutritional status

Before initiation of nutrition, assessment of nutritional status should include evaluation of weight loss and nutrient intake before admission, level of disease severity, comorbid conditions, and function of the gastrointestinal tract [4,18,19].

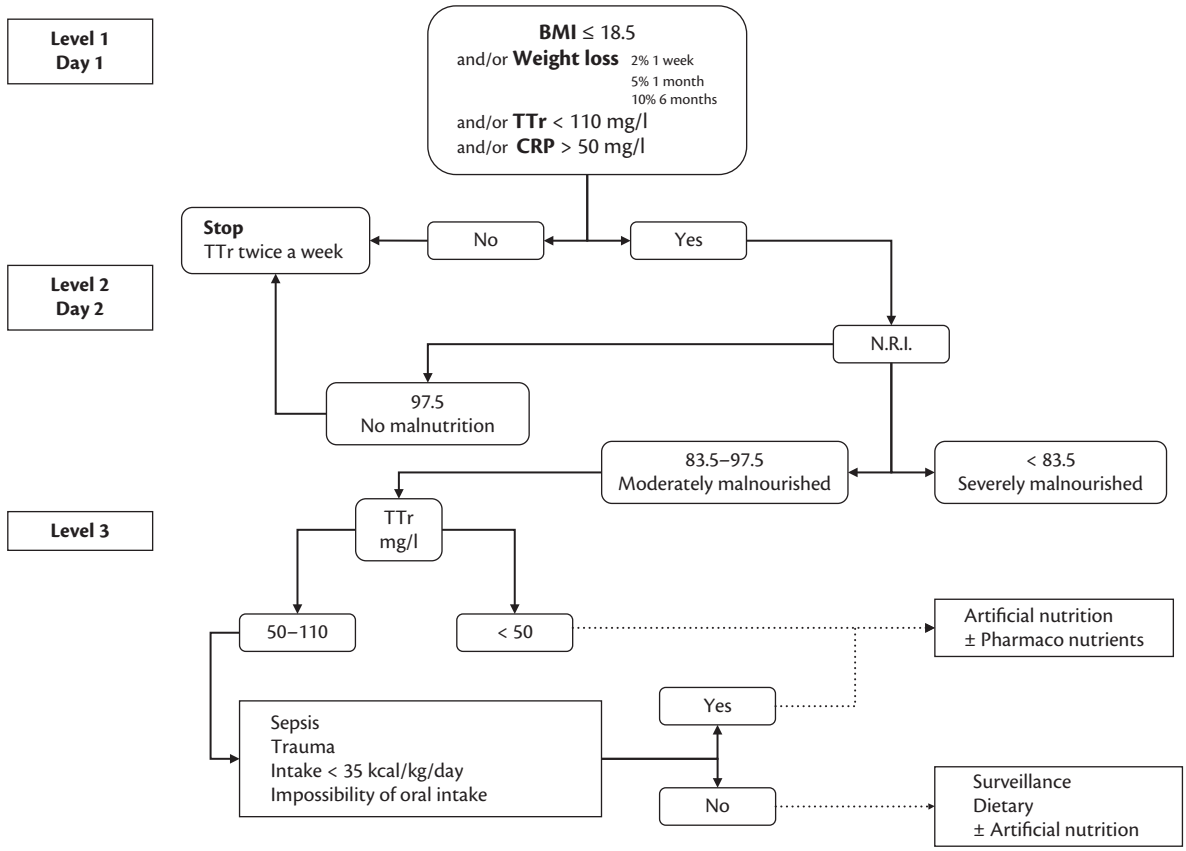


Fig. 204.1 Algorithm to screen for malnutrition.

Obese patients should be assessed similarly. Guidelines require body weight (usual, actual, and ideal) and BMI as 'vital signs'. Biomarkers of the metabolic syndrome (serum levels of triglyceride, cholesterol, and glucose) and the degree of systemic inflammatory reaction should also be assessed [20].

An algorithm to screen for malnutrition using BMI, weight loss, TTr, CRP, NRI, and critical illness severity should be performed upon admission and during the ICU stay (Fig. 204.1).

References

1. Hiesmayr M. (2012). Nutrition risk assessment in the ICU. *Current Opinion in Clinical Nutrition and Metabolic Care*, **15**(2), 174–80.
2. Jensen GL and Wheeler D. (2012). A new approach to defining and diagnosing malnutrition in adult critical illness. *Current Opinion in Critical Care*, **18**(2), 206–11.
3. Jensen GL, Mirtallo J, Compher C, et al. (2010). Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. *Clinical Nutrition*, **29**(2), 151–3.
4. White JV, Guenter P, Jensen G, Malone A, and Schofield M. (2012). Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *Journal of Parenteral and Enteral Nutrition*, **36**(3), 275–83.
5. Ravasco P, Camilo ME, Gouveia-Oliveira A, Adam S, and Brum G. (2002). A critical approach to nutritional assessment in critically ill patients. *Clinical Nutrition*, **21**(1), 73–7.
6. Klidjian AM, Foster KJ, Kammerling RM, Cooper A, and Karran SJ. (1980). Relation of anthropometric and dynamometric variables to serious postoperative complications. *British Medical Journal*, **281**(6245), 899–901.
7. Zeiderman MR and McMahon MJ. (1989). The role of objective measurement of skeletal muscle function in the pre-operative patient. *Clinical Nutrition*, **8**(3), 161–6.
8. Raguso CA, Dupertuis YM, and Pichard C. (2003).The role of visceral proteins in the nutritional assessment of intensive care unit patients. *Current Opinion in Clinical Nutrition and Metabolic Care*, **6**(2), 211–16.
9. Sheean PM, Peterson SJ, Gurka DP, and Braunschweig CA. (2010). Nutrition assessment: the reproducibility of subjective global assessment in patients requiring mechanical ventilation. *European Journal of Clinical Nutrition*, **64**(11), 1358–64.
10. Buzby GP, Mullen JL, Matthews DC, Hobbs CL, and Rosato EF. (1980). Prognostic nutritional index in gastrointestinal surgery. *American Journal of Surgery*, **139**(1), 160–7.
11. Buzby GP, Knox LS, Crosby LO, et al. (1988). Study protocol: a randomized clinical trial of total parenteral nutrition in malnourished surgical patients. *American Journal of Clinical Nutrition*, **47**(2 Suppl.), 366–81.
12. Ingenbleek Y and Carpentier YA. (1985). A prognostic inflammatory and nutritional index scoring critically ill patients. *International Journal for Vitamin and Nutrition Research*, **55**(1), 91–101.
13. Malnutition Advisory Group (2000). In: Elia M (ed.) Guidelines for the Detection and Management of Malnutrition. A report by the Malnutrition Advisory Group, a standing committee of the British Association for Parenteral and Enteral Nutrition, Proceedings of a Consensus Conference, organized by BAPEN.
14. Kondrup J, Allison SP, Elia M, Vellas B, and Plauth M. (2003). ESPEN guidelines for nutrition screening 2002. *Clinical Nutrition*, **22**(4), 415–21.
15. Kyle UG, Kossovsky MP, Karsegard VL, and Pichard C. (2006). Comparison of tools for nutritional assessment and screening at hospital admission: a population study. *Clinical Nutrition*, **25**(3), 409–17.

16. Heyland DK, Dhaliwal R, Jiang X, and Day AG. (2011). Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Critical Care*, **15**(6), R268.
17. Lee SY and Gallagher D. (2008). Assessment methods in human body composition. *Current Opinion in Clinical Nutrition and Metabolic Care*, **11**(5), 566–72.
18. Kreymann KG, Berger MM, Deutz NE, et al. (2006). ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clinical Nutrition*, **25**(2), 210–23.
19. Martindale RG, McClave SA, Vanek VW, et al. (2009). Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: Executive Summary. *Critical Care Medicine*, **37**(5), 1757–61.
20. McClave SA, Kushner R, Van Way CW, et al. (2011). Nutrition therapy of the severely obese, critically ill patient: summation of conclusions and recommendations. *Journal of Parenteral and Enteral Nutrition*, **35**(5 Suppl.), 88S–96S.

CHAPTER 205

Indirect calorimetry in the ICU

Joseph L. Nates and Sharla K. Tajchman

Key points

- Oxygen consumption can be used to determine a patient's energy expenditure.
- Indirect calorimetry is the gold standard for determining nutrition requirements in critically-ill patients.
- Interpretation of indirect calorimetry results should be performed in conjunction with the patient's clinical condition and should take into consideration any factors that may potentially alter energy expenditure.
- Despite the potential benefits of indirect calorimetry to prevent adverse effects associated with over- and underfeeding, widespread utilization is limited due to its cost and the need for trained personnel to perform gas exchange measurements.
- Aside from nutrition purposes, indirect calorimetry can assist clinicians in weaning mechanical ventilation in patients with limited respiratory reserve and increased work of breathing.

Introduction

Despite the advancement in nutrition and medicine since Antoine Lavoisier conducted the first indirect calorimetry study over 200 years ago, the assessment of energy expenditure (EE) in critically-ill patients remains a clinical challenge. The metabolic stress response, acuity of illness, and underlying comorbidities commonly present in ICU patients yield a wide variation of unpredictable metabolic derangements that are difficult, if not impossible, to quantify. Unmet metabolic demand has deleterious consequences in critically-ill patients and accurately assessing energy expenditure throughout a patient's ICU stay is vital to optimizing care and preventing adverse outcomes.

Indirect calorimetry methodology

Calorimetry is a direct measurement of heat production and usually requires 24-hour patient isolation in a hermetically-sealed room to assess temperature change. Indirect calorimetry (ICal) quantifies the amount of heat generated by the body (or resting energy expenditure (REE)) in relation to the amount of substrate used and by-product generation. Fuel substrates (carbohydrates, protein, and lipids) are oxidized to CO_2, water, and heat in the presence of O_2. By measuring the amount of O_2 consumed (VO_2) and CO_2 produced (VCO_2), ICal can be used to calculate EE. ICal was validated using direct calorimetry and is considered to be the gold standard for determining EE in the intensive care unit (ICU).

$$O_2 + \text{substrate} \rightarrow CO_2 + H_2O + \text{heat} \qquad \text{[eqn 1]}$$

Circulatory ICal (CICal) is based on a thermodilution technique that requires the insertion of a pulmonary artery catheter to measure cardiac output and mixed venous O_2 saturation. EE is calculated using measurements taken from an arterial blood gas via the Fick method (eqn 2). Catheter and arterial cannula measurements are both instantaneous and do not allow for continuous assessment of values. While CICal can provide useful results, it is an invasive technique that requires placement of a pulmonary artery catheter that may contribute to complications. This method of calorimetry is reserved for patients who already have a catheter inserted and who are not eligible for respiratory ICal due to major air leaks or other contraindications.

Fick method for determining EE

$$\text{EE}(\text{kcal/day}) = \text{CO} \times \text{Hb}(\text{SaO}_2 \times \text{SvO}_2) \times 95.18 \qquad \text{[eqn 2]}$$

where CO is cardiac output in L/min, Hb is haemoglobin concentration in mg/L, SaO_2 is the oxygen saturation of arterial blood, and SvO_2 is the oxygen saturation of mixed venous blood.

Respiratory ICal is what most clinicians refer to as 'indirect calorimetry'. By measuring VO_2 and VCO_2 via pulmonary gas exchange, EE can be calculated using the Weir equation (eqn 3). The urinary nitrogen component (uN_2) is often omitted from EE calculations (eqn 4) as it accounts for <4% of true EE in critically-ill patients and results in <2% error in the final EE calculation. The VO_2 accounts for 70–80% and the VCO_2 for 20–30% of the equation [1,2]. The Weir equation can also facilitate the identification of the substrate that is predominantly being metabolized for fuel, although it is not commonly used in this capacity.

Weir equation

$$\text{EE}\,(\text{kcal/day}) = \left[\begin{array}{l}(\text{VO}_2 \times 3.941) + (\text{VCO}_2 \times 1.11) \\ + (\text{uN}_2 \times 2.17)\end{array}\right] \times 1440 \qquad \text{[eqn 3]}$$

Simplified Weir equation

$$\text{EE}\,(\text{kcal/day}) = \left[(\text{VO}_2 \times 3.941) + (\text{VCO}_2 \times 1.11)\right] \times 1440 \qquad \text{[eqn 4]}$$

where VO_2 and VCO_2 are both measured in L/min, uN_2 is the urinary nitrogen component measured in g/day and 1440 accounts for the number of minutes in a day.

Box 205.1 Common contraindications for performing ICal

- Mechanical ventilation with $FiO_2 \geq 0.6$.
- Mechanical ventilation with positive end expiratory pressure >12 cmH_2O.
- Hyper- or hypoventilation.
- Leak in the sampling system.
- Moisture in the system, which can affect the oxygen analyser.
- Continuous flow through the system >0 L/min during exhalation.
- Inability to collect all expiratory flow.
- Unstable inspiratory FiO_2 (>± 0.01).
- Chest tube with air leak.
- Bronchopleural fistula.
- Supplemental oxygen in spontaneously breathing patients.
- Haemodialysis in progress.
- Indirect calorimeter calibration error.

Data from Branson RD and Johannigman JA, 'The measurement of energy expenditure', *Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition*, 2004, 19, 6, pp. 622–636. Epub 2005/10/11.

ICal can be performed on mechanically-ventilated or spontaneously breathing patients. Canopies, face masks, mouthpieces, or nose pieces used to trap all gas exchange can be utilized to perform ICal in spontaneously breathing patients. Mechanical ventilators may be equipped with ICal modules to measure VO_2 and VCO_2 continuously in ventilated patients. In order to achieve the most accurate results, all patients should be screened for ICal study eligibility and only trained personnel should perform the test. Technical factors that can affect the accuracy of ICal results and are thus considered exclusion criteria for ICal are listed in Box 205.1 [3]. Many of the exclusion criteria listed can be linked to the addition or elimination of O_2 or CO_2 from the ICal study circuit, which will alter VO_2 and VCO_2 measurements. The duration of an ICal study will depend on the achievement of steady state conditions, defined as stable VO_2 and VCO_2 that vary by <10% for 5 consecutive minutes or the coefficient of variation for the two values is <5% for 5 minutes [4]. Steady state represents a period of metabolic equilibrium and ensures the reliability of the measurements obtained from the ICal study. When performed under appropriate conditions, respiratory ICal is non-invasive, reliably reproducible, and accurate. Although the use of ICal has expanded significantly over the past 25 years, its use remains limited by availability, cost, and the need for trained personnel for its correct use.

Determining energy expenditure

A patient's total daily energy expenditure is the summation of basal energy expenditure (BEE) or basal metabolic rate, diet-induced thermogenesis, and activity-related thermogenesis. The BEE is the energy required to maintain the body's basic cellular metabolic activity and organ function. Many factors may affect or alter the body's BEE and are listed in Table 205.1 [5,6]. BEE can only be measured when a person is in a deep sleep. ICal measures resting EE (REE), which has traditionally been described as the energy expended when a patient is lying in bed, awake, and aware of his or her surroundings. To measure REE, ICal should be performed under strict testing conditions including a minimum of 5 hours of fasting, at least 30 minutes to an hour of resting with no physical activity, and in the absence of any stimulants or depressants. Critically-ill patients rarely meet the previously mentioned conditions, thus the term measured energy expenditure (MEE) is more commonly used to describe EE in critically-ill patients.

Table 205.1 Factors affecting energy expenditure

Non-modifiable	Modifiable
Age	Acute or chronic respiratory distress syndrome
Body composition (e.g. obesity, ascites, oedema)	Burn
Disease processes (e.g. malignancy)	Diet
Gender	Fever/Infection
Genetics	Large or multiple open wounds
Hormonal status	Nutrition status
Limb amputation	Medications (e.g. sedatives, paralytics)
Post-operative organ transplantation	Multisystem organ failure
	Sepsis
	Systemic inflammatory response syndrome
	Trauma
	Use of paralytic agents or sedation

Data from Brandi LS et al., 'Indirect calorimetry in critically ill patients: clinical applications and practical advice', Nutrition, 1997, 13, 4, pp. 349–358. Epub 1997/04/01; McClave SA and Snider HL, 'Use of indirect calorimetry in clinical nutrition', *Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition*, 1992, 7, 5, pp. 207–221. Epub 1992/10/01.

Clinical measurement of REE

At least four different organizations have published guidelines for the provision of nutrition support in critically-ill patients, although none of them provide specific recommendations on the use of ICal in the ICU [7–10]. Ideally, all critically-ill patients should receive ICal if their ICU length of stay is estimated to be >72 hours, especially if they are mechanically-ventilated (Fig. 205.1) However, due to cost considerations, and the availability of equipment and trained personnel, obtaining ICal may not be possible for all patients or at every institution. All factors considered, it is strongly recommended that ICU patients with any of the following conditions have an ICal study performed:

- Any clinical condition that significantly alters EE (e.g. acute or chronic respiratory distress syndrome, acute pancreatitis, burns, multiple trauma, multisystem organ failure, sepsis, systemic inflammatory response syndrome).
- Failure to respond to presumed adequate nutritional support (wound dehiscence, loss of lean body mass).
- Long-term ICU patients with multiple insults for the provision of individualized nutrition support (baseline and serial ICal measurements).

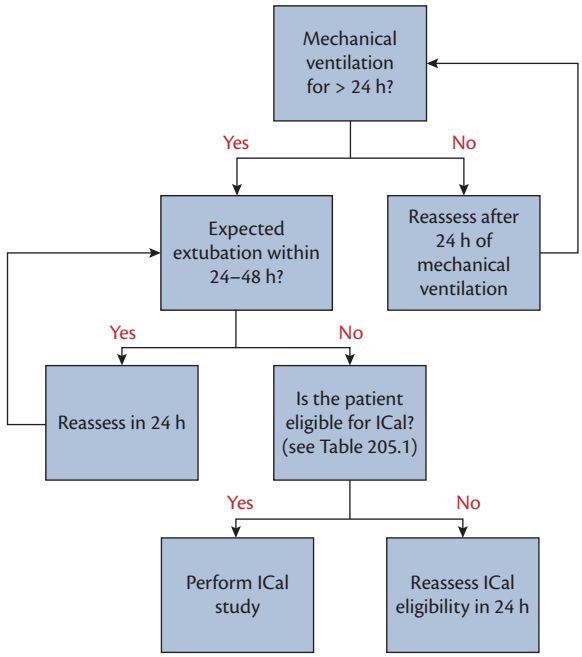


Fig. 205.1 Algorithm for performing indirect calorimetry.

Interpretation of ICal results

It is important to note the ICal study results are a MEE and may not accurately represent the BEE or REE depending on patient conditions during the study. Ideally, ICal should be measured under resting conditions. Many patient, environmental, and equipment-related factors can affect the accuracy of ICal measurements (Box 205.2) [3,6,11,12]. Keeping this in mind, ICal results give an accurate measure of the EE for the patient under the specific testing conditions. If patient conditions drastically change (discontinuation of paralytic agents, sedatives, initiation of nutrition, etc.) a follow-up ICal should be considered to evaluate the change in EE.

The MEE should serve as the daily caloric target for the provision of nutrition support in critically-ill patients. The addition of stress or activity factors to the MEE is not necessary and can increase the risk of overfeeding as the MEE has been shown to closely approximate 24-hour EE [6]. Also, since most ICU patients are receiving continuous feeding, diet-induced thermogenesis is accounted for in the MEE. However, if nutrition is intermittent, MEE should be increased by 5% to account for thermogenesis.

Another value derived from ICal is the respiratory quotient (RQ), which is defined as the ratio between VO_2 and VCO_2. The RQ value is a reflection of substrate utilization. Complete oxidation of glucose in a closed system yields an RQ value of 1. The use of protein and lipids as substrates for fuel yield different values within the physiological range of RQ values (see Fig. 205.2). It is important to remember the RQ value is a summation of whole body substrate utilization. Also, since many factors can influence the RQ, and result in false or inaccurate RQ values, the RQ value is mainly used as a measure of ICal study quality. An RQ value around 0.7 suggests underfeeding and a shift toward lipolysis for fuel substrate; alternatively, an RQ > 1 suggests overfeeding due to lipogenesis as substrate is stored as fat.

Box 205.2 Recommendations to improve the accuracy of ICal

Resting conditions

- Supine position at least 30 minutes prior to the study.
- Quiet, thermoneutral environment.
- Normal voluntary muscle movement is present during the study.
- No/minimum involuntary muscle movement is present during the study.
- Adequate pain control.
- No/minimal agitation.
- All sedatives and/or analgesics should be administered at least 30 minutes prior to the study when clinically feasible.

Nutrition considerations

- **Intermittent nutrition:**
  - If thermogenesis is to be included in the REE—perform study 1 hour after feeding.
  - If thermogenesis is **not** to be included in the REE—perform study 4 hours after feeding.
- **Continuous nutrition**: no changes to the rate and/or composition of continuous nutrition for at least 12 hours prior to the study.

Oxygen considerations

- Non-mechanically ventilated patients—no supplemental oxygen provided during the study.
- **Mechanically-ventilated patients**:
  - FIO_2 must remain constant during the study.
  - No changes in ventilatory settings for at least 90 minutes.
  - No leaks are present in the ventilation or sampling system.

Procedural considerations

- **Haemodialysis:**
  - *Intermittent*—must wait 3–4 hours after completion of haemodialysis.
  - *Continuous*—cannot perform study until continuous renal replacement therapy is discontinued.
- No general anaesthesia within 6–8 hours prior to the study.
- **Painful procedures**: wait at least 1 hour and ensure pain is adequately controlled prior to study.
- Avoid routine nursing care or procedures during the study.

Measurement considerations

- Data used to calculate EE and RQ are taken from steady state conditions.

Data from Branson RD and Johannigman JA, 'The measurement of energy expenditure', *Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition*, 2004, 19, 6, pp. 622–636. Epub 2005/10/11; McClave SA and Snider HL, 'Use of indirect calorimetry in clinical nutrition', *Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition*, 1992, 7, 5, pp. 207–221. Epub 1992/10/01; Matamis D et al., 'Influence of continuous haemofiltration-related hypothermia on haemodynamic variables and gas exchange in septic patients', *Intensive care medicine*, 1994, 20, 6, pp. 431–436. Epub 1994/07/01; Matarese LE, 'Indirect calorimetry: technical aspects', *Journal of the American Dietetic Association*, 1997, 97, 10, Suppl 2, pp. S154–160. Epub 1997/10/23.

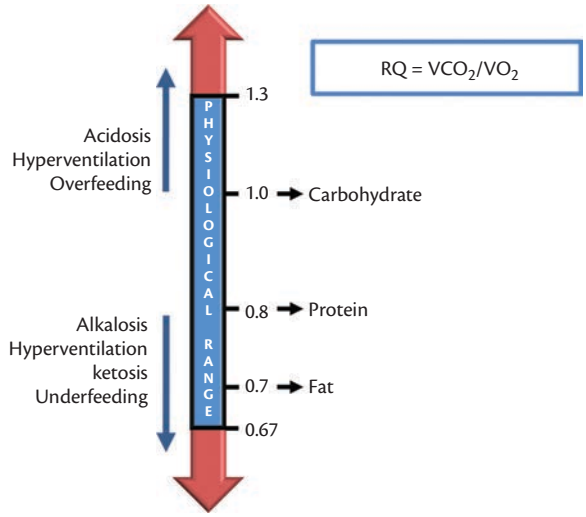


Fig. 205.2 Interpretation of the RQ value.

Clinical benefits of ICal

Malnutrition occurs in approximately 43–88% of ICU patients and accurate determination of energy requirements is essential to avoid feeding-associated adverse effects [13]. Underfeeding may result in the development of malnutrition and associated adverse outcomes, such as decreased wound healing, increased infectious complications, increased duration of mechanical ventilation, and increased ICU length of stay [14,15]. Recent literature has suggested that a negative caloric balance in the ICU may lead to injurious consequences, including an increased ICU length of stay, duration of mechanical ventilation, overall rate of complications (pressure ulcers, acute kidney insufficiency, acute respiratory distress syndrome, and sepsis), and death [15–17]. Conversely, overfeeding critically-ill patients can lead to hyperglycaemia, hepatic dysfunction, prolonged mechanical ventilation, fluid overload including pulmonary oedema, and congestive heart failure [18]. More recently, the concept of tight caloric control has been advocated that critically-ill patients should avoid the deleterious effects of under- and overfeeding, although the studies have had conflicting results [19,20].

Weaning from mechanical ventilation

Determination of accurate daily caloric needs with ICal can also assist in the facilitation of weaning from mechanical ventilation. Overfeeding results in excessive production of CO_2 and results in increased work of breathing, which can be detrimental to weaning efforts, especially in patients with limited respiratory reserves such as those with chronic obstructive pulmonary disease and acute respiratory distress syndrome. Performing ICal allows clinicians to determine whether overfeeding is contributing to unsuccessful ventilator weaning attempts. Subsequently, decreasing caloric intake can help reduce excessive CO_2 production and decrease respiratory efforts required to successfully wean a patient from mechanical ventilation. Due to the dynamic metabolic profile of critically-ill patients, it is difficult to estimate daily caloric needs accurately.

References

1. Bursztein S, Saphar P, Singer P, and Elwyn DH. (1989). A mathematical analysis of indirect calorimetry measurements in acutely ill patients. *American Journal of Clinical Nutrition*, **50**(2), 227–30.
2. Ferrannini E. (1988). The theoretical bases of indirect calorimetry: a review. Metabolism, **37**(3), 287–301.
3. Branson RD and Johannigman JA. (2004). The measurement of energy expenditure. *Nutrition in Clinical Practice*, **19**(6), 622–36.
4. McClave SA, Spain DA, Skolnick JL, et al. (2003). Achievement of steady state optimizes results when performing indirect calorimetry. *Journal of Parenteral and Enteral Nutrition*, **27**(1), 16–20.
5. Brandi LS, Bertolini R, and Calafa M. (1997). Indirect calorimetry in critically ill patients: clinical applications and practical advice. *Nutrition*, **13**(4), 349–58.
6. McClave SA and Snider HL. (1992). Use of indirect calorimetry in clinical nutrition. *Nutrition in Clinical Practice*, 7(5), 207–21.
7. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, and Dodek P. (2003). Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *Journal of Parenteral and Enteral Nutrition*, **27**(5), 355–73.
8. Kattelmann KK, Hise M, Russell M, Charney P, Stokes M, and Compher C. (2006). Preliminary evidence for a medical nutrition therapy protocol: enteral feedings for critically ill patients. *Journal of the American Dietetic Association*, **106**(8), 1226–41.
9. Kreymann KG, Berger MM, Deutz NE, et al. (2006). ESPEN Guidelines on enteral nutrition: intensive care. *Clinical Nutrition*, **25**(2), 210–23.
10. McClave SA, Martindale RG, Vanek VW, et al. (2009). Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *Journal of Parenteral and Enteral Nutrition*, **33**(3), 277–316.
11. Matamis D, Tsagourias M, Koletsos K, et al. (1994). Influence of continuous haemofiltration-related hypothermia on haemodynamic variables and gas exchange in septic patients. *Intensive Care Medicine*, **20**(6), 431–6.
12. Matarese LE. (1997). Indirect calorimetry: technical aspects. *Journal of the American Dietetic Association*, **97**(10 Suppl. 2), S154–60.
13. Giner M, Laviano A, Meguid MM, and Gleason JR. (1996). In 1995 a correlation between malnutrition and poor outcome in critically ill patients still exists. *Nutrition*, **12**(1), 23–9.
14. Singer P, Pichard C, Heidegger CP, and Wernerman J. (2010). Considering energy deficit in the intensive care unit. *Current Opinion in Clinical Nutrition and Metabolic Care*, **13**(2), 170–6.
15. Villet S, Chiolero RL, Bollmann MD, et al. (2005). Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clinical Nutrition*, **24**(4), 502–9.
16. Dvir D, Cohen J, and Singer P. (2006). Computerized energy balance and complications in critically ill patients: an observational study. *Clinical Nutrition*, **25**(1), 37–44.
17. Faisy C, Lerolle N, Dachraoui F, et al. (2009). Impact of energy deficit calculated by a predictive method on outcome in medical patients requiring prolonged acute mechanical ventilation. *British Journal of Nutrition*, **101**(7), 1079–87.
18. Port AM and Apovian C. (2010). Metabolic support of the obese intensive care unit patient: a current perspective. *Current Opinion in Clinical Nutrition and Metabolic Care*, **13**(2), 184–91.
19. Singer P, Anbar R, Cohen J, et al. (2011). The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Medicine*, **37**(4), 601–9.
20. Strack van Schijndel RJ, Weijs PJ, et al. (2009). Optimal nutrition during the period of mechanical ventilation decreases mortality in critically ill, long-term acute female patients: a prospective observational cohort study. *Critical Care*, **13**(4), R132.

CHAPTER 206

Enteral nutrition in the ICU

Shaul Lev and Pierre Singer

Key points

- Enteral feeding is an integral part of patient care and should be started early as soon as the patient is stabilized.
- Nasogastric or nasojejunal tubes are the main routes of enteral nutrition (EN) administration.
- Monitor gastric residual volume and follow protocols to start enteral feeding.
- Choice of feed composition should depend on the main disease—acute lung injury, diabetes, trauma, or others.
- The main complications are aspiration and diarrhoea.

Introduction

Artificial nutritional support is considered an integral part of critical care. Artificial feeding can be in the form of enteral nutrition (EN), parenteral nutrition (PN) or as a combination. The primary goal of nutrition support in the critically ill is to supply patients with macro- and micronutrients that are needed for new protein synthesis, energy production, and to sustain enzymatic function. A secondary goal is to modulate immune function in order to improve infection rates, wound healing, and to avoid non-adaptive proteolysis of vital proteins and hyper-inflammatory reactions. This field of nutrition is called immunonutrition. The intensive care unit (ICU) population is very heterogenic and the appropriate nutritional intervention should be chosen with care. First the calorie–protein targets should be defined followed by the timing for commencing EN and choice of route of feeding. EN is currently viewed as the first line of feeding for critically-ill patients who cannot be fed by mouth and has many benefits in maintaining the functionality of the intestine. The timing for starting feeding is a matter of controversy, but it is usually started in the early stages of ICU hospitalization, during the first 2 days, in order to avoid major caloric and protein deficits. The concept of commencing early nutrition for critically-ill patients is based on observation that feeding started within short time frame is associated with less gut permeability, diminished activation, and release of inflammatory cytokines and reduced systemic endotoxaemia. A meta-analysis by Heyland et al. [1] showed a trend toward reduced mortality and infectious morbidity. A systematic review by Marik and Zaloga [2] showed significant reduction in infectious morbidity and hospital stay with early EN compared with delayed feedings. While most experts agree that patients who can tolerate feeding should be nourished as soon as they are stabilized, controversy exists regarding the best management of patients who cannot tolerate EN matched to their estimated needs.

Indications

The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends 'all patients who are not expected to be on a full oral diet within 3 days should receive enteral nutrition' [3]. The European [3], American [4], and Canadian [1] guidelines recommend that ventilated, haemodynamically stable patients, with a functioning digestive system, will begin enteral nutrition 24–48 hours after admission to the ICU. Bowel sounds are a poor indicator of small bowel activity, particularly in patients subject to tracheal intubation and mechanical ventilation. Their absence should not delay a trial of enteral nutrition.

Methods of administration

Enteral feeds are usually given continuously by gravity feed or pump-assisted infusion. Intermittent bolus feeds may also be given every 6 hours and may have a more positive effect on protein synthesis than the same quantity of continuous feeds. The administration set must be sterile and have connectors incompatible with intravenous infusions to minimize the risk of confusion with fluids intended for intravenous use. Enteral feeds should not be left hanging at the bedside for more than 24 hours at room temperature, since bacterial colonization of enteral feeds have been found in up to 24% of enteral feed reservoirs at 24 hours.

Routes of feeding: stomach versus small bowel

Routes of feeding include nasogastric (NG), nasoduodenal, nasojejunal (NJ), gastrostomy, and jejunostomy. Nasal tube feeding should be performed via a soft, fine-bore tube in order to avoid ulceration of the nose or oesophagus. Patients tolerate nasal tubes better than oral tubes, but the nasal route is associated with increased frequency of bleeding during insertion and with sinusitis. Nasal intubation is relatively contraindicated in patients with a fractured base of skull. Nasogastric feeding usually starts using a 12–14-French tube to allow aspiration of gastric contents to check feed absorption, and administration of viscous elixirs or crushed tablets.

The placement of nasoduodenal tubes should be considered if gastric residues are large (250–500 mL). This kind of feeding, directly to the small bowel, bypasses the stomach, enables nutritional goals to be reached faster and eliminates the need for parenteral feeding. Direct feeding to the small bowel does not cause special complications. The main disadvantage relates to the difficulty in tube placement. Fewer than 50% of fine-bore tubes pass through the pylorus spontaneously within 24 hours of insertion.

Tubes can be guided through the pylorus using fluoroscopy or endoscopy. The position of the tip of a feeding tube should be confirmed by radiography before feeding starts in order to avoid accidental tracheal intubation.

In selected patients creation of a feeding jejunostomy is considered, especially when there is a laparotomy. This procedure allows the administration of early enteral nutrition in most patients, but may be complicated by leaks, peritonitis, wound infection, and bowel obstruction.

Monitoring tolerance of enteral feeding

Up to 47% of patients in the ICU suffer from GI motility problems. Gastric residual volume (GRV) is viewed as the most common indicator of tolerance for enteral feeding, although many studies found no correlation between GRV and pneumonia rate [4]. Serial GRV measurements may decrease the amount of nutrition that is actually given. According to the American Society for Parenteral and Enteral Nutrition (ASPEN) [4], when GRV levels are 200–500 mL, and with the absence of other indicators for intolerance of feeding, enteral feeding should not be stopped [4]. One of the recommended approaches to tackle motility problems is the use of prokinetic medication. If the nasogastric aspirates are significant (i.e. more than 150 mL), prokinetic drugs such as metoclopramide (10–20 mg intravenously (iv) every 6 hours), or erythromycin (80–300 mg iv) are used to decrease gastric paresis and to assist transpyloric placement of transpyloric tube [4]. Several studies and meta-analyses have questioned the advantages of post-pyloric feeding in the ICU. A small number of studies demonstrated that post-pyloric feeding benefits by reducing gastro-oesophaegeal reflux and rate of aspirations, especially if the tip of tube is located distally in the duodenum. A meta-analysis that covered 11 studies of 637 ICU patients, did not demonstrate any advantage in the clinical outcome of patients fed directly into the small bowel, with respect to mortality, duration of hospitalization, rate of pneumonia, and aspirations [5]. A recent meta-analysis of 15 randomized clinical trials enrolling 966 participants found that post-pyloric feeding was associated with a reduction in pneumonia compared with gastric feeding (relative risk (RR) 0.63, 95% CI 0.48–0.83, $p = 0.001$; $I^2 = 0\%$) [6]. The risk of aspiration (RR, 1.11; 95% CI, 0.80–1.53, $p = 0.55$; $I^2 = 0\%$) and vomiting (RR, 0.80; 95% CI, 0.38–1.67, $p = 0.56$; $I^2 = 65.3\%$) were not significantly different between patients treated with gastric and post-pyloric feeding [6]. A recent multicentre Australian study did not find an increase in the amount of energy delivered in 181 ventilated patients with medium GRV when an early NJ tube was introduced as compared to NG tube [7].

EN composition

Many formulas are commercially available, and may differ in their caloric density, amount of proteins, and their enrichment with specific components, such as fibres, specific amino acids, fish oil, specific fatty acids, nucleotides, and other nutrients and antioxidants. Most standard formulations contain 1 kcal/mL. 'Energy dense' formulation with high fat content may contain up to 2 kcal/mL. Formulations also vary in osmolality, electrolyte, mineral, and vitamin content. All the feeds are lactose and gluten free. Carbohydrates are provided as sucrose, fructose, or glucose polymers. Proteins are provided as whole proteins. New formulations with high protein content have recently been introduced into the market. The value of a very high protein-to-energy ratio is still unproven, but allows delivery of higher amounts of proteins without fluid overload. Elemental or semi-elemental feeds contain a mix of oligopeptides and free amino acids. They are used in patients with short bowel syndrome, severe diarrhoea, radiation enteritis and pancreatic insufficiency. Fats may be provided as medium-chain fatty acids or long-chain triglycerides. Special feeds are constantly being developed, including feeds with nucleotides and arginine, and formulations enriched with fish oils. Electrolyte content varies and may affect the choice of feed when sodium or potassium restriction is important; these electrolytes can always be added to a feed when supplementation is needed. Most of the commercial formulations meet the daily recommended intake of healthy adults if given in an amount higher than 1000–1500 mL/day. The daily needs might be higher for some vitamins in settings of increased losses, such as continuous haemodiafiltration.

Specific nutrients

Some nutrients have been intensively research both in animal models and humans due to their specific biological effects, rather than their use as energy sources or substrates for protein synthesis.

Glutamine

Glutamine is a conditionally essential amino acid and is the most abundant amino acid in plasma. Glutamine is involved in many biochemical reactions in the cells. The glutamine stores in muscle tissue are depleted and low plasma glutamine concentrations are an independent prognostic factor for an unfavourable outcome in the critically-ill patient. Under catabolic conditions, such as sepsis and shock, release of glutamine from muscle tissue serves as a 'stress signal' to the organism that leads to gene activation in order to promote cellular protection and immune regulation. Glutamine serves as a precursor of nucleotides and glutathione, and is the major metabolic fuel for the enterocytes of the gut mucosa, lymphocytes, and macrophages. Several other properties are associated with glutamine, including antioxidant activity, promotion of production of heat shock proteins and protection of gut barrier functionality. In most enteral formulations glutamine is present in low concentrations and glutamine supplementation is given intravenously for burns, trauma and ICU patients.

'Immune-enhancing' enteral formulas (arginine, omega-3 fatty acids, probiotics, nucleotides)

Specific formulas designed with the aim of improving immune function and reducing the risk of infections, are called immune-enhancing enteral feeds.

These formulas are usually enhanced with omega-3, γ-linolenic acid (GLA), arginine, and/or nucleotides (low molecular weight intracellular compounds that are composed of a purine and pyridimine backbone). The effect of these feeds is controversial and might be related to a specific formula. Well-designed large clinical trials did not show improved outcome in critically-ill patients.

Arginine

Arginine-enriched formulas reduced the risk of infections and shortened the duration of hospitalization in elective surgical patients. Heyland et al. [8] suggest in a systematic review that

immune modulating formulas decrease rate of infections in elective surgical patients, but may increase mortality rates in general ICU patients, although the data to support such conclusion was weak [8]. Arginine enriched formulas might be beneficial to patients before and after major surgery and trauma, but in the meantime should not be provided to patients suffering from severe sepsis.

Omega-3 fatty acids and γ-linolenic acid

Omega-3 fatty acids help down-regulate the inflammatory response and improve overall immune function. Both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) show benefits in membrane structure and function and gene transcription. Animal models have established the ability of fish oil solutions to reduce lung permeability in acute lung injury (ALI) compared with solutions with omega-6 or saturated fat. Preclinical data supported the concept that EPA and DHA may be beneficial in ALI/acute respiratory distress syndrome (ARDS) by reducing inflammation. Most of the animal studies have involved a pre-injury supplementation protocol and have delivered the fish oil supplementation before or soon after the insult to the lungs. Patients with ALI/ARDS have been found to have very low omega-3 levels compared with normal individuals, suggesting a potential role for omega-3 dietary supplementation in these patients [9].

Clinical data regarding the use of formulas enhanced with EPA and GLA in ALI/ARDS patients come from five randomized controlled studies. Three studies demonstrated an association between the administrations of an enteral formula enriched in EPA, GLA, and antioxidants and improved clinical outcome as compared with high-fat formula. A meta-analysis done on these three trials showed a significant reduction in the risk of mortality as well as relevant improvements in oxygenation and clinical outcomes of ventilated patients with ALI/ARDS [10]. Nevertheless, there are two recent studies that addressed the same question in patients with ALI or ARDS with mixed results. In a Spanish multicentre study [11], the EPA-GLA diet group showed a trend toward a decreased SOFA score, but it was not significant. In this study, no improvement in the gas exchange measured by the PaO_2/FiO_2 ratio was measured in the omega-3-treated group [11]. Liver function tests, glycaemia, cholesterol and triglycerides were similar in both groups [11]. The control group stayed longer in the ICU than the EPA-GLA diet group [11]. In a recent study [12], the authors used a different approach of twice-daily bolus administration of omega-3 fatty acids instead of continuous enteral infusions to deliver the supplements. In contrast to the previous studies in this study enteral supplementation of omega-3 fatty acids, GLA, and antioxidants did not improve the rate of nosocomial infections, non-pulmonary organ function, lung physiology, or clinical outcomes in patients with ALI compared with supplementation of an isocaloric control [12]. Furthermore, the study was stopped early for futility despite an 8-fold increase in plasma eicosapentaenoic acid levels [12]. The use of the omega-3 supplement resulted in increased duration of diarrhoea [12]. The study had sustained heavy criticism since the control formula contained five times more protein and the omega-3 supplements were given up to 5 days after the respiratory deterioration. Moreover, half the patients were underfed and the omega-3 fatty acids might have been catabolized as an energy source.

Fibres

Fibres are non-digestible, sugar-based, long molecules that are subject to bacterial breakdown to short-carbon molecules, such as acetate, propionate, and butyrate. These serve as important substrates for the cells of the colonic mucosa, and their uptake enhances absorption of water and electrolytes from the bowel lumen. Fibres also bind bile salts, which would otherwise be irritants to the colonic mucosa, promotes glucose absorption, and provides substrate for the normal bowel flora. The main importance of fibres is their ability to improve stool consistency. Despite concern being raised about their utility in patients who suffer from gut ischaemia, no adverse effects have been reported from including fibre in enteral feeds, and most new formulations contain a fibre source.

Probiotics

Probiotic therapy can be defined as any supplemental micro-organisms that are safe and stable and, when administered in adequate amounts, confer a health benefit to the patient. Looking at patients' microbiota profile over time in hospital reveals profound changes. These changes are due to broad spectrum antibiotics, ulcer prophylaxis, vasoactive-pressor agents, alterations in motility, and decreases in luminal nutrient delivery. These agents act by competitively inhibiting pathogenic bacterial growth, blocking epithelial attachment of invasive pathogens, eliminating pathogenic toxins, enhancing the mucosal barrier function, and favourably modulating the host inflammatory response. There is an inverse correlation between the changes in patients' microbiota and clinical outcome [13]. Unfortunately, despite the fact that the administration of probiotics agents has been shown to decrease infection rate in specific critically-ill patient populations involving transplantation, major abdominal surgery, and severe trauma [13], no recommendation has currently been made for use of probiotics in the general ICU population due to a lack of consistent outcome effect.

Many experts believe that as the ease and reliability of taxonomic classification will improve, stronger recommendations could be made for the use of specific probiotics in specific populations of critically-ill patients.

Complications

The most severe complication of EN is aspiration and is a main cause of pneumonia. Some patients have increased risk factors for aspiration, such as mechanical ventilation, old age, decreased consciousness, supine position, poor oral health, etc. In order to reduce the risk of aspiration, it is important to maintain a posture where the upper body is raised to 30–45° and to assess the tolerance for feeding. Gastrointestinal complications, especially diarrhoea, affecting up to 60%, are commonly encountered, as well as regurgitation, nausea, vomiting, constipation, abdominal pain, and bloating. Soluble fibre-enriched solutions can be used in cases of diarrhoea and in severe cases a use of a polypeptide-based formula may be tried. Metabolic complications, such as hyperglycaemia, electrolyte disturbance, especially hypokalaemia, are mainly linked to the medical condition of the patient and the content of the formula. Special attention should be given to the possible development of refeeding syndrome, a group of symptoms that appear after sudden feeding of a patient who was in a starved state. The sudden change affects insulin secretion that, in turn, causes changes in electrolytes and fluids. These changes could cause cardiac, respiratory, haematological, metabolic, and neurological disturbances and, in severe cases, a multi-organ failure and death [14]. The electrolytic

disturbances include hypophosphataemia, hypokalaemia, and hypomagnesaemia.

References

1. Heyland DK, Dhaliwal R, and Drover JW. (2003). Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *Journal of Parenteral and Enteral Nutrition*, **27**, 355–73.
2. Marik PE and Zaloga GP. (2001). Early enteral nutrition in acutely ill patients: a systematic review. *Critical Care Medicine*, **29**, 2264–70.
3. Kreymann KG, Berger MM, and Deutz NEP. (2006). ESPEN guidelines on enteral nutrition: intensive care. *Clinical Nutrition*, **25**, 210–23.
4. Stephen A, McClave MD, and Robert G. (2009). Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient. *Journal of Parenteral and Enteral Nutrition*, **33**, 277.
5. Ho KM, Dobb GJ, and Webb SA. (2006). A comparison of early gastric and post-pyloric feeding in critically ill patients: a meta-analysis. *Intensive Care Medicine*, **32**, 639–49.
6. Jiyong J, Tiancha H, Huiqin W, and Jingfen J. (2013). Effect of gastric versus post-pyloric feeding on the incidence of pneumonia in critically ill patients: observations from traditional and Bayesian random-effects meta-analysis. *Clinical Nutrition*, **32**, 8–15.
7. Davies AR, Morrison SS, Bailey MJ, et al. (2012). ENTERIC Study Investigators; ANZICS Clinical Trials Group. A multicenter, randomized controlled trial comparing early nasojejunal with nasogastric nutrition in critical illness. *Critical Care Medicine*, **40**, 2342–8.
8. Heyland DK, Novak F, Drover JW, Jain M, Su X, and Suchner U. (2001). Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *Journal of the American Medical Association*, **286**, 944–53.
9. Singer P, Theilla M, and Fisher H. (2006). Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. *Critical Care Medicine*, **34**, 1033–8.
10. Pontes-Arruda A, Demichele S, Seth A, and Singer P. (2008). The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data. *Journal of Parenteral and Enteral Nutrition*, **32**, 596–605.
11. Grau-Carmona T, Moran-Garcia V, Garcia-de-Lorenzo A, et al. (2011). Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and anti-oxidants on the outcome of mechanically ventilated, critically ill, septic patients. *Clinical Nutrition*, **30**, 578–84.
12. Rice TW, Wheeler AP, Thompson BT, et al. (2011). Acute Respiratory Distress Syndrome Network of Investigators. *Journal of the American Medical Association*, **306**, 1574–81.
13. Shimizu K, Ogura H, Asahara T, et al. (2013). Probiotic/synbiotic therapy for treating critically ill patients from a gut microbiota perspective. *Digestive Diseases and Sciences*, **58**, 23–32.
14. Byrnes MC and Stangenes J. (2011). Refeeding in the ICU: an adult and pediatric problem. *Current Opinion in Clinical Nutrition and Metabolic Care*, **14**, 186–92.

CHAPTER 207

Parenteral nutrition in the ICU

Jonathan Cohen and Shaul Lev

Key points

- The parenteral nutrition formula should be designed to meet nutritional needs.
- Daily writing of parenteral nutrition orders needs to include laboratory evaluation, fluid, caloric, and protein requirements.
- Calorie and protein requirements should be calculated daily.
- Laboratory assessment should be performed daily.
- Monitor drug and nutrient interactions, and their effects on laboratory variables.

Introduction

Parenteral nutrition (PN) is a technique of artificial nutrition support, which consists of the intravenous administration of macronutrients (glucose, amino acids, and triglycerides), micronutrients (vitamins and trace elements) and water. While enteral nutrition (EN) is recognized as the optimal method for providing energy and protein needs, it is not always an option in many patients and may fail to meet patient requirements. For this reason, PN has become integrated into ICU patient management with the aim of preventing energy deficits and preserving lean body mass. The addition of PN to enteral nutrition is known as supplemental PN.

Indications and modes of administration

Indications for parenteral feeding

Parenteral feeding should be considered in the following circumstances:

- **Enteral nutritional support is contraindicated**: e.g. in the presence of gut obstruction, high output fistulae, severe gut ischaemia or gut failure.
- **Enteral nutrition alone is unable to meet energy and nutrient requirements and PN is given as supplemental nutrition**: this approach may be especially relevant in high risk patients who are chronically malnourished.

Approach and clinical evidence for supplemental PN

International guidelines differ considerably regarding the indications for PN [1–3]. Thus, the European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines [3] recommend initiating PN in critically-ill patients who do not meet caloric goals within 2–3 days of commencing EN. The Canadian guidelines [2] recommend PN only after extensive attempts to feed with EN have failed, while the American Society of Parenteral and Enteral Nutrition (ASPEN) guidelines [1] advocate administering PN after 8 days of attempting EN unsuccessfully.

Five randomized prospective trials have been published regarding the early use of supplemental PN [4–8]. The first trial was published in 2000, by a French group [4] and randomized 120 patients to receive either EN plus PN from day one or conventional EN given as early as possible. Despite a significant energy delivery difference between the two groups and better biochemical parameters, the only clinical improvement noted in the PN group was a decrease in the length of hospital stay. Due to these disappointing results and to a strong negative sentiment in the medical community, the use of PN was largely neglected for many years. Recently, however, there has been renewed interest in the use of PN and four randomized controlled trials (RCTs) have been published in the last 3 years [5–8]. The TICACOS study [5] was performed on 130 patients randomized to receive either EN or PN where required according to indirect calorimetry measurements and a control group targeted to 25 kcal/kg/day. The study did not find a difference in ICU mortality, but reported a significantly better hospital survival for the study group when analysing the results per protocol. The very recent bicentre Swiss trial (SPN) [6] allocated 301 patients to receive PN on the fourth day of admission if it was shown that energy delivery was less than 60% of measured EE. The study reported significantly better outcomes regarding infection rates, days of antibiotic administration and length of ventilation when analysing the results after 9 days of admission. The largest study on very early PN administration, the EPANIC study [7], recruited more than 4000 patients to receive either PN on the first 2 days of admission versus adding PN on the 8th day of admission. The study group received a low protein formulation, severely malnourished patients were excluded and most of the population comprised non-high risk patients. The study did not find any positive outcome and even suggested harm. However, the results should be interpreted with caution and the main conclusion that can be drawn is that patients who are not high risk, who are not chronically malnourished should not receive early supplemental PN. A sub-analysis of the trial also did not find any benefit in any subgroup analysed, including the patients with higher illness severity scores or patients with high malnutrition scores. A very recent multicentre Australian study prospectively randomized patients to receive complimentary PN as soon as possible if they were not expected to be orally fed for at least for 24 hours. The study did not find any significant clinical improvement except for length of ventilation, which was reduced by 1 day and a slightly improved quality of life after 1 month, which was not considered to be clinically meaningful. Interestingly, the infection rate, including blood stream infections, was not increased in the PN group [8].

Methods of administration

PN is usually delivered by programmable pumps and requires reliable vascular access. A dedicated catheter or lumen is needed.

PN should be prescribed by trained health care professionals applying validated protocols. Energy delivery should be matched to the energy target, preferably defined by indirect calorimetry or calculated by a trained dietitian. Meticulous glucose control is important, with a therapeutic goal targeting levels between 140 mg/dL to 180 mg/dL.

Choice of parenteral feeding route

Central venous

The central venous route is preferred for administration of hyperosmolar solutions (>850 mOsmol/kg) in cases where high energy intake (> 1500 kcal) is to be infused. The femoral route should not be used if possible due to a higher risk of catheter-related infections.

Peripheral venous

Parenteral nutrition via the peripheral route is possible when the prescribed solution is of low osmolality. In order to achieve this, the volume of the solution can be increased or the energy content (particularly from carbohydrate) reduced. Peripheral cannula sites should be changed every 72–96 hours.

PN composition

Carbohydrate is normally provided as concentrated glucose while 30–40% of total calories are usually given as lipids (e.g. soya bean emulsion). The nitrogen source is synthetic, crystalline L-amino acids, which should contain appropriate quantities of all essential and most non-essential amino acids. Carbohydrate, lipid, and nitrogen sources are typically mixed into a large bag in a sterile pharmacy unit. Vitamins, trace elements, and appropriate electrolyte concentrations can then be added to the infusion, thus avoiding multiple connections. Volume, protein, and calorie content of the feed should be determined on a daily basis in conjunction with the appropriate health care professional.

Stability

Commercial solutions are highly stable after preparation and can be stored for months in cool storage conditions. After opening the bag, the solution should be given within 24–48 hours depending on manufacturer's recommendations. The vitamin solutions are usually stable for up to 24 hours.

Immunonutrition

The concept of immunomodulating formulae has been extensively studied in relation to EN, but not substantiated regarding PN. In this regard, glutamine and omega-3 fatty acids have received the most attention. Glutamine is an important metabolic fuel for the cells of the gut and the immune system. It is also involved in the regulation of muscle and liver protein balance, probably mediated by an increase in cellular hydration, a triggering signal or protein anabolism. Several studies have demonstrated that parenteral glutamine supplementation may improve outcome, and the ESPEN guidelines give a grade A recommendation to the use of glutamine in critically-ill patients who receive PN. Three large multicentre trials have been published since the release of the ESPEN guidelines. The Scandinavian multicentre, double-blind, RCT of intravenous (iv) glutamine supplementation for ICU patients was recently published [9]. In this trial, patients were given supplemental iv glutamine (0.283 g/kg body weight/24 hours) for their entire ICU stay. They demonstrated a lower ICU mortality in the treatment arm compared with controls, which was not significant at 6 months. No change in the SOFA (Sequential Organ Failure Assessment) scores were noted. The SIGNET trial [10] recruited 502 patients to receive glutamine via PN, which was given as a supplement to EN. This study did not find any benefit from iv glutamine administration to unselected critically-ill patients. A trial conducted on 1223 mechanically ventilated critically-ill patients reported disappointing results and concluded that glutamine administration in this critically-ill population might in fact cause harm [11]. The harm was noted mainly in patients with multi-organ failure, haemodynamic instability, and renal failure. The doses used in this trial were higher than those recommended and glutamine was given very early in the course of hospitalization.

Studies on IV omega-3 fatty acids have yielded promising results in animal models of acute respiratory distress syndrome and proved superior to solutions with omega-6 composition. The clinical experience with the use of these solutions in critically-ill patients is not as yet proven. The discrepancy between animal models and clinical practice could be related to different time frames. Thus, while in the animal studies the fish oil solutions were given in proximity to the insults, the administration in clinical trials was much later after the primary insults.

Complications

The use or misuse of PN may be associated with many potential complications [12], which may be divided into mechanical, infectious, and metabolic complications. Most of the complication can be avoided by optimum hand hygiene, maximal barrier precautions, and close medical care by specialized total parenteral nutrition (TPN) team.

Mechanical complications

- Catheter misplacement.
- Catheter-related mechanical complications (pneumothorax, arterial injury, bleeding).
- Thrombosis or thromboembolism.

Infectious complications

- Bacteraemia.
- Fungaemia.
- Tunelitis.
- Phlebitis.
- Cellulitis.

Metabolic complications

Fluid excess

- Fatty liver and liver failure.
- Hyperosmolar, hyperglycaemic, and hypoglycaemic states.
- Hypophosphataemia and hyperphosphataemia.
- Hypercalcaemia.

- Metabolic acidosis with hyperchloraemia.
- High endogenous insulin levels.
- Vitamin deficiencies—folate, thiamine, vitamin K.
- Encephalopathy.
- Hypoprothrombinaemia.
- Vitamin excess or deficiency—vitamins A and D.
- Dermatitis.

Conclusion

Timely and adequate parenteral nutritional support administered according to guidelines recommendations, may help to achieve balanced nutritional support. Both under- and overfeeding should be avoided. In addition to energy balance, careful attention should be devoted to the adequacy of protein and micronutrient administration. Avoiding infectious complications by applying meticulous sterile techniques in catheter insertion and avoiding metabolic complications by close metabolic follow-up can be achieved as shown by studies reporting low rates of PN complications.

References

1. Stephen A, McClave MD, and Robert G. (2009). Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. *Journal of Parenteral and Enteral Nutrition*, **33**, 277.
2. Heyland DK, Dhaliwal R, and Drover JW. (2003). Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *Journal of Parenteral and Enteral Nutrition*, **27**, 355–73.
3. Singer P, Berger MM, and Van den Berghe G. (2009). ESPEN Guidelines on parenteral nutrition: intensive care. *Clinical Nutrition*, **28**, 387–400.
4. Bauer P, Charpentier C, Bouchet C, Nace L, Raffy F, and Gaconnet N. (2000). Parenteral with enteral nutrition in the critically ill. *Intensive Care Medicine*, **26**, 893–900.
5. Singer P, Anbar R, Cohen J, et al. (2011). The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Medicine*, **37**, 601–9.
6. CP Heidegger, Berger MM, Graf S, et al. (2013). Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet*, **2**, 354–5.
7. Casaer MP, Mesotten D, Hermans G, et al. (2011). Early versus late parenteral nutrition in critically ill adults. *New England Journal of Medicine*, **365**, 506–17.
8. Doig GS, Simpson F, Sweetman EA, et al. Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition: A Randomized Controlled Trial. *JAMA*. 2013; **309**(20), 2130–2138.
9. Wernerman J, Kirketeig T, Andersson B, et al. for the Scandinavian Critical Care Trials Group. (2011). Scandinavian glutamine trial: a pragmatic clinical multi-centre randomised clinical trial of intensive care unit patients. *Acta Anaesthesiologica Scandinavica*, **55**, 812–18.
10. Andrews PJ, Avenell A, Noble DW, et al. (2011). Scottish Intensive Care Glutamine or Selenium Evaluation Trial (SIGNET) Trials Group. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. *British Medical Journal*, **342**, d1542.
11. Heyland D, Muscedere J, Wischmeyer PE, et al. (2013). A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients. *New England Journal of Medicine*, **368**,1489–97.
12. Jeejeebhoy KN. (2012). Parenteral nutrition in the intensive care unit. *Nutrition Reviews*, **70**, 623–30.

SECTION 8

The renal system

PART 8.1

Physiology

CHAPTER 208

Normal physiology of the renal system

Bruce Andrew Cooper

Key points

- The kidney has many important roles other than just urine production.
- The impact of kidney disease is often predictable.
- The kidney plays a critical role in fluid and electrolyte balance via many specialized trans-membrane pathways.
- The kidney is also involved in the production and modification of two key hormones and one enzyme.
- Understanding normal renal physiology can help determine clinical management.

Renal structure

General anatomy

Standard renal anatomy consists of two kidneys situated either side of the L2–5 lumbar vertebrae in a retroperitoneal position each with a single feeding artery, a single draining vein and a single ureter each connecting to the urinary bladder, which acts as a reservoir to be emptied on demand through a single urethra. Some anatomical variants include a fused or single kidney (1 in 750–1000 people), multiple renal arteries (32%) and veins (30%; usually right-sided) and duplication of the collecting system (<1%) which can be at the level of the renal pelvis, ureter, or down to the level of the bladder. Vascular duplication is usually functionally unimportant although can result in complexity at times of surgery or other invasive procedures. Ureteric duplication if often associated with obstruction or reflux. Sympathetic nerves travel within the renal artery adventitia to supply the kidney.

Internal structure

The macroscopic internal structure of the kidney can be divided into several key areas: renal cortex, renal medulla, renal pyramids, and the calyceal system including the renal pelvis. The microscopic structure of the renal parenchyma consists of between 900,000 to 1 million nephron units [1] and the renal interstitium which includes arcuate arteries, peritubular capillaries, and interstitial fibroblasts. The nephron unit begins with the renal glomerulus, a delicate tuft of capillaries supported by specialized epithelial cells (podocytes and mesangial cells) that is supplied and drained by an afferent and efferent arteriole respectively. Each glomerulus sits within a capsule (Bowman's) that is drained by a single renal tubule. Each tubule consists of a single layer of epithelial cells that have a luminal membrane (urine side) and basolateral membrane (interstitial side). The sections of the renal tubule include the proximal convoluted tubule (PxCT), the loop of Henle (LOH: consisting of the thin descending limb, thin ascending limb, and thick ascending limb), and distal convoluted tubule (DCT) several of which join together to form a collecting duct (CD). The renal cortex consists of mostly glomeruli and the PxCT and DCT, the renal medulla consists of mostly the LOH and the renal pyramids contain the CD that drain the final urine into the calyceal system. The calyceal system acts to funnel the urine via the renal pelvis into the muscular ureter that then propels the urine towards the bladder. The most metabolically active cells within the nephron unit include the PxCT and DCT, the thick ascending limb of the LOH and the glomerular podocyte. Therefore, these are the areas of the kidney that are most susceptible to toxic or ischaemic injury.

Renal function

The combined blood flow to both kidneys is in the order of 1 L/min, i.e. 20% of the entire cardiac output. The blood flow to each glomerulus is controlled by the afferent (feeder) arteriolar tone, i.e. vasodilatation will result in an increase in pressure and flow into the glomerulus and vasoconstriction will result in a decrease in pressure and flow into the glomerulus. This mechanism is under the control of prostaglandins which when present results in vasodilatation and when absent or inhibited (e.g. by non-steroidal anti-inflammatory drugs) results in vasoconstriction. The glomerular tuft is therefore subject to variable pressure loads (glomerular filtration pressure) that are not only determined by the afferent arteriolar inflow, but also the efferent arteriolar outflow. The efferent arteriolar tone is under the control of angiotensin II and vasoconstricts when present, causing an increase in the glomerular pressure and vasodilates when absent or inhibited (e.g. by angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB)) resulting in a decrease in glomerular pressure. The glomerular tuft acts as a semi-permeable membrane consisting of a basement membrane that is only 330 ± 50 (SD) nm thick in the males and 305 ± 45 nm thick in the females supported on the blood side by a single layer of endothelial cells and on the urine side by a single layer of podocytes. Therefore, changes in the glomerular pressure will result in an increased or decrease in the filtration rate when the pressure is increased or decreased respectively. This filtration rate is described as the glomerular

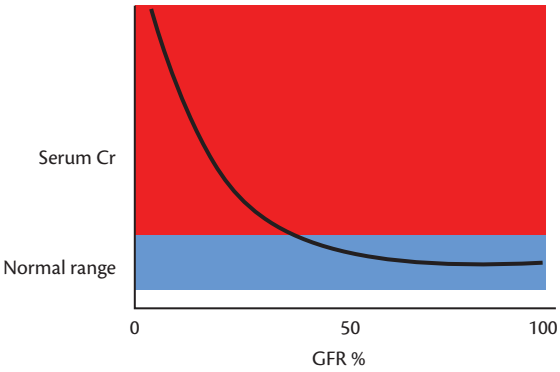


Fig. 208.1 Association between GFR and creatinine.

filtration rate (GFR) and in a normal adult male is approximately 120 mL/min or 170 L/day.

GFR is often used synonymously with 'renal function' although as described later in this chapter there are many other aspects of kidney function beyond GFR. GFR can be defined as the rate of clearance of a substance from the blood into the urine by glomerular filtration assuming that it passes through the nephron unit without undergoing any metabolism, tubular secretion, or reabsorption. As GFR can be difficult to measure accurately in a clinical setting (laboratory based settings use inulin infusions) surrogate estimates of GFR are often used. As creatinine is a continuously produced endogenous substance (muscle derived) that undergoes glomerular filtration without any subsequent reabsorption and only minimal tubular secretion it can be used as a simple measure of GFR. Creatinine clearance (CrCl) can be calculated using a timed urine collection by measuring the urinary flow rate (V) (mL/min) and urinary creatinine concentration (U) (μmol/L) with a simultaneously drawn plasma creatinine concentration (P) (μmol/L) using the simple equation: CrCl = UV/P. (**Note**: plasma creatinine should now universally be measured by the standardized isotope dilution mass spectrometry (IDMS) method, which is considered the best reference standard measure [2]). However, as creatinine production is significantly influenced by age, gender, and muscle mass and as there is often the need to compare renal function between different patient groups, various estimating equations for GFR (eGFR) have been derived (Cockcroft and Gault [3], modification of diet in renal disease (MDRD) [4], CKD Epidemiology Collaboration CKD-EPI [5]). It is important to remember that these are estimating equations derived in specific patient populations (e.g. MDRD equation was derived from patients with GFRs between 15 and 60 mL/min/1.73 m^2); they are inaccurate in patients not at steady state (i.e. during acute renal failure or its recovery) and in patients on dialysis. The units of GFR are usually millilitres per minute (mL/min) corrected for body size to an average body surface area of 1.73 m^2, i.e. mL/min/1.73 m^2. This enables the comparison of renal function in two or more individuals of different body size. Creatinine concentration can be used as a simple measure of renal function. Again assuming that creatinine production remains unchanged an increase in creatinine in a given individual reflects worsening renal function whereas a decrease reflects improving renal function. It is important to remember that the relationship between GFR and serum creatinine is inverse and non-linear (see Fig. 208.1).

From Fig. 208.1, it can also be seen that up to 50% of GFR can be lost before the serum creatinine rises outside of the normal range, and at lower levels of GFR further small reductions in GFR can result in a significant rise in the blood concentration of creatinine and other important solutes (urea and potassium).

Due to the semi-permeable nature of the glomerulus, the composition of the glomerular filtrate is effectively identical to that of the blood plasma minus the proteins which under normal circumstances are too large to cross. Given that the daily GFR is 170 L a significant recovery mechanism is needed to prevent major solute and fluid loss. This is achieved by the subsequent luminal fluid manipulation, both active and passive, that occurs in various segments of the renal tubule. The final urine produced is therefore a highly modified version of the glomerular filtrate and is so well balanced that subtle adjustments in various elements and fluid balance can be achieved.

Tubular reabsorption

The majority of the filtered solute (sodium, potassium, chloride, calcium, phosphate, and bicarbonate) is recovered in the PxCT [6] (see Table 208.1) via specific pathways driven by a sodium/potassium adenosine 5'-triphosphatase (Na^+/K^+ ATPase) found on the basolateral membrane. ATPase generates an electrochemical gradient by removing sodium from the cell and moving potassium

Table 208.1 Summary of renal handling

Element	PxCT	DL of the LOH	AL of the LOH	DCT	CD	Urine content as % of filtered load
Na^+	65–70%	0%	20–25%	5–9%	0%	<1%
K^+	65–70%	0%	25%	Secretion	0%	>20%
Ca^{2+}	55–70%	0%	20–25%	5–10%	<2%	1–3%
$PO4^{3-}$	80–95%	0%	0%	0%	0%	5–20%
HCO_3^-	80–85%	0%	10–15%	5%	0%	0%
H_2O	65–70%	15%	0%	5%	10–14%	<1%

% indicates the percentage of filtered elements reabsorbed in different part of the nephron.

PxCT, proximal convoluted tubule; DL, descending limb; AL, ascending limb; LOH, Loop of Henle; DCT, distal convoluted tubule; CD, collecting duct.

Data from Maddox DA and Gennari FJ, 'The early proximal tubule: a high-capacity delivery-responsive reabsorptive site', *American Journal of Physiology*, 1987, **252**(4 Pt 2), pp. F573–84.

into the cell. Amino acids and glucose, when at normal levels, are completely recovered by the PxCT via luminal sodium-amino acid and sodium–glucose cotransporters. Significant water recovery also occurs in parallel to this active solute uptake in the proximal tubules. The thick ascending limb of the loop of Henle selectively recovers another 20–25% sodium and chloride via a luminal sodium potassium chloride co-transporter, without any passage of water. This mechanism is blocked by frusemide. The distal convoluted tubule absorbs small amounts of sodium and chloride again utilizing a basolateral Na^+/K^- ATPase and a luminal sodium-chloride co-transporter (the latter is blocked by thiazide diuretics [7]).

Water balance

As mentioned earlier, a large volume of fluid is filtered by the glomerulus and so several mechanisms exist to prevent significant fluid losses. The majority of filtered water (65–70%) returns to the circulation along with the filtered solute in the PxCT. The second location for water reabsorption is in the thin descending limb of the LOH. This part of the LOH is permeable only to water and as it travels deeper into the renal medulla it is exposed to increasing osmotic forces, from the iso-osmolar (300 mOsm/kg) cortex through to the hyperosmolar (up to 1200 mOsm/kg) medulla. This osmotic concentration gradient is generated by the active solute exchange (counter current exchange [8]) that occurs in the LOH. Aquaporin channels selectively allow the movement of water across the cell membrane under the influence of the osmotic gradient. The solute reabsorption in the DCT also results in water reabsorption (approximately 5%). The final location for water reabsorption is in the CD. The CD again utilizes the increasing osmotic gradient as it traverses from the cortex to the medulla and water is reabsorbed via aquaporin channels under the control of anti-diuretic hormone (ADH). ADH is produced by osmoreceptors (neurosecretory neurons) in the hypothalamus under circumstances of dehydration and secreted by the posterior pituitary into the blood. ADH then travels via the blood to the kidney where it binds to a basolateral membrane receptor that initiates a cyclic AMP dependent protein kinase pathway that results in insertion of preformed aquaporin channels onto the luminal membrane of the CD [9] allowing water reabsorption. The action of ADH is to produce a reduced volume of more concentrated urine. ADH secretion is inhibited by over hydration and in the absence of ADH the CD aquaporin channels are removed from the luminal surface rendering the CD impervious to water. This absence of ADH results in the passage of a larger urine volume with a low osmolality. Through these processes serum osmolality is maintained between 285 and 295 mOsm/kg by the kidney's ability to produce urine with a concentration varying between 50 and 1200 mOsm/kg [10].

Acid balance

Normal metabolic function results in the production of acid. Some of these acids can be removed in the form of carbon dioxide via respiration. Other acids can only be removed by passage in the urine. Two areas of the nephron are critical in managing acid base balance via proximal tubular bicarbonate recovery and acid secretion in the late distal tubule/cortical collecting duct [11].

Proximal tubule

As bicarbonate is freely filtered by the glomerulus a recovery mechanism is required to prevent massive bicarbonate loss that would result in acidosis (i.e. proximal renal tubular acidosis (RTA), also known as type II RTA); the PxCT is a site of major bicarbonate recovery. The mechanism used to recover bicarbonate relies on a luminal sodium-hydrogen exchange carrier molecule (NHE-3) and luminal carbonic anhydrase (CA). Freely filtered HCO_3^- combines with actively secreted hydrogen to form H_2CO_3. In the presence of CA, H_2CO_3 dissociates to H_2O and CO_2, the latter can then diffuse into the PxCT. Within this cell and again in the presence of CA the CO_2 combines with H_2O to form H_2CO_3. This can then dissociate into H^+ and HCO_3^- of which the former can move via the NHE-3 into the luminal fluid and the latter into the blood via a basolateral Na^+/HCO_3^- co-transporter. Any defect in this system results in bicarbonate remaining within the tubule (although the distal tubule can compensate for some of these losses) resulting in a metabolic acidosis. The most common cause of this in adults is the use of a carbonic anhydrase inhibitor (acetazolamide) and in children due to a congenital tubular defect (Fanconi's syndrome which is also associated with increase urinary losses of amino acids, glucose, phosphate, and uric acid).

Distal tubule

The distal tubule is responsible for active acid secretion into the lumen via two separate mechanisms involving H^+-ATPase located on the luminal membrane (intercalated cell). This mechanism is again dependent on intracellular CA producing H_2CO_3, which then dissociates into H+ and HCO_3^-. The HCO_3^- moves across the basolateral cell membrane via a chloride-bicarbonate exchange carrier. The H^+ is actively transported into the lumen via the H^+-ATPase and then binds with either filtered HPO_4^{2-} to form $H_2PO_4^-$, or luminal ammonia (NH_3), produced by proximal tubule glutaminase from the amino acid glutamine [12], to form ammonium (NH_4^+) both of which are trapped within the lumen and excreted. This process not only results in the secretion of acid, but also generates bicarbonate and hence partly compensate for proximal losses if they occur. Significant up-regulation of acid excretion can occur through increased NH_3 production. Any defect in this distal system will result in failure of acid secretion and this usually results in a significant metabolic acidosis (distal renal tubular acidosis, also known as type I RTA). The most common causes of this condition in adults include tubular diseases seen with autoimmune diseases (Sjögrens syndrome and SLE) and drugs (lithium and amphotericin), and in children due to a congenital tubular defect (hereditary RTA).

Insulin and gluconeogenesis

The kidney has an important role in the control of blood glucose through several mechanisms. Under normal physiological conditions freely filtered glucose is completely reabsorbed by the proximal tubule leaving the resultant urine free of glucose. However, as the maximal re-absorptive capacity of filtered glucose is only 11 mM, filtered glucose loads above this level (i.e. during diabetes induced hyperglycaemia) will result in glycosuria. The process of glucose reabsorption is achieved by luminal membrane based sodium-glucose linked transporters (SGLT1/2) [13], again driven by a basolateral based Na^+/K^+ ATPase, and the passive removal of intracellular glucose via basolateral glucose transporters (GLUT1/2) [14]. The kidney is now also considered to be an important site of glucose production (up to 40%) [15], after that of the liver, through the process of gluconeogenesis. This results in

the generation of glucose from non-carbohydrate carbon substrates (principally lactate). A final factor that impacts on blood glucose control is the kidneys role in insulin clearance. Insulin is freely filtered by the glomerulus and then reabsorbed by the PxCT where it undergoes proteolytic degradation into small peptide fragments that are then returned to the circulation.

Hormonal function

Erythropoietin

Erythropoietin is a critical glycoprotein hormone that controls erythropoiesis. If the oxygen concentration of the blood passing through the kidney is low, specialized fibroblasts within the peritubular interstitium are stimulated to produce erythropoietin [16]. This erythropoietin then travels through the blood to the bone marrow where it stimulates the proliferation of erythrocyte precursors into mature red blood cells. In kidney disease erythropoietin levels can be inappropriately low or absent causing significant anaemia. This can easily be corrected by administration of synthetic erythropoietic agent [17].

Vitamin D and parathyroid hormone

Vitamin D is a critical hormone for calcium homeostasis and bone metabolism. The kidney converts 25-hydroxycholecalciferol into its activated form 1,25-dihydroxycholecalciferol [18]. In the presence of kidney disease activated vitamin D levels fall resulting in a decrease in serum calcium concentration. Decreasing calcium concentration are countered by increasing parathyroid hormone (PTH) concentration, which stimulates the release of calcium from bones in an attempt to return the serum calcium concentration to normal. PTH concentration also increases in kidney disease due to reduced phosphate clearance resulting in elevated serum phosphate concentration. PTH increases renal phosphate clearance in the attempt to return the serum phosphate to normal. This stimulation of the parathyroid gland to produce PTH is termed secondary hyperparathyroidism although if prolonged can result in the production of uncontrolled parathyroid adenomas (tertiary hyperparathyroidism) [19].

Renin

Renin is an enzyme produced by specialized cells within the afferent arteriole adjacent to the DCT (juxtaglomerular apparatus). Factors that stimulate renin production include a decrease in blood pressure, reduced sodium delivered to the DCT and increased sympathetic activity [20], i.e. situations suggesting dehydration or hypotension. Once in the blood, renin hydrolyses angiotensinogen (produced by the liver) into angiotensin I, which in turn is converted to angiotensin II by ACE within the lungs. Angiotensin II increases blood pressure through arteriolar vasoconstriction, aldosterone production, sympathetic nervous system activation, increased thirst, and direct stimulation of proximal tubular sodium reabsorption. Important factors that result in inappropriate renin production and resulting systemic hypertension include renal artery stenosis and kidney disease.

Influencing hormones

Aldosterone is an important steroid hormone that is produced in the adrenal gland (zona glomerulosa) in the presence of angiotensin II or high potassium concentration. Aldosterone acts to stimulate sodium reabsorption (via luminal epithelial sodium channels ENaC which is blocked by amiloride) and potassium secretion (via K^+ channels in the luminal membrane) in the cortical collecting duct (principal cell), again driven by a basolateral Na^+/K^- ATPase, resulting in salt and water retention.

References

1. Bertram JF, Douglas-Denton RN, Diouf B, Hughson MD, and Hoy WE. (2011). Human nephron number: implications for health and disease. *Pediatric Nephrology*, **26**(9), 1529–33.
2. Stevens PE and Levin A. (2013). Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Annuals of Internal Medicine*, **158**(11), 825–30.
3. Cockcroft DW and Gault MH. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**(1), 31–41.
4. Levey AS, Coresh J, Greene T, et al. (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Annuals of Internal Medicine*, **145**(4), 247–54.
5. Levey AS, Stevens LA, Schmid CH, et al. (2009). A new equation to estimate glomerular filtration rate. *Annals of Internal Medicine*, **150**(9), 604–12.
6. Maddox DA and Gennari FJ. (1987). The early proximal tubule: a high-capacity delivery-responsive reabsorptive site. *American Journal of Physiology*, **252**(4 Pt 2), F573–84.
7. Beaumont K, Vaughn DA, and Fanestil DD. (1988). Thiazide diuretic drug receptors in rat kidney: identification with [3H]metolazone. *Proceedings of the National Academy of Sciences USA*, **85**(7), 2311–14.
8. Barrett KE and Ganong WF. (2012). *Ganong's Review of Medical Physiology*, 24th edn. New York, London: McGraw-Hill Medical.
9. Katsura T, Gustafson CE, Ausiello DA, and Brown D. (1997). Protein kinase A phosphorylation is involved in regulated exocytosis of aquaporin-2 in transfected LLC-PK1 cells. *American Journal of Physiology*, **272**(6 Pt 2), F817–22.
10. Halperin ML, Kamel KS, and Oh MS. (2008). Mechanisms to concentrate the urine: an opinion. *Current Opinion in Nephrology and Hypertension*, **17**(4), 416–22.
11. Unwin RJ and Capasso G. (2001). The renal tubular acidoses. *Journal of the Royal Society Medicine*, **94**(5), 221–5.
12. Adeva MM, Souto G, Blanco N, and Donapetry C. (2012). Ammonium metabolism in humans. *Metabolism*, **61**(11), 1495–511.
13. Lee WS, Kanai Y, Wells RG, and Hediger MA. (1994). The high affinity Na+/glucose cotransporter. Re-evaluation of function and distribution of expression. *Journal of Biological Chemistry*, **269**(16), 12032–9.
14. Sacktor B. (1989). Sodium-coupled hexose transport. *Kidney International*, **36**(3), 342–50.
15. Meyer C, Stumvoll M, Dostou J, Welle S, Haymond M, and Gerich J. (2002). Renal substrate exchange and gluconeogenesis in normal postabsorptive humans. *American Journal of Physiology: Endocrinology Metabolism*, **282**(2), 428–34.
16. Bachmann S, Le Hir M, and Eckardt KU. (1993). Co-localization of erythropoietin mRNA and ecto-5'-nucleotidase immunoreactivity in peritubular cells of rat renal cortex indicates that fibroblasts produce erythropoietin. *Journal of Histochemicals and Cytochemicals*, **41**(3), 335–41.
17. Macdougall IC and Ashenden M. (2009). Current and upcoming erythropoiesis-stimulating agents, iron products, and other novel anemia medications. *Advanced Chronic Kidney Disease*, **16**(2), 117–30.
18. Perwad F and Portale AA. (2011). Vitamin D metabolism in the kidney: regulation by phosphorus and fibroblast growth factor 23. *Molecular Cell Endocrinology*, **347**(1–2), 17–24.
19. Jamal SA and Miller PD. (2013). Secondary and tertiary hyperparathyroidism. *Journal of Clinical Densitom*, **16**(1), 64–8.
20. Kurtz A. (2012). Control of renin synthesis and secretion. *American Journal of Hypertension*, **25**(8), 839–47.

PART 8.2

Renal monitoring and risk prediction

CHAPTER 209

Monitoring renal function in the critically ill

Paul M. Palevsky

Key points

- Renal function needs to be closely monitored in patients at high risk for acute kidney injury (AKI).
- Urine output should be monitored continuously in all patients.
- Serum creatinine should be measured at least daily, with more frequent measurement in patients at increased risk for AKI as the result of underlying susceptibilities and acute exposures.
- Calculated estimates of glomerular filtration rate (eGFR) are unreliable in critically-ill patients with unstable kidney function.
- Biomarkers of tubular injury may be helpful in the differential diagnosis of AKI and for assessment of prognosis, however, they do not have a role in routine monitoring of kidney function.

Introduction

The manifestations of kidney dysfunction in critically-ill patients range from asymptomatic laboratory abnormalities associated with early or mild disease to a constellation of symptoms including oliguria, volume overload and overt uremic manifestations accompanied by acidaemia and electrolyte derangements in patients with severe acute kidney injury (AKI). A fundamental difficulty in the assessment of kidney function is the absence of reliable bedside methods to measure glomerular filtration rate (GFR) and rapidly detect changes in kidney function. In the critical care setting, kidney function is commonly monitored based on changes in the concentration of urea and/or creatinine in the blood or as the result of sustained reduction in urine output and these are the parameters that are used for the consensus definitions and staging of AKI Tables 209.1 and 209.2 [1].

Urine volume

Although reductions in urine volume may be a manifestation of both AKI and advanced chronic kidney disease (CKD), urine volume is neither a sensitive nor specific index of kidney function. Sustained acute oliguria, which is defined as a urine output of <20 mL per hour or <400–500 mL per day, in the absence of effective intravascular volume depletion almost always indicates the presence of AKI. While oliguria is often considered to be a cardinal feature of AKI, the majority of critically-ill patients with AKI are non-oliguric. Thus, although the acute onset of sustained oliguria should prompt the evaluation for AKI, the presence of a well-maintained urine output should not be equated with the absence of impaired kidney function. Anuria (the absence of urine output) always demands prompt attention. True anuria is most often caused by complete urinary obstruction, but may also be seen with vascular catastrophes resulting in bilateral renal infarction and less commonly with severe forms of rapidly progressive glomerulonephritis. Rarely, severe intrinsic AKI due to acute tubular necrosis may result in transient anuria. In patients with CKD, urine output is generally preserved until kidney function is severely impaired and may even be sustained in occasional patients requiring chronic dialysis.

Markers of glomerular filtration rate

GFR is the primary index used to assess kidney function. While most rigorously measured from the clearance of exogenous markers

Table 209.1 Kidney Disease: Improving Global Outcomes (KDIGO) definition and staging of acute kidney injury

	Serum creatinine	Urine output
Definition	Increase by ≥26.5 µmol/L (≥0.3 mg/dL) within 48 hours; *or* Increase to ≥1.5 times baseline, which is known or presumed to have occurred within the previous 7 days	<0.5 mL/kg per hour for 6 hours
Stage 1	1.5–1.9 times baseline *or* ≥26.5 µmol/L (≥0.3 mg/dL) increase	< 0.5 mL/kg per hour for 6–12 hours
Stage 2	2.0–2.9 times baseline	<0.5 mL/kg/hour for ≥12 hours
Stage 3	≥3.0 times baseline *or* Increase to ≥353.6 µmol/L (≥4.0 mg/dL) *or* Initiation of renal replacement therapy *or* In patients <18 years, decrease in eGFR to <35 mL/min/1.73 m^2	<0.3 mL/kg/hour for ≥24 hours *or* Anuria for ≥12 hours

Either serum creatinine or urine output criteria satisfied.

Table 209.2 Comparison of RIFLE, AKIN, and KDIGO creatinine-based definitions of acute kidney injury*

	RIFLE	AKIN	KDIGO
Definition	Increase to ≥1.5 times baseline that is both abrupt (within 1–7 days) and sustained (>24 hours)	Increase of ≥26.5 μmol/L (≥0.3 mg/dL) *or* Increase to ≥1.5 times baseline within 48 hours	Increase of ≥26.5 μmol/L (≥0.3 mg/dL) within 48 hours; *or* Increase of ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
RIFLE –R AKIN/KDIGO Stage 1	Increase to 1.5–2 times baseline	Increase of 1.5–2 times baseline *or* Increase of ≥26.5 μmol/L (≥0.3 mg/dL)	Increase of 1.5–1.9 times baseline *or* Increase of ≥26.5 μmol/L (≥0.3 mg/dL)
RIFLE –I AKIN/KDIGO Stage 2	Increase to 2–3 times baseline	Increase of 2–3 times baseline	Increase of 2.0–2.9 times baseline
RIFLE –F AKIN/KDIGO Stage 3	Increase to >3.0 times baseline *or* Increase to >353.6 μmol/L (>4.0 mg/dL) with an acute rise >44 μmol/L (>0.5 mg/dL)	Increase of >3 times baseline *or* Increase to ≥ 353.6 μmol/L (≥4.0 mg/dL) with an acute rise >44 μmol/L (>0.5 mg/dL) *or* On RRT	Increase of ≥3.0 times baseline *or* Increase to ≥353.6 μmol/L (≥4.0 mg/dL) *or* Initiation of RRT *or* In patients <18 years, decrease in eGFR to <35 mL/min/1.73 m^2
RIFLE-L	RRT > 4 weeks		
RIFLE-E	Need for RRT for >3 months		

RIFLE, risk, injury, failure, loss, end-stage; AKIN, acute kidney injury network; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, renal replacement therapy.

The urine output criteria for these three definition and classification systems for acute kidney injury are the same (see Table 209.1).

of glomerular filtration such as inulin, iothalamate, or iohexol, GFR is more commonly assessed based on the concentrations of endogenous solutes that are primarily excreted by glomerular filtration such as urea, creatinine, and less frequently cystatin C. A sudden decrease in GFR will result in rising concentrations of these solutes in the blood. However, the relationship between the GFR and the concentration of these solutes is nonlinear and may be affected by a variety of additional factors.

Urea

Urea is the major end product of nitrogen metabolism. Blood urea concentration, often assayed as blood urea nitrogen (BUN), is dependent upon the balance between synthesis in the liver and excretion by the kidneys. Although increases in urea concentration are often assumed to be due to reduced kidney excretion, increases in urea generation as a result of excessive dietary protein intake, from amino acid loading during nutritional support and from breakdown of the endogenous protein load from gastrointestinal haemorrhage as well as during the hypercatabolic states associated with fever, sepsis, or glucocorticoid administration can cause elevations in the urea concentration in the absence of significant decrease in GFR. Conversely, when hypercatabolic states are superimposed on AKI, the increase in urea may be exaggerated and exceed the increase of 4–8 mmol/L (10–20 mg/dL) per day that is typically seen in patients who are functionally anephric.

Normally, urea is freely filtered at the glomerulus and partially reabsorbed along the length of the nephron. Urea reabsorption is increased in states of low urine flow, such as volume depletion and severe heart failure, resulting in increases in urea concentration that are disproportionate to the decrease in GFR. This variability in urea generation and renal tubular reabsorption contribute to the poor performance of urea as a marker of GFR. However, the urea concentration generally correlates with symptoms of renal failure, with uremic manifestations usually absent until the urea concentration is greater than 30–35 mmol/L (85–100 mg/dL).

Creatinine

Creatinine is generated from the non-enzymatic hydrolysis of muscle creatine and is excreted primarily by glomerular filtration, although there is a variable component of tubular secretion. Creatinine generation is relatively constant, correlating with lean muscle mass, averaging 175–220 μmol/kg (20–25 mg/kg) per day in healthy young adult males and 130–175 μmol/kg (15–20 mg/kg) per day in healthy young adult females. Creatinine generation declines with age, malnutrition, and in chronic disease. Creatinine is freely filtered at the glomerulus and is not reabsorbed along the length of the nephron. In patients with normal kidney function,

less than 10% of urinary creatinine is due to tubular secretion. However, this percentage increases as GFR decreases in patients with CKD. Hence, given the relatively predictable generation rate and predominant excretion by glomerular filtration, the plasma creatinine concentration is inversely related to GFR, with increased creatinine concentration associated with decreased GFR. This has allowed the development of equations to estimate GFR based on serum creatinine with adjustments for demographic and clinical variables [2–5].

In the absence of glomerular filtration, such as during severe AKI, serum creatinine typically increases by 90–175 μmol/L (1–2 mg/dL) per day. This increase is influenced by multiple factors including the degree of decrease in GFR, the rate of creatinine production and changes in the volume of distribution of creatinine. For example, creatinine production is often reduced in sepsis [6], and may be markedly increased in rhabdomyolysis. In addition, aggressive volume resuscitation may mask an increase in serum creatinine by rapidly expanding its volume of distribution and diminishing or obscuring the rise in serum concentration [7]. Several other factors may also impair the reliability of serum creatinine as a marker of kidney function in critical illness. Some medications, most notably trimethoprim and cimetidine, block tubular secretion of creatinine, leading to an increase in serum creatinine concentration in the absence of decreased kidney function [8]. While this effect is generally minimal in patients with normal kidney function, the increase in serum creatinine may exceed 30% in patients with underlying CKD. Reported creatinine concentrations may also be increased as a result of chemical interference with some assay methods by ketone bodies or by medications, such as cefoxitin [8]. One final drawback to the use of creatinine as a marker of kidney function in patients with AKI is the inverse relationship between serum creatinine concentrations and GFR. Thus, significant reductions in GFR may occur prior to the change in serum creatinine concentration being recognized.

Cystatin C

Given the limitations of urea and creatinine as markers of kidney function, other readily available markers of glomerular filtration have been sought. Cystatin C, a cysteine protease inhibitor that is released into the bloodstream at a constant rate from all nucleated cells, has been proposed as a more sensitive endogenous marker of glomerular filtration rate, including in ICU patients. Cystatin C is filtered at the glomerulus and reabsorbed and catabolized by renal proximal tubular epithelial cells such that normally virtually no cystatin C appears in the urine. The inter-individual variability in cystatin C production appears to be less than that for creatinine. Thus, in steady-state situations cystatin C may be a more reliable marker of glomerular filtration [9]. In addition, the serum half-life of cystatin C is shorter than that of creatinine, making it a more sensitive marker for acute changes in glomerular filtration. However, cystatin C assays are not currently readily available in the acute clinical setting, and the optimal role for cystatin C in the detection of AKI in critically-ill patients remains to be determined.

Quantification of glomerular filtration rate

Precise quantification of GFR requires the measurement of clearance of endogenous or exogenous solutes that are removed primarily by glomerular filtration. Creatinine clearance may be measured by performing a timed urine collection and dividing the rate of urinary creatinine excretion by the concentration of creatinine in the blood, expressed as:

$$\text{Creatinine Clearance} = U_{creat} \times V/P_{creat} \quad \text{[eqn 1]}$$

where U_{creat} is the urine concentration of creatinine, V is the urine flow, expressed as volume per unit time, and P_{creat} is the average concentration of plasma creatinine during the urine collection [10]. When plasma creatinine is in steady state, a single measurement is sufficient. However, when creatinine concentration is changing, as is generally the case in AKI, a time averaged concentration based on serial measurements during the urine collection is necessary. Alternatively, if the timed collection is relatively brief, a mid-point serum creatinine may be sufficient [10]. Measured creatinine clearance is prone to errors in quantification of the precise duration and volume of the urine collection, small errors in quantification of these parameters, especially when collection time is shorter than 12 hours or urine volume is less than 1 litre may result in substantial error in the calculated creatinine clearance. In addition, since creatinine is excreted by tubular secretion as well as by glomerular filtration, measured creatinine clearance will generally overestimate true GFR. For these reasons, measurement of creatinine clearance is rarely used to monitor kidney function in the critically-ill patient. While the use of exogenous filtration markers such inulin, iothalamate, and iohexol provide more precise quantification of GFR, they are rarely used outside of research settings and are not practical tools for monitoring kidney function in the ICU setting. Newer techniques, using differential plasma disappearance of a large non-filterable plasma volume marker and smaller filterable reporter molecule, have been developed and may provide a means for real-time bedside measurement of GFR in the future [11].

Estimated glomerular filtration rate and creatinine clearance

Methods for estimating creatinine clearance and glomerular filtration have been developed based on serum creatinine and/or cystatin C concentrations and using demographic and clinical variables such as age, gender, race, or weight to adjust for inter-individual variability in creatinine and cystatin C generation [2–5]. These equations, including the Cockroft–Gault equation for estimated creatinine clearance and the Modification of Diet in Renal Disease (MDRD) and the CKD Epidemiology Collaboration (CKD-EPI) equations for estimated GFR can only be used when serum creatinine is in steady state. In addition, these equations were developed in cohorts of non-hospitalized patients and have not been validated in the setting of acute illness. Thus, laboratory reported estimates of GFR should not be relied upon in critically-ill patients with unstable kidney function.

Markers of tubular injury

A number of markers of tubular injury including kidney injury molecule-1 (KIM-1) [12], neutrophil gelatinase-associated lipocalin (NGAL) [13], interleukin (IL)-18 [14,15], liver fatty acid binding protein (L-FABP) [16], alpha and pi-glutathione-S-transferase (GST) [17], insulin-like growth factor-binding protein-7 (IGFBP7) [18], and tissue inhibitor of metaloprotinases-2 (TIMP-2) [18], among others, have been described. These markers have shown promise for the early diagnosis of AKI, for differentiation between

Table 209.3 Risk factors for the development of acute kidney injury

Underlying susceptibilities	Acute exposures
◆ Chronic kidney disease	◆ Sepsis
◆ Advanced age	◆ Circulatory shock
◆ Female gender	◆ Cardiac surgery/Cardiopulmonary bypass
◆ Black race	◆ Major non-cardiac surgery
◆ Volume depletion	◆ Burns
◆ Heart failure	◆ Trauma
◆ Liver failure	◆ Nephrotoxic medications (e.g. aminoglycosides, amphotericin B, cisplatin)
◆ Diabetes mellitus	◆ Radiocontrast agents
◆ Non-steroidal anti-inflammatory drugs	◆ Toxins (e.g., ethylene glycol)
◆ RAAS inhibition (e.g. ACEI, ARB)	

RAAS, renin-angiotensin-aldosterone system; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

volume responsive (e.g. pre-renal) AKI and intrinsic tubular injury, and for prediction of the need for renal replacement therapy and hospital mortality [19]. However, the optimal marker or panel of markers and their role in the clinical care of patients at risk for AKI remains uncertain and is an active area of clinical investigation [19].

Approach to monitoring of kidney function

Monitoring kidney function in critically-ill patients should be based primarily on measurements of serum creatinine and urine output [1]. Urine output should be monitored continuously. Oliguria or anuria should be promptly evaluated for evidence of volume depletion or haemodynamic compromise. Persistent oliguria following adequate volume resuscitation should prompt further evaluation of causes of AKI, including obstruction, abdominal compartment syndrome, non-volume responsive haemodynamic compromise and intrinsic causes of AKI. Serum creatinine should be measured at least daily, with more frequent measurement in patients at increased risk for AKI as the result of underlying susceptibilities and acute exposures Table 209.3 [1].

Patients with an acute decline in kidney function should undergo a prompt, systematic evaluation to identify the specific cause, with particular attention to the identification and treatment of reversible aetiologies of AKI. Evaluation should include a careful assessment of medication and environmental exposures, ingestion of toxins, and episodes of sepsis or hypotension. Haemodynamic status, including cardiac output, preload responsiveness, and intra-abdominal pressure should be assessed as appropriate to the clinical context. Additional laboratory testing, including a comprehensive metabolic profile, complete blood count with examination of the peripheral smear, urinalysis with microscopy and urine chemistries may be helpful in elucidating the underlying cause of AKI. Renal imaging studies, particularly renal ultrasound, are also helpful in the evaluation of AKI, particularly for the assessment of acute obstruction. Biomarkers of tubular injury may be helpful in the differential diagnosis of AKI and in assessment of prognosis, although their precise role remains the subject of investigation [19].

In patients with established AKI, continued close monitoring of urine output and serum creatinine is required to stage the severity of AKI and assess the response to treatment. Just as increases in serum creatinine and urea and decreased urine output are the cardinal manifestations of AKI, spontaneous recovery of urine output and fall in blood urea and creatinine concentrations generally herald recovery of kidney function.

References

1. (2012). Kidney disease: improving global outcomes (KDIGO) AKI Definition. *Kidney International Supplements*, **2**, 19–36.
2. Cockcroft DW, and Gault MH. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**, 31–41.
3. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, and Roth D. (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Annals of Internal Medicine*, **130**, 461–70.
4. Levey AS, Stevens LA, Schmid CH, et al. (2009). A new equation to estimate glomerular filtration rate. *Annuals of Internal Medicine*, **150**, 604–12.
5. Stevens LA, Coresh J, Greene T, and Levey AS. (2006). Assessing kidney function—measured and estimated glomerular filtration rate. *New England Journal of Medicine*, **354**, 2473–83.
6. Doi K, Yuen PS, Eisner C, et al. (2009). Reduced production of creatinine limits its use as marker of kidney injury in sepsis. *Journal of American Society of Nephrology*, **20**, 1217–21.
7. Macedo E, Bouchard J, Soroko SH, et al. (2010). Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Critical Care*, **14**, R82.
8. Muther RS. (1983). Drug interference with renal function tests. *American Journal of Kidney Disease*, **3**, 118–20.
9. Inker LA, Schmid CH, Tighiouart H, et al. (2012). Estimating glomerular filtration rate from serum creatinine and cystatin C. *New England Journal of Medicine*, **367**, 20–9.
10. Palevsky PM, Zhang JH, O'Connor TZ, et al. (2008). Intensity of renal support in critically ill patients with acute kidney injury. *New England Journal of Medicine*, **359**, 7–20.
11. Wang E, Meier DJ, Sandoval RM, et al. (2012). A portable fibre optic ratiometric fluorescence analyzer provides rapid point-of-care determination of glomerular filtration rate in large animals. *Kidney International*, **81**, 112–17.
12. Han WK and Bonventre JV. (2010). Biologic markers for the early detection of acute kidney injury. *Current Opinion in Critical Care*, **10**, 476–82.
13. Cruz DN, de Cal M, Garzotto F, et al. (2010). Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. *Intensive Care Medicine*, **36**, 444–51.
14. Parikh CR, Abraham E, Ancukiewicz M, and Edelstein CL. (2005). Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. *Journal of the American Society of Nephrology*, **16**, 3046–52.
15. Parikh CR, Mishra J, Thiessen-Philbrook H, et al. (2006). Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. *Kidney International*, **70**, 199–203.
16. Doi K, Katagiri D, Negishi K, et al. (2012). Mild elevation of urinary biomarkers in prerenal acute kidney injury. *Kidney International*, **82**, 1114–20.
17. Koyner JL, Vaidya VS, Bennett MR, et al. (2010). Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. *Clinical Journal of American Society Nephrology*, **5**, 2154–65.
18. Kashani K, Al-Khafaji A, Ardiles T, et al. (2013). Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Critical Care*, **17**, R25.
19. Koyner JL and Parikh CR. (2013). Clinical utility of biomarkers of AKI in cardiac surgery and critical illness. *Clinical Journal of American Society of Nephrology*, **8**(6), 1034-42.

CHAPTER 210

Imaging the urinary tract in the critically ill

Andrew Lewington and Michael Weston

Key points

- Imaging of the urinary tract should be considered in patients with acute kidney injury if the cause is not clear.
- Ultrasound is the first choice imaging modality of the urinary tract on the ICU due to its portability and non-invasive nature.
- Contrast-enhanced ultrasound using non-nephrotoxic microbubble contrast agents allows imaging of kidney perfusion.
- Pyonephrosis is a cause of septic shock and needs urgent radiological intervention.
- If iodinated contrast is to be used then measures to prevent contrast –induced AKI must be employed.

Introduction

There are a large number of radiological techniques available to image the urinary tract. However there are limitations as to which of these imaging techniques can be used in a critically-ill patient on the intensive care unit (ICU) in terms of whether the technique can be utilized bedside or whether the patient is stable enough to be transferred to the radiology department. This chapter will therefore focus on those radiological techniques that are most commonly used to image urinary tract in critically-ill patients on the ICU. It will consider imaging of the native kidneys and also consider kidney transplants.

Imaging of the urinary tract in the critically-ill patient is predominantly required to assess renal anatomy in the clinical context of impaired kidney function and to aid diagnosis. Critically-ill patients commonly develop acute kidney injury (AKI) in association with multi-organ failure [1]. The most common cause of AKI in this setting is sepsis which results in renal hypoperfusion [2]. Initially, the AKI can be considered as pre-renal with a reduction in renal blood flow. This can be considered as a functional process. If the hypoperfusion is prolonged intrinsic AKI occurs whereby there is damage to the tubules. It is important to recognize that there are a variety of rarer disorders that should be considered if there is no clear cause. Post-renal AKI is due to urinary tract obstruction and is initially functional but will lead to structural damage if the obstruction is not relieved promptly. Pyonephrosis must be treated as an emergency and is a cause of septic shock.

Ultrasound is the most commonly used radiographic technique to image the urinary tract in critically-ill patients due to its non-invasive nature and ability to be used bedside. Gray scale ultrasound allows an assessment of kidney size (small and/or scarred kidneys implies chronic kidney disease) and the rapid exclusion of urinary tract obstruction. Doppler ultrasound of the intra-renal vasculature can be useful in the investigation of the cause of AKI. Computed tomography (CT) and vascular imaging can be performed in patients who are deemed stable enough for transfer to the radiology department. In both CT and vascular imaging of the urinary tract there should be consideration surrounding the use of iodinated contrast media and the risk of contrast-induced acute kidney injury (CI-AKI). Measures should be taken to reduce exposing patients at risk of or with AKI to nephrotoxins [3]. There is an increased awareness about the longer-term consequences of patients who have had an episode of AKI and the risk of progressive chronic kidney disease (CKD) [4]. It is important to reduce nephron loss and maintain functional reserve of the kidneys [5]. Magnetic resonance imaging (MRI) may be preferred in patients at high risk of CI-AKI but will need to be connected to specific monitoring equipment that can be safely used in the environment of MRI scanner.

Types of imaging

Ultrasound imaging

Gray scale ultrasound

Despite ultrasound findings often being non-specific gray scale and colour Doppler ultrasound are the most commonly used imaging techniques of the urinary tract in critically-ill patients because of its portability and non-invasive nature. Patients with critical illness often present with AKI as part of multi-organ failure and may have pre-existing CKD. The cause of any pre-existing CKD should always be considered and the baseline kidney function should always be sought as this is important when assessing recovery of function. However in the absence of recent biochemical tests of kidney function the demonstration of small (Fig. 210.1 and/or scarred kidneys using gray scale Doppler will favour a diagnosis of pre-existing CKD, whereas the presence of normal sized kidneys would support a diagnosis of AKI. The echogenicity and parenchymal thickness of the kidneys are usually preserved in patients with previously normal kidney function. Patients with CKD often have reduced parenchymal thickness and reduced corticomedullary differentiation. The identification of kidneys of two different sizes in patients presenting with AKI in the setting of known hypertension and treatment with angiotensin-converting enzyme

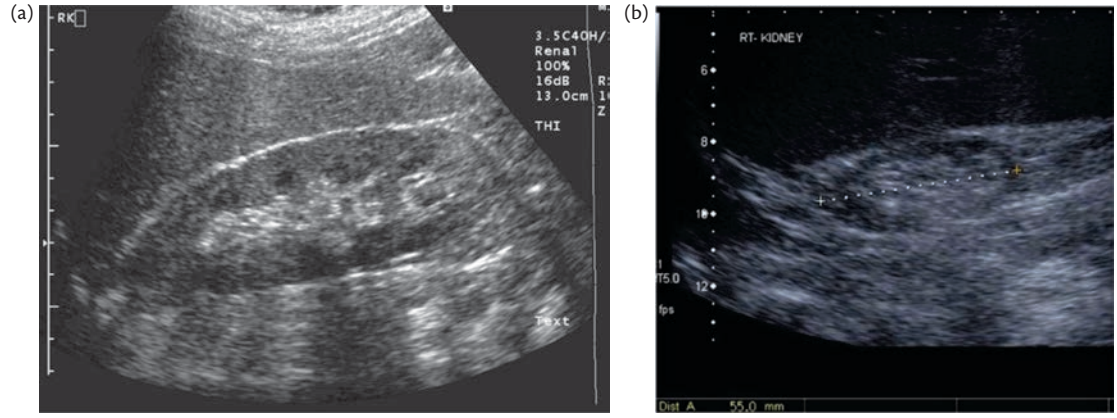


Fig 210.1 (a) Normal longitudinal ultrasound scan of right kidney. Notice the echogenic renal sinus fat, the dark evenly spaced pyramids and the even cortical echogenicity (a little darker than the adjacent liver). (b) Atrophic right kidney, 5.5 cm long. Note reduction in cortical thickness and the cortex is brighter than the adjacent liver.

(ACE) inhibitors would imply the possibility of renal artery stenosis. Further imaging of the renal arteries should be performed using colour Doppler ultrasound but may require magnetic resonance angiography (MRA) or renal arteriography for a definitive diagnosis.

The kidney size is important to assess particularly in patients presenting with AKI of unknown origin. In such patients rarer causes of AKI should be considered especially if there are features of systemic disease (e.g. uveitis, joint pains, rash, haemoptysis) and an active urinary sediment (blood and protein on urinalysis). An ultrasound demonstrating normal sized kidneys in this clinical context should prompt discussions about the utility of performing a kidney biopsy to identify rarer forms of AKI (e.g. vasculitis) and guide further management. Ultrasound guided kidney transplant biopsy maybe required in critically-ill patients to exclude the possibility of rejection as a cause of AKI.

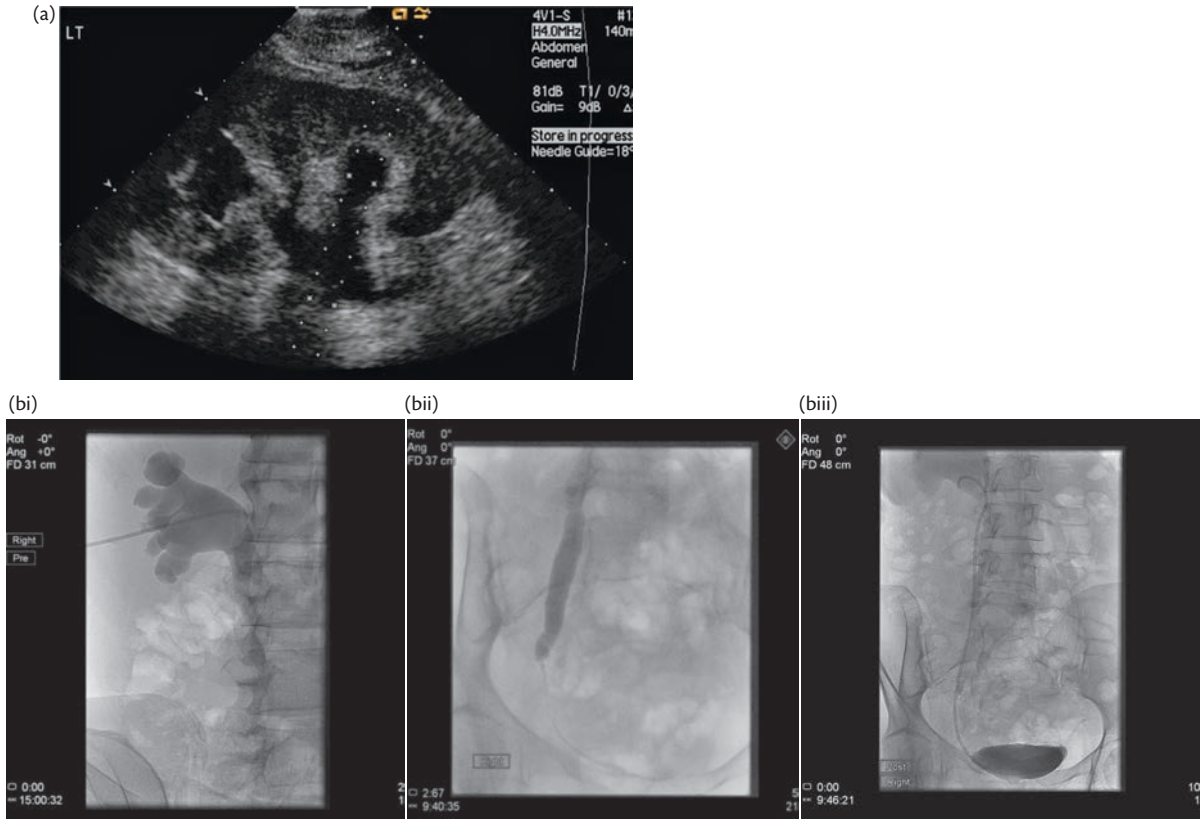


Fig 210.2 (a) Hydronephrotic kidney. The dilated pelvicalyceal system shows up as an echo-free branching structure within the renal sinus fat. Note that the guidelines for an ultrasound guided nephrostomy are aimed at the lower pole calyx. (b) Sequence of three fluoroscopic images. The first shows the dilated pelvicalyceal system is opacified by contrast medium instilled via a nephrostomy catheter. The second shows a distal extrinsic ureteric stricture that has produced the hydronephrosis. The third shows a ureteric stent in place across the stricture.

Ultrasound imaging is the technique of choice to exclude urinary tract obstruction, hydronephrosis (Fig. 210.2a). However it is recognized that in 5% of cases urinary tract obstruction may not be initially present and if it is suspected should be repeated [6]. In patients where obstruction is identified, the insertion of a nephrostomy can be performed radiologically (Fig. 210.2b). Alternatively retrograde ureteric stenting may be preferred and a urological opinion should be requested. The cause of the obstruction should always be sought and may require further imaging such as CT scanning. For obstruction of the urinary tract to cause AKI the function of both kidneys must be affected, either secondary to bilateral obstruction of the urinary tract or obstruction of a single functioning kidney. If urinary tract obstruction is suspected in patients with sepsis and AKI it is important to consider whether there could be an underlying pyonephrosis. Pus secondary to infected urine in an obstructed collecting system will appear as diffuse fine echoes on ultrasound. The associated hypotension and renal microvascular circulatory dysfunction secondary to sepsis may be of sufficient severity to result in pre-renal AKI of the other kidney. The relief of a pyonephrosis must be achieved as soon as possible to prevent the development of septic shock and irreversible damage to the renal parenchyma. Ultrasound is capable of identifying diffusely dispersed fine echoes in the obstructed collecting system which is consistent with infected urine or pus.

Contrast-enhanced ultrasonography (CEUS) of urinary tract using non-nephrotoxic microbubble contrast agents is a new technique which allows imaging of kidney perfusion. The contrast consists of microbubbles of gas stabilized in a coating of lipid, protein or polymer and has a half-life of a few minutes. Ultrasound causes the microbubbles to oscillate and resonate at an appropriate diagnostic frequency. The technique also has the advantage that the imaging is not as sensitive to movement artefacts [7]. The resolution achieved is superior to Doppler ultrasound and can be used to identify areas of non-perfusion and infarction associated with thromboembolism (e.g. trauma, vasculitis, atrial fibrillation or bacterial endocarditis). Contrast-enhanced ultrasound (CEUS) has been validated to assess and quantify the microcirculation up to capillary perfusion in several organs. A recent study utilizing CEUS 24 hours post-surgery demonstrate a decrease in renal perfusion in patients at risk of acute kidney injury [8]. It has also been shown to quantify cortical renal microcirculation in patients undergoing cardiac surgery [9]. These studies provide new possibilities for the assessment of cortical renal microcirculation in ICU patients.

Doppler ultrasonography

Duplex

Doppler ultrasonography of the renal arterial blood flow has been employed to identify patients suspected to have renal artery stenosis (RAS) [10]. Doppler ultrasonography for RAS scanning is very difficult, and is affected by the depth of the arteries, the motion imposed by respiration, and intra-abdominal gas. It has also been used to differentiate pre-renal and intrinsic AKI. Patients with pre-renal AKI generally have a normal intra-renal vascular waveform. In contrast patients with intrinsic AKI have an increased renal resistive index but this is a non-specific finding and does not distinguish the different causes of intrinsic AKI [11]. Improvements in blood flow have been described in patients prior to functional recovery. Doppler ultrasonography is useful in assessing the arterial blood flow in the critically-ill patient with a kidney transplant. Such patients developing AKI should have regular assessment of the arterial blood supply due to the increased risks of renal artery stenosis associated with the anastomotic site. Assessment of the renal transplant veins is also important to exclude renal vein thrombosis as a cause of AKI [12]. Colour Doppler ultrasound gives enhanced imaging of intra-renal blood flow and can identify focal areas of infarction.

Computed tomography

Unenhanced computed tomography

The use of computed tomography (CT) will depend upon the clinical status and stability of the patient. Critically-ill patients need continuous monitoring on transfer to the radiology department. Unenhanced CT of the urinary tract is rarely used as a first-line radiological investigation. It is usually used following ultrasonography to provide useful information on the presence of calcification if obstruction of the urinary tract has been demonstrated (Fig. 210.3) or if suspected but not identified on ultrasonography. It will also identify solid or cystic masses in the kidneys or extra renal masses causing obstruction (e.g. retroperitoneal fibrosis).

Enhanced computed tomography

Enhanced CT uses iodinated contrast media and allows imaging of the renal arteries and veins. In patients with normal kidney function the iodinated contrast is excreted through the urinary tract. However in patients with AKI contrast media will not be excreted and so is not of any clinical utility in assessing the flow through the urinary tract (Fig. 210.4). The contrast will remain in the kidney tubules for up to 24–48 hours. Iodinated contrast media is nephrotoxic and therefore contrast enhanced CT scanning to image the urinary tract system must be approached cautiously in critically-ill patients at risk of AKI. Computed tomography angiography can be used to investigate suspected renal artery stenosis or identify potential sites of active haemorrhage following kidney biopsy (Fig. 210.5).

Magnetic resonance imaging

Magnetic resonance imagining (MRI) allows assessment of both morphological (Fig. 210.6a, b) and functional changes of the urinary tract system. It is an attractive alternative to CT to visualize the renal arteries as it does not require iodinated contrast

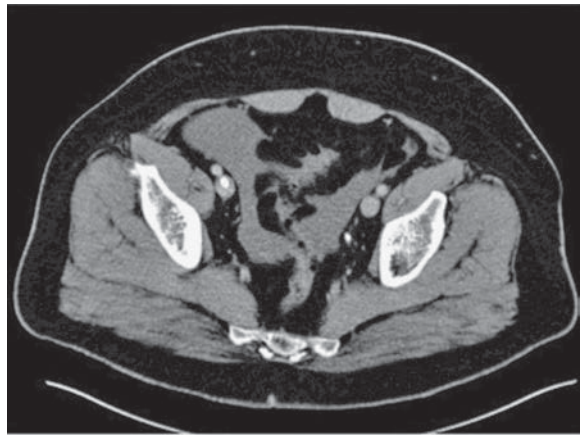


Fig 210.3 Axial CT scan in the lower abdomen. The calculus in the left ureter is visible as a high density focus. There is also free fluid in the peritoneal cavity.

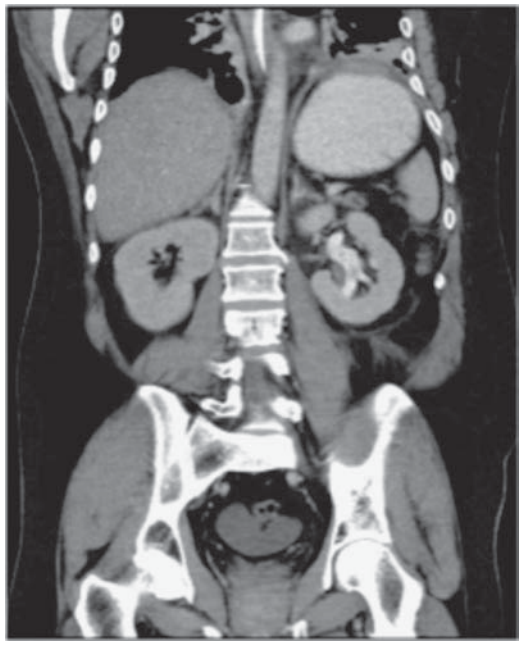


Fig. 210.4 Coronal reformatted CT image. This shows the left kidney has mild distension of the pelvicalyceal system and has retained excreted contrast medium. The right kidney has cleared of contrast medium. One of the typical features of an obstructed system is delayed excretion and persistence of the enhancement. Note that acutely obstructed systems may not be very dilated.

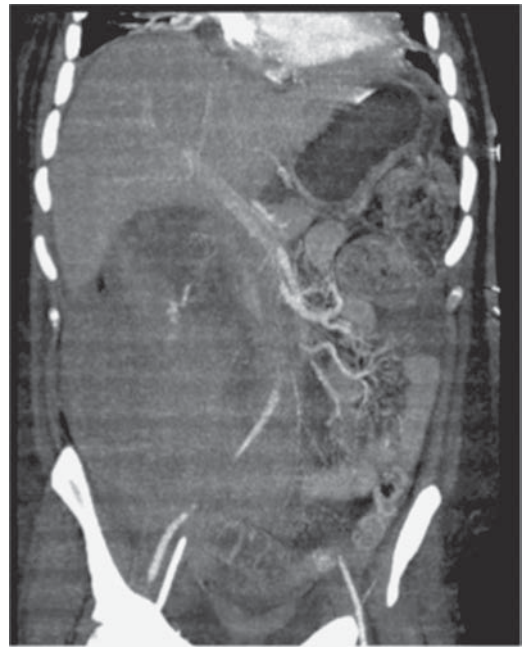


Fig. 210.5 Coronal reformatted CT image in the arterial phase following intravenous contrast medium enhancement. The site of arterial blood leak into the perinephric haematoma is shown.

media and is therefore not associated with CI-AKI (Fig. 210.6c). Magnetic resonance angiography (MRA) should be considered in patients with AKI that is suspected to be the secondary to renal artery stenosis. Demonstration of renal artery stenosis using MRA reduces the subsequent exposure to iodinated contrast which will be required to confirm the findings using renal angiography prior to intervention. Critically-ill patients that require MRI will need to be transferred to non-magnetic life support equipment. Magnetic resonance imaging uses gadolinium (Gd) which is non-nephrotoxic but has rarely been associated with the risk of developing Nephrogenic Systemic Fibrosis (NSF) [13]. Nephrogenic systemic fibrosis is a severe fibrosis of the skin resulting in extensive limitation in mobility.

Renal angiography

Renal angiography is used less often due to the availability and improved resolution of CTA and MRA. Is most often performed for therapeutic interventions such as angioplasty and stenting of confirmed renal artery stenosis or complications from such procedures (Fig. 210.7a) and embolization of sites of renal haemorrhage (Fig. 210.7b).

Iodinated contrast agents

Contrast–induced AKI (CI-AKI) is the third most common cause of AKI in hospital after renal hypoperfusion and nephrotoxic medication [3]. The risk of CI-AKI has been reported to be as high as 25% in patients with a combination of chronic kidney disease (CKD) and diabetes, cardiac failure, older age and exposure to nephrotoxic drugs. The CI-AKI Consensus Working Panel has recommended that the risk of CI-AKI becomes clinically important with an eGFR < 60 mL/min/1.73 m^2 [14]. Critically-ill patients with sepsis and/or hypotension are particularly vulnerable to injury following iodinated contrast exposure. There is currently no validated CI-AKI risk assessment available to recommend for routine use.

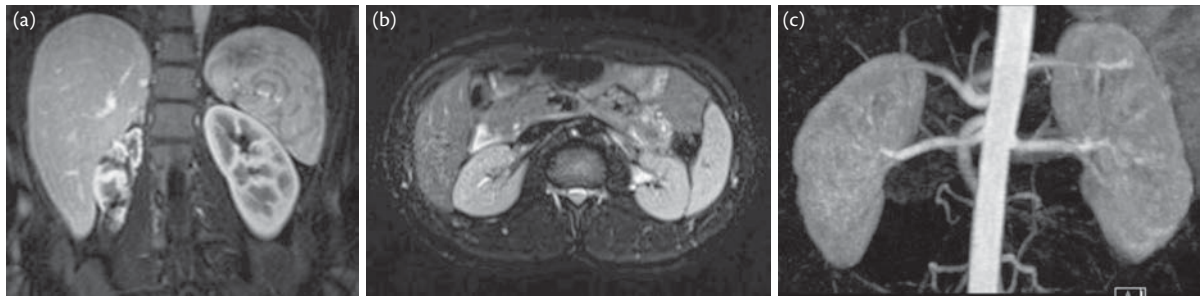


Fig 210.6 Normal magnetic resonance image (MRI) of the kidneys: coronal gadolinium-enhanced magnetic resonance image of the kidneys, scarred atrophic right kidney and normal left kidney (a), axial pyelographic phase image of kidneys (b), coronal maximum intensity projection of an magnetic resonance angiogram (MRA) (c).

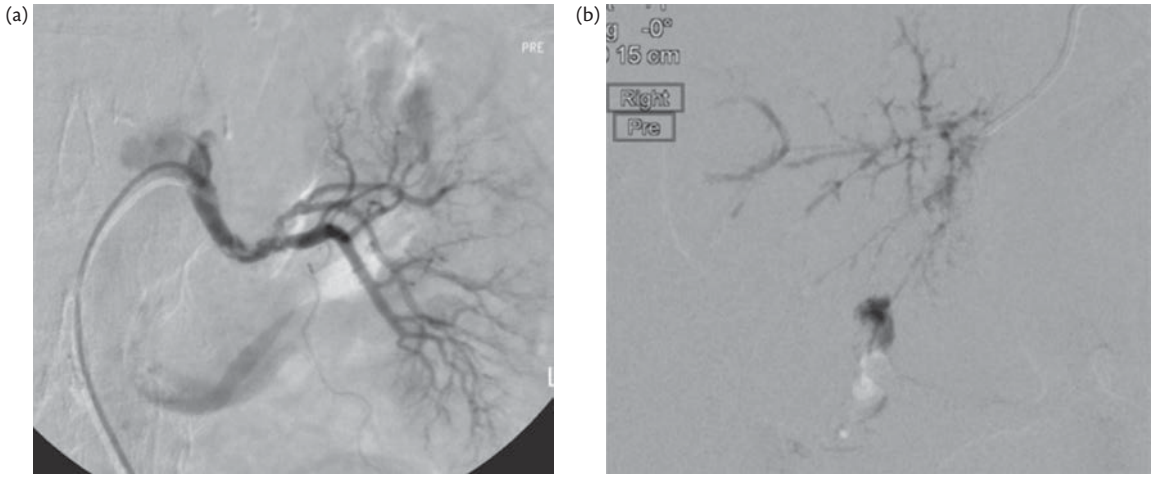


Fig 210.7 Left renal angiogram. The catheter is in the aorta with its tip lying in the ostium of the left renal artery. A spiral lucency corresponding to a dissection flap can be seen within the main renal artery (a). Subtraction renal angiogram technique showing the site of bleeding in the lower pole of the right kidney (b). This was subsequently successfully embolized to stop the bleeding.

Prevention of CI-AKI is important as there is no specific treatment and involves identification of patients at increased risk of CI-AKI. It should also be considered whether alternative imaging could be utilized such as ultrasound or whether carbon dioxide can be used to reduce the amount of iodinated contrast agent required.

Acutely ill patients and patients who are identified at high risk of CI-AKI should have an assessment of their volume status and receive appropriate volume expansion prior to the procedure. It is currently recommended that either intravenous 0.9% sodium chloride or isotonic sodium bicarbonate should be used for volume expansion in patients at risk of CI-AKI. Potentially nephrotoxic medications such as non-steroidal anti-inflammatory drugs and aminoglycosides should be withheld or avoided.

More controversial is the debate regarding whether iso-osmolar contrast media is safer than low-osmolar contrast media in patients at risk of CI-AKI. Currently, there is only one type of iso-osmolar media which has failed to demonstrate any clear benefit compared to different low-osmolar media in preventing CI-AKI. The volume of contrast media should be minimized and further exposure to contrast media should be delayed until full recovery of renal function unless absolutely necessary. Currently there is no compelling evidence for the routine use of N-acetylcysteine to prevent CI-AKI [3].

Table 210.1 summarizes the preferred imaging for common renal conditions.

Box 210.1 Risk factors for patients developing contrast–induced AKI

- Chronic kidney disease (CKD) eGFR < 60 mL/min/1.73m^2.
- Age > 75 years old.
- Cardiac failure.
- Nephrotoxic medication.
  - Aminoglycosides.
  - NSAIDs.
  - Amphotericin B.
- Hypovolaemia.
- Sepsis.
- Volume (dose) of contrast.
- Intra-arterial administration.

Table 210.1 Preferred mode of imaging the renal tract on the ICU

Clinical condition	Preferred radiological investigation on ICU
AKI or CKD	Ultrasound (size and shape of kidneys)
Renal artery stenosis	Doppler ultrasound/CT angiography or MR Angiography
Renal vein thrombosis	Doppler ultrasound
Renal infarction	Contrast-enhanced ultrasound
Pyelonephritis	Ultrasound
Obstruction	Ultrasound
Renal calculus	CT scan
Retroperitoneal Fibrosis	CT scan
Haematuria	Ultrasound/renal arteriography

References

1. Bagshaw SM, Uchino S, Bellomo R, et al. (2007). Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. *Clinical Journal of the American Society of Nephrology*, **2**(3), 431–9.
2. Koyner JL. (2012). Assessment and diagnosis of renal dysfunction in the ICU. *Chest*, **141**(6), 1584–94.
3. Acute Kidney Work Group. (2012). Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International*, **2**(Suppl.), 1–138.
4. Chawla LS, Amdur RL, Amodeo S, et al. (2011). The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney International*, **79**, 1361–9.

5. Ronco C and Rosner MH. (2012). Acute kidney injury and residual renal function. *Critical Care*, **16**(4), 144.
6. Canavese C, Mangiarotti G, Pacitti A, et al. (1998). The patient with acute renal failure and nondilated urinary tract. *Nephrology Dialysis Transplantation*, **13**(1), 203–5.
7. Cokkinos DD, Antypa EG, Skilakaki M, et al. (2013). Contrast enhanced ultrasound of the kidneys: what is it capable of? *Biomedical Research International*, **2013**, 595873.
8. Harrois A and Duranteau J. (2013). Contrast-enhanced ultrasound: a new vision of microcirculation in the intensive care unit. *Critical Care*, **17**(4), 449.
9. Schneider AG, Goodwin MD, Schelleman A, et al. (2013). Contrast-enhanced ultrasound to evaluate changes in renal cortical perfusion around cardiac surgery: a pilot study. *Critical Care*, **17**(4), R138.
10. Granata A, Fiorini F, Andrulli S, et al. (2009). Doppler ultrasound and renal artery stenosis: an overview. *Journal of Ultrasound*, **12**(4), 133–43.
11. Kalantarinia K. (2009). Novel imaging techniques in acute kidney injury. *Current Drug Targets*, **10**(12), 1184–9.
12. Naesens M, Heylen L, Lerut E, et al. (2013). Intrarenal resistive index after renal transplantation. *New England Journal of Medicine*, **369**(19), 1797–806.
13. Thomsen HS. (2006). Nephrogenic systemic fibrosis: a serious late adverse reaction to gadodiamide. *European Radiology*, **16**(12), 2619–21.
14. Fliser D, Laville M, Covic A, et al. (2012). A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury: Part 1: definitions, conservative management and contrast-induced nephropathy. *Nephrology Dialysis Transplantation*, **27**(12), 4263–72.

PART 8.3

Oliguria and acute kidney injury

CHAPTER 211

Pathophysiology of oliguria and acute kidney injury

Rinaldo Bellomo and John R. Prowle

Key points

- The concept that global renal ischaemia accounts for the development of acute kidney injury (AKI) in critically-ill patients in general and patients with sepsis in particular is flawed.
- In patients with severe sepsis, septic shock, and increased cardiac index, global renal blood flow is most likely also either normal or increased.
- In animals and patients with sepsis global renal blood flow is dissociated from glomerular filtration rate.
- Even in the presence of adequate global renal blood flow, there can be tissue ischaemia, especially in the medulla, a finding that suggests intra-renal shunting.
- Inflammation and microvascular changes are likely major contributors to tubular injury and loss of renal excretory function.

Introduction

The term acute kidney injury (AKI) has replaced acute renal failure [1] to emphasize that there is a continuum of kidney injury that begins long before loss of excretory kidney function can be detected with standard laboratory tests. In ICU patients, several conditions trigger and/or predispose to AKI: severe sepsis/septic shock, major surgery (especially open heart surgery), severe liver disease, cardiogenic shock, pre-morbid chronic kidney disease (CKD), and the presence of rhabdomyolysis [2]. As the clinical syndrome common to all of these conditions AKI has conventionally been treated as a single pathophysiological entity. However, much evidence now suggests that the pathophysiology of AKI differs in clinical situations and that septic AKI (S-AKI), in particular, is profoundly different form other forms of AKI.

Key concepts and problems with current paradigms

Most clinicians are familiar with two key AKI-related terms. The first is 'acute tubular necrosis' (ATN). In classic teaching, ATN describes a form of 'intrinsic' (structural) AKI which follows severe and persistent 'pre-renal AKI'. The assumption that ATN results from continued hypoperfusion is widely accepted in textbooks and by clinicians, but may in fact be false. ATN conflates a histological diagnosis (tubular necrosis) that is rarely confirmed by biopsy with a complex clinical syndrome. In both animal experiments and human disease the clinical syndrome is commonly *not* linked with the specific histopathological appearance of ATN [3].

A second concern is that ATN is believed to represent the consequence of sustained or severe 'pre-renal azotemia' which, in contrast to ATN, is considered free of histopathological changes. 'Pre-renal azotemia' is typically expected to resolve over, at most, two to three days. Again, 'pre-renal azotemia', like ATN, is conceptually flawed [4], because it implies that clinicians can know by taking a history, examining the patient and performing urine and blood tests, that there is no histopathological injury.

The third concern is that such concepts are biologically flawed because they imply that AKI does not represent (like all other diseases known to man) a continuum of injury [5].

Pathophysiology

The pathophysiology of inflammatory diseases of the kidney parenchyma (glomerulonephritis and/or vasculitis) is complex. Detailed discussion of these mechanisms is outside the scope of this chapter and can be found in dedicated reviews [6,7]. The same principle applies to acute (but uncommon) vascular events which can cause parenchymal injury and to obstructive disease of urinary tract. In this review, we will mostly focus on AKI secondary to pre-renal factors because it is by far the most common form of AKI in ICU patients.

Animal models of acute kidney injury

The majority of our conceptions of the pathophysiology of AKI due to pre-renal causes are derived from animal models [8]. Most animal models involve the induction of 30–45 minutes of ischaemia by the acute and complete occlusion of the vascular pedicle of the kidney. The associated injury then causes increased organ oedema, decreased renal blood flow (RBF), ATN, and apoptosis, loss of glomerular filtration rate (GFR), evidence of tubular casts with tubular obstruction, and back-leak of tubular solutes and solvent.

However, the clinical relevance of such models is limited, possibly even negligible to conditions like sepsis (the most common form of AKI in ICU patients). Their relevance even to periods of decreased perfusion (e.g. during major surgery) is also limited, given that 80% renal artery occlusion for 2 hours leads to no sustained renal dysfunction.

Unfortunately, animal models of septic AKI which fully resemble the human phenotype are difficult to develop. In small animals endotoxin bolus often induces a hypodynamic (low cardiac output)

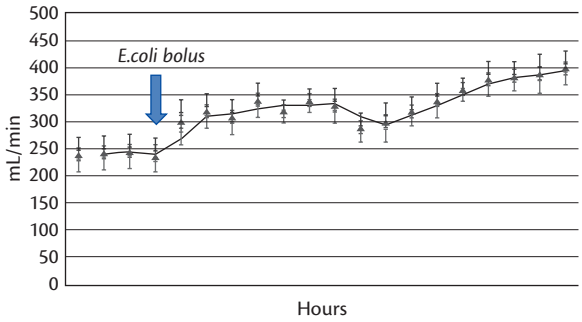


Fig. 211.1 Changes in renal blood flow (with moving average line fit) measured by transit-time flow probe placed around the renal artery in sheep after the induction of Gram negative bacteraemia through intravenous bolus of *E. coli*. Renal blood increases by almost 60% over several hours (values are shown hourly).

[9] shock state resembling more cardiogenic shock, than the human sepsis phenotype. In septic patients a hyperdynamic state (high cardiac output, low blood pressure) is most common. When a hyperdynamic sepsis phenotype of septic AKI is produced in large animals, RBF actually increases to supranormal levels (Fig. 211.1) and renal histopathology is normal.

If experimental septic AKI can occur in the setting of increased RBF, it is impossible to know for sure that such hyperaemia does not also happen in man (RBF cannot be measured continuously and non-invasively in man). Also, if loss of GFR can occur in the absence of histopathological changes in septic animals and humans, it is impossible to assume that ATN occurs due to sepsis in man.

Human studies

Given the uncertainties mentioned previously, it would seem logical to pursue pathophysiological investigations in man. However, renal biopsy is dangerous and ethically unwarranted in critically-ill patients and no accurate, non-invasive, reproducible bedside techniques exist to measure RBF in man. Urinary analysis is similarly of limited pathophysiological value.

The challenge of assessing perfusion

While complete renal ischaemia and reperfusion is associated with AKI both experimentally and clinically, in patients surviving cardiac arrest (a clinically relevant cause of global ischaemia), AKI is uncommon in the absence of post-resuscitation cardiogenic shock. Thus, a major, but relatively short lived (20–30 minutes) reduction in global RBF **alone** appears insufficient to initiate AKI. Conversely, there is considerable historical and recent clinical data to suggest that **established AKI** is associated with reduction in RBF **as a proportion of cardiac output** [10]. To reconcile these seemingly contradictory observations, we need to know how clinical conditions like sepsis and major surgery affect not only global RBF, but also blood flow distribution within the kidney and renal oxygenation in the cortex and medulla, how these changes are related to renal injury (histological and/or functional), and whether reductions in RBF seen in man during established AKI are a cause or a consequence of AKI.

The complexity of renal blood flow

Auto-regulation of RBF is impaired in critical illness prior to and during AKI so that global RBF varies with cardiac output which may be normal, elevated or depressed in different clinical contexts. Renal vasodilatation in experimental sepsis may be due to nitric oxide derived from the endothelial and neural isoforms of nitric oxide synthase (NOS). However, reversal of renal vasodilation by non-selective NOS-blockade does not restore renal function. Furthermore, GFR decreases even during mild hyperdynamic sepsis not associated with systemic hypotension. These observations suggest that an imbalance in pre- and post-glomerular resistance or the development of intra-renal shunting or both account for a fall in glomerular filtration. Thus, outside of extreme situations, what matters to GFR and AKI is not global RBF, but intra-renal blood flow. To confirm these concerns, recent studies have shown that increased renal capillary permeability occurs prior to falls in RBF and that alterations in global renal blood flow are accompanied by changes in cortical microcirculatory hypoperfusion [11], peri-tubular capillary leakage and reactive nitrogen species [11]. In this setting, increased renal blood flow can hide medullary hypoxia due to shunting (Fig. 211.2).

The possible role of bioenergetic failure

Recently experimental studies of septic shock showed that, despite shock, renal hypoperfusion and AKI, tissue hypoxia does not appear to a major pathophysiological issue; mitochondrial respiration remained normal and the gradient between microvascular PO_2 and tissue oxygen tension remained unchanged in both the renal cortex and outer medulla.

Experimental studies have used magnetic resonance technology to measure ATP in the kidney during mammalian hyperdynamic sepsis with or without the infusion of a vasopressor drug. Under both circumstances global renal ATP was preserved. Observations like these undermine the hypothesis that tissue ischaemia is an initiating event in S-AKI [12].

The role of inflammation

Collectively, much evidence suggests that inflammatory responses and inflammatory alterations in the microcirculation are responsible for the progression and maintenance of S-AKI. Toll-like receptors (TLR) recognize molecules that are broadly shared by common pathogens and play a key role in triggering inflammatory responses. In an ovine model of hyperdynamic S-AKI, a TLR-4 antagonist improved renal function during lipopolysaccharide infusion and attenuated renal tubular injury [13]. Thus, in a model of AKI associated with renal hyperaemia, blockade of an early inflammatory pathway prevented biochemical AKI and tubular injury.

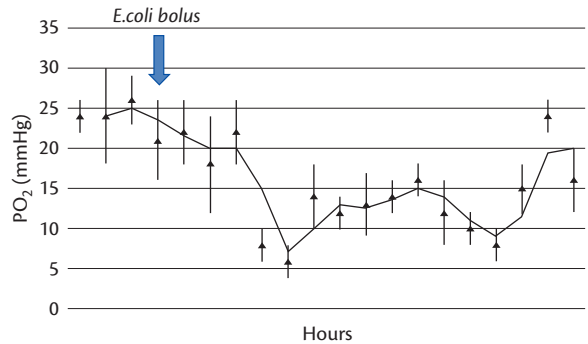


Fig. 211.2 Changes in tissue oxygen pressure in the renal medulla during experimental sepsis in sheep with moving average line fit. In animals that have increased renal blood flow as displayed in Fig. 211.1, there can be substantial undetected medullary hypoxia (values shown hourly).

The reduction in RBF during sustained AKI may occur as a consequence of inflammatory tubular injury contributing to sustained reduction in GFR.

Given that most renal oxygen consumption is related to active sodium reabsorption, the kidney might be relatively protected against ischaemia when GFR is lost. However, recent data for post-cardiac surgery patients also found that sodium reabsorption is inefficient in post-operative AKI compared with no AKI, suggesting that renal oxygenation may remain impaired, despite decreased GFR. This raises the concern that recurrent ischaemia and inflammation may cause repeated renal injury during AKI, leading to delayed recovery and/or non-recovery of renal function. Specific pathways for cellular regeneration or fibrosis may be involved in these processes.

The lessons from attempts to increase global renal blood flow

Treatment choices to optimize renal perfusion during AKI are not clear-cut. For instance prevention of endotoxaemia-induced systemic hypotension by immediate fluid resuscitation in a rat model reduced renal inflammation, but did not prevent reduced renal microvascular oxygenation. In humans, administration of un-buffered isotonic saline solutions has been shown to cause renal vasoconstriction suggesting buffered crystalloids should be used in patients with or at risk of AKI. Conversely, use of vasopressors to raise mean blood pressure from 60 to 75 mmHg has been shown to raise global RBF in humans with AKI after cardiac surgery [14], suggesting renal perfusion pressure is important in determining RBF in AKI. However, use of vasopressors to restore blood pressure will not affect the inflammatory pathogenesis of S-AKI.

An integrated view

A new renal blood flow related paradigm and working hypothesis for the development of AKI is emerging from the accumulating data. Transient alterations in glomerular filtration pressure gradient may cause reversible reduction GFR. Depending on circumstances, this may be associated with reduced, unchanged or elevated RBF. However, sustained AKI likely occurs as a result of tubular injury, which may or may not be preceded by haemodynamic alterations in GFR. If haemodynamic alterations occur, they may be related to intra-renal haemodynamics. If microvascular events occur, global renal blood flow may be maintained or even increased and yet GFR can be markedly decreased. This dissociation between global renal blood flow and function has been recently shown in critically-ill patients by cine phase contrast magnetic resonance [10]. In such patients RBF is related to cardiac index (Fig. 211.3), but not to GFR. Once established tubular injury may then be associated with reduction in RBF secondary to oedema and inflammatory congestion.

Neurohormonal mechanisms

Despite all of the observations mentioned previously, it seems likely that sympathetic system activation and neuro-hormonal responses unique to the kidney are activated in the setting of AKI (Fig. 211.4). They include activation of the renin-angiotensin system (RAAS), activation of the renal sympathetic system, and activation of the tubuloglomerular feedback (TGF) system. Such paradigms, however, do not provide information on which particular pathway of injury has primacy in terms of importance or timing or both. As such, these paradigms do not yet guide the development of novel

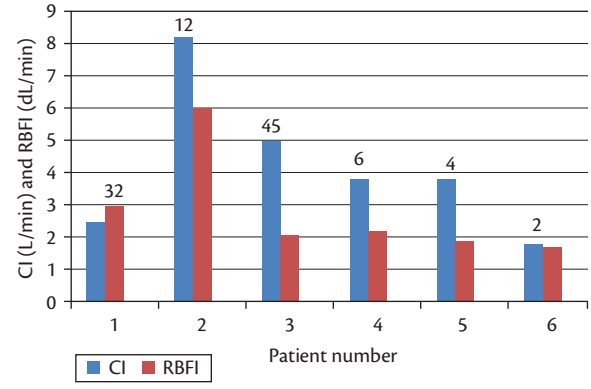


Fig. 211.3 Histogram showing the cardiac index (CI, L/min) and renal blood flow index (RBFI, dL/min) in a cohort of critically-ill patients with AKI. In these patients, CI and RBFI were closely related as shown, although GFR (presented as mL/min above each bar) did not show any correlation with RBFI.

interventions aimed at preventing or attenuating AKI. Finally, it remains unknown whether neurohormonal changes are fundamental to specific forms of AKI like the so-called hepatorenal syndrome (HRS) [15].

In the HRS, like in experimental sepsis, AKI appears to occur in the absence of histopathological and, therefore, is essentially 'functional' in nature. The characteristic finding of intense renal vascular vasoconstriction associated with high levels of RAAS activation suggests that neuro-hormonal cause the HRS. Although the mechanisms for such activation are debated, decreased systemic blood pressure secondary to splanchnic vasodilatation is considered a key event. As a consequence the renal circulation may suffer. Whether this eventually occurs in other states of hypotension and systemic vasodilatation (inflammation or sepsis) remains unknown, but is theoretically possible. Thus, elevations in norepinephrine, renin, and angiotensin II levels may participate in other forms of AKI suggesting that, in some situations, neurohormonal renal vasoconstriction may be a fundamental mechanism of loss of excretory function.

Other forms of acute kidney injury

In large observational studies, rhabdomyolysis-associated AKI accounts for close to 5–10% of cases of AKI in ICUs depending on the setting. Its pathogenesis likely involves pre-renal (hypovolaemia), renal (neurohormonal vasoconstriction, and myoglobin cast formation) and post-renal factors (intra-abdominal hypertension) [16].

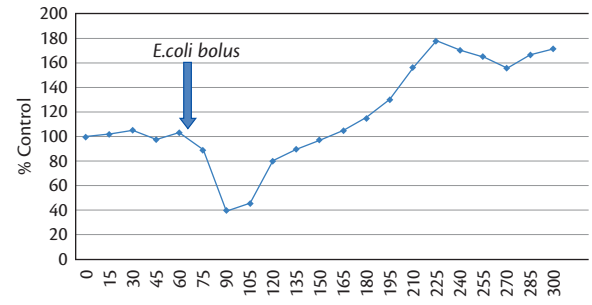


Fig. 211.4 Renal sympathetic nerve activity (RSNA) after the induction of sepsis in sheep. After the initial fall, there is a progressive increase in RSNA.

The changing demographics of patients in developed countries and the increasing incidence of both chronic heart failure and CKD have seen the emergence of more and more patients who combine the presence of heart disease with AKI, often superimposed on CKD and frequently triggered by an acute decompensation of heart failure 'cardiorenal syndromes'. Although focused work in this field is only in its inception, initial insights are emerging that organ congestion may be more important to the pathogenesis of AKI in this setting than low blood pressure and cardiac output [17].

Cardiac surgery associated AKI is increasingly common as older patients undergo such surgery. Its pathophysiology is complex and likely involves multiple mechanisms of injury (cardiopulmonary bypass [CPB]-induced inflammation and haemolysis, low cardiac output states, organ oedema, renin-angiotensin system activation, sympathetic system activation, cholesterol embolism, etc.). These mechanisms likely interact and carry different weight in different patients [18]. With the exclusion of CPB-derived events, similar mechanisms likely play a role in other forms of **major surgery** (another common cause of AKI in critically-ill patients).

Finally, drug- induced AKI accounts for or significantly contributes to 10–15% of AKI in the ICU [19]. The pathophysiology is dependent on the drug in question and varies from direct tubular toxicity from accumulation with aminoglycosides to profound afferent arteriolar vasoconstriction with calcineurin inhibitors [19]. Whatever the mechanism, no effective therapies allow toxic drug therapy to be safely continued; drug withdrawal, lesser dosage or avoidance remain the only therapeutic options.

Oliguria

Our limited understanding of the pathophysiology of AKI in critically-ill patients is reflected in our similarly limited understanding of the pathophysiology of oliguria. Although urine output is the only real time signal that clinicians have to assess what might be happening in the kidney, it is a profoundly flawed biomarker of developing AKI. Several prospective studies show that even several hours of oliguria have limited specificity in diagnosing subsequent AKI [20]. Moreover, clinicians seek to increase such urine output by means of intravenous fluid loading or diuretic therapy or both either in a sequence or together. The pathophysiological basis for such interventions is weak and the potential for harm is real. Whether such interventions are useful in critically-ill patients with adequate mean arterial pressure, intravascular filling, and cardiac output is doubtful.

Conclusion

Although we refer to AKI as if it were a single condition, it represents multiple different aetiologies. Accordingly, its pathophysiology differs depending on the disease or clinical event triggering its development. For the most common type of AKI (S-AKI) in critically-ill patients, novel insights suggest that intra-renal haemodynamic events coupled with/or triggered by inflammation and neurohormonal responses are responsible for loss of kidney function. Establishing, the timing, hierarchy, and links that govern these events will provide a challenge for decades to come. Until such pathophysiological mechanisms are better understood, the development of effective therapies will continue to prove elusive.

References

1. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, and the ADQI workgroup (2004). Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the ADQI Group. *Critical Care*, **8**, 204–12.
2. Uchino S, Kellum JA, Bellomo R, et al. (2005). Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Acute renal failure in critically ill patients: a multinational, multicenter study. *Journal of the American Medical Association*, **294**(7), 813–8.
3. Langenberg C, Bagshaw S, May CN, and Bellomo R. (2008). The histopathology of septic acute kidney injury: a systematic review. *Critical Care*, **6**(12), 38–44.
4. Bellomo R, Bagshaw SM, Langenberg C, and Ronco C. (2007). Pre-renal azotemia: a flawed paradigm in critically ill septic patients? *Contributors to Nephrology*, **156**, 1–9.
5. Uchino S, Bellomo R, Bagshaw SM, et al. (2010). Transient azotemia is associated with a high risk of death in hospitalised patients. *Nephrology Dialysis and Transplantation*, **25**, 1833–9.
6. Stoegeman CA and Kallenberg CGM. (2005). Pathogenesis of angiitis. In: Davison AM (ed.) *Oxford Textbook of Clinical Nephrology*, pp. 741–52. Oxford: Oxford University Press.
7. Falk RJ and Jennette JC. (2010). ANCA disease: where is this field heading? *Journal of American Society Nephrology*, **21**, 745–52.
8. Heyman SN, Rosenberger C, and Rosen S. (2009). Critical assessment of animal models of acute renal failure. In: Ronco C, Bellomo R, Kellum JA (eds) *Critical Care Nephrology*, pp. 237–50. Philadelphia, PA: Saunders Elsevier.
9. Langenberg C, Wan L, Egi M, May CN, and Bellomo R. (2006). Renal blood flow in experimental septic acute renal failure. *Kidney International*, **69**, 1996–2002.
10. Prowle JR, Molan MP, Hornsey E, and Bellomo R. (2012). Measurement of renal blood flow by phase-contrast magnetic resonance imaging during septic acute kidney injury: A pilot investigation. *Critical Care Medicine*, **40**, 1768–76.
11. Wang Z, Holthoff JH, Seely KA, et al. (2012). Development of oxidative stress in the peritubular capillary microenvironment mediates sepsis-induced renal microcirculatory failure and acute kidney injury. *American Journal of Pathology*, **180**, 505–16.
12. May CN, Ishikawa K, Wan L, et al. (2012). Renal bioenergetics during early Gram negative mammalian sepsis and angiotensin II infusion. *Intensive Care Medicine*, **38**, 886–93.
13. Fenhammar J, Rundgren M, Forestier J, et al. (2011). Toll-like receptor 4 inhibitor TAK-242 attenuates acute kidney injury in endotoxemic sheep. *Anesthesiology*, **114**, 1130–7.
14. Redfors B, Bragadottir G, Sellgren J, et al. (2011). Effects of norepinephrine on renal perfusion, filtration and oxygenation in vasodilatory shock and acute kidney injury. *Intensive Care Medicine*, **37**, 60–7.
15. Wong F, Nadim MK, Kellum JA, et al. (2011). ADQI Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut*, **60**, 702–9.
16. Bosch X, Poch E, and Grau JM. (2009). Rhabdomyolysis and acute kidney injury. New England Journal of Medicine, **361**, 62–72.
17. Damman K, Navis G, Smilde TD, et al. (2007). Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. *European Journal of Heart Failure*, **9**, 872–8.
18. Bellomo R, Auiremma S, Fabbri A, et al. (2008). The pathophysiology of cardiac surgery associated acute kidney injury. *International Journal of Artificial Organs*, **31**, 166–78.
19. Pannu N and Nadim MK. (2008). An overview of drug-induced acute kidney injury. *Critical Care Medicine*, **36**(4), 216–23.
20. Prowle JR, Liu YL, Licari E, et al. (2011). Oliguria as predictive biomarker of acute kidney injury in critically ill patients. *Critical Care*, **15**, 172.

CHAPTER 212

Diagnosis of oliguria and acute kidney injury

John A. Kellum

Key points

- Acute kidney injury or impairment (AKI) may be defined as an abrupt reduction in kidney function to a level that is insufficient to meet the needs of the patient.
- Urine output is both a reasonably sensitive functional index for the kidney as well as a biomarker of tubular injury. However, the relationship between urine output and renal function/injury is complex.
- Neither oliguria nor azotaemia alone provide sufficient sensitivity, specificity, or time responsiveness to be useful to define AKI.
- The KDIGO criteria, based on changes in serum creatinine or low urine output represent a broad international consensus for diagnosing and staging AKI.
- Sepsis is the most common cause of AKI in the intensive care unit; although AKI is often multifactorial it is important to rule out or treat preventable causes.

Introduction

For practical purposes acute kidney injury (AKI) is conceptualized entirely through changes in glomerular function even though there are other important functions of the kidney (e.g. tubular, hormonal) that are not considered and even though **injury** to the kidney may not manifest as a change in glomerular function. Also for practical purposes the definition of AKI is based on changes in serum creatinine and urine output—in the near future this is likely to change with the introduction of specific biomarkers of renal cell damage. Unlike other vital organs, the kidney reduces its function when it senses that there is insufficient circulating blood volume, either because blood volume is indeed reduced (e.g. haemorrhage, dehydration) or because other pathologic conditions make it appear that way by reducing renal perfusion (e.g. acute decompensated left heart failure, renal artery stenosis). Much confusion can result when AKI is thought of only as an intrinsic disease of the kidney when factors external to the kidney frequently cause injury or impair function. Similar to the concept that a cardiac arrest is still a cardiac arrest even when the heart is empty and the myocardium is normal; AKI is still AKI when the kidney itself is structurally normal. Finally, when the opposite occurs and there is damage to the kidney without clinical signs, a subclinical form of AKI is said to exist.

Definitions

Oliguria

Although urine output is a reasonably sensitive functional index for the kidney as well as a biomarker of tubular injury, the relationship between urine output and renal function/injury is complex. For example oliguria may be more profound when tubules are patent, but tubular reabsorbtive function is preserved. Volume depletion and hypotension are profound stimuli for vasopressin secretion, as a consequence the distal tubules and collecting ducts become fully permeable to water and thus, urine volume is minimized and urine concentration maximized (>500 mOsm/kg). Conversely, when the tubules are injured, maximal concentrating ability is impaired and urine volume may even be normal (i.e. non-oliguric renal failure). Analysis of the urine to determine tubular function has a long history in clinical medicine. Indeed, a high urine osmolality coupled with a low urine sodium concentration in the face of oliguria and azotemia is strong evidence of intact tubular function. However, this should not be interpreted as 'benign' or even 'pre-renal'. Intact tubular function, particularly early on, may be seen with various forms of renal disease (e.g. glomerulonephritis). Sepsis, the most common condition associated with acute renal failure in the ICU [1], may alter renal function without any characteristic changes in urine indices [2,3]. Finally, although severe oliguria and even anuria may result from renal tubular damage, it can also be caused by urinary tract obstruction and by total arterial or venous occlusion. These conditions will result in rapid and irreversible damage to the kidney and require prompt recognition and management.

Azotaemia

Classically, high blood nitrogen levels, in the form of urea nitrogen, are referred to as azotaemia. The upper limits of the normal ranges for serum urea or blood urea nitrogen (BUN) vary by age, race, and sex (due in part to differences in muscle mass) and by diet (vegetarians will have lower levels), but in general are less than 8.5 mmol/L and 24 mg/dL, respectively. In more recent years, the term is azotaemia is often used for a reduction in GFR regardless of the cause and is manifest by elevations in, but while creatinine is only slighted reabsorbed (with also some tubular secretion), urea is reabsorbed in a manner that is flow dependent. Thus, as flow through the tubules decreases, urea reabsorption, and hence the serum concentration, increases. This difference in renal physiology for urea and creatinine can be exploited to help delineate the aetiology of azotaemia, though important limitations apply.

Acute kidney injury or impairment

Neither oliguria nor azotaemia alone provide sufficient sensitivity, specificity, or time responsiveness to be useful to define acute kidney disease.

The term AKI has been proposed to encompass the entire spectrum of renal impairment from minor changes in renal function to the requirement for renal replacement therapy. Thus, the concept of AKI creates a new paradigm. AKI is not synonymous with acute tubular necrosis (ATN), nor with 'renal failure'. Instead, it encompasses both and also includes less severe conditions (even pre-renal azotaemia). Indeed, AKI can really be thought of as including all forms of **injury** to the kidney as well as **impairment** of function regardless of the cause. This is important because rather than focusing exclusively on patients with renal failure or on those who receive dialysis or on those that have a clinical syndrome defined by pathology that is rarely confirmed (e.g. ATN), the strong association of AKI with hospital mortality demands that we change the way we think about this disorder. In a study by Hoste et al. [4], only 14% of patients reaching RIFLE 'F' received renal replacement therapy yet these patients experienced hospital mortality more than 5 times that of the same ICU population without AKI.

Damage, sub-clinical acute kidney injury, and renal reserve

Damage to the kidney may precede, follow or occur simultaneously with functional decline. This is because reductions in renal function may be adaptive, for example in response to a decrease in circulating blood volume. While the concept of AKI is intended to include damage without loss of function, common forms of AKI (e.g. sepsis) do not produce structural changes that are easily detected with existing imaging techniques. Histopathology does reveal evidence of damage, though often very mild and patchy, but kidney biopsies are rarely obtained from patients with AKI. Studies using sensitive biomarkers of renal damage (e.g. neutrophil gelatinase-associated lipocalin, and kidney injury molecule-1) suggest that some patients have functional decline without evidence of damage while others have biomarker evidence of damage without manifesting functional decline [4]. This second group may be thought off as having a form of AKI that is 'sub-clinical' meaning that it is below our ability to detect clinically [5]. It is important to appreciate that subclinical does not equate to 'mild' or 'unimportant'. This is because the healthy kidney can suffer significant loss of nephrons before there is a change in renal function under normal conditions. A young, healthy individual has significant renal reserve and can sustain significant renal damage without manifesting AKI, while a much smaller degree of injury to a patient with chronic kidney disease (CKD) will result in clinical AKI. The biological consequences of subclinical AKI are currently unknown. The damage may heal or there may be some permanent loss of functional renal reserve. The outcome may be determined by the characteristics of the patient (especially age, but possibly also genetic factors determining recovery), as well as the type and duration of the renal insult.

Diagnosis and staging

Rifle criteria

In order to standardize the definition of AKI, the Acute Dialysis Quality Initiative (ADQI) proposed the RIFLE criteria through a broad consensus of experts [5]. The acronym RIFLE stands for the increasing severity classes Risk, Injury and Failure, and the 2 outcome classes loss and end-stage kidney disease. The three severity grades were defined on the basis of the changes in serum creatinine or urine output where the worst of each criterion is used. The two outcome criteria, loss and end-stage kidney disease, are defined by the duration of loss of kidney function. Since the RIFLE criteria were initially proposed, they have been widely adopted and have ushered in a new era of precision for the diagnosis, treatment, and study of AKI. However, almost from the beginning, there was a concern that using a relative change in serum creatinine to define AKI would mean that patients with pre-existing CKD (and elevated baseline creatinine) would have to incur a larger absolute increase in serum creatinine to fulfil the diagnosis. For example a patient with a serum creatinine of 70 mmol/L (0.8 mg/dL) would meet the criteria for AKI once the serum creatinine reached 105 mmol/L (1.2 mg/dL) or a 35 mmol/L absolute increase. Conversely a patient with serum creatinine of 200 mmol/L (2.26 mg/dL) would not meet the criteria for AKI until the serum creatinine reached 300 mmol/L (3.39 mg/dL) or an absolute increase of 100 mmol/L. Although relative changes in serum creatinine can be equated across different patients because they relate to relative changes in GFR (a doubling of serum creatinine corresponds to a 50% decline in GFR regardless of the baseline creatinine), it is likely that an increase in serum creatinine <100 mmol/L is still clinically significant. Furthermore, compared to patients with normal renal function, patients with CKD will require a much longer time in order to observe a relative change (e.g. 50%) than will be required to observe a fixed increase (e.g. 35 mmol/L).

Beyond rifle: acute kidney injury network and kidney disease improving global outcomes

The Acute Kidney Injury Network (AKIN), an international, interdisciplinary group proposed to modify the RIFLE criteria to include a small (26.5 mmol/L) absolute increase in serum creatinine as an alternative criterion for AKI as long as it was observed to occur within 48 hours [6]. In 2012, Kidney Disease Improving Global Outcomes (KDIGO) adopted the modified RIFLE criteria proposed by AKIN and also included modifications proposed for paediatric patients Table 212.1 [7]. The KDIGO AKI clinical practice guideline emphasizes the need to begin management of AKI in high risk patients even before evidence of AKI is apparent. This approach is predicated on the assumption that AKI is preventable in some proportion of patients. Evidence that this is indeed the case is available only for some forms AKI (most notably nephrotoxic). Nevertheless, the expectation that AKI can only be avoided or attenuated if it can be either predicted or detected early seems reasonable.

Finally, there is hope that the use of functional makers (urine output and serum creatinine) will be replaced or augmented in the near future by injury biomarkers. Several potential serum and urinary markers have been identified Table 212.2 [8]. In the future, markers of cellular injury in the kidney will likely define AKI and offer the potential to diagnose the disorder before functional decline. Until then, the 'tried and true' markers of urine output and serum creatinine, disciplined by (modified) RIFLE criteria, will be the best we can provide.

Risk stratification

Given the risks associated with AKI and the likelihood that early intervention will result in better outcome, it is important to

Table 212.1 Definition and staging of acute kidney injury. Based on the original RIFLE criteria and the modification to include a small absolute increase in serum creatinine for stage 1 as proposed by AKIN, the KDIGO definition of AKI is shown. For staging of AKI, the worse criterion (creatinine or urine output) is used

AKI is defined as any of the following:

- Increase in SCr by ≥ ≥26.5 μmol/L (0.3 mg/dL) within 48 hours; or
- Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 mL/kg/hour for 6 hours.

AKI is staged for severity according to the following criteria

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR >0.3 mg/dL (>26.5 μmol/L) increase	<0.5 mL/kg/hour for 6–12 hours
2	2.0–2.9 times baseline	<0.5 mL/kg/hour for >12 hours
3	3.0 times baseline *or* Increase in serum creatinine to >4.0mg/dL (>353.6μmol/L) *or* Initiation of renal replacement therapy *or* in patients <18 years, decrease in eGFR to <35 mL/min/1.73 m^2	<0.3 mL/kg/hour for >24 hours *or* Anuria for >12 hours

Adapted by permission from Macmillan Publishers Ltd: 'KDIGO Clinical Practice Guideline for Acute Kidney Injury', *Kidney International Supplements*, 2012, **2**(1), pp. 1–138, copyright KDIGO 2012.

determine a patient's risk for AKI. The general concept of risk for AKI can be thought of as comprising both the patient's susceptibilities and their exposures [7]. Table 212.2 provides a list of common susceptibilities and exposures. Intuition would suggest that the presence of multiple susceptibilities and exposures would lead to greater risk. Indeed most patients with AKI have more than one susceptibility and/or exposure; many have multiple. However, there is no reliable way to risk stratify patients based on clinical or laboratory criteria. Lack of adequate risk stratification can result in over or under utilization of resources or 'renal sparing' therapies (e.g. admitting a low risk patient to hospital because of concern for AKI; not stopping a nephrotoxic drug for failure to appreciate a high risk patient). Neither is desirable and efforts are under way to develop better risk prediction tools.

Table 212.2 Causes of AKI: exposures and susceptibilities for non-specific AKI

Exposures	Susceptibilities
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	CKD
Cardiac surgery (especially with CPB)	Chronic diseases (heart, lung, liver)
Major non-cardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anaemia
Poisonous plants and animals	

CKD, chronic kidney disease; CPB, cardiopulmonary bypass.

Reprinted by permission from Macmillan Publishers Ltd: 'KDIGO Clinical Practice Guideline for Acute Kidney Injury', *Kidney International Supplements*, 2012, **2**(1), pp. 1–138, copyright KDIGO 2012.

Aetiology

Acute tubular necrosis

When mammalian kidneys are subjected to prolonged (most studies use more than one hour) warm ischaemia followed by reperfusion there is extensive necrosis destroying the proximal convoluted tubules and the proximal tubules of the outer stripe of the medulla. Distal nephron involvement in these animal experiments is minimal, unless medullary oxygenation is specifically targeted. Although these animals develop severe acute renal failure, not much else resembles the clinical syndrome in humans [6] and the term ATN does not accurately reflect the morphological changes in AKI [6]. Instead, ATN describes a clinical situation in which there is adequate renal perfusion to largely maintain tubular integrity, but not to sustain glomerular filtration. Renal biopsies in patients with ATN dating back to the 1950s [7] confirm the limited parenchymal compromise in spite of severe organ dysfunction [6]. Thus, the syndrome of ATN has very little to do with the animal models traditionally used to study it. More recently, investigators have emphasized the role of endothelial dysfunction, coagulation abnormalities, systemic inflammation, and oxidative stress in causing renal injury, particularly in sepsis [9,10]. True ATN does, in fact, occur. Patients with arterial catastrophes (ruptured aneurysms, acute dissection) can suffer prolonged periods of warm ischaemia just like animal models. However, these cases comprise <1% of AKIs and ironically, these patients are often excluded from

studies seeking to enrol patients with the more common clinical syndrome known as ATN.

Pre-renal azotaemia

At the other end of the spectrum from ATN is the condition that occurs when the kidneys are structurally normal, but something extrinsic is impairing their function. While the causes of AKI are traditionally classified as prerenal, renal, and post-renal, the imprecision of this approach leads to diagnostic and therapeutic confusion. For instance, the treatment of intravascular dehydration, often cited as the classic example of pre-renal azotemia, includes rapid rehydration. However, other 'pre-renal' conditions, including nephrotic, hepatorenal, and cardiorenal syndromes can present with similar laboratory findings, yet the management for these conditions requires fluid restriction. Unfortunately, for many clinicians, the statement that a patient is 'pre-renal' has become synonymous with being dehydrated.

Similarly, reversibility of renal dysfunction does not define 'pre-renal' nor the absence of harm. Several large cohort studies and the prospective EARLYARF study [11] identified that transient (less than 48 hour) AKI was associated with increased need for dialysis and risk of death, even when AKI resolved within 24 hours. The concept of purely functional loss is also challenged by recent studies providing evidence that some, albeit less, damage is actually present in patients with transient AKI. If 'pre-renal' AKI is defined as transient AKI combined with evidence of preservation of renal tubular function (e.g. with a fractional sodium excretion less than 1%), then biomarkers of damage are increased above that observed in 'No-AKI' patients [11]. Even the earliest studies of reversible azotaemia induced in volunteers by water deprivation noted kidney damage as shown by the development of haematuria and proteinuria, which reversed after rehydration [12]. On the other hand, there is good evidence, that when AKI biomarkers are positive, even in the absence of apparent change in function, patients have worse hospital survival and even increased need for dialysis than patients without AKI [4]. Of course the biomarkers may simply predict changes in function that would manifest later except that competing endpoints such as death or dialysis occur first.

Differential diagnosis for AKI

Thus, like many other syndromes, AKI is caused by multiple diseases and should be viewed from the perspective of the disease or diseases causing it, rather than as syndrome comprised of pre-renal, renal, and post-renal conditions. Furthermore, AKI occurring in critically ill patients is frequently multi-factorial. Table 212.2 lists common causes of AKI. It is important to determine the cause of AKI when possible, and in particular, to determine reversible causes. Fig. 212.1 provides a diagnostic flow diagram for patients at risk of or diagnosed with AKI. The longer the AKI condition persists the more likely the injury will become irreversible.

Clinical judgement

While the definitions and classification system discussed above provide a framework for the clinical diagnosis of AKI, they should not be interpreted to replace or to exclude clinical judgment. While the vast majority of cases will fit both AKI diagnostic criteria as well as clinical judgment, AKI is still a clinical diagnosis—not all cases of AKI will fit within the proposed definition and not all cases fitting the

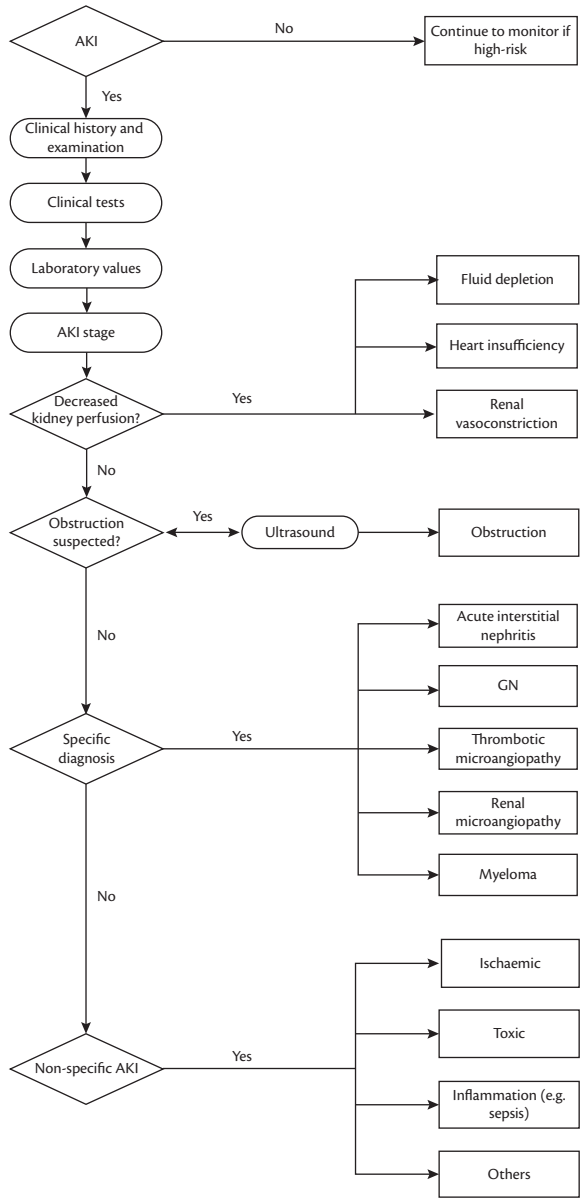


Fig. 212.1 Diagnostic flow diagram for patients at risk of or diagnosed with AKI.

definition should be diagnosed as AKI. However, exceptions should, in general, be very rare. For example, endogenous chromogens (e.g. bilirubin, ascorbic acid, uric acid) and various drugs (e.g. cephalosporins, trimethoprim, cimetidine) may interfere with the creatinine assay, which it could impact the diagnosis of AKI. A similar problem exists with urine output. Particularly outside the ICU, urine output is not often reported and urine collections may be inaccurate, especially in non-catheterized patients. Finally, a weight-based criterion for urine output will mean that some very obese patients will fulfil the definition of AKI without any kidney abnormality. Clinical judgment should always be exercised in interpreting such data.

Conversely, there are situations where a case of AKI fails to meet the definition. These cases should be distinguished from conditions in which data are simply missing and refer to situations in which existing data are unreliable. For example, a patient might receive very large quantities of intravascular fluids such that SCr is falsely

lowered. Similarly, massive blood transfusions will result in the SCr more closely reflecting the kidney function of the blood donors than the patient. It is unusual for these cases not to result in oliguria and, thus, most patients will be diagnosed with AKI even if SCr is not increased. Nevertheless, the clinician should be cognizant of possibility that SCr may be falsely lowered by large-volume fluid resuscitation or transfusion. Changes in creatinine production are also well known in conditions such as muscle breakdown where production increases and in muscle wasting (including advanced liver disease) where production is decreased. Creatinine production may also be decreased in sepsis possibly due to decreased muscle perfusion.

Conclusion

Small changes in kidney function in hospitalized patients are important and associated with significant changes in short and possibly long-term outcomes. The shift of terminology from ATN and acute renal failure to AKI has been well received by the research and clinical communities. AKI severity grades represent patient groups with increasing severity of illness as illustrated by an increasing proportion of patients treated with RRT, and increasing mortality. Like CKD stages AKI stages have now been linked to specific treatment recommendations [7].

References

1. Uchino S, Kellum JA, Bellomo R, et al. (2005). Acute renal failure in critically ill patients: a multinational, multicenter study. *Journal of the American Medical Association*, **294**(7), 813–18.
2. Bagshaw SM, Langenberg C, Wan L, May CN, and Bellomo R. (2007). A systematic review of urinary findings in experimental septic acute renal failure. *Critical Care Medicine*, **36**(6), 1592–8.
3. Bagshaw SM, Langenberg C, and Bellomo R. (2006). Urinary biochemistry and microscopy in septic acute renal failure: a systematic review. *American Journal of Kidney Disease*, **48**(5), 695–705.
4. Hoste EA, Clermont G, Kersten A, et al. (2006). RIFLE criteria for acute kidney injury is associated with hospital mortality in critical ill patients: a cohort analysis. *Critical Care*, **10**(3), 73.
5. Bellomo R, Ronco C, Kellum JA, Mehta RL, and Palevsky P. (2004). Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Critical Care*, **8**(4), 204–12.
6. Rosen S and Heyman S. (2001). Difficulties in understanding human 'acute tubular necrosis': limited data and flawed animal models. *Kidney International*, **60**(4), 1220–4.
7. Brun C and Munk O. (1957). Lesions of the kidney in acute renal failure following shock. *Lancet*, **1**, 603–9.
8. Venkataraman R and Kellum JA. (2007). Defining acute renal failure: the RIFLE criteria. *Journal of Intensive Care Medicine*, **22**(4), 187–93.
9. Klenzak J and Himmelfarb J. (2005). Sepsis and the kidney. *Critical Care Clinics*, **21**, (2), 211–22.
10. Lameire NH. (2005). The Pathophysiology of Acute Renal Failure. *Critical Care Clinics*, **21**, (2), 197–210.
11. Endre ZH, Walker RJ, Pickering JW, et al. (2010). Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial). *Kidney International*, **77**, 1020–30.
12. Coller FA and Maddock WG (1935). A study of dehydration in humans. *Annals of Surgery*, **102**, 947–60.

CHAPTER 213

Management of oliguria and acute kidney injury in the critically ill

Mohammed Ahmed and Sean M. Bagshaw

Key points

- Acute kidney injury (AKI) is common and increasingly encountered in critically-ill patients and portends a greater risk of morbidity, mortality, and resource utilization.
- Identification of those at highest risk and intensive monitoring for early intervention of AKI can reduce risk of developing severe or worsening AKI.
- There are generally no 'magic bullets' to prevent or treat AKI once established, rather management for ALL critically-ill patients should ideally focus on restoration of systemic and renal haemodynamics; along with discontinuing, dose-adjusting or avoiding potentially nephrotoxin exposures.
- Fluid therapy remains the cornerstone for prevention and management of early AKI; however, fluid resuscitation with potentially nephrotoxin solutions should be avoided, and fluid accumulation and overload should be limited.
- Selected clinical contexts, such as contrast media-associated AKI (CA-AKI), hepatorenal syndrome (HRS), rhabdomyolysis, and sepsis, may involve specific interventions to reduce risk of AKI.

Introduction

Acute kidney injury (AKI) is exceedingly common and increasingly encountered amongst hospitalized patients with critical illness. Those with AKI suffer worse clinical outcomes, including overt kidney failure and need for renal replacement therapy (RRT), higher mortality, prolonged hospitalization, and amongst survivors, non-recovery of kidney function, and chronic kidney disease (CKD). AKI often occurs in association with clearly identifiable patient- and/or intervention-related risks and can be anticipated as a consequence or complication of critical illness. Intensivists are often the key care providers for these critically-ill patients who are at high risk of AKI. Accordingly, working knowledge of the scope, complexity, and general principals of prevention and management of AKI are indispensable in the care of these patients.

It is important to recognize these patients are often exposed to multiple discrete risks that may accumulate (i.e. multiple insults) over their course and exert an important modifying influence on the duration and severity of AKI, along with the probability of recovery of kidney function. Evidence has consistently shown that timely identification for those at high risk of or who have developed milder forms of AKI can afford opportunity for earlier intervention. The implementation of a real-time electronic alert system (i.e. 'AKI sniffer') to an ICU was found to contribute to earlier identification and more aggressive intervention in those with worsening AKI, including fluid therapy, diuretics and/or vasoactive support, along with a higher likelihood of resolution of AKI within 8 hours [1].

Multiple different therapies have been investigated over the last several decades that while showing benefit in experimental studies for preventing or mitigating damage after an acute kidney insult, these have not translated into effective interventions in humans. In essence, there is essentially no specific therapeutic intervention for the vast majority of critically-ill patients developing AKI. Accordingly, strategies to prevent or mitigate AKI should be individualized, while avoiding further exposure to kidney insults, and mitigating the complications associated with kidney failure. In general, the over-arching tenets for **all** potentially susceptible patients are shown in Box 213.1. Selected examples of acute physiology and interventions with the potential for negative effects on kidney function are shown in Table 213.1.

Specific interventions for acute kidney injury

Fluid therapy

Type of fluid therapy

Fluid therapy represents the cornerstone for the prevention and management of AKI. Of the numerous strategies evaluated for prevention of AKI, only fluid therapy has been shown to be consistently effective. There are a variety of fluid types available for resuscitation. These are broadly categorized as crystalloid solutions (i.e. 0.9% saline or balanced Ringer's Lactate), and colloid solutions (i.e. hydroxyethylstarch [HES], dextran, gelatin, albumin, blood products). There remains controversy, along with conflicting data, about which type of fluid (i.e. crystalloid vs. colloid) should ideally be used during resuscitation. The most common resuscitation fluid administered worldwide is synthetic colloid (i.e. HES); however, it

Box 213.1 Summary of approach to management and intervention in AKI

Approach to management and interventions

- Restore/optimize arterial filling.*
- Restore/optimize cardiac output.*
- Restore/optimize mean arterial pressure.*
- Restore/optimize oxygen carrying capacity (i.e. haemoglobin).*
- Monitor/maintain fluid and electrolyte homeostasis.
- Remove/avoid all non-essential nephrotoxins or performed appropriate therapeutic monitoring/dose-adjustment when necessary.
- Consider context-specific interventions (i.e. contrast-media; hepatorenal syndrome; rhabdomyolysis; sepsis).
- Monitor for/avoid excess fluid accumulation.
- Monitor for/avoid complications of overt kidney failure (i.e. hyperkalaemia; metabolic acidosis; intravascular volume overload) and, when appropriate, plan for RRT.

*There should be early use of invasive/functional haemodynamic monitoring (i.e. arterial catheter, central venous pressure, echocardiography, pulmonary artery catheter, or methods to measure stroke or pulse pressure variation) to guide timely and appropriate resuscitation.

is likely the majority of critically-ill patients receive some combination of crystalloids, colloids, and/or blood products.

Recent data have suggested HES contributes to or exacerbates AKI, in particular in sepsis. Three multi-centre, randomized trials comparing HES to control resuscitation fluids (3% modified gelatin; 0.9% saline; Ringer's acetate) in critically ill septic patients have found HES results in worse clinical outcomes, including increased risk of AKI, greater rate of RRT use, and higher mortality [2–4]. These data of potential harm, coupled with no improvement in outcomes and excessive cost compared with crystalloids, have led to consensus guideline recommendations that HES not be used in patients with severe sepsis or at risk of AKI [5].

Resuscitation with saline solution (i.e. 0.9% saline) compared with balanced crystalloid solution (i.e. Ringer's lactate; Plasmalyte) may predispose to metabolic acidosis and AKI in peri-operative and critically-ill patients. Observational data have suggested the use of balanced crystalloids, when compared with 0.9% saline, for peri-operative resuscitation in patients undergoing major abdominal surgery reduced post-operative complications, including need for RRT [6]. In a small non-randomized study, balanced crystalloid resuscitation in patients with diabetic ketoacidosis resulted in more rapid correction of base deficit when compared to 0.9% saline [7]. Similarly, in a non-randomized before-and-after study, the restriction of chloride-rich solutions in critically-ill patients can decrease the incidence of severe metabolic acidosis and contribute to lower adjusted-rates of AKI and RRT [8].

Fluid volume and accumulation

It is important to recognize there is currently no evidence that fluid therapy will reverse AKI once established. In fact, AKI patients, whether oliguric or not, require judicious monitoring of volume status, not only to correct preload deficits, but also because of the adverse consequences of fluid accumulation. The unnecessary accumulation of fluid can negatively impact clinical outcomes, in particular in oliguric patients with established AKI [9,10]. For example, observational data in patients with septic shock have shown higher mortality in those not achieving a negative fluid balance in at least one of the first three days after ICU admission. The impact of a maintaining a neutral or negative fluid balance has been shown to improve outcomes in acute lung injury (ALI) [9], pulmonary oedema and is predictive of successful weaning from mechanical ventilation. In patients with sepsis and AKI, excessive fluid therapy, despite optimal systemic haemodynamics and a high rate of diuretic use, does not necessarily improve kidney function, but may worsen gas exchange. Observational data of fluid accumulation in critically ill children with AKI has consistently been identified as a predictor of mortality [11]. Similarly, in adult critically-ill patients with septic AKI, fluid accumulation predicted 60-day mortality. In AKI patients, fluid overload independently predicts higher likelihood of RRT requirement and mortality [10]. These observations highlight the importance for monitoring of fluid balance in critical illness, in particular after the initial phase of resuscitation, where obligatory fluid intake (i.e. medications, nutrition) may greatly exceed output (i.e. relative oliguria) leading to rapid fluid accumulation, in particular in AKI, where water and solute excretion in impaired.

Vasodilator therapy

The use of vasodilators is theoretically attractive to restore renal blood flow (RBF) and mitigate renal vasoconstriction in AKI. Dopamine (DA), via the DA receptors present in renal tissue, can reduce renal vascular resistance and has long been used to mitigate AKI; however, evidence from a large randomized trial failed to show any benefit for 'renal-dose' DA in critically-ill patients with early AKI [12]. Moreover, DA has been associated with arrhythmic complications. Additional therapies, including the DA_1 receptor agonist fenoldopam; atrial natriuretic peptide (ANP); and B-type natriuretic peptide (i.e. nesiritide) merit further investigation; however, have not yet conclusively been proven effective.

Diuretic therapy

The role of diuretic therapy in the management of AKI remains controversial. Yet, diuretics are extensively used in critically-ill patients despite a lack of definitive evidence of effectiveness for improved clinical outcomes and concern for harm [13]. There has long been the hypothesis that the oliguria and reduced glomerular filtration rate (GFR) observed with AKI, mediated largely by glomerulotubular feedback (TFG), is an adaptive physiological response for kidney protection. However, this has recently been challenged. In a prospective observational study, Redfors et al. evaluated the renal oxygen supply/demand relationship in 49 post-cardiac surgery patients with and without AKI. In those with AKI, GFR, RBF, sodium reabsorption was reduced, but also associated with a significant increase in rVO2, such that for each unit of reabsorbed sodium, there was a 2.4-fold higher utilization of oxygen for those with AKI compared with those who did not have AKI. These data challenge the hypothesis that oliguria and reduced GFR in AKI are simply adaptive/protective mechanisms. These data further indirectly support a potential 'renal protective' role for furosemide, to attenuate and/or reduce the severity of kidney injury, when administered in the early phases of AKI. Diuretics also have an important role for managing fluid accumulation and

Table 213.1 Selected examples of acute physiology and interventions with the potential for negative effects on kidney function

Intervention	Example	Action
Altered systemic haemodynamics		
Reduced arterial filling	Diuretics	Discontinue
Negative inotropic therapy	β-blockers	Discontinue
Anti-hypertensive therapy	CCB	Discontinue
Altered renal haemodynamics		
Afferent arteriolar vasoconstrictors	NSAIDs	Discontinue
Efferent arteriolar vasodilators	ACEi/ARB*	Discontinue
Altered renal venous pressure		
Elevated intra-abdominal pressure	Excess fluid accumulation	Avoid
Nephrotoxins		
Antibiotics	Aminoglycosides; vancomycin; colistin; sulfamethoxezole; foscarnet	Discontinue, monitor or dose-adjust
Antifungals	Amphotericin	Discontinue, monitor or dose-adjust
Antivirals	Acyclovir; HAART	Discontinue, monitor or dose-adjust
Immunosuppression	Tacrolimus; cyclosporin	Discontinue, monitor or dose-adjust
Fluid therapy	Dextrans; hydroxyethyl starch	Avoid
Diagnostic imaging	Radio-contrast media	Avoid
Cytotoxic chemotherapy	Cisplatin; methotrexate	Discontinue, monitor or dose-adjust

*ACEi and ARB lead to reduction in glomerular blood flow, which has beneficial effects for kidney survival in chronic kidney disease patients but may lead to worsening kidney function in patients with AKI.

CCB, calcium channel blockers; NSAID, non-steroidal anti-inflammatory drugs; ACE, angiotensin enzyme converting; ARB, angiotensin receptor blocker; HAART, highly active anti-retroviral therapy; IAP, intra-abdominal pressure.

in the delivery of optimal nutritional support. Numerous studies have evaluated loop diuretics in the treatment of AKI; however, most have failed to find consistent clinical benefit and some have suggested worse clinical outcome. Additional small trials have suggested that diuretics might reduce the severity of kidney injury by converting 'oliguric' to 'non-oliguric' AKI, shorten the duration of AKI, improve renal recovery, and perhaps delay or ameliorate need for RRT. Importantly; however, improved survival or renal recovery has yet to be confirmed by high-quality evidence. Recent data from a large randomized trial of fluid strategies in critically-ill patients with acute lung injury (ALI) have suggested potential improved outcome with furosemide use. In the subgroup with AKI, those received greater cumulative furosemide were observed to have lower mortality, while greater fluid balance was associated with higher mortality. Importantly, there was no observed threshold of furosemide dose above which mortality was observed to increase [9]. These data imply the selective use of furosemide is likely effective and safe in most patients with AKI; however, further randomized trials are needed.

Cytoprotective and antioxidant therapy

Additional 'cytoprotective' interventions for prevention of AKI, such as remote ischaemic preconditioning, hypothermia, thyroxine, erythropoietin, statins, ascorbic acid (vitamin C), and insulin-like growth factor are theoretically attractive. However, they have not yet been proven consistently beneficial in randomized trials. Tight glycaemic control with intensive insulin therapy has been shown to reduce the incidence of severe AKI requiring RRT in single centre trials, however, this was not replicated in a large multi-centre trial.

Specific syndromes

Contrast media-associated acute kidney injury

Contrast media-associated AKI (CA-AKI) is a leading cause of iatrogenic kidney injury following diagnostic and interventional procedures. The pathophysiology of CA-AKI remains incompletely understood; however, is believed to involve a combination of renal vasoconstriction, corticomedullary ischaemia, direct tubular toxicity, and tubular cast formation/obstruction. An estimated 16.3% of critically-ill patients receiving contrast media with imaging procedures develop CA-AKI [14]. Those developing CA-AKI were more likely to need RRT, less likely to recovery kidney function, had longer durations of hospitalization and higher mortality. Approaches to preventing CA-AKI are largely categorized into three strategies based on our current understanding of its pathophysiology:

- Interventions to induce a forced diuresis and high urine flow rates.
- Interventions to induce renal vasodilatation.
- Interventions to attenuate oxidative stress and inflammation in the kidney.

Most interventions to date, with the exception of fluid hydration, have proven either ineffective or inconsistent, including forced diuresis, N-acetylcysteine, sodium bicarbonate, and prophylactic haemofiltration. Pragmatically, in critically-ill patients, the perceived benefits and risks of undergoing a diagnostic/therapeutic procedure involving contrast media must be carefully explored and strategies to mitigate the risk, such as alternative modalities of imaging in those at increased risk, or alternatively, if proceeding with the procedure, ensuring volume repletion, avoiding the use of concomitant nephrotoxins, and minimizing the volume of contrast media administered. In those at high risk, a plan for potential need for RRT should be considered.

Hepatorenal syndrome

Hepatorenal syndrome (HRS) refers to the development of functional AKI in advanced cirrhosis. HRS develops in nearly 40% of patients with advanced cirrhosis by 5 years. HRS may be associated with a precipitating event, such as spontaneous bacterial peritonitis (SBP), gastrointestinal bleeding, or volume depletion due to diuretic therapy or large volume paracentesis or may follow a more indolent path whereby kidney function may deteriorate over a period of weeks to months, often in association with refractory

ascites. Strategies to prevent HRS should focus on directed treatment of precipitants such as rapid restoration of effective circulation volume with albumin, haemodynamic support with vasoactive therapy as indicated, antimicrobials, and albumin for SPB, and strict avoidance of nephrotoxins. While in established HRS, liver transplantation (LT) is the only definitive intervention; additional bridging therapies are available. Vasoconstrictor therapy, to mitigate splanchnic vasodilatation and restore mean arterial pressure and renal perfusion, can reverse HRS and improve outcome. Evidence from randomized trials supports the use of the synthetic vasopressin-analogue terlipressin, when administered with albumin, to restore of kidney function and improve patients survival to transplantation [15]. Terlipressin has been associated with secondary organ ischaemia, including cardiac arrhythmias and splanchnic ischaemia, therefore, this therapy is contraindicated in those with significant coronary, cerebral and/or peripheral artery disease. If terlipressin is unavailable or too costly, alternative vasopressors to reverse of HRS may be used including intravenous infusions of arginine vasopressin and norepinephrine or oral therapy with the α-adrenergic agonist midodrine coupled with subcutaneous octreotide. For refractory ascites and progressive HRS, small clinical studies have found transjugular portosystemic intrahepatic shunting (TIPS) may attenuate or improve kidney function over several weeks to months.

Rhabdomyolysis and myoglobinuric acute kidney injury

Rhabdomyolysis is a syndrome characterized by the breakdown of striated muscle, resulting in the release of myoglobin and other muscle constituents into the extracellular fluid. The cornerstone for prevention and treatment of myoglobinuric AKI remains aggressive volume resuscitation to expand the vascular compartment to restore and maintain kidney perfusion. This is primarily achieved initially with isotonic crystalloid solutions (10–15 mL/kg/hour) titrated to physiologic endpoints such as central venous pressure and urine output (target 200–300 mL/hour for persisting myoglobinuria). In the context of crush syndrome associated with disaster, fluid resuscitation should be initiated prior to evacuation. Following initial resuscitation, bicarbonate (50–100 mEq/L) may be added, titrated to achieve a urine pH >6.5, to increase the solubility and renal excretion of tubular myoglobin and uric acid casts, along with attenuation of concomitant acidosis, hyperkalaemia, and release of free iron from myoglobin. Importantly, if urinary alkalization is unsuccessful or symptomatic hypocalcaemia ensues, bicarbonate-containing solutions should be discontinued. There are theoretical benefits for the use of mannitol (1–2 g/kg over 24 hours) including provoking an osmotic diuresis to flush intra-tubular myoglobin deposition and cast formation, remove sequestered water from injury muscle and mitigate compartment syndrome; and potentially acting as a free radical scavenger; however, these benefits are currently not supported by evidence from randomized trials. Further augmentation of urine output with loop diuretics may be beneficial for patients with relative oliguria and excessive fluid accumulation. While controversial, myoglobin clearance can be augmented by haemofiltration with high-flux haemofilters (molecular weight cut-off 30–60 kDa). Additional controversial strategies have been hypothesized, including allopurinol to reduce uric acid production, improving microcirculatory blood flow with pentoxyifylline, attenuating oxidant injury with glutathione, chelation of circulating free iron with deferoxamine and dantrolene to reduce intracellular calcium; however, all lack robust data to support recommending. Unfortunately, in patients with myoglobinuria and overt kidney failure, no specific therapy is available and patients should be supported early by initiation of RRT.

Sepsis-associated acute kidney injury

Sepsis is a key contributing factor for AKI in critically-ill patients that portends higher risk of poor clinical outcome. Yet, our understanding of its pathophysiology remains incomplete. Recent experimental data in hyperdynamic septic AKI have shown GFR and urine output can be restored by infusion of the potent efferent arteriolar vasoconstrictor angiotensin II (ATII) [16]. Experimental models have also suggested mitigation of the immune response with dexamethasone may improve kidney function [17]. While restoration of systemic haemodynamics is a principal mechanism to prevent and treat AKI, supraphysiological augmentation of mean arterial pressure has not been shown to improve kidney function and may contribute harm. More recently, the addition of arginine vasopressin to norepinephrine in septic shock was shown to reduce the incidence of worsening AKI in those at risk [18]. Several studies have suggested fluid resuscitation with albumin may be associated with improve survival in septic shock; however, improvements in kidney function have not been assessed and further confirmatory trials are ongoing. Alternatively, fluid resuscitation with HES in septic shock and in those at risk for AKI has consistently been associated with worse clinical outcome and recently practice guidelines have recommended against their use in these settings [2,3,5]. The administration of alkaline phosphatase (AP) may reduce renal tubular expression of inducible nitric oxide synthase and mitigate AKI. A recent phase II randomized trial of a continuous 48 hour AP infusion started early after AKI onset found greater reduction in systemic and kidney-injury specific mediators and improvement in creatinine clearance at 28 days [19]. Observational data have also suggested that delay to effective antimicrobial therapy in septic shock is an important independent factor for AKI [20]. Finally, following the acute resuscitative phase, excessive fluid accumulation has been associated with worse clinical outcome. In these circumstances, there should be concerted effort to minimize or avoid non-essential fluid administration.

Conclusion

AKI remains a challenging clinical problem in the care of critically-ill patients due largely to the paucity of specific therapeutic interventions aimed at reducing poor outcome. Those patients most at risk for the development of AKI can often be identified by an assessment of demographic, clinical, diagnostic and procedure-related factors couple with early and intensive bedside monitoring. All critically-ill patients at risk of or with milder forms of AKI should have their support individualized with a particular focus on: restoring systemic and renal haemodynamics; avoidance of potentially exacerbating nephrotoxin exposures; opportunities for context-specific therapies in selected circumstances, and prevention monitoring for life-threatening complications of kidney failure with RRT planning if necessary.

References

1. Colpaert K, Hoste EA, Steurbaut K, et al. (2012). Impact of real-time electronic alerting of acute kidney injury on therapeutic intervention and progression of RIFLE class. *Critical Care Medicine*, **40**(4), 1164–70.
2. Schortgen F, Lacherade JC, Bruneel F, et al. (2001). Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. *Lancet*, **357**(9260), 911–16.
3. Brunkhorst FM, Engel C, Bloos F, et al. (2008). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *New England Journal of Medicine*, **358**(2), 125–39.
4. Perner A, Haase N, Guttormsen AB, et al. (2012). Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *New England Journal of Medicine*, **367**(2), 124–34.
5. Reinhart K, Perner A, Sprung CL, et al. (2012). Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Medicine*, **38**(3), 368–83.
6. Shaw AD, Bagshaw SM, Goldstein SL, et al. (2012). Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Annuals of Surgery*. **255**(5), 821–9.
7. Chua HR, Venkatesh B, Stachowski E, et al. (2012). Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. *Journal of Critical Care*, **27**(2), 138–45.
8. Yunos NM, Kim IB, Bellomo R, et al. (2011). The biochemical effects of restricting chloride-rich fluids in intensive care. *Critical Care Medicine*, **39**(11), 2419–24.
9. Grams ME, Estrella MM, Coresh J, Brower RG, and Liu KD. (2011). Fluid balance, diuretic use, and mortality in acute kidney injury. *Clinic Journal of American Society Nephrology*, **6**(5), 966–73.
10. Bouchard J, Soroko SB, Chertow GM, et al. (2009). Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney International*, **76**(4), 422–7.
11. Sutherland SM, Zappitelli M, Alexander SR, et al. (2010). Fluid overload and mortality in children receiving continuous renal replacement therapy: the Prospective Pediatric Continuous Renal Replacement Therapy Registry. *American Journal of Kidney Disease*, **55**(2), 316–25.
12. Bellomo R, Chapman M, Finfer S, Hickling K, and Myburgh J. (2000). Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet*, **356**(9248), 2139–43.
13. Bagshaw SM, Delaney A, Haase M, Ghali WA, and Bellomo R. (2007). Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis. *Critical Care Resuscitation*, **9**(1), 60–8.
14. Hoste EA, Doom S, De Waele J, et al. (2011). Epidemiology of contrast-associated acute kidney injury in ICU patients: a retrospective cohort analysis. *Intensive Care Med*icine, **37**(12), 1921–31.
15. Martin-Llahi M, Pepin MN, Guevara M, et al. (2008). Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology*, **134**(5), 1352–9.
16. May CN, Ishikawa K, Wan L, et al. (2012). Renal bioenergetics during early Gram-negative mammalian sepsis and angiotensin II infusion. *Intensive Care Medicine*, **38**(5), 886–93.
17. Johannes T, Mik EG, Klingel K, Dieterich HJ, Unertl KE, and Ince C. (2009). Low-dose dexamethasone-supplemented fluid resuscitation reverses endotoxin-induced acute renal failure and prevents cortical microvascular hypoxia. *Shock*, **31**(5), 521–8.
18. Gordon AC, Russell JA, Walley KR, et al. (2010). The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Medicine*, **36**(1), 83–91.
19. Pickkers P, Heemskerk S, Schouten J, et al. (2012). Alkaline phosphatase for treatment of sepsis-induced acute kidney injury: a prospective randomized double-blind placebo-controlled trial. *Critical Care*, **16**(1), R14.
20. Bagshaw SM, Lapinsky S, Dial S, et al. (2009). Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. *Intensive Care Medicine*, **35**(5), 871–81.

PART 8.4

Renal replacement techniques

CHAPTER 214

Continuous haemofiltration techniques in the critically ill

Zaccaria Ricci and Claudio Ronco

Key points

- Critically-ill patients with severe acute kidney injury (AKI) should be supported with extracorporeal renal replacement therapy. Timely and correctly prescribed treatments produce the best outcomes.
- Intermittent techniques are reserved for haemodynamically stable patients, and are less commonly used in critical care.
- Continuous veno-venous haemofiltration/haemodialysis/haemodiafiltration may all be used in critically-ill patients. Each modality has advantages and pitfalls. Haemodiafiltration possibly combines the best of both purification techniques.
- A continuous renal replacement therapy dose of at least 25 mL/kg/hour should be delivered. Due to machines inaccuracies and downtime, a prescription of 30–35 mL/kg/hour may be needed to achieve a dose of 25 mL/kg/hour.
- Heparin remains the gold standard for circuit anticoagulation. Alternatives to heparin are available, and should be considered if there is particular concerns about haemorrhage or if heparin induced thrombocytopaenia is suspected.

Introduction

The mainstay of severe acute kidney injury (AKI) treatment is extracorporeal renal support. Advances in modern technology have provided different modalities to perform renal replacement therapies (RRT), but the optimal time to start and stop RRT is not yet established.

Indications to start renal replacement therapies

Renal replacement is indicated when renal dysfunction leads to one or more of the following:

- Oligo/anuria (0–0.2 mL/kg/hour).
- Severe fluid overload.
- Pulmonary oedema.
- Hyperkalaemia.
- Metabolic acidosis.

However, recent greater ease of use, novel so called 'extra-renal indications' and a relatively low associated morbidity has brought clinicians to standardize treatment timing and explore new indications (i.e. severe sepsis and multi organ dysfunction syndrome). As a matter of fact, indication to start RRT remains a matter of debate and no clear recommendations have been provided. As a general rule, early RRT is considered beneficial, in a clinical state where renal dysfunction is clearly worsening, but before one of the above-mentioned indications has been reached. However, this hypothesis has not been definitively proven [1–3].

Indications to stop renal replacement therapies

There is no hard evidence on how and when RRT should be stopped. It is generally accepted, however, that re-appearance of urine output (>500 mL/day) in a previously anuric patient is a signal that the kidneys are improving. RRT might also be weaned to lighter forms (i.e. from intense to less intense treatments, or from continuous to semi-continuous or intermittent therapies) if the patient demonstrates haemodynamic stability and improving severity of critical illness.

Principles of renal replacement

The glomeruli filter the blood to remove excess water and waste products. Renal replacement uses semi-permeable membranes to achieve a similar result. The membrane may be artificial, as in a filter, or autologous, as in the peritoneum. Many molecules, including water, urea, and solutes of various molecular weights, are transported across the membrane by variable combinations of the processes of diffusion (dialysis) and convection (ultrafiltration).

During diffusion the movement of solutes depends on their tendency to reach the same concentration (equilibrium) on each side of the membrane: this results in the passage of solutes from the compartment with the higher concentration to the compartment with the lower concentration. Diffusion is affected by characteristics of the semi-permeable membrane including thickness, surface area, temperature, and diffusion coefficient. Diffusion is provided by dialysis, in which a solution (the dialysate) flows on the other side of the membrane, counter-current to blood flow, in order to maintain a solute gradient.

In convection, the movement of solute across a semi permeable membrane is a result of transfer of water across the membrane. In other words, as the solvent (plasma water) crosses the membrane, solutes are carried with it if the pore size of the membrane allows such passage. Convection can be achieved by ultrafiltration (UF),

which creates a transmembrane pressure (TMP) gradient. UF depends on the rate of flow (Qf), the membrane coefficient (Km) and the TMP gradient between the pressures on both sides of the membrane:

$$Qf = Km * TMP \quad \text{[eqn 1]}$$

The TMP gradient is the difference between the pressure in the blood compartment which is directly related to blood flow (Qb), and filtrate compartment pressure which is modulated by a pump in modern RRT machines. The machines are designed to maintain a constant filtration rate (Qf): when the filter is 'fresh' and highly permeable, the pumps retard UF production, generating a positive pressure in the filtrate compartment (TMP is initially dependent only on blood flow). As the membrane fibres become degraded, a negative pressure on the filtrate side is necessary to achieve a constant Qf. With time, TMP progressively increases up to a maximum level at which solute clearance is compromised and clotting of the filter or membrane rupture is possible.

The size of molecules cleared during convection and UF exceeds that during diffusion, because they are physically dragged to the UF side, however, this gradually becomes limited by the protein layer that progressively closes filter pores during convective treatments. In addition, the membrane itself can adsorb molecules, and this is important for higher molecular weight toxins. The membrane adsorptive capacity is generally saturated in the first few hours of filter use and has a relatively minor impact on mass separation processes. During UF, plasma water and solutes are filtered from blood, leading to a decrease in blood hydrostatic pressure and increase in blood oncotic pressure. The fraction of plasma water that is removed from blood during UF is called filtration fraction and should be kept in the range of 20–25% to prevent excessive haemoconcentration within the filtering membrane. Otherwise, the oncotic pressure gradient could neutralize the TMP gradient resulting in equilibrium.

Replacing plasma water with a substitute solution completes the haemofiltration (HF) process. The replacement fluid can be administered after the filter (post- filter dilution HF, often called simply 'post-dilution'), before (pre- filter dilution HF, often called simply 'pre-dilution'), or both. Post-filter dilution leads to a higher urea clearance, but pre-filter dilution may prolong circuit life by reducing haemoconcentration and protein build-up in the filter fibres. Conventional haemofiltration is performed with a highly permeable, steam-sterilized membrane with a surface area of about 1–2 m^2. The addition of convection to the diffusion process allows haemodiafiltration: dialysis and replacement solutions run simultaneously within the same filter to obtain additional solute removal.

Choice of mode

The ideal renal replacement treatment should include:

- Efficient solute removal.
- Low impact on haemodynamics.
- Low anticoagulant needs.
- Minimal interference with patient mobility.

Continuous RRT (CRRT) exhibits many of these features. Advantages of CRRT include using a low UF rate and slowing solutes exchanges which reduces the risk of as solute disequilibrium which can give rise to neurological symptoms and cerebral oedema, and the ability to adjust the CRRT prescriptions to individual patient's needs on an hour to hour basis. Different CRRT modalities are shown in Fig. 214.1.

Practical CRRT prescription

During CRRT, clearance (K) depends on circuit blood flow (Qb), haemofiltration flow (Qf), or dialysis flow (Qd), molecular weight of solutes, and filter type, and size. Circuit blood flow is mainly dependent on vascular access and operational characteristics of the individual RRT machine.

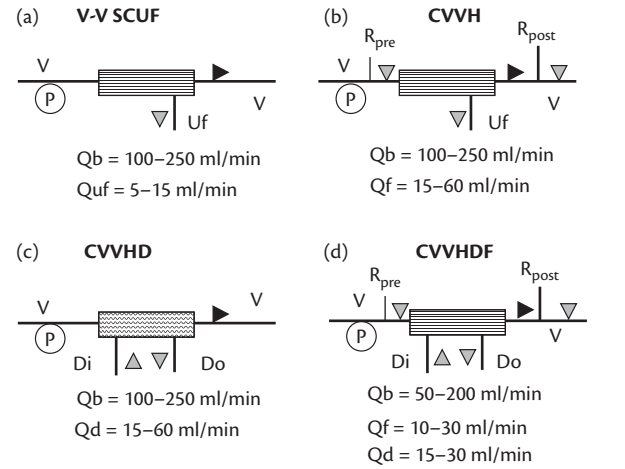


Fig. 214.1 Techniques of CRRT. (a) Slow continuous ultrafiltration (SCUF): blood is driven by a pump (P) through a highly permeable filter via an extracorporeal circuit, using veno-venous (V) access. The ultrafiltrate produced during membrane transit is not replaced and it corresponds to weight loss. It is used only for fluid removal in overloaded patients. Circuit blood flow: (Qb) 100–250 mL/min; ultrafiltrate flow (QUF): 5–15 mL/min. (b) Continuous veno-venous haemofiltration (CVVH): CVVH is similar to SCUF above except that the ultrafiltrate produced during membrane transit is partly or completely replaced (R) to maintain intravascular volume. Replacement fluid may be delivered before (R PRE), after (R POST) or both sides of the filter (pre- or post-dilution). Clearance for all solutes is convective and equals UF rate. Qb: 100–250 mL/min; QR: 15–60 mL/min; QUF: QR+ 5–15 mL/min. A variant of CVVH is high volume haemofiltration (HVHF): this treatment uses highly permeable membranes and haemofiltration with a high volume setting: Qb >200 mL/min and QUF> 35 mL/kg/hour in order to increase removal of high molecular weight solutes (e.g. inflammatory mediators). It is currently reserved to research purposes and experimental studies, as evidence for its use in the treatment of human sepsis is limited to small and inconclusive trials. (c) Continuous veno-venous haemodialysis (CVVHD): In CVVHD, blood is driven through a low permeability dialyser via an extracorporeal circuit in veno-venous mode and a countercurrent flow of dialysate (Di-Do) is delivered on the dialysate compartment. The ultrafiltrate produced during membrane transit corresponds to patient's weight loss. Solute clearance is mainly diffusive and efficiency is limited to small solutes only. Qb: 100–250 mL/min; QDi: 15–60 mL/min; QDo: QDi + QUF. (d) Continuous veno-venous haemodiafiltration (CVVHDF): Technique where blood is driven through a highly permeable dialyser via an extracorporeal circuit in veno-venous mode and a countercurrent flow of dialysate is delivered on the dialysate compartment. The ultrafiltrate produced during membrane transit is in excess of the patient's desired weight loss and replacement solution is needed to maintain fluid balance. Solute clearance is both convective and diffusive. CVVHDF has the main advantage of getting the most solute clearance with the lowest blood flow rate and should be reserved to heavier adult patients. Qb: 100–250 mL/min; QDi: 15–60 mL/min; Do: Di + QR + QUF.

Table 214.1 Different anticoagulation types

	Indication	Contra-indication	Advantages	Disadvantages
Unfractionated Heparin	Standard treatments	Heparin induced thrombocytopenia, high risk of bleeding	Relatively easy to manage, easy to reverse	Relative high risk of bleeding, relative low efficacy
No Anticoagulation	Post-operative patients with high risk of bleeding; critically-ill patients with severe coagulopathy	Standard treatments	Reduced adjunctive bleeding risk	Potentially reduced circuit lifespan
Regional heparinization	Patients at high risk of bleeding with excessively low circuit lifespan	Heparin induced thrombocytopenia	Easy to manage	Relative low efficacy
Low molecular weight heparin	Need for alternatives to continuous heparin infusion	Heparin induced thrombocytopenia	No need for continuous infusion	Difficult to reverse
Bivalirudine	Heparin induced thrombocytopenia	Blood stagnation	Fair anticoagulant efficacy	Scarce clinical experience, cost
Argatroban	Heparin induced thrombocytopenia	Liver insufficiency	Reliable anticoagulant efficacy	Scarce clinical experience, cost
Prostacycline	Heparin induced thrombocytopenia	Haemodynamic instability	Short half-life, no effect on coagulation cascade	Relative low efficacy
Epoprostenol	Heparin induced thrombocytopenia; standard treatment in experienced centres	Liver insufficiency	Significantly prolonged circuit patency	Metabolic alkalosis, cumbersome technique in non-experienced centres
Non-thrombogenic surfaces	High risk of bleeding	High risk of circuit clotting	Prolonged filter patency	Costly, scarce clinical validation

In haemofiltration, Qf is strictly linked to Qb by filtration fraction. In dialysis however, even if Qd is not limited by filtration fraction, still Qd/Qb ratio should not exceed 0.3, in order to optimize dialysis efficiency.

Urea and creatinine concentrations are generally used as reference solutes and their serum concentrations used to monitor the effectiveness of the RRT prescription; because their clearance has a 1:1 correlation with Qd/Qf rate (e.g. urea clearance of 10 mL/min corresponds to a Qf –or Qd- of 10 mL/min). However, it is important to be aware that serum urea and creatinine (typically and rapidly decreasing during the first CRRT days) are determined by the effectiveness of RRT and are not indicative of underlying renal function or eventual AKI outcome. The role of RRT is to maintain the patient's homeostasis in the period of AKI, providing the time necessary for the kidneys to recovery. RRT is used as a therapy, for example in patients with severe sepsis, to remove inflammatory mediators, but the effectiveness of such use has not yet been proven.

During continuous treatments, a standard initial therapy prescription should target a minimum urea clearance of 25–35 mL/kg /hr (1.7–2.5 l/hr of Qf/Qd in a 70 kg patient): this recommendation derives from the results of two recent large trials (RENAL and ATN trials) that reported no improvement in outcomes when CRRT doses higher than this were used. As yet there has been no prospective trial comparing same doses of different modalities (i.e. continuous haemodialysis vs. haemofiltration) and choice of modality generally relies on personal and institutional expertise and protocols. Current recommendations are to provide a CRRT dose that is not lower than 25 mL/kg/hour [4–6].

A negative fluid balance has recently been identified as having a strong association with outcome in critically-ill patients with AKI: it is possible that a negative fluid balance should be targeted in haemodynamically stable patients being treated with CRRT. However, the link between fluid balance and outcome has reported from observational data only and currently we recommend the net UF rate should be tailored to the individual patient's needs [7–12].

Anticoagulation

During RRT blood comes into contact with the artificial surfaces and in most patients some form of anticoagulation is needed Table 214.1. To reduce the risk of filter clotting, vascular access should to be of adequate size, and blood flow rate should exceed 100 mL/min. Pump flow fluctuations should be prevented (in modern machines this is mainly due to increased circuit resistances rather than flow rate inaccuracies). Venous bubble traps, where air/blood contact occurs, are used to prevent systemic air embolus, and the machine will alarm if bubbles are detected.

There is evidence that, when set-up is perfectly optimized, anticoagulants contribute little to the maintenance of circuit patency. When anticoagulants are relatively contra-indicated (risk of bleeding, pre-existing coagulopathy, thrombocytopaenia) RRT can still be performed safely and filter life may not be compromised.

Unfractionated heparin is the most commonly used anticoagulant. The dose ranges from 5 to 10 IU/kg/hour. In patients in whom systemic anticoagulation is to be avoided, heparin can be used in combination with post-filter administration of protamine (regional anticoagulation); with a 1 to 1 ratio (1mg of protamine per 150 IU of unfractionated heparin) and monitoring of activated partial thromboplastin time (aPTT). The response to heparin administration can be unpredictable due to altered bioavailability, antithrombin III (ATIII) depletion and the risk of heparin induced thrombocytopenia (HIT).

Low molecular weight heparins (LMWH) may also be used, but prospective studies have not yet shown them to be superior in prolonging circuit life. Bioavailability is more reliable than with

unfractionated heparin and the risk of HIT is lower. However, the anticoagulant effect cannot be reversed and there may be a higher risk of haemorrhage.

Epoprostenol is potentially useful for RRT anticoagulation, being a potent inhibitor of platelet aggregation with a short half-life. It is infused at a dose of 4–8 ng/kg/hour with or without the adjunct of low dose heparin. Hypotension may be induced by higher doses. High cost and the risk of hypotension may limit its use to short-term treatment.

Citrate chelates calcium to prevent clot formation and can be used to produce regional anticoagulation. The effect of citrate is reversed by post-filter administration of calcium chloride to maintain systemic normocalcaemia. This approach is effective in maintaining filter patency and compares favourably with heparin. It also avoids the risk of HIT and does not lead to systemic anticoagulation. However, the risk of potentially fatal hypocalcaemia, metabolic alkalosis, and the need for special fluids and the increased complexity of circuit set-up currently limit its use.

Finally direct thrombin inhibitors (bivalirudine, argatroban) have been proposed as alternative anticoagulants in cases where unfractionated heparin is contraindicated, but clinical experience is still limited to case series [13].

References

1. Ronco C and Bellomo R. (1998). Principles of solute clearance during continuous renal replacement therapy. In: Ronco C and Bellomo R (eds) *Critical Care Nephrology*, pp. 1213–23. Dordrecht: Kluwer Academic Publishers.
2. Bellomo R, Ronco C, Kellum JA, Mehta R, and Palevsky P (2004). The ADQI workgroup: acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Critical Care*, **4**, R204–12.
3. Uchino S, Kellum JA, Bellomo R, et al. (2005). Acute Renal Failure in Critically Ill Patients A Multinational, Multicenter Study. *Journal of the American Medical Association*, **294**, 813–18.
4. Ronco C, Bellomo R, Homel P, et al. (2000). Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet*, **356**, 26–30.
5. Saudan P, Niederberger M, De Seigneux S, et al. (2006). Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney International*, **70**, 1312–17.
6. Vinsonneau C, Camus C, Combes A, et al. (2006). Continuous veno-venous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. *Lancet*, **368**, 379–85.
7. Bellomo R, Baldwin I, and Ronco C (2001). High Volume Hemofiltration. *Contributors to Nephrology*, **132**, 375–82.
8. Uchino S, Bellomo R, Kellum JA, et al. (2007). Patient and kidney survival by dialysis modality in critically ill patients with acute kidney injury. *International Journal of Artificial Organs*, **30**, 281–92.
9. Ricci Z, Ronco C, Bachetoni A, et al. (2006). Solute removal during continuous renal replacement therapy in critically ill patients: convection versus diffusion. *Critical Care*, **10**, R67.
10. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, et al. (2009). Intensity of continuous renal-replacement therapy in critically ill patients. *New England Journal of Medicine*, **361**, 1627–38.
11. VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, et al. (2008). Intensity of renal support in critically ill patients with acute kidney injury. *New England Journal of Medicine*, **359**, 7–20.
12. Ricci Z, Polito A, Polito A, and Ronco C. (2011). The implications and management of septic acute kidney injury. *National Review of Nephrology*, 7, 218–25.
13. Tan HK, Baldwin I, and Bellomo R. (2000). Continuous veno-venous hemofiltration without anticoagulation in high-risk patients. *Intensive Care Medicine*, **26**, 1652–7.

CHAPTER 215

Haemodialysis in the critically ill

Rolando Claure-Del Granado and Ravindra L. Mehta

Key points

- Several new methods of dialysis are now available to treat critically ill patients with acute kidney injury (AKI). Haemodialysis remains an important technique to treat these patients.
- Rational use of haemodialysis requires an understanding of its operational factors and appreciation of the advantages and disadvantages of this technique.
- Delivered dose of dialysis needs to be measured and dose assessment should be a continuous process.
- Intermittent Haemodialysis should be preferred over slow low-efficiency dialysis (SLED) or Continuous renal replacement therapy (CRRT) in the case of severe hyperkalaemia or metabolic acidosis where rapid correction is required; for pulmonary oedema with fluid overload in patients without severe haemodynamic impairment; when high risk of bleeding and when anticoagulation is contraindicated; and to treat poisoning.
- IHD, SLED and CRRT are complementary methods that can be used in critically ill patients with AKI. They can be used at different times in the same patient as the patient's condition changes.

Introduction

Haemodialysis is used worldwide to manage patients with acute kidney injury (AKI). In recent years, there have been many advances in haemodialysis technology including biocompatible synthetic membranes, bicarbonate buffers, adjustments in blood, and dialysate flow rates, and improved monitoring of patient parameters. These have facilitated the widespread use of haemodialysis in the intensive care unit (ICU) despite which considerable controversy exists regarding the optimal use of haemodialysis in this setting. In this chapter we provide a brief review of the current status of haemodialysis to treat AKI in critically-ill patients.

Operational characteristics of haemodialysis techniques

Haemodialysis techniques utilize diffusion for solute removal by developing a concentration gradient between the vascular and dialysis compartments in the dialysis filter. This gradient facilitates bidirectional transport of solutes across a highly permeable membrane to allow effective removal of waste products (e.g. urea and creatinine) while replenishing the blood with base and electrolytes. Three main factors govern the rate of solute and fluid removal; blood and dialysate flow rates, membrane permeability and therapy duration.

In most haemodialysis sessions solute and fluid removal are optimized by having the blood flow rate (Qb) set at 200–400 mL/min based on the desired clearance for metabolic control. The site and type of access (femoral vs. jugular, tunnelled versus non-tunnelled catheter) contribute significantly to getting an adequate Qb particularly in hypotensive patients. Dialysate flow rate (Qd) usually is set at 500–800 mL/min to run countercurrent to blood flow and results in a solute saturation of approximately 40%. Ultrafiltration (UF) rate is set depending on patient's volume status and haemodynamic variables. Standard therapy for IHD is a treatment length of 3 to 4 hours, and treatment frequency ranges from 3 to 6 days per week [1].

Anticoagulation

Using an anticoagulant; most commonly heparin, helps to ensure membrane permeability, and to maintain circuit patency. Clotting of the filter reduces its longevity, and more importantly, reduces the efficiency of solute clearance and is a major barrier to delivery of effective dialysis [2]. Inefficient anticoagulation reduces dialyzer performance by diminishing the surface of the membrane available for diffusion or convection. The mainstay of anticoagulation for intermittent haemodialysis (IHD) is heparin, which is usually administrated as a bolus, followed by a continuous infusion into the arterial line. The target is to maintain a partial thromboplastin time of 1.5–2 times the normal level.

In patients with thrombocytopenia and coagulation disorders, systemic anticoagulation should be avoided; and regional citrate anticoagulation can be performed with calcium-containing or calcium-free dialysate, preferred for short and long sessions, respectively. The citrate infusion rate depends on the blood flow; therefore, during IHD with a blood flow ≥300 mL/min a citrate infusion of 50–60 mmol/hour would be appropriate. A common approach is to adjust the citrate infusion to maintain a post-filter calcium concentration of 0.25–0.35 mmol/L [3]; the patients serum ionized calcium must be maintained within the normal range through calcium administration on the return side of the filter. Regional citrate anticoagulation is increasingly used for CRRT and some studies have shown increased filter life, fewer bleeding complications, and in one study, increased survival [4]. Anticoagulation-free strategies postpone clotting by intermittent flushing of the arterial line of the circuit every 15–30 minutes with saline [5]. While successful, the saline volume administered must be included in the net ultrafiltration.

These operational parameters are used in the majority of IHD procedures and in most instances are effective in achieving reductions in solute levels and in maintaining fluid balance. However,

Table 215.1 Some operational characteristics of different renal replacement therapies

	CVVH	CVVHD	CVVHDF	IHD	SLED	EDD
Access	VV	VV	VV	VV	VV	VV
Blood flow (mL/min)	150–200	150–200	150–200	300–350	100–150	100–150
Dialysate flow (mL/min)	0	1000	1000	500	100–200	100–200
Replacement fluid (mL/min)	15–60	0	10–30	0	0	0
Ultrafiltration rate (L/h)	1	0.3	0.8	0.5	1	1
Urea Clearance (mL/min)	16.7	21.7	30	150–180	78	78

VV, venous-venous; CVVH, continuous venous-venous haemofiltration; CVVHD, continuous venous-venous haemodialysis; CVVHDF, continuous venous-venous haemodiafiltration; IHD, intermittent haemodialysis; SLED, slow low-efficiency dialysis; EDD, extended daily dialysis.

Reproduced from Mehta RL, 'Renal replacement therapy for acute renal failure: matching the method to the patient', *Seminars in Dialysis*, 1993, **6**(4), pp. 253–9, copyright 1993, with permission from John Wiley and Sons and American Society of Diagnostic and Interventional Nephrology.

the resulting high clearance (>200 mL/min for urea) causes a rapid decrease in the concentration gradient, which reduces the removal rate, limiting the total amount of solute removed. Additionally, critically-ill patients with AKI are generally fluid overloaded and hypoperfused and urea refilling from the interstitium to the blood results in compartmentalization that reduces operational efficiency. To counteract these limitations, strategies have emerged to reduce the Qb and Qd to 100 and 300 mL/min respectively and prolong the duration to 6–12 hours. These slow low-efficiency dialysis (SLED) or extended daily dialysis (EDD) techniques improve haemodynamic stability, provide adequate solute and fluid balance and are being utilized in some ICUs in lieu of CRRT Table 215.1. These hybrid modalities can be performed for 6–12 hours at night using ICU staff, thereby eliminating interruption of therapy, reducing staff requirements, and avoiding scheduling conflicts. Studies comparing EDD/SLED to CRRT have revealed favourable haemodynamic tolerance in critically-ill patients while achieving dialysis adequacy and ultrafiltration targets, since fluid removal and solute clearance are more gradual [6].

As shown in Table 215.2 haemodialysis techniques have some advantages and disadvantages in comparison with CRRT [7]. However, since dialysis techniques depend on diffusive clearance, they are subject to losses of key components (e.g. phosphorus and amino acids) and are limited in removing larger molecules. The rapid rate of solute and fluid removal may also contribute to haemodynamic instability and reduce plasma osmolality promoting osmotic water movement into cells and therefore reducing plasma volume. Osmolality changes may also induce or worsen cellular oedema, including cerebral oedema [8]. Several technological advancements in recent years have focused on features that could help physicians to optimize patient's volume status while avoiding haemodynamic instability and further kidney insults. Some of these features include: UF profiling, sodium profiling, blood volume monitoring, and blood temperature monitoring. In a prospective, randomized, crossover stratified study, Paganini et al. [9] compared a fixed dialysate sodium (140 mEq/L) and fixed UF rate (Protocol A), or a variable sodium dialysate (160–140 mEq/L) and variable UF (50% UF during the first third of treatment time, 50% UF over the last two thirds treatment time) (Protocol B). They found greater haemodynamic stability, significantly less need of interventions, and relative less blood volume changes with Protocol B [9]. Two small-randomized control trials have compared haemodynamic parameters between SLED and CRRT; in both studies no significant differences were found in all measured haemodynamic parameters [10,11].

Timing of initiation of haemodialysis

The optimal timing of dialysis for AKI is not defined. The initiation of dialysis for critically-ill patients with AKI is largely empirical and is subject to wide variation. In most instances, physicians start therapy based on a number of patients and process of care factors, e.g. blood concentrations of potassium, bicarbonate, sodium, and urea, liver function, bleeding risk, clinical parameters like body weight and arterial blood pressure, and finally the availability of equipment and staff, logistical considerations, and departmental protocols need also to be considered.

Table 215.2 Advantages and disadvantages of intermittent haemodialysis, sustained low-efficiency dialysis, extended daily dialysis, and continuous renal replacement therapies

	IHD	SLED/EDD	CRRT
Haemodynamic stability	++	+++	++++
Treatment duration	++	+++	++++
Patient mobility	++++	++	+
Fluid control	+	++	++++
Low osmolality variations	+	++	++++
No anticoagulation	++++	++	+
Small solute clearance	++++	+++	+++
Removal of medium molecular weight solutes	+	++	+++
Need of water production	+	+	-
1 machine several patients per day	++++	++	-
Continuous and adaptable therapy	+	++	++++
Cost	++	+++	++++
Nurse training	++++	++	+
Nurse workload	++	++	+

IHD, intermittent haemodialysis; SLED, slow low-efficiency dialysis; EDD, extended daily dialysis; CRRT, continuous renal replacement therapies.

Studies suggest that the decision when to start renal replacement therapy (RRT) should be individualized and based on trends in the patient's severity of illness, the presence of oliguria and fluid overload trying to minimize and avoid the complications of uraemia and volume overload rather than specific serum creatinine or urea values [12]. In a recent study Ostermann et al. evaluated optimal triggers for RRT in critically-ill patients with AKI. They examined data from 2 randomized controlled trials, 2 prospective studies and 13 retrospective trials and found large variation in the different parameters and cut-offs for RRT initiation. They found that no single biochemical parameter was able to define the optimal indication and time to start RRT. They also concluded that the degree of fluid overload, oliguria, and associated non-renal organ failure were more appropriate parameters for RRT initiation [13]. These data highlight the need to develop evidence-based and patient-specific indications for dialysis initiation in AKI.

Haemodialysis prescription and dose for acute kidney injury

Haemodialysis prescription for critically-ill patients with AKI is also largely empirical and is influenced by desired blood concentrations of solutes (e.g. serum urea, potassium, bicarbonate), fluid balance and haemodynamic stability. It is often influenced by logistic considerations including the availability of equipment and staff, and departmental protocols. As with timing of RRT, haemodialysis prescription should be individualized and operational characteristics of IHD/SLED must be considered before selecting different machine settings (i.e. Qb, Qd, ultrafiltration rate), choosing the type of anticoagulation (heparin versus regional citrate versus no anticoagulation), treatment time, and treatment frequency.

Haemodialysis prescription must also incorporate an assessment of the delivered dialysis dose. Traditionally Kt/V_{urea} has been employed as dialysis dose measurement in patients with end stage renal disease (ESRD). Kt/V_{urea} is defined as the dialyzer clearance of urea (K, obtained from manufacturer in mL/min) multiplied by the duration of the dialysis treatment (t, in minutes) and divided by the urea volume of distribution in the body (V, in mL), which is approximately equal to the total body water distribution. Based on studies in patients with ESRD that showed the influence of dose expressed as Kt/V_{urea} on outcomes, the same dose method has been employed for assessing delivered dose in acute haemodialysis. Nonetheless, some assumptions needed for calculating Kt/V_{urea} in chronic dialysis cannot be applied in patients with AKI. Routine measures of Kt/V_{urea} are unsuitable for quantifying haemodialysis regimens that vary in frequency because cumulative Kt/V_{urea} does not change proportionally to cumulative solute removal [14]. Another problem is that there is no standard method for assessing dose of dialysis in AKI; studies that have explored dose-outcomes relationships and prescribed vs. delivered dose of dialysis have used several different dose expressions (single-pool Kt/V, equilibrated Kt/V, frequency of dialysis per week, etc.).

The concept of providing higher dialysis doses in order to improve patients' outcomes has also been applied to critically-ill patients with AKI. However, recent trials did not confirm this benefit. The acute tubular necrosis (ATN) study, a randomized multicenter trial in 1124 critically-ill AKI patients compared intensive dosage (defined in IHD/SLED as 6 times per week) and less-intensive dosage (as IHD/SLED 3 times per week) [15]. There were no differences in day 60 all-cause mortality, duration of RRT, recovery rate of kidney function, or non-renal organ failure between the groups.

However, dose is still an important factor in the care of patients with AKI, and the actual delivered dose should be continuously assessed to ensure that operational characteristics of the treatment (e.g. filter function) do not preclude the delivery of a prescribed dose [14]. Dialysis dose should also consider fluid balance as an additional parameter as emerging evidence strongly support the influence of fluid overload as a major factor influencing outcomes [16]. Current dialysis machines incorporate on-line measurements of solute clearances and provide information on the delivered Kt/V making this a versatile tool for managing patients [17].

Effect of haemodialysis on outcomes

There is still an ongoing debate of which dialysis modality is better for critically-ill patients with AKI. Several studies have compared IHD and CRRT; most have found no significant differences in terms of mortality, as well as no differences in secondary outcomes such as renal recovery, RRT dependence, or haemodynamic tolerance. Even if CRRT confers a haemodynamic benefit; it is unclear whether this translates into improvements in the patient-relevant outcomes of survival and renal recovery [18]. There are few studies that have compared SLED vs. CRRT, those studies have found no significant differences in all measured haemodynamic parameters (mean arterial pressure, systemic vascular resistance, cardiac output) and fluid removal, with comparable removal of small solutes (e.g. creatinine and urea) [10,11].

Current evidence suggests that there is no superior method of RRT for critically-ill patients with AKI, since the three methods seem to provide similar outcomes. The choice between different modalities should consider the operational characteristics of each method with its advantages and limitations, patients' characteristics and clinical scenario, making sure that an adequate dose of dialysis is delivered and haemodynamic stability is maintained. Examples of situations where IHD may be preferred include severe hyperkalaemia, severe metabolic acidosis, pulmonary oedema with fluid overload in oliguric patients without severe haemodynamic impairment, high bleeding risk and when anticoagulation is contraindicated, and to treat poisoning with a substance of low molecular weight (<500 Da), high water solubility, low protein bound fraction, and low volume of distribution (<1.5 L/kg). On the other hand, in patients with severe haemodynamic instability with fluid overload and when risk of cerebral oedema is present CRRT or SLED should be chosen over IHD.

Van Berendoncks et al. found no difference in 2-year survival when conservative treatment, IHD, and CRRT where compared. Separate survival analysis comparing the conservative treated AKI with the total group of RRT; and sub analysis comparing the two types of RRT did not show a significant difference in long-term outcome. Of patients with chronic kidney disease, one half of the patients stayed in the same category, one quarter decreased, and one quarter increased. Mean serum creatinine did not differ between discharge and follow-up [19].

Finally, the question of the overall effect of RRT vs. conservative management of AKI has not been tested in an RCT. An observational study of Elseviers et al. noted increased mortality in patients treated with RRT vs. conservative management and this difference persisted even after adjustment of disease severity

using the SHARF score [20]. As with other aspects we have previously discussed (timing, type of RRT, and dose) the decision to start RRT requires an integrated and individualized approach, considering conservative management as well as different RRT options in each patient.

Conclusion

Haemodialysis constitutes an important technique to treat critically-ill patients with AKI. The choice of dialysis over conservative treatment, deciding when to start dialysis, and which modality to use, should be based on the operational characteristics of each method with due regard for its advantages and limitations. Haemodialysis techniques should be considered as part of an arsenal for RRT that can be used in critically-ill patients with AKI and based on the individual patient's need at any given time.

References

1. Overberger P, Pesacreta M, and Palevsky PM. (2007). Management of renal replacement therapy in acute kidney injury: a survey of practitioner prescribing practices. *Clinical Journal of the American Society of Nephrology*, **2**(4), 623–30.
2. Uchino S, Fealy N, Baldwin I, Morimatsu H, and Bellomo R. (2003). Continuous is not continuous: the incidence and impact of circuit 'down-time' on uraemic control during continuous veno-venous haemofiltration. *Intensive Care Medicine*, **29**(4), 575–8.
3. Davenport A. (2011). What are the anticoagulation options for intermittent hemodialysis? *National Review in Nephrology*, **7**(9), 499–508.
4. Hetzel GR, Schmitz M, Wissing H, et al. (2011). Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. *Nephrology Dialysis Transplantation*, **26**(1), 232–9.
5. Hoste EA and Dhondt A. (2012). Clinical review: use of renal replacement therapies in special groups of ICU patients. *Critical Care*, **16**(1), 201.
6. Liao Z, Zhang W, Hardy PA, et al. (2003). Kinetic comparison of different acute dialysis therapies. *Artificial Organs*, **27**(9), 802–7.
7. Srisawat N, Lawsin L, Uchino S, Bellomo R, and Kellum JA. (2010). Cost of acute renal replacement therapy in the intensive care unit: results from The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study. *Critical Care*, **14**(2), R46.
8. Schortgen F, Soubrier N, Delclaux C, et al. (2000). Hemodynamic tolerance of intermittent hemodialysis in critically ill patients: usefulness of practice guidelines. *American Journal of Respiratory Critical Care Medicine*, **162**(1), 197–202.
9. Paganini EP, Sandy D, Moreno L, Kozlowski L, and Sakai K. (1996). The effect of sodium and ultrafiltration modelling on plasma volume changes and haemodynamic stability in intensive care patients receiving haemodialysis for acute renal failure: a prospective, stratified, randomized, cross-over study. *Nephrology Dialysis Transplantation*, **11**(8), 32–7.
10. Kielstein JT, Kretschmer U, Ernst T, et al. (2004). Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: a randomized controlled study. *American Journal of Kidney Disease*, **43**(2), 342–9.
11. Baldwin I, Bellomo R, Naka T, Koch B, and Fealy N. (2007). A pilot randomized controlled comparison of extended daily dialysis with filtration and continuous veno-venous hemofiltration: fluid removal and hemodynamics. *International Journal of Artificial Organs*, **30**(12), 1083–9.
12. Macedo E and Mehta RL. (2011). When should renal replacement therapy be initiated for acute kidney injury? *Seminars in Dialysis*, **24**(2), 132–7.
13. Ostermann M, Dickie H, and Barrett NA. (2012). Renal replacement therapy in critically ill patients with acute kidney injury—when to start. *Nephrology Dialysis Transplantation*, **27**, (6), 2242–8.
14. Claure-Del Granado R and Mehta RL. (2011). Assessing and delivering dialysis dose in acute kidney injury. *Seminars in Dialysis*, **24**(2), 157–63.
15. Palevsky PM, Zhang JH, O'Connor TZ, et al. (2008). Intensity of renal support in critically ill patients with acute kidney injury. *New England Journal of Medicine*, **359**(1), 7–20.
16. Bouchard J, Soroko SB, Chertow GM, et al. (2009). Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney International*, **76**(4), 422–7.
17. Chesterton LJ, Priestman WS, Lambie SH, et al. (2006). Continuous online monitoring of ionic dialysance allows modification of delivered hemodialysis treatment time. *Hemodialysis International*, **10**(4), 346–50.
18. Fieghen H, Wald R, and Jaber BL. (2009). Renal replacement therapy for acute kidney injury. *Nephron Clinical Practice*, **112**(4), c222–9.
19. Van Berendoncks AM, Elseviers MM, and Lins RL. (2010). Outcome of acute kidney injury with different treatment options: long-term follow-up. *Clinical Journal of American Society of Nephrology*, **5**(10), 1755–62.
20. Elseviers MM, Lins RL, Van der Niepen P, et al. (2010). Renal replacement therapy is an independent risk factor for mortality in critically ill patients with acute kidney injury. *Critical Care*, **14**(6), R221.

CHAPTER 216

Peritoneal dialysis in the critically ill

Jeffrey C. Sirota and Isaac Teitelbaum

Key points

- Peritoneal dialysis (PD), the first modality of renal replacement therapy (RRT) used in the acute setting, dates back nearly 100 years. However, haemodialysis has now largely replaced PD in the treatment of acute kidney injury.
- PD is technically simpler to perform than haemodialysis, requiring simple, inexpensive, and widely available equipment and less specialized staff. As such, acute PD may be particularly important in resource-deprived areas or when natural disasters render haemodialysis impossible.
- Acute PD should be considered when haemodialysis is not available; when central venous access cannot be obtained or should be avoided; when AKI is accompanied by hypothermia or hyperthermia; and in patients with acute haemorrhagic pancreatitis, diuretic-refractory heart failure, or increased intracranial pressure.
- Close monitoring for various infectious, mechanical, pulmonary, and metabolic complications must be performed when acute PD is chosen, but these potential issues should not dissuade clinicians from considering this modality.
- Small observational studies have shown that PD can achieve favourable outcomes in non-hypercatabolic AKI, but there is a paucity of data comparing acute PD to acute haemodialytic techniques.

Introduction: the advantages of peritoneal dialysis

Acute kidney injury (AKI) is a widespread problem with increasing incidence, occurring in up to 20% of critically-ill patients and requiring renal replacement therapy (RRT) in approximately 0.5% of those affected [1]. Initially explored in the 1920s and made commonplace by the 1970s, peritoneal dialysis (PD) was the first modality of RRT used in AKI [2]. However, the emergence of haemodialysis (HD) has resulted in a significantly diminished role for PD; in a recent multinational survey PD was used in less than 5% patients who required RRT in an intensive care unit (ICU) [3].

However, despite its decline in popularity, PD still boasts a number of potential advantages over extracorporeal blood purification techniques, chief among which is the technical ease with which it can be performed. In comparison to HD, PD involves simpler access as well as inexpensive and widely available materials. Additionally, PD can be performed by nurses without specialized HD training in resource-deprived settings that may even lack electricity [4].

Some evidence has also suggested faster renal recovery with PD than with HD [5]. Despite these advantages, however, contemporary use of PD in AKI has been confined to resource-poor settings, following natural disasters when resources and capacity for HD may be exceeded, and to use in children, where its relatively gentle nature and its ease of dosing make it particularly attractive [6,7].

This chapter will review the indications and contraindications for PD in AKI, technical considerations, the available data on outcomes, and possible complications.

Indications and contraindications for peritoneal dialysis in acute kidney injury

Indications

Advances in extracorporeal RRT have led to a paradigm in which the only absolute indication for PD during AKI is the need for RRT when extracorporeal RRT cannot be performed, either due to resource limitations or technical constraints. In addition to this single absolute indication, relative indications also exist in which PD may be considered.

First, PD should be considered when central venous access cannot be obtained or should be avoided. Second, because PD does not require anticoagulation, patients with haemorrhagic conditions may benefit from PD instead of HD, although this advantage is lessened by the emergence of HD approaches that minimize systemic anticoagulation. Thirdly, PD can be beneficial when AKI is accompanied by hypothermia or hyperthermia, as the dialysate temperature can be manipulated to normalize body temperature [8,9]. PD may also have particular benefit in acute haemorrhagic pancreatitis where it may remove active inflammatory mediators [10]. PD can also achieve gentle volume removal without causing significant haemodynamic instability and so may be beneficial in patients requiring ultrafiltration (UF), such as those with diuretic-refractory heart failure [11]. Finally, PD's gentle solute removal may be safer than HD in patients with increased intracranial pressure in whom rapid solute removal may precipitate cerebral oedema.

Contraindications

Contraindications to acute PD are those related to the limitations of the dialytic modality and those related to mechanical concerns.

The former involves potentially inadequate therapy related to the gradual nature of fluid and solute clearance in PD. For example, although life-threatening hyperkalaemia can be treated with acute PD, HD is preferred if available. Similarly, hypercatabolic patients with emergent complications of high solute burden are better suited for HD modalities that provide more rapid solute clearance. Finally, patients who require more precise control of fluid removal might be better treated with HD.

The second category of relative contraindications involves mechanical issues. Instillation of PD fluid may increase intra-abdominal pressure and cause restrictive pulmonary physiology; therefore, caution should be used in patients with respiratory compromise. Certain post-operative conditions may also limit the use of PD, including the presence of new abdominal wall incisions, paralytic ileus, or presence of peritoneal drains (although PD can be performed successfully following abdominal surgery [12]). PD is also relatively contra-indicated in patients with anatomical conditions that preclude adequate filling of the peritoneal cavity (e.g. abdominal adhesions, hernias). Finally, infections such as abdominal wall cellulitis and peritonitis are relative contraindications PD.

Technical considerations

While a variety of different PD modalities exist, they affect solute and fluid clearance by the same principles. Sterile, potassium-free dialysate is instilled through a catheter into the peritoneal cavity and allowed to 'dwell', permeable solutes with a higher concentration in blood than dialysate (such as urea) move down the concentration gradients into the fluid. Additionally, the high dialysate glucose concentration draws water out of the blood, producing net UF. The dwell is followed by fluid drainage, and the instill–dwell–drain cycle is repeated. Cycling of PD fluid bags can be performed manually or automatically by a cycler machine. If available, the latter option is technically easier and requires less supervision.

Peritoneal access

The first step in initiating PD is placement of a peritoneal catheter, of which there are two types. The semi-rigid acute catheter can be placed at the bedside by a trained proceduralist without general anaesthesia. However, semi-rigid catheters carry risks of discomfort, peritonitis, and a risk of bowel perforation which increases with duration of catheter placement [13]. Placing a softer cuffed catheter is a surgical procedure that often requires general anaesthesia with its attendant risks. Laparascopic placement using less anaesthesia is also possible. Cuffed catheters carry less risk of bowel perforation and infection and are more comfortable, they do not require frequent replacement (as semi-rigid catheters do) and are less likely to trigger cycler alarms that cause dialysis interruptions [14,15].

Peritoneal dialysis modalities

High volume PD (HVPD), accomplished through a large number of daily exchanges, is the modality best suited for critically-ill patients who require high solute clearance. Another option for critically ill, hypercatabolic patients is continuous flow PD (CFPD), which involves one peritoneal access for instilling dialysate and another for draining; this arrangement allows higher dialysate flow rates and solute clearances.

Acute intermittent PD is a simpler technique that involves two or three 24-hour sessions per week of rapid cycling fluid into the peritoneal cavity (20–30 exchanges per day) [16]. This approach may not provide adequate small solute clearance in hypercatabolic critically-ill patients [2] and is better suited for maintenance therapy of AKI. Similarly, chronic equilibrated PD (CEPD), which involves an average of four exchanges daily with longer dwells, is also better-suited for patients following resolution of life-threatening AKI.

Finally, tidal PD involves leaving a residual volume of fluid (10–50% of the instilled volume) in the peritoneal cavity after each drain. Tidal PD should theoretically allow for improved solute clearance because fresh dialysate is instilled more frequently and faster [16], but as yet studies have not proven this to be the case [17].

Peritoneal dialysis prescription

PD requires orders for the following variables, all of which require frequent re-evaluation due to the dynamic nature of AKI:

- **PD fluid glucose concentration**: dialysate tonicity (and therefore fluid removal) can be varied by choosing different glucose concentrations. Three standard glucose concentrations are available—1.36, 2.25, and 3.86 g/dL; these correspond to 1.5, 2.5, and 4.25% dextrose, with an osmolarity of 346, 396 and 485 mOsm/L, respectively. Glucose concentration is chosen based on desired fluid removal with a more concentrated glucose solution being chosen when greater fluid removal is desirable.
- **PD fluid volume**: the volume of dialysate infused per exchange is largely determined by patient size. A typical adult can tolerate 2 L, while children are often prescribed 30 mL/kg of body weight. Smaller volumes may be warranted in the first few days after PD catheter insertion (to minimize leaks from the catheter site) and in patients with respiratory compromise or abdominal wall hernias.
- **Times**: 'inflow time' (i.e. time required to instill dialysate) should be minimized in order to maximize dialysis efficiency; if it exceeds 15 minutes, then increased catheter resistance should be suspected (e.g. from catheter kinking or reduced abdominal compliance). 'Dwell time' depends on the PD modality, but should be at least 30 minutes to allow for adequate solute clearance. 'Outflow time' (i.e. time required to drain the peritoneal cavity), like inflow time, should be kept to a minimum to improve overall dialysis efficiency.
- **Dialysate additives**: PD fluid is commonly supplemented with additives. Insulin may be added in diabetic or critically-ill patients who can become hyperglycaemic from the PD fluid's glucose load. Potassium can be added to avoid hypokalaemia. If fibrin clots cause catheter obstruction, heparin can be added (there is no risk of systemic anticoagulation as heparin is not absorbed). Finally, antibiotics can be administered via the PD fluid.

Outcomes using peritoneal dialysis in the treatment of acute kidney injury

Adequate control of metabolic derangements and favourable outcomes can be achieved using various modes of PD in non-hypercatabolic AKI. A limited number of prospective trials are available as well.

In a randomized trial comparing PD with continuous veno-venous haemofiltration (CVVH) in 70 adults with AKI due to malaria [18], outcomes were better in the CVVH group; metabolic abnormalities resolved faster, duration of treatment with RRT was shorter and the mortality was lower. However, as PD practices in the trial were not optimal, the external validity of the results is unclear. In addition, patients with AKI due to malaria may benefit from specific non-dialytic aspects of haemodialysis such as the use of heparin, which may have rheologic benefits to the red blood cells. Another randomized trial assigned 120 patients with AKI, mostly due to sepsis, to either daily HD or HVPD [5]. Mortality in the two groups was similar, but renal recovery occurred significantly earlier in the PD group. These seemingly contradictory results emphasize that in the absence of large, robust clinical trials the relative effects of PD and other forms of RRT in patients with AKI remain unclear.

Complications of peritoneal dialysis

Infectious complications

Peritonitis is the most important infectious complication during acute PD, with a reported incidence of 12% [19]. Typically resulting from contamination of the peritoneal cavity with Gram-positive or Gram-negative organisms, peritonitis usually arises in the first two days of acute PD. Cloudy drain fluid should prompt fluid analysis for cell count, Gram stain and culture, and initiation of empiric antibiotic treatment. Local skin and soft tissue infections can also occur at the PD catheter insertion site.

Mechanical complications

A variety of mechanical complications may occur with acute PD. The most dangerous is bowel perforation, which can present with pain and blood or faecal material in the peritoneal fluid. Bladder perforation is less common and can present with urine leakage into the PD effluent. Perforation requires prompt antibiotic and surgical care. Acute PD can also cause abdominal discomfort, usually from catheter placement and the distension of the peritoneal cavity with dialysate.

Pulmonary complications

The increase in intra-abdominal pressure caused by PD fluid can restrict diaphragmatic excursion resulting in impaired secretion clearance and basal atelectasis. Increased intra-abdominal pressure can promote gastro-oesophageal reflux predisposing to aspiration. Respiratory impairment can also occur if PD fluid enters the thorax through congenital or iatrogenic defects in the diaphragm which occurs in up to 1% of patients starting PD [20] and should be suspected if pleural fluid glucose concentration is significantly higher than that of serum.

Metabolic complications

The glucose load of PD fluid may cause or worsen hyperglycaemia particularly in patients with diabetes mellitus. Cessation of PD can result in hypoglycaemia in critically-ill patients being treated with insulin infusions if the insulin infusion rate is not decreased at the same time. Hypernatraemia can result from free water losses in the hypotonic ultrafiltrate and prolonged PD can result in hypokalaemia. PD can contribute to malnourishment in critically-ill patients due to the protein loss through the dialysate.

Conclusion

RRT in patients with AKI has long been achieved with PD, and available evidence suggests that this approach is reasonable and safe in many circumstances. By virtue of its technical simplicity, PD remains an important modality for RRT in resource-deprived areas and may be life-saving when no alternative exists. In addition, it should also be considered in all settings when its advantages over HD may be particularly beneficial.

References

1. Lameire N, Van Biesen W, and Vanholder R. (2006). The changing epidemiology of acute renal failure. *Nature Clinical Practice Nephrology*, **2**(7), 364–77.
2. Burdmann EA and Chakravarthi R. (2011). Peritoneal dialysis in acute kidney injury: lessons learned and applied. *Seminars in Dialysis*, **24**(2), 149–56.
3. Uchino S, Kellum JA, Bellomo R, et al. (2005). Acute renal failure in critically ill patients: a multinational, multicenter study. *Journal of the American Medical Association*, **294**(7), 813–18.
4. Callegari JG, Kilonzo KG, Yeates KE, et al. (2012). Peritoneal dialysis for acute kidney injury in sub-Saharan Africa: challenges faced and lessons learned at Kilimanjaro Christian Medical Centre. *Kidney International*, **81**(4), 331–3.
5. Gabriel DP, Caramori JT, Martim LC, Barretti P, and Balbi AL. (2008). High volume peritoneal dialysis vs daily hemodialysis: a randomized, controlled trial in patients with acute kidney injury. *Kidney International Supplement*, **108**, S87–93.
6. Goldstein SL. (2009). Overview of pediatric renal replacement therapy in acute kidney injury. *Seminars in Dialysis*, **22**(2), 180–4.
7. Flynn JT, Kershaw DB, Smoyer WE, Brophy PD, McBryde KD, and Bunchman TE. (2001). Peritoneal dialysis for management of pediatric acute renal failure. *Peritoneal Dialysis International*, **21**(4), 390–4.
8. Reuler JB and Parker RA. (1978). Peritoneal dialysis in the management of hypothermia. *Journal of the American Medical Association*, **240**(21), 2289–90.
9. Horowitz BZ. (1989). The golden hour in heat stroke: use of iced peritoneal lavage. *American Journal of Emergency Medicine*, **7**(6), 616–19.
10. Kauste A, Hockerstedt K, Ahonen J, and Tervaskari H. (1983). Peritoneal lavage as a primary treatment in acute fulminant pancreatitis. *Surgery, Gynecology & Obstetrics*, **156**(4), 458–63.
11. Gotloib L, Fudin R, Yakubovich M, and Vienken J. (2005). Peritoneal dialysis in refractory end-stage congestive heart failure: a challenge facing a no-win situation. *Nephrology, Dialysis, Transplantation*, **20**(7), vii32–6.
12. Shah H, Chu M, and Bargman JM. (2006). Perioperative management of peritoneal dialysis patients undergoing hernia surgery without the use of interim hemodialysis. *Peritoneal Dialysis International*, **26**(6), 684–7.
13. Wong SN and Geary DF. (1988). Comparison of temporary and permanent catheters for acute peritoneal dialysis. *Archives of Disease in Childhood*, **63**(7), 827–31.
14. Chadha V, Warady BA, Blowey DL, Simckes AM, and Alon US. (2000). Tenckhoff catheters prove superior to cook catheters in pediatric acute peritoneal dialysis. *American Journal of Kidney Diseases*, **35**(6), 1111–16.
15. Ash SR. (2004). Peritoneal dialysis in acute renal failure of adults: the under-utilized modality. *Contributions to Nephrology*, **144**, 239–54.

16. Passadakis P and Oreopoulos D. (2003). Peritoneal dialysis in acute renal failure. *International Journal of Artificial Organs*, **26**(4), 265–77.
17. Piraino B, Bender F, and Bernardini J. (1994). A comparison of clearances on tidal peritoneal dialysis and intermittent peritoneal dialysis. *Peritoneal Dialysis International*, **14**(2), 145–8.
18. Phu NH, Hien TT, Mai NT, et al. (2002). Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. *New England Journal of Medicine*, **347**(12), 895–902.
19. Daugirdas JT, Blake PG, and Ing TS. (2001). *Handbook of Dialysis*, 3rd edn. Philadelphia: Lippincott Williams & Wilkins.
20. Van Dijk CM, Ledesma SG, and Teitelbaum I. (2005). Patient characteristics associated with defects of the peritoneal cavity boundary. *Peritoneal dialysis International*, **2**5(4), 367–73.

PART 8.5

Established renal failure

CHAPTER 217

The effect of renal failure on drug handling in critical illness

Myrna Y. Munar and Ali J. Olyaei

Key points

- Acute and chronic kidney injury alters the pharmacokinetic of most commonly used drugs.
- For most agents, the dose or dosing interval should be adjusted to be appropriate for the individual patient's renal function.
- For drugs with narrow therapeutic window, plasma concentration should be monitored and dosage adjusted accordingly.
- For most patients with kidney disease, exposure to nephrotoxins should be avoided as much as possible.
- It is important to accurately estimate renal function to improve drug dosing in patients with chronic kidney disease (CKD).

Introduction

The kidneys play an important role in the elimination of many drugs as well as their pharmacologically active metabolites. Chronic kidney disease (CKD) affects not only glomerular blood flow and filtration, but also tubular secretion and reabsorption, and renal metabolism. Several pharmacokinetic processes such as drug absorption, bioavailability, protein binding, volume of distribution, and non-renal clearance are also affected. Patients with CKD require medication dosing appropriate for their level of kidney function to avoid adverse drug events, to prevent further renal injury, and to optimize outcomes.

Many medications are frequently administered orally. Oral bioavailability, defined as the fraction of an oral dose that actually reaches systemic circulation, is determined by the fraction of the dose that undergoes absorption, the fraction that escapes gut metabolism and drug transport from the intestinal wall back into the gut lumen, and the fraction that escapes hepatic metabolism. Drug absorption may be altered in patients with CKD as a result of vomiting secondary to azotemia or uraemia, delays in gastric emptying, changes in gastric pH, and the presence of gastrointestinal tract oedema.

Absorption is characterized by the maximum drug concentration (C_{max}), the time it was achieved (T_{max}), and area-under-the plasma concentration-time curve (AUC). Delays in gastric emptying and sluggish gastrointestinal (GI) motility may result from diabetic or uremic gastroparesis, or both. The result is delayed absorption with a prolonged T_{max} and a lower C_{max}. Eventually the administered dose is absorbed; therefore, the overall extent of absorption (AUC) is unaffected. Delayed drug absorption becomes clinically significant for medications in which a rapid onset of pharmacologic effect is needed.

Several medications taken by patients with CKD can alter gastric pH and, to a lesser extent, gut motility including: histamine-2 receptor blockers, proton-pump inhibitors, and antacids. Ammonia formation in the gut can also contribute to an increase in gastric pH. Elevated blood urea nitrogen in CKD can be converted by gastric urease enzymes to ammonia, resulting in an increase in gastric pH. Regardless of aetiology, an increase in gastric pH can result in either an increase or a decrease in drug absorption. For example, some imidazole antifungals (e.g. itraconazole) are dependent upon a low gastric pH for disintegration and dissolution. Gastric alkalinization reduces drug disintegration and dissolution, resulting in reduced absorption and bioavailability [1]. Conversely, the oral bioavailability of weakly acidic medications such as NSAIDS or oral hypoglycaemics (e.g. glipizide) can be enhanced in an alkaline gastric environment by increasing drug dissolution and subsequent absorption [1].

Drug interactions involving antacids, which are used to treat gastrointestinal symptoms or as dietary phosphate binders to treat the hyperphosphataemia of chronic renal disease, can occur through various mechanisms: alterations in drug dissolution by changing gastric pH, alterations in gastric motility, complexing with certain medications reducing absorption, alterations in drug ionization whereby weak acids are more ionized and less absorbed and weak bases are less ionized and more likely to be absorbed, and alterations in drug elimination by changing urinary pH [1]. Aluminum-, magnesium- and calcium-containing antacids, can form insoluble complexes with co-administered medications leading to reduced absorption. These medications can also interfere with oral iron absorption by two mechanisms: decreasing iron solubility by increasing gastric pH, and formation of non-absorbable insoluble complexes [2]. Two classes of antibiotics, tetracyclines and fluoroquinolones, are also susceptible to these absorption interactions [1]. Other phosphate binders, such as sevelamer and lanthanum have also been reported to decrease the absorption of fluoroquinolones [3,4]

Another factor that can affect drug absorption is gastrointestinal tract oedema caused by congestive heart failure or by hypoalbuminaemia due to liver cirrhosis or nephrotic syndrome. Acidic drugs such as penicillins, cephalosporins, salicylates, phenytoin, valproic acid, and furosemide mainly bind to albumin, while basic drugs, such as propranolol, morphine, disopyramide, and oxazepam, bind mainly to alpha 1-acid glycoprotein (AAG). AAG is an acute-phase

protein whose serum concentration is increased in CKD. Although the binding of most basic drugs to AAG is unaffected in CKD, the binding of certain drugs, such as disopyramide, may be increased.

The decrease in protein binding of acidic drugs in patients with renal impairment may be caused by:

- Hypoalbuminaemia which may occur in association with uraemia and in nephrotic syndrome.
- Accumulation of competitive endogenous substances (e.g. organic acids in uraemia, drugs, and/or drug metabolites) that can compete with the acidic drugs for protein binding sites.
- Conformational or structural changes in the binding site in uraemia resulting in decreased affinity of binding sites for the acidic drug.

Total plasma drug concentrations represent both drug bound to plasma proteins and unbound or free drug. Only free drug is pharmacologically active and capable of crossing membranes. The decrease in protein binding results in a greater fraction of unbound drug available for distribution as well as drug elimination by hepatic metabolism, or in patients with end-stage renal disease, by dialysis. Therefore, an increase in the apparent volume of distribution and an increase in total body clearance may be observed. The overall effect is no change in the unbound or active drug concentration, but a reduction in the total plasma concentration. The classic example of this effect is with the acidic drug, phenytoin. Total phenytoin concentrations may be misinterpreted in patients with renal impairment and hypoalbuminaemia, resulting in erroneous upward dose titration in response to low measured total phenytoin concentrations. Therefore, it is recommended to monitor unbound or free phenytoin concentrations instead.

Tissue binding is reduced in uremic states resulting in an increase in the fraction of drug unbound in tissues. Changes in tissue binding are not clinically significant for most drugs, with the exception of digoxin. The volume of distribution of digoxin is reduced in patients with end stage renal disease (ESRD) [5]. Decreased tissue uptake combined with impaired renal excretion may result in increased digoxin serum concentrations if loading doses are not reduced.

Drug metabolism is classified as either phase I or phase II reactions. Phase I reactions consist of oxidation, hydrolysis, and reduction mediated by cytochrome P-450 isoenzymes, while phase II reactions involve conjugation via glucuronidation, sulphation, acetylation, methylation, and glutathione conjugation. Both phase I and phase II reactions are slowed in renal impairment [2], which can result in increased serum drug concentrations. Phase I and phase II metabolism result in the formation of water soluble metabolites that are subsequently excreted by the kidney. Thus, pharmacologically active and toxic metabolites can accumulate in renal impairment. A notable example is the narcotic analgesic, pethidine. Pethidine is metabolized to norpethidine, a toxic metabolite with little analgesic activity, but with the propensity to lower the seizure threshold [6]. It should not be used in patients with severe kidney disease and renal failure.

Last of all, metabolic enzymes found in the liver are also found in the kidney within the renal cortex. However, the total weight of the kidneys are less than the total weight of the liver, therefore the contribution of renal metabolism to overall drug clearance is probably low in comparison to liver metabolism.

The effect of CKD on renal drug metabolism could be clinically important for two medications: vitamin D and insulin. The kidneys play an important role in the activation of vitamin D to calcitriol. Therefore, patients with severe kidney disease should receive the active form of vitamin D as calcitriol, paricalcitol, or doxercalciferol. The kidneys, in addition to the liver and muscle, are important sites for insulin degradation and clearance. CKD can have variable effects on insulin and glucose homeostasis. On one hand, impaired renal insulin degradation and clearance, malnutrition from gastroparesis or anorexia, and deficient renal gluconeogenesis lower the threshold for hypoglycaemia [7,8]. On the other hand, increased insulin resistance may mitigate these effects.

Renal clearance represents the sum of three processes that control the movements of drugs between plasma and urine: glomerular filtration, tubular secretion, and tubular reabsorption. Drug clearance by glomerular filtration (CL_{GFR}) is dependent on the patient's glomerular filtration rate (GFR) and the fraction of drug not bound to plasma proteins. Drugs that are highly protein bound are not readily filtered at the glomerulus for two reasons: plasma proteins, such as albumin carry an anionic charge that is repelled by anionic sites within the glomerulus, and protein bound drugs are too large to be filtered. However, highly protein bound drugs are actively secreted into the proximal convoluted tubules. However, tubular secretion is a transport-mediated process that can be saturated, thus, with high drug concentrations tubular secretion can reach a limit resulting in a longer elimination half-life. Other drugs can also compete for tubular secretion (e.g. penicillin and probenecid). Finally, CKD can reduce tubular reabsorption resulting in higher urinary concentrations and increased elimination of drugs. Caution should be exercised when prescribing drugs that are potentially nephrotoxic and undergo tubular reabsorption (e.g. methotrexate and lithium).

It is vital to accurately estimate renal function to improve drug dosing in patients with CKD. GFR is a high-quality estimate of renal index in both healthy and diseased kidneys. Inappropriate drug dosing in CKD may adversely affect patient outcomes. Overexposure and underexposure are major concerns in CKD. To reduce potential toxicities or sub-therapeutic exposures, a number of biomarkers and mathematical models have been developed to accurately estimate GFR [9].

Serum creatinine

Creatinine is a product of muscle metabolism. Creatinine is unbound and is filtered through the glomerulus with minimal tubular secretion. These properties make serum creatinine a good marker for measuring GFR. However, since creatinine is a function of muscle breakdown, it is affected by differences in muscle mass, age, gender, race, diet, and certain drugs. Additionally, since serum creatinine (SCr) accumulation is time dependent, it does not adequately reflect the change in GFR due to an acute kidney injury (AKI). Likewise when resolution of kidney injury occurs, SCr levels may 'lag' behind kidney recovery. Lastly, creatinine secretion from the proximal tubules depends on GFR so for patients with renal insufficiencies, may have an inaccurate lower creatinine [10].

Cockcroft–Gault

The most common method to estimate renal function is use of the Cockcroft-Gault (CG) equation. The CG formula was developed in 1976, and today is the most widely used formula for assessment of

kidney function [11]. Variables in the equation include age, body weight, and SCr. For females, the equation is multiplied by 0.85.

$$\text{CrCl} = (140 - \text{age}) \times \text{Wt (kg)} \times (0.85 \text{ for females})/72 \times \text{SCr} \quad \text{[eqn 1]}$$

It is important to note that the CG method estimates creatinine clearance (CrCl) not GFR. However, CrCl is recommended by the FDA for drug dosing adjustment in CKD. The CG formula places heavy emphasis on age, weight, and muscle mass. As such, it is not an accurate measure of renal function in obese or malnourished patients or patients with muscle disease, or advanced or unstable renal function.

Modification of diet in renal disease

The Modification of Diet in Renal Disease (MDRD) equation was developed in 1999 in an attempt to improve accuracy compared to the CG formula. It was derived from the MDRD study involving 1628 patients who were assessed to determine the most accurate measure of GFR [12]. Compared to the CG formula, the MDRD includes additional variables that may affect SCr. In total, four

Table 217.1 Therapeutic drug monitoring in chronic kidney disease

Drug name	When to draw sample	Therapeutic range	How often to draw levels
Aminoglycosides (conventional dosing): gentamicin, tobramycin, amikacin	*Trough*: immediately prior to dose *Peak*: 30 minutes after a 30–45-minute infusion	**Gentamicin and tobramycin** *Trough*: 0.5–2 mg/L *Peak*: 5–8 mg/L **Amikacin** *Trough*: < 10 mg/L *Peak*: 20–30 mg/L	Check peak and trough with 3rd dose For therapy less than 72 hours, levels not necessary. Repeat drug levels weekly or if renal function changes
Aminoglycosides (24-h dosing): gentamicin, tobramycin, amikacin	Obtain random drug level 12 hours after dose	0.5–3 mg/L	After initial dose, repeat drug level in 1 week or if renal function changes
Carbamazepine	*Trough*: immediately prior to dosing	4–12 μg/mL	Check 2–4 days after first dose or change in dose
Ciclosporin	*Trough*: immediately prior to dosing	150–400 ng/mL	Daily for first week, then weekly
Digoxin	12 hours after maintenance dose	0.8–2.0 ng/mL	5–7 days after first dose for patients with normal renal and hepatic function; 15–20 days in anephric patients
Enoxaprin	4 hours after 2nd or 3rd dose	0.7–1.1	Weekly and as needed
Lidocaine	8 hours after iv infusion started or changed	1–5 μg/mL	As needed
Lithium	*Trough*: before a.m. dose, at least 12 hours after last dose	*Acute*: 0.8–1.2 mmol/L *Chronic*: 0.6–0.8 mmol/L	As needed
Phenobarbital	*Trough*: immediately prior to dosing	15–40 mcg/mL	Check 2 weeks after first dose or change in dose. Follow-up level in 1–2 months
Phenytoin: free phenytoin	*Trough*: immediately prior to dosing	10–20 mcg/mL 1–2 mcg/mL	5–7 day after first dose or after change in dose
Procainamide **NAPA** (n-acetyl procainamide): a procainamide metabolite	*Trough*: immediately prior to next dose or 12–18 hours after starting or changing an infusion. Draw with procainamide sample	4–10 μg/mL *Trough*: 4 μg/mL *Peak*: 8 μg/mL 10–30 μg/mL	As needed
Sirolimus	*Trough*: immediately prior to next dose	10–20 ng/dL	Weekly for first month, then as needed
Tacrolimus	*Trough*: immediately prior to next dose	5–10 ng/mL	Daily for first week, then weekly
Valproic acid (valproate semisodium)	*Trough*: immediately prior to next dose	40–100 mcg/mL	Check 2–4 days after first dose or change in dose
Vancomycin	*Trough*: immediately prior to dose *Peak*: 60 minutes after a 60-minute infusion	*Trough*: 10–20 mg/L *Peak*: 25–40 mg/L	With 3rd dose (when initially starting therapy, or after each dosage adjustment). For therapy less than 72 hours, levels not necessary. Repeat drug levels if renal function changes

Data from: Olyaei AJ and Steffl JL, 'A quantitative approach to drug dosing in chronic kidney disease', *Blood Purification*, 2011, **31**(1–3), pp. 138–145; Olyaei AJ and Bennett WM, 'Drug dosing in the elderly patients with chronic kidney disease', *Clinics in Geriatric Medicine*, 2009, **25**(3), pp. 459–527.

variables are included: age, SCr, race, and gender (6-variable equation (MDRD6) includes BUN and albumin).

$$\text{GFR} = 175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212\,(\text{if black}) \times 0.742\,(\text{if female}) \quad \text{[eqn 2]}$$

MDRD has been validated in a number of patient populations and most importantly does not require body weight. This allows for reporting of eGFR along with the routine chemistries. Recently, this method was adopted by the National Kidney Foundation as the primary equation for determining estimated GFR and CKD staging. The MDRD can significantly underestimate the GFR in patients with good kidney function (GFR >90 mL/min/17.3 m^2). Additionally, its accuracy has not been established in paediatrics, elderly, hospitalized, and other ethnic origins (only blacks). Most important MDRD does not address the patient's weight and obesity factor.

Chronic kidney disease epidemiology collaboration equation

CKD Epidemiology Collaboration Equation (CKD-EPI) was developed in 2009 to match the accuracy of the MDRD equation at GFR < 60 mL/min/1.73 m^2 and to offer greater accuracy at GFR >90 mL/min/1.73 m^2.

$$\text{eGFR} = 141 \times \min(\text{SCr}/\text{k},1)^{\text{a}} \times \max(\text{SCr}/\text{k},1)^{-1.209} \times 0.993^{\text{age}} \times 1.159\,(\text{if black}) \times 1.018\,(\text{if female}) \quad \text{[eqn 3]}$$

CKD-EPI has shown to be as accurate as MDRD in patients with GFR<60 and substantially more accurate in the subgroup with GFR >90 [13]. In a recent review paper and recommendation, CKD-EPI was more accurate and the least biased when compared to CG and MDRD [14]. However, it has not been validated for most drugs and there is a lack of information in older patients [15].

Today, the CG method is the most commonly used formula to assess kidney function. It has been around the longest, has been well validated, is easy to remember, and is fairly accurate in estimating kidney function. Also, most drugs are dosed based on the patient's weight (mg/kg) which makes the CG method easier to use for most estimates. In some circumstances all three formula should be utilized to improve patient outcomes while reducing adverse drug reactions related to overexposure. A patient's renal function should always be estimated based on the best available evidence for that specific patient [16].

Drug dosing in chronic kidney disease

Many drugs require loading doses to rapidly achieve therapeutic plasma concentrations. This is particularly true for antimicrobial and cardiovascular agents. For most drugs no renal dose adjustment is required for the loading dose. However, maintenance doses should be adjusted for drugs that are excreted primarily unchanged through the urine. The maintenance doses can be adjusted in two different ways, 1) reduce each dose, but maintain the same dosing interval to avoid the risks of toxicity due to drug accumulation, or 2) maintain the same dose, but lengthen the dosing interval to decrease the risk of sub-therapeutic dosing for concentration dependent drugs. In addition, for drugs with proven therapeutic drug monitoring (TDM), measuring plasma or whole blood concentrations can optimize therapeutic regimens while reducing toxicities (Table 217.1) [17,18].

However, hypoalbuminaemia may affect TDM for drugs that are highly protein bound, such as phenytoin, and the results of TDM should be interpreted with caution. Although the total drug concentration may be low, active unbound drug concentrations are high and the patients are at risk for drug toxicity. Therefore, hypoalbuminaemia should be considered in the interpretation of measured total drug concentrations. Finally patients with CKD are at great risk of developing kidney injury from drugs or diagnostic agents. Exposure to nephrotoxins should be avoided as much as possible [19].

References

1. Ogawa R and Echizen H. (2011). Clinically significant drug interactions with antacids: an update. *Drugs*, **71**(14), 1839–64.
2. Pruchnicki MC, Coyle JD, Hoshaw-Woodard S, and Bay WH. (2002). Effect of phosphate binders on supplemental iron absorption in healthy subjects. *Journal of Clinical Pharmacology*, **42**(10), 1171–6.
3. Kays MB, Overholser BR, Mueller BA, Moe SM, and Sowinski KM. (2003). Effects of sevelamer hydrochloride and calcium acetate on the oral bioavailability of ciprofloxacin. *American Journal of Kidney Disease*, **42**(6), 1253–9.
4. How PP, Fischer JH, Arruda JA, and Lau AH. (2007). Effects of lanthanum carbonate on the absorption and oral bioavailability of ciprofloxacin. *Clinical Journals on American Society Nephrology*, **2**(6), 1235–40.
5. Jusko WJ, Szefler SJ, and Goldfarb AL. (1974). Pharmacokinetic design of digoxin dosage regimens in relation to renal function. *Journal of Clinical Pharmacology*, **14**(10), 525–35.
6. Szeto HH, Inturrisi CE, Houde R, Saal S, Cheigh J, and Reidenberg MM. (1977). Accumulation of norpethidine, an active metabolite of pethidine, in patients with renal failure of cancer. *Annuals of Internal Medicine*, **86**(6), 738–41.
7. Stumvoll M, Meyer C, Mitrakou A, Gerich JE. (1999). Important role of the kidney in human carbohydrate metabolism. *Medical Hypotheses*, **52**(5), 363–6.
8. Duckworth WC. (1988). Insulin degradation: mechanisms, products, and significance. *Endocrinology Review*, **9**(3), 319–45.
9. Hudson JQ and Nyman HA. (2011). Use of estimated glomerular filtration rate for drug dosing in the chronic kidney disease patient. *Current Opinion in Nephrology and Hypertension*, **20**(5), 482–91.
10. Steffl JL, Bennett W, and Olyaei AJ. (2012). The old and new methods of assessing kidney function. *Journal of Clinical Pharmacology*, **52**(1), 63S–71S.
11. Cockcroft DW, and Gault MH. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**(1), 31–41.
12. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, and Roth D. (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Annuals of Internal Medicine*, **130**, (6), 461–70.
13. Stevens LA, Schmid CH, Greene T, et al. (2010). Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m^2. *American Journal of Kidney Disease*, **56**(3), 486–95.
14. Dowling TC, Matzke GR, Murphy JE, and Burckart GJ. (2010). Evaluation of renal drug dosing: prescribing information and clinical pharmacist approaches. *Pharmacotherapy*, **30**(8), 776–86.

15. Stevens LA and Levey AS. (2009). Use of the MDRD study equation to estimate kidney function for drug dosing. *Clinical Pharmacology & Therapeutics*, **86**(5), 465–7.
16. Jones GR. (2011). Estimating renal function for drug dosing decisions. *Clinical Biochemistry Reviews*, **32**(2), 81–8.
17. Olyaei AJ and Steffl JL. (2011). A quantitative approach to drug dosing in chronic kidney disease. *Blood Purification*, **31**(1–3), 138–45.
18. Olyaei AJ and Bennett WM. (2009). Drug dosing in the elderly patients with chronic kidney disease. *Clinical Geriatric Medicine*, **25**(3), 459–527.
19. Pannu N and Nadim MK. (2008). An overview of drug-induced acute kidney injury. *Critical Care Medicine*, **36**(4), S216–23.

CHAPTER 218

The effect of chronic renal failure on critical illness

Sinead Kinsella and John Holian

Key points

- The prevalence of chronic and end stage kidney disease (CKD and ESKD) is increasing and these patients are frequently admitted to Intensive Care Units (ICU).
- Sepsis and cardiovascular events are the most frequent causes of ICU admission in patients with CKD and ESKD.
- Patients with ESKD and CKD requiring ICU admission have better ICU and in-hospital survival than patients with acute kidney injury (AKI) requiring renal replacement therapy (RRT).
- ESKD patients who survive an episode of critical illness have higher ICU re-admission rates and may benefit from closer monitoring following ICU discharge.
- Mortality in critically-ill ESKD patients is related to their co-morbid conditions rather than to ESKD status, therefore appropriately selected ESKD patients benefit from ICU admission.

Introduction

The incidence and prevalence of chronic and end stage kidney disease (CKD and ESKD) are increasing world-wide, reflecting an increase in Type 2 diabetes, hypertension, and an ageing population. Patients with ESKD treated with dialysis have significant co-morbidities due both to their underlying disease and specific to their ESKD. These patients are more likely to become critically ill and require admission to an ICU. It is reported that between 1.3 and 11% of ICU admissions are patients with dialysis-dependent ESKD [1–4]. It is estimated that the risk of requiring ICU admission in the ESKD population is 4-fold higher than that of the general population [1]. Cardiovascular events including sudden death, myocardial infarction, cardiac arrest, and malignant arrhythmias are the major cause of death accounting for 43% of all-cause mortality among haemodialysis patients [5]. Cardiovascular events and infectious complications are the leading causes of hospitalizations in patients with ESKD [6] and account for approximately 24 and 20.5% of ICU admissions respectively [7]. In addition, patients with ESKD are almost twice as likely to have received cardio-pulmonary resuscitation prior to ICU admission, compared to patients without ESKD [1].

Outcomes

Despite their chronic co-morbidities, several studies have reported lower ICU mortality for patients with ESKD than for patients with Acute Kidney Injury (AKI) requiring Renal Replacement Therapy (RRT). Clermont et al. in a study of 1530 ICU admissions reported that patients with ESKD had intermediate mortality (11%), compared with patients with AKI (23%) and those without renal failure, (5%) [2]. Unchino et al. found that ICU mortality matched for illness severity score was similar for patients with ESKD and AKI [3]. Similarly in a systematic review of 16 studies including 6591 patients, Arulkumaran et al. report an ICU mortality of 21.4% and an in-hospital mortality of 34.5% for patients with ESKD. In-hospital mortality for patients with AKI requiring RRT was significantly higher compared to patients with ESKD, (55 versus 24%, $p < 0.0001$). The 90-day mortality among patients with AKI requiring RRT was also higher compared to ESKD, (56% versus 38%, $p = 0.0007$). In most studies, the unadjusted in-hospital mortality of patients with ESKD is significantly less than for patients with de novo AKI requiring RRT, however, following adjustment for confounders, these studies consistently show that mortality in critically-ill patients with ESKD is largely related to their co-morbid conditions rather than to ESKD status [1,2,4]. Similarly while pre-existing non-dialysis requiring CKD is a risk factor for the development of acute kidney injury in the ICU, Mehta et al. observed in the PICARD study that patients with CKD and super-imposed AKI had lower mortality rates than those with new-onset AKI (31 versus 41%, $p = 0.03$) [8].

While critical illness associated with AKI requiring RRT has a less favourable ICU outcome compared to patients with ESKD admitted to the ICU, re-admission rates to the ICU are reportedly higher in the patients with ESKD and patients with ESKD have significantly longer hospital stays [1,4].

Data on long-term survival of patients with ESKD following an episode of critical illness is limited. Bell et al. observed that the risk of death was 2.86-fold higher during the first year and 1.95-fold higher during the second year following ICU admission when compared to patients with ESKD not admitted to the ICU. Conversely, Chapman et al. found that once patients who died within a month of ICU discharge were excluded; there was no difference in 2-year survival between patients with ESKD admitted to the ICU and a comparator group of patients with ESKD without a history of critical illness [9].

Outcome predictors

Illness severity scores and non-renal organ failure are important predictors of outcome in critically-ill patients with ESKD in the ICU. However, the accuracy of outcome prediction scoring systems such as Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score (SAPS) and the Acute Physiology and Chronic Health Evaluation (APACHE) score in patients with ESKD is controversial. In most studies the predicted ICU and in-hospital mortality based on illness severity scores over-estimate the actual mortality in patients with ESKD [1–4]. One potential explanation for the over-estimation of mortality in ESKD patients may be that illness severity scoring systems allocate high points for renal variables such as oliguria, and elevated urea and creatinine. These variables, which may be indicative of systemic inflammatory response syndrome (SIRS), haemodynamic instability and systemic vasodilatation in patients with AKI, are baseline characteristics of the patient with ESKD. As such, unmeasured changes in acute physiology which result in AKI, along with non-renal organ responses to AKI may account for the observed difference in mortality in patients with AKI vs. those with ESKD, despite similar illness severity scores. It has also been suggested that patients with ESKD respond differently to critical illness compared to patients without kidney disease. Unchino et al. found that even after matching for diagnosis and illness severity score, patients with ESKD required less vasoactive drugs, required mechanical ventilation for shorter periods of time and had a lower incidence of SIRS compared to patients with AKI [3]. Plasma levels of pro and anti-inflammatory cytokines which are associated with SIRS are predictive of mortality in patients with AKI and plasma cytokine levels have been shown to be significantly higher in critically-ill patients with AKI compared with patients with ESKD and CKD [10]. It has been suggested that the state of immunosuppression inherent to CKD [11] is responsible for the differences in cytokine production, development of SIRS and response to critical illness and may contribute to the observed differences in mortality [3]. The development of novel sensitive serum and urinary biomarkers to detect AKI, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and interleukin 18 may allow the detection of super-imposed AKI in patients with CKD or ESKD who have residual renal function and help distinguish between the effects of loss of organ function and acute physiological responses on outcomes of critical illness [12].

The reason for admission to the ICU is an important predictor of outcome for patients with ESKD, as it is for other patients. The relative risk of death for patients with ESKD admitted to ICU with a medical diagnosis is twice that of patients with ESKD admitted with a surgical diagnosis [9]. This may reflect an appropriately low threshold for admitting patients with ESKD patients to ICU following surgery, given their co-morbidities and increased mortality after major surgery.

Practical considerations

Cardiovascular disease

Cardiovascular disease accounts for up to 50% of mortality in patients with ESKD. In addition, the majority of patients with CKD die of cardiovascular events before progressing to ESKD. Atherosclerotic coronary artery disease is highly prevalent in both CKD and ESKD patients and is frequently asymptomatic. Left Ventricular Hypertrophy (LVH) is also highly prevalent in patients with CKD and ESKD, with over 70% of incident dialysis patients demonstrating evidence of LVH [13]. Both eccentric LVH, due to volume overload and concentric LVH, due to hypertension and exacerbated by anaemia, hyperparathyroidism and elevated angiotensin II, occur. The predominant effect of these changes in patients with ESKD is diastolic dysfunction, often with preserved ejection fraction. Modest increases in Left Ventricular volume in these patients results in a large increase in LV pressure, pre-disposing to acute pulmonary oedema. In addition, relatively small volume ultrafiltration on dialysis can result in an abrupt fall in LV diastolic pressure, predisposing to hypotension and haemodynamic instability.

Given the prevalence of LVH and diastolic dysfunction, acute pulmonary oedema is a frequent cause of admission to the ICU in the dialysis population and has been associated with respiratory infection, excessive interdialytic weight gain and inappropriate dry weight. Admissions to the ICU with pulmonary oedema are also more likely to occur towards the end of the 2-day weekend dialysis gap [14]. Patients with dialysis-dependent ESKD are frequently anuric and more likely to develop pulmonary oedema and hypertension due to volume overload and salt excess. These patients demonstrate resistance to diuretic therapy and require ultrafiltration to restore salt and water balance. Similarly patients with CKD and residual urine output may require higher diuretic doses in order to achieve a response.

Cardiac arrhythmias and sudden cardiac death are also more common in patients with renal disease due to abnormalities in coronary micro-circulation, impaired coronary reserve, myocardial fibrosis, impaired vascular compliance, and increased sympathetic nervous system activity. Fluxes in electrolytes such as potassium, calcium, and magnesium which occur during dialysis also increase the risk of arrhythmia.

Sepsis

Infectious complications are the most common cause of hospitalization in patients with ESKD. Factors resulting in increased susceptibility to infection include immunocompromise related to chronic disease [11], increased exposure to nosocomial infection, hypoalbuminaemia, anaemia, malnutrition [15] and widespread use of in-dwelling dialysis catheters. It is estimated that half of all catheter related blood stream infections in dialysis patients are due to Gram positive cocci, one third due to Gram negative organisms and approximately 20–30% are polymicrobial [16]. In addition the risk of Meticillin-resistant Staphylococcus aureus (MRSA) bacteraemia is substantially higher in the dialysis population compared to the general population as up to 9.5% of haemodialysis patients are carriers of MRSA [17]. It is therefore prudent to administer empiric antibiotic treatment which includes MRSA and Gram negative cover to the ESKD patient with sepsis until causative organisms have been identified. In addition, in the case of catheter–related sepsis, dialysis patients often improve dramatically on removal of the source.

Vascular access

The use of arteriovenous fistulae for continuous haemofiltration should be avoided as lower pump speeds may predispose to thrombosis of the fistulae and prolonged needle placement predisposes to infection. The insertion of a dedicated haemodialysis catheter

is preferred for continuous RRT, but insertion of catheters into the subclavian vein should be avoided due to the increased risk of central vein stenosis. Catheters should be placed contralateral to any existing permanent dialysis access and catheter placement may be difficult due to multiple previous venous access procedures.

Anti-coagulation and bleeding risk

Renal failure is associated with an increased risk of bleeding with the most common manifestations being gastro-intestinal bleeding and prolonged bleeding from needle and venous access insertion sites. Bleeding diathesis in uraemia is due to dysfunctional platelet adherence, abnormal von Willebrand factor metabolism and anaemia.

Anti-coagulation is required to maintain patency of the extra-corporeal dialysis circuit both during intermittent and continuous dialysis therapies. While low molecular weight heparin is frequently used in chronic stable haemodialysis patients, the use of unfractionated heparin is preferred in the acute or critically-ill patient as it is easily monitored and readily reversible. Haemodialysis catheters are routinely 'locked' with heparin to maintain patency when not in use and care should be taken to withdraw the instilled heparin volume prior to catheter use to avoid systemic anticoagulation. Regional citrate anticoagulation is an increasingly popular alternative to heparin as it restricts anticoagulation to the extracorporeal circuit, where it acts by chelating ionized calcium. Calcium is then replaced by infusion at the end of the extracorporeal circuit. Use of citrate anticoagulation requires monitoring for hypocalcaemia and the development of metabolic alkalosis, as citrate is metabolized by the liver to bicarbonate. Other anticoagulation strategies for RRT include thrombin antagonists (lepirudin, argatroban), platelet inhibiting agents (epoprostenol) and Factor Xa inhibitors (fondaparinux).

Anaemia

CKD and ESKD patients are frequently anaemic due to erythropoietin and iron deficiency and are often prescribed Erythropoiesis Stimulating Agents (ESA's) to maintain haemoglobin levels. Anaemia is a common complication in critical illness due to blood loss, reduced red cell production, increased red cell destruction, decreased erythropoietin production and hyporesponsiveness of the bone marrow to erythropoietin. The use of erythropoietin in critically-ill patients has not been shown to reduce red blood cell transfusions in the ICU and has been associated with an increased incidence of thrombotic events. The benefit of continuing ESA's in critically ill ESKD patients has not been evaluated [18].

Peritoneal dialysis

Peritoneal dialysis has several advantages over haemodialysis based modalities including non-vascular access, greater haemodynamic stability, and no requirement for systemic anticoagulation. It is also less expensive. Contra-indications to PD include recent intra-abdominal surgery, peritonitis, and respiratory compromise, as intra-peritoneal fluid may further impair lung function and gas-exchange. PD is the modality of choice for RRT in critically ill paediatric patients. Despite the advantages of PD, it is ineffective in the management of life-threatening hyperkalaemia and it is less effective than haemodialysis based modalities in severe acute illness, pulmonary oedema, drug overdose, and hypercatabolic states. As such, PD is not commonly used in the ICU setting. If PD is used in this setting, care should be taken to monitor venous blood glucose levels, as icodextrin containing PD fluid may interfere with point-of-care blood sugar monitoring resulting in overestimation of capillary glucose and severe undetected hypoglycaemia [19].

In patients with ESKD treated with chronic PD, peritonitis is a significant cause of morbidity and mortality and such patients may require admission to the ICU. Clinical presentations of PD peritonitis include abdominal pain, fever, nausea and vomiting, and cloudy peritoneal effluent. If PD peritonitis is suspected, empiric antibiotic treatment should be initiated promptly. Peritoneal effluent should be sent for cell count and differential, Gram stain and culture. A diagnosis of PD peritonitis is confirmed if two or more of the following criteria are met:

- Signs and symptoms.
- PD effluent white cell count >100/μL (after a dwell time of at least 2 hours) with at least 50% neutrophils.
- A positive culture of an organism from the PD effluent.

PD peritonitis is usually caused by a single organism. Culture of multiple Gram negative or mixed Gram negative and positive organisms from the PD effluent should raise immediate concern for presence of a perforated viscus and prompt appropriate investigations for 'surgical' peritonitis.

Intra-peritoneal administration of antibiotics is superior to intravenous administration for treating PD peritonitis and should be initiated without delay. Empiric antibiotics must cover both Gram positive and Gram negative organisms and the selection of empiric antibiotics is based on the centre-specific history of sensitivities of peritonitis associated organisms. Gram positive organisms can be covered by vancomycin or a cephalosporin, Gram negative organisms by a third-generation cephalosporin, aminoglycoside or ciprofloxacin. Failure of the effluent to clear after 5 days of appropriate antibiotic therapy or identification of fungal infection by microscopy or culture should prompt removal of the PD catheter [20].

Drug dosing

Drug dosing in CKD and ESKD can be particularly challenging as care must be taken to ensure therapeutic drug levels while avoiding toxicity or inadequate plasma levels. Correct dosing of drugs in these patients requires consideration of drug-protein binding, volume of distribution and residual renal function. In addition extracorporeal drug clearance differs depending on the modality of RRT used.

Conclusion

The incidence of CKD and ESKD is increasing and these patients with CKD or ESKD frequently require treatment in an ICU. Mortality in critically-ill patients with ESKD is frequently related to their co-morbid conditions rather than their ESKD status, therefore appropriately selected patients benefit from ICU admission. Cardiovascular disease and sepsis account for the majority of ICU admissions in this population and the aetiology of these conditions differs from that in patients without kidney disease. Optimal critical care management of patients with ESKD and CKD requires that these differences are recognized.

References

1. Hutchison CA, Crowe AV, Stevens PE, et al. (2007). Case mix, outcome and activity for patients admitted to intensive care units requiring chronic renal dialysis: a secondary analysis of the ICNARC Case Mix Programme Database. *Critical Care*, **11**, R50.
2. Clermont G, Acker CG, Angus DC, et al. (2002). Renal failure in the ICU: comparison of the impact of acute renal failure and end-stage renal disease on ICU outcomes. *Kidney International*, **62**, 986–96.
3. Uchino S, Morimatsu H, Bellomo R, et al. (2003). End-stage renal failure patients requiring renal replacement therapy in the intensive care unit: incidence, clinical features, and outcome. *Blood Purification*, **21**, 170–5.
4. Strijack B, Mojica J, Sood M, et al. (2009). Outcomes of chronic dialysis patients admitted to the intensive care unit. *Journal of American Society Nephrology*, **20**, 2441–7.
5. Kanbay M, Afsar B, Goldsmith D, et al. (2010). Sudden death in hemodialysis: an update. *Blood Purification*, **30**, 135–45.
6. Collins AJ, Foley RN, Gilbertson DT, et al. (2009). The state of chronic kidney disease, ESRD, and morbidity and mortality in the first year of dialysis. *Clinical Journal of the American Society for Nephrology*, **4**(1), S5–11.
7. Arulkumaran N, Annear NM, and Singer M. (2013). Patients with end-stage renal disease admitted to the intensive care unit: systematic review. *British Journal of Anaesthetics*, **110**, 13–20.
8. Mehta RL, Pascual MT, Soroko S, et al. (2004). Spectrum of acute renal failure in the intensive care unit: the PICARD experience. *Kidney International*, **66**, 1613–21.
9. Chapman RJ, Templeton M, Ashworth S, et al. (2009). Long-term survival of chronic dialysis patients following survival from an episode of multiple-organ failure. *Critical Care*, **13**, R65.
10. Himmelfarb J, Le P, Klenzak J, et al. (2004). Impaired monocyte cytokine production in critically ill patients with acute renal failure. *Kidney International*, **66**, 2354–60.
11. Vanholder R, Van Loo A, Dhondt AM, et al. (1996). Influence of uraemia and haemodialysis on host defence and infection. *Nephrology Dialysis Transplantation*, **11**, 593–8.
12. Bagshaw SM and Uchino S. (2009). End-stage kidney disease patients in the intensive care unit. *Nephrology Dialysis Transplantation*, **24**, 1714–7.
13. Foley RN, Parfrey PS, Harnett JD, et al. (1995). Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney International*, **47**, 186–92.
14. Halle MP, Hertig A, Kengne AP, et al. (2012). Acute pulmonary oedema in chronic dialysis patients admitted into an intensive care unit. *Nephrology Dialysis Transplantation*, **27**, 603–7.
15. Dalrymple LS and Go AS. (2008). Epidemiology of acute infections among patients with chronic kidney disease. *Clinical Journal of the American Society for Nephrology*, **3**, 1487–93.
16. Alexandraki I, Sullivan R, Zaiden R, et al. (2008). Blood culture isolates in hemodialysis vascular catheter-related bacteremia. *American Journal of Medical Science*, **336**, 297–302.
17. Lai CF, Liao CH, Pai MF, et al. (2011). Nasal carriage of methicillin-resistant *Staphylococcus aureus* is associated with higher all-cause mortality in hemodialysis patients. *Clinical Journal of the American Society for Nephrology*, **6**, 167–74.
18. Corwin HL, Gettinger A, Fabian TC, et al. (2007). Efficacy and safety of epoetin alfa in critically ill patients. *New England Journal of Medicine*, **357**, 965–76.
19. Korsatko S, Ellmerer M, Schaupp L, et al. (2009). Hypoglycaemic coma due to falsely high point-of-care glucose measurements in an ICU-patient with peritoneal dialysis: a critical incidence report. *Intensive Care Medicine,* **35**, 571–2.
20. Li PK, Szeto CC, Piraino B, et al. (2010). Peritoneal dialysis-related infections recommendations: 2010 update. *Peritoneal Dialysis International*, **30**, 393–423.

SECTION 9

The neurological system

PART 9.1

Anatomy and physiology

CHAPTER 219

Normal anatomy and physiology of the brain

Simona Ferioli and Lori Shutter

Key points

- Central nervous system dynamics such as blood flow, cerebrospinal fluid circulation, and intracranial pressure are tightly regulated by its different compartments. Knowledge of basic physiological mechanisms is essential in understanding how the brain can be affected by systemic diseases encountered in the intensive care unit.
- The cerebral cortex attends complex functions including memory, language, abstraction, judgment, emotion, attention, and synthesis of movements. These can be selectively impaired in patients with primary central nervous system pathologies depending on their location.
- Consciousness is commonly affected in critically-ill patients. Its integrity depends on arousal and content, which are regulated by distinct structures within the central nervous system.
- Ventilation is controlled by a multi-level network of peripheral and central nervous structures that are crucial in diagnosis and treatment of respiratory failure.
- Motor and sensory systems are hierarchically organized along tracts involving nerves, muscles spinal cord, and central structures. Identification of their localization and function is important for diagnosis of different patterns of weakness and sensory loss that occur in critically-ill subjects.

Meninges, cerebral spinal fluid, and the blood–brain barrier

The brain is protected from mechanical trauma within the skull by three meningeal layers and the cerebral spinal fluid (CSF). The outer meningeal layer is the dura, which is attached to the inner surface of the skull and extends caudally around the spinal cord to form the dural sac. The two layers that constitute the dura separate to form the intracranial walls of the venous sinuses where cerebral spinal fluid gets reabsorbed. The epidural space (between the inner skull and dura) contains the middle meningeal artery, a branch of the external carotid artery. The subdural space (between the inner side of the dura and subarachnoid) is traversed by bridging veins that drain into the dural sinuses which continue into the jugular veins. The middle meningeal layer is the arachnoid, which adheres loosely to the inner dura, defines the subarachnoid space and is filled by CSF (Table 219.1). The inner meningeal layer is the pia, a thin epithelial layer that tightly covers the parenchyma. All these spaces can become sites for life-threatening haemorrhages, particularly in the setting of trauma (epidural and subdural haematomas) or aneurysm rupture (subarachnoid space). CSF is produced by the choroid plexus, which is a vascular structure lying within the ventricles. CSF circulates through the ventricular system, enters the subarachnoid space, surrounds the spinal cord and is ultimately reabsorbed by the arachnoid granulations into dural venous sinuses. The total volume of CSF is about 150 cm^3, with a production of approximately 500 cm^3 every 24 hours. The blood–CSF barrier maintains osmolality, electrolytes, proteins, and glucose content of CSF within constant limits. Substances in serum typically can only move into CSF by active transportation across the blood–brain barrier, a highly selective filter made up of tight junctions around capillaries (Fig. 219.1), but inflammation can produce a breakdown of this barrier and allow direct CSF penetration. Bacteraemia is the most common example of meningeal colonization and paramenin-geal spread [1,2]. Once in the CSF, substances can freely diffuse to the brain parenchyma.

Cerebral blood flow

Cerebral blood flow (CBF) is dependent on cerebral perfusion pressure (CPP) and cerebral vasculature resistance. According to the Kelly–Monroe doctrine, due to the rigid skull compartment, CPP is calculated by subtracting the intracranial pressure (ICP)

Table 219.1 Normal CSF composition

Proteins	Glucose	White blood cells	Red blood cells	Appearance
15–40 g/L	2.7–4.7 mmol/L (2/3 plasma glucose concentration)	0–3 (Lymphocytes)	None	Clear

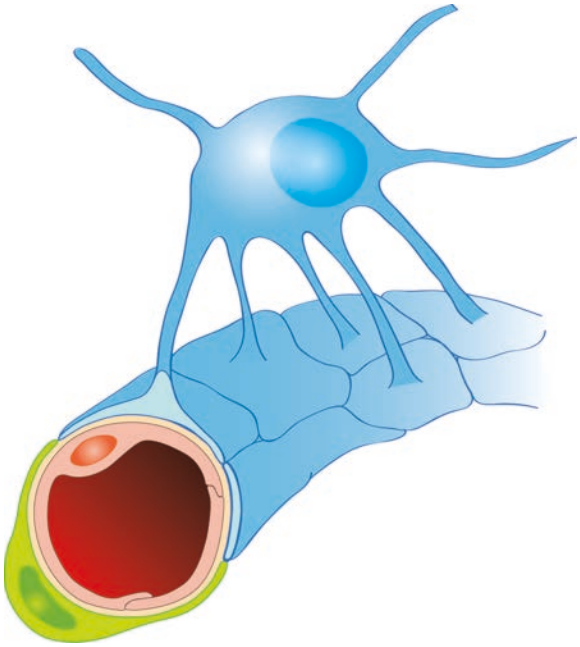


Fig. 219.1 The blood–brain barrier. Brain capillary endothelial cells are connected by tight junctions and most of the capillary is covered by astrocytes foot processes.
Printed with permission from Glia Media.

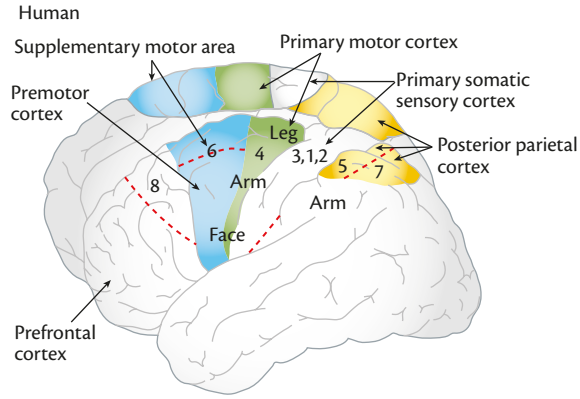


Fig. 219.2 The principle motor control areas of the cortex are shown on the convexity (in front) and the medial aspects (behind) of the cerebral hemispheres.
Reproduced with permission from Kandel ER et al. (eds), *Principles of Neural Science*, © 1991 McGraw-Hill Education.

from the mean arterial pressure (MAP) according to the formula: CPP = MAP – ICP. Normal ICP is less than 20 cmH_2O (or less than 15mmHg), but physiological variations occur with Valsalva manoeuvres, sneezing, or coughing. Any space-occupying lesion can increase ICP. This is initially compensated by reduction in CSF and cerebral blood volume (CBV). Severely elevated ICP ultimately affects CBF causing ischaemia and may lead to cerebral herniation. CBF is maintained at a constant level in normal brain by the intrinsic process of autoregulation through myogenic and metabolic mechanisms that allow adjustments in arterial calibre in response to many different parameters, including arterial blood pressure, $PaCO_2$, PaO_2, and several pharmacological agents. Any increase in $PaCO_2$ results in cerebral vasodilation. In contrast, variation of PaO_2 does not affect cerebral blood flow until it decreases below 50 mmHg (6.7 kPa). Autoregulation normally maintains constant blood flow between a MAP of 50 and 150 mmHg, but MAPs below this range can allow a drop in cerebral perfusion, which can lead to ischaemia. Conversely, MAPs above this range may cause damage to the blood–brain barrier, leading to oedema and hemorrhagic events. Autoregulation is also impaired in primary brain pathologies where the blood–brain barrier is damaged and CBF becomes linearly dependent on MAP [3].

Functional cortical regions

The cerebral cortex provides the necessary substrate for several sophisticated intellectual and cognitive functions that determine behaviour, motor planning, and sensory processing. The dominant hemisphere (usually the left hemisphere) controls language which is primarily localized in the inferior frontal lobe (Broca's area), temporal lobe (Wernicke's area), and the interconnecting parietal lobe area. Lesions to these areas cause problems generating and understanding spoken and written language, depending on the precise location.

The non-dominant hemisphere is involved in mechanisms of attention and visual-spatial analysis, which are localized primarily in parietal frontal areas. Bilateral frontal lobes are responsible for inhibition of inappropriate behaviours, motivation, judgment, and working memory. In addition, the frontal eye fields control horizontal conjugate eyes movements; a damage to one of these areas generates a gaze deviation ipsilateral to the lesion typically seen, for example, after hemispheric strokes. The visual area lies in the occipital lobes where each hemisphere receives information from the contralateral halves of both visual fields. Damage to this region is responsible for visual field deficits (quadrantianopia, hemianopia) or cortical blindness. Motor and somatosensory cortex are represented in the frontal and parietal lobes respectively, and are somatotopically-organized so the size of each body region is related to its sensory or motor importance (see Fig. 219.2) [1].

Consciousness

Consciousness refers to a state of awareness of self and environment that depends on intact arousal and content [4]. Arousal is clinically related to the level of alertness or wakefulness. It is mediated through a core of nuclei that extend through the brainstem (known as reticular formation) and project to the cortex bilaterally through the diencephalon (thalamus and hypothalamus). The content of consciousness includes sensory, motor, emotional, executive, and mnemonic systems, localized throughout multiple levels of both cortical hemispheres. Coma is usually caused by lesions of the upper brainstem or diffuse bilateral cortical areas, but could also result from mass effect of lesions above the brainstem compressing the reticular formation and thalamus. The arousal system can also be affected by metabolic abnormalities that impair the state of consciousness and resemble coma in the absence of a structural lesion (encephalopathy). The major neurotransmitters released by the arousal system that regulate the level of alertness are norepinephrine, dopamine, serotonin, histamine, orexin and acetylcholine (see Fig. 219.3) [5].

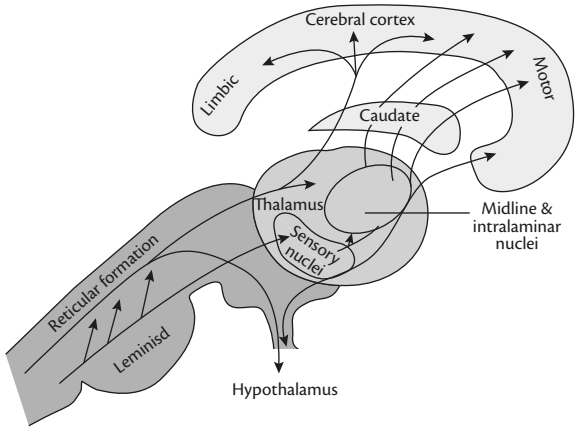


Fig. 219.3 The ascending reticular system and its projections. This diagram depicts the brainstem, containing the reticular formation and the ascending sensory pathways (lemnisci), the thalamus, the caudate nucleus, and the higher structures (limbic system, motor areas, and cerebral cortex). Projections to the hyopthalamus are also shown.

Respiration

Breathing occurs automatically under control of a network of neurons in the lower medulla. Afferent inputs, including chemoreceptors for oxygen, carbon dioxide, and lung stretch receptors, project to the cardiorespiratory centre of the nucleus solitarius and modulate the respiratory pattern. The central nervous system can also stimulate breathing via medullary serotoninergic neurons or temporarily regulate ventilation through voluntary cortical control. The medullary breathing centres project via the lateral columns of the spinal cord and modulates the phrenic nerve control of the diaphgram and the (cervical nerve roots C3–C5), intercostal nerves that innervate thoracic inspiratory and expiratory muscles. Distinct abnormal respiratory patterns can be associated with central nervous system pathologies. Extensive bilateral medullary lesions lead to respiratory arrest, whereas partial damage may produce ataxic breathing (disorganized breathing pattern with random periods of apnoea). Higher pontine lesions can cause apneustic respiration, which is marked by prolonged end-inspiratory pauses. Central neurogenic hyperventilation (sustained tachypnoea) is encountered with damage at different brainstem levels and can lead to metabolic derangements (alkalosis). Cheyne–Stokes respiration, which is generally not harmful, consists of cyclic phases of incremental hyperventilation followed by hypoventilation to the point of apnoea. It has been associated with left ventricular dysfunction, as well as bilateral upper pons or higher cerebral lesions [6].

Autonomic control

The nervous system is directly responsible for maintenance of homeostasis through a complex network of interactions among hypothalamus, limbic system, midbrain nuclei, and peripheral autonomic nervous system. It regulates intravascular volume, regional blood flow, thermoregulation, motility and secretions of gastrointestinal and respiratory tracts, micturition, and reproduction. The hypothalamus integrates emotional input from the limbic system with autonomic responses, and regulates endocrine function through control of pituitary hormones. It activates mechanisms of heat dissipation or conservation in response to variations in body temperature, and regulates food intake and thirst. Heart rate and blood pressure control are mediated through the nucleus solitarius in the medulla, which receives input from carotid and aortic arch baroreceptors, and projects to brainstem and spinal cord autonomic neurons. The peripheral autonomic system regulates involuntary control of visceral functions and consists of three subdivisions—sympathetic, parasympathetic, and enteric nervous systems. The sympathetic is involved in 'fight or flight' functions, such as increasing heart rate, blood pressure, bronchodilation, and pupil size. In contrast, the parasympathetic slows heart rate, decreases pupil size, and promotes peristalsis and gastric secretions. Acetylcholine is the neurotransmitter that activates all preganglionic autonomic neurons, and is the final neurotransmitter of parasympathetic and sweat glands neurons. Norepinephrine is the sympathetic system post-ganglionic neurotransmitter. Other substances such as vasoactive intestinal peptide (VIP), substance P, and neuropeptide Y have also been found to have a role in autonomic modulation [7].

Motor control

The motor cortex follows a somatotopic pattern, where parts of the body responsible for elaborate movements have a larger representation than those responsible for gross movements. It projects to contralateral lower motor neurons that innervate specific muscle groups through peripheral nerves. The cranial nerves lower motor neurons are located at different levels throughout the brainstem, and integrate vestibular, visual, and somatosensory inputs to eye movements and postural control. The anterior horns of the spinal cord contain lower motor neurons for skeletal muscles, with each spinal cord segment corresponding to specific muscles group and receiving sensory inputs from related dermatomes. The cerebellum and basal ganglia connect to the motor cortex through complex feedback loops that regulate coordination and motor planning. Pathological posturing reflexes can be seen in extensive lesions interrupting upper motor neuron pathways, with flexor posturing seen after damage at the midbrain or higher, and extensor posturing seen with lesions of the lower brainstem. Reflex responses, such as pupil light reflex or deep tendon reflexes are motor responses to external stimuli that depend only on brainstem or spinal cord pathways, and do not require conscious participation. Weakness caused by an upper motor neuron lesion is characterized by increased tone and hyper-reflexia (secondary to loss of cortical modulation of the reflex response and tone), whereas lower motor neuron weakness is characterized by hypotonia and hyporeflexia [8].

Peripheral nervous system

Cranial and spinal peripheral nerves are responsible for somatosensory afferents to the central nervous system, motor output, and autonomic regulation to target organs. The majority of peripheral nerves are mixed, containing axons that carry both sensory input of a specific skin region (dermatome) and others that innervate distinct muscle groups (myotome). Autonomic fibres also travel along the peripheral nerves and synapse at paravertebral ganglia (sympathetic ganglia) or near end organs (parasympathetic ganglia). Nerve roots that exit the cervical and lumbosacral region are organized in bundles (brachial plexus and lumbosacral plexus) that provide somatosensory innervation of the upper and lower extremities.

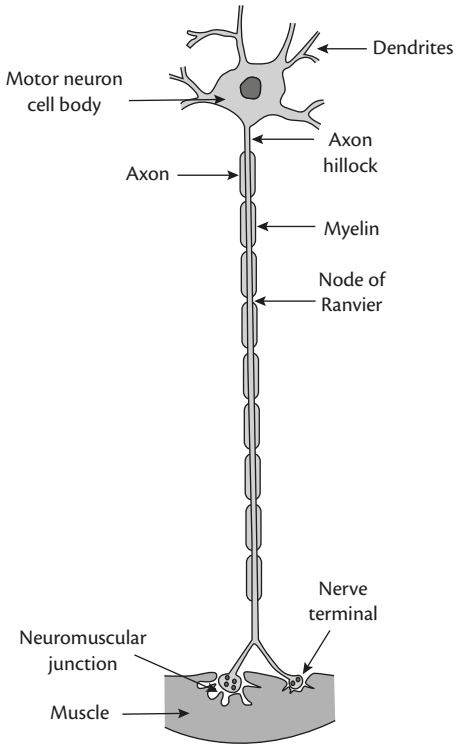


Fig. 219.4 Schematic diagram of the motor neuron and its components, the neuromuscular junction, and muscle.

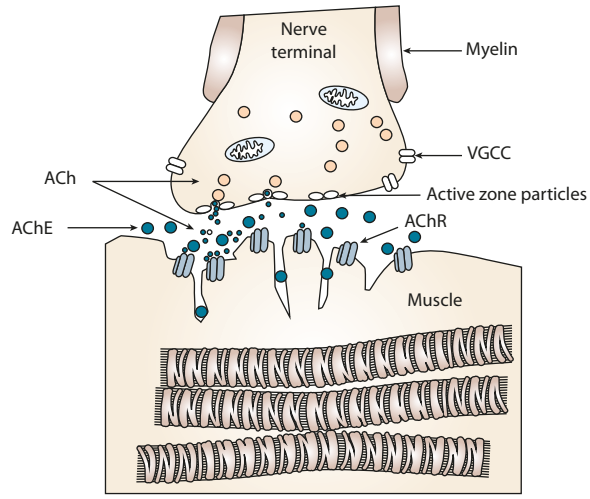


Fig. 219.5 The neuromuscular junction.
The nerve terminal synaptic cleft, and muscle endplate are shown: Ach, acetylcholine; AChE, acetylcholinesterase; VGCC, voltage-gated Ca2+ channels; AChR, acetylcholine receptors.

Sensory fibres begin with receptors in cutaneous or visceral muscles and tendon receptors, and then travel to the cell body in the dorsal root ganglia. Its central process enters the spinal cord in the region of the dorsal horns and travels centrally. Motor fibres start at the motor neuron cell body in the anterior horns of the spinal cord, and the axon travels within the peripheral nerve to the neuromuscular junction. Compression neuropathies or 'plexopathies' can be encountered in the ICU as consequence of prolonged positioning or from initial injuries. Critical illness polyneuropathies have also been documented in ICU patients, and may present with difficult ventilator weaning or evidence of diffuse usually symmetric weakness and sensory loss (see Fig. 219.4).

Neuromuscular transmission

Motor and sensory stimuli travel along nerves through generation of action potentials. Conduction velocity is determined by fibre size and myelination. Myelin is a protein-lipid complex produced by Schwann cells that insulates axons, leaving gaps of exposed axons (nodes of Ranvier) where action potential conduction occurs through voltage gate sodium channels. Unmyelinated sensory fibres (pain and temperature) have a smaller diameter and conduction is slower when compared with myelinated larger fibres for motor and sensory (proprioception and joint position) transmission. Demyelination of peripheral nerves, as seen in acute inflammatory demyelinating syndrome (AIDP or Guillain–Barré), may slow and block nerve conduction, causing respiratory muscle weakness and autonomic instability, which often requires treatment in an intensive care unit. Muscle contraction initiates when depolarization opens calcium channels concentrated in the nerve terminal membrane and stimulates release of acetylcholine at the neuromuscular junction level. Acetylcholine acts on post-synaptic muscle receptors and allows sodium into muscle fibres, which then implements muscle contraction by release of intracellular calcium. The action of acetylcholine is terminated by hydrolysis by acetylcholinesterases. Antibodies against acetylcholine receptors results in the classic form of myasthenia gravis, which can lead to diffuse weakness and respiratory failure. Muscles can also be severely compromised in critically-ill patients (critical illness myopathy) or develop wasting and muscle necrosis (necrotizing myopathy of intensive care). Both are distinguished by profound weakness with spared sensation (see Fig. 219.5) [9].

References

1. Blumenfeld H. (2010). *Neuroanatomy Through Clinical Cases*. Sunderland, MA: Sinauer Associates.
2. Greenberg MS, Duckworth M, and Nichols T. (2005). *Handbook of Neurosurgery*. New York: Thieme.
3. Torbey MT, Bhardwaj A. (2004). Cerebral blood flow physiology and monitoring. In: Suarez JI (ed.) *Critical Care Neurology and Neurosurgery*, pp. 23–7. Totowa, NJ: Humana Press.
4. Posner JB, Saper CB, Schiff ND, and Plum F. (2007). *Plum and Posner's Diagnosis of Stupor and Coma*, 4th edn. New York, NY: Oxford University Press.
5. Cooper JR and Roth RH. (2003). *The Biochemical Basis of Neuropharmacology*. New York, NY: Oxford University Press.
6. Pal PK, Chen R. (2014). Breathing and the nervous system. In: Aminoff MJ (ed.) *Neurology and General Medicine*, pp. 3–23. Philadelphia: Churchill Livingstone Elsevier; 2008.
7. Buczek M, Suarez JI, Chelimsky TC(2004). Treatment of autonomic disorders requiring intensive care management. In: Suarez JI (ed.) *Critical Care Neurology and Neurosurgery*, pp. 168–9. Totowa: Humana Press.
8. Brazis PW, Masdeu JC, and Biller J. (2011). *Localization in Clinical Neurology*, 6th edn. China: Lippincott Williams & Wilkins.
9. Torbey TM, Suarez JI, Geocardin R (2004). Less common causes of quadriparesis. In: Suarez JI (ed.) *Critical Care Neurology and Neurosurgery*, pp. 509–10. Totowa, NJ: Humana Press.

CHAPTER 220

Normal anatomy and physiology of the spinal cord and peripheral nerves

Steve Casha and Philippe Mercier

Key points

- The spinal cord contains efferent and afferent sensory, motor, and autonomic pathways connecting the body with the cerebrum.
- A cross-section of the spinal cord reveals a very organized structure containing ascending, descending and bidirectional tracts.
- Each mixed spinal nerve innervates a particular area of skin called a dermatome and a discrete set of muscles called a myotome.
- Neurological problems affecting the spine and peripheral nerves are frequently encountered in the intensive care unit.
- A basic understanding of the anatomy of the spine and peripheral nerves is essential to localize pathology.

Introduction

Pathology of the spine and peripheral nerves is common in the intensive care unit. Critical care specialists may be asked to provide supportive care to patients already under the care of a neurologist or neurosurgeon, provide the care and management of patients from initial presentation such as in trauma or may consult neurologists and neurosurgeons regarding secondary neurological complications occurring in patients with other medical or surgical diseases. Regardless, the critical care specialist must have a working knowledge of the anatomy of the spine and peripheral nerves in order to localize pathology, formulate a differential diagnosis and initiate treatment of a diverse group of disease states.

The spinal cord

Gross anatomy

The spinal cord is the major conduction pathway for both afferent and efferent pathways between the brain and the body and is a component of the reflex centre. It is a cylindrical structure slightly flattened in the anterior–posterior plane beginning as an extension of the medulla and ending as the conus medularis [1]. During development the spinal cord extends to the end of the dural sac that is attached at the level of the second sacral vertebrae. The spine and dura grow more rapidly than the spinal cord such that at birth the conus medularis lies at the level of the third lumbar vertebrae and eventually it is located at the level of first or second lumbar vertebrae [1].

The spinal cord is contained within the vertebral canal and protected throughout its length by the vertebral column. The spinal cord is surrounded by the pia mater, the arachnoid membrane and a single layer of dura mater that is a continuation of the inner dural layer of the brain [1]. The spinal cord is bathed in cerebrospinal fluid (CSF) that is continuous with cerebral CSF and it is also protected by a layer of epidural fat [1].

The spinal cord, like the vertebral column, is organized in a segmental fashion. There are eight cervical, 12 thoracic, five lumbar, five sacral, and one coccygeal spinal segments [1]. The cord is enlarged in two regions corresponding to upper and lower extremities. The cervical enlargement extends between spinal cord segments C4–T1 and its spinal roots form the brachial plexus. The lumbosacral enlargement extends from T11 to S3 gives rise to spinal roots that form the lumbosacral plexus (Fig. 220.1) [1].

Spinal nerves for each segment are formed from a merger of anterior and posterior roots formed from a series of rootlets that emerge from each segment of the spinal cord [1]. The posterior nerve roots form a ganglion (dorsal root ganglion) in the intervertebral foramen before the anterior and posterior roots evaginate the dura separately and unite to form a mixed spinal nerve [1]. Each spinal nerve divides into a posterior primary and anterior primary ramus almost immediately. The anterior roots of the spinal nerve carry efferent (motor) fibres to skeletal muscle and many contain presynaptic autonomic fibres [1]. The cell bodies of the somatic axons contributing to the ventral roots are contained within the anterior horns of the grey matter of the spinal cord [1]. The posterior roots contain afferent (sensory) fibres from the skin, subcutaneous and deep tissues, and the viscera. The cell bodies of the posterior fibres are found within the dorsal root ganglia and synapse within the dorsal aspect of the grey matter of the spinal cord [1].

Internal structure of the spinal cord

The spinal cord in cross-section consists of central grey matter in the shape of a butterfly. Within the grey matter can be divided

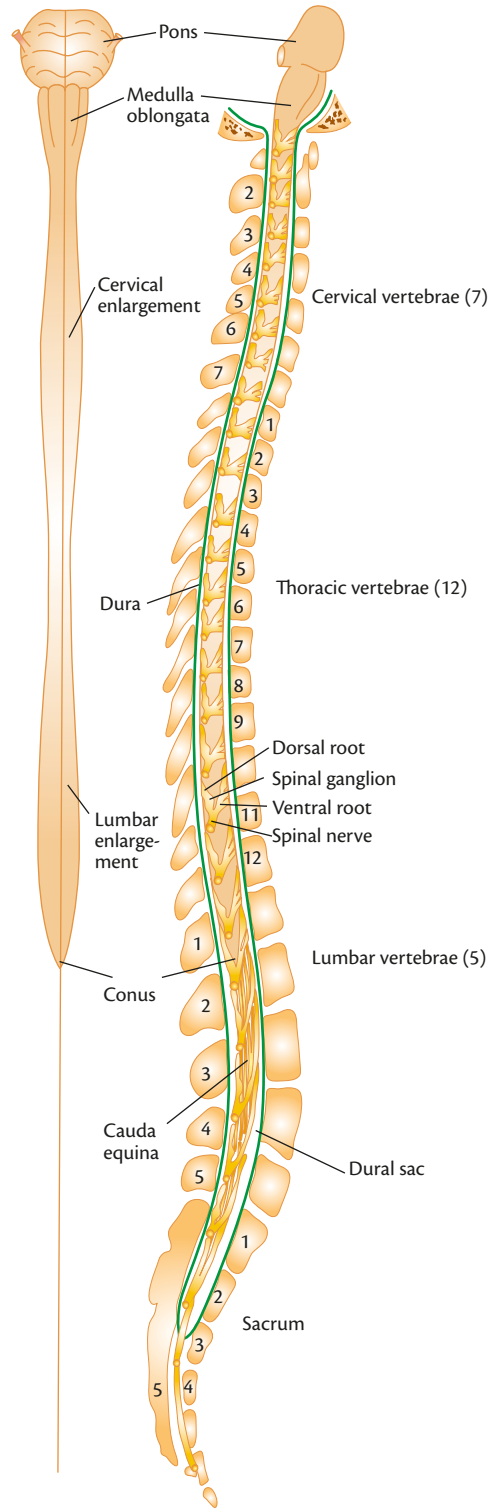


Fig. 220.1 Sagittal view of the spinal cord. Spinal nerve roots exit through the bilateral neuroforamina (not shown) and are named for each vertebral level. The spinal cord typically ends as the conus medullaris between the L1 and L2 levels in the adult.

Reproduced from Brodal P (editor), *The Central Nervous System*, Fourth Edition, 2010, Figure 6.3, by permission of Oxford University Press, USA.

into rexed laminae that have different specific roles [1]. A number of afferent or ascending tracts, efferent or descending tracts, and bidirectional tracts can be identified and are summarized in Fig. 220.2.

Autonomic nervous system

Sympathetic efferents arise from the interomediolateral nucleus of the grey matter of the spinal cord and exit through the ventral roots forming paired paravertebral ganglia that form a continuous

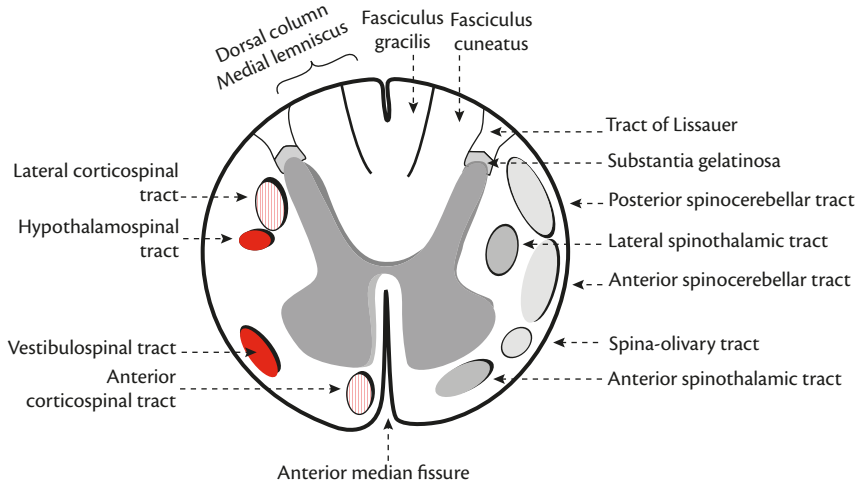


Fig. 220.2 Cross-section of the cervical spinal cord. Descending white matter motor tracts (red) include the anterior corticospinal tract involved in skilled movement, the vestibulospinal tract that facilitates extensor muscle tone, and the lateral corticospinal tract that is involved in skilled movement. The hypothalamospinal tract carries autonomic efferents to the thoracic spine. Bi-directional white matter tracts include the dorsolateral fasciculus of lissauer and the fasciculus proprius that contains short spinospinal connections. Ascending white matter sensory tracts (grey) include the fasciculus gracilis and cuneatus that are involved in joint position, fine touch and vibration for lower and upper limbs, respectively, the posterior spinocerebellar tracts that carries stretch receptor innervation, the lateral spinothalamic tract that conveys pain and temperature sense, anterior spinocerebellar tracts, which convey whole limb position, spinotectal tract and the anterior spinothalamic tract that convey light touch, and spino-olivary tract, which carries information from muscles, tendons, and cutaneous impulses.
Reproduced from Samandouras G (editor), *The Neurosurgeon's Handbook*, 2010, figure 6.21, with permission from Oxford University Press.

chain from contributions from T1 to L2 or L3 called the sympathetic trunk [1]. The head and neck sympathetic efferents are supplied by three sympathetic chain ganglia called the superior, middle, and inferior stellate cervical ganglia [1]. The sympathetic chain supplies sympathetic efferents to the body. Presynaptic neurons either enter or synapse with a paravertebral ganglion at that level, ascend or descend in the sympathetic trunk to synapse with a post-synaptic neuron in a higher or lower paravertebral ganglion or pass through the sympathetic trunk without synapsing [1]. Sympathetic post-ganglionic neurons release predominately norepinephrine activating noradrenergic receptors resulting in 'fight or flight' responses, including pupil dilatation, inhibition of salivation and lacrimation, airway dilatation, accelerated heartbeat, sweating, pilo-erection, hepatic glucose production and release, inhibition of digestion, adrenal secretion of adrenaline and noradrenaline, relaxation of the urinary bladder, and stimulation of ejaculation [1].

Parasympathetic efferents arise from cranial nerve parasympathetic nuclei (CN III, VII, IX, and X) and from sacral parasympathetic nuclei located in the lateral grey matter of levels S2–S4 [1]. Preganglionic nerve fibres travel longer distances to terminal ganglia that are typically located close to the effector organs [1]. Parasympathetic post-ganglial neurons release predominantly acetylcholine activating muscarinic cholinergic receptors on end organs resulting in a 'rest and digest' response opposite to the sympathetic response [1].

Vascular supply

The vascular supply to the spinal cord includes a single anterior spinal artery, as well as paired posterior spinal arteries running longitudinally. The anterior spinal artery is a midline vessel that is formed by a union of branches from both vertebral arteries [2]. The paired posterior spinal arteries also arise directly from the vertebral arteries or the posterior inferior cerebellar arteries. All three vessels run from the level of the foramen magnum to the conus medularis within the subarachnoid space [2]. The anterior spinal artery supplies the whole spinal cord anterior to the posterior grey columns, whereas the posterior spinal arteries supply the grey and white posterior columns [2]. The spinal arteries also form anastomoses with a number of segmental medullary arteries that form the more important vascular supply of the distal cord [2]. The medullary arteries enter the spinal canal through the intervertebral foramina as branches of the vertebral, costocervical, posterior intercostal, lumbar, and lateral sacral arteries [1]. The largest medullary artery is named the artery of Adamkiewicz that accompanies a nerve root between T8 and L1. It forms the major vascular supply of the distal two thirds of the cord including the lumbosacral enlargement [1]. A few radicular arteries that perfuse a small portion of the spinal cord do not form anastomoses with the anterior and posterior spinal arteries [1].

Anterior and posterior spinal veins communicate freely with each other and 12 anterior and posterior medullary and radicular veins. The spinal veins join the internal vertebral venous plexus in the extradural space that is continuous with the draining veins and sinuses of the cranium as well as communicating with the external venous plexus on the surface of the vertebrae [2].

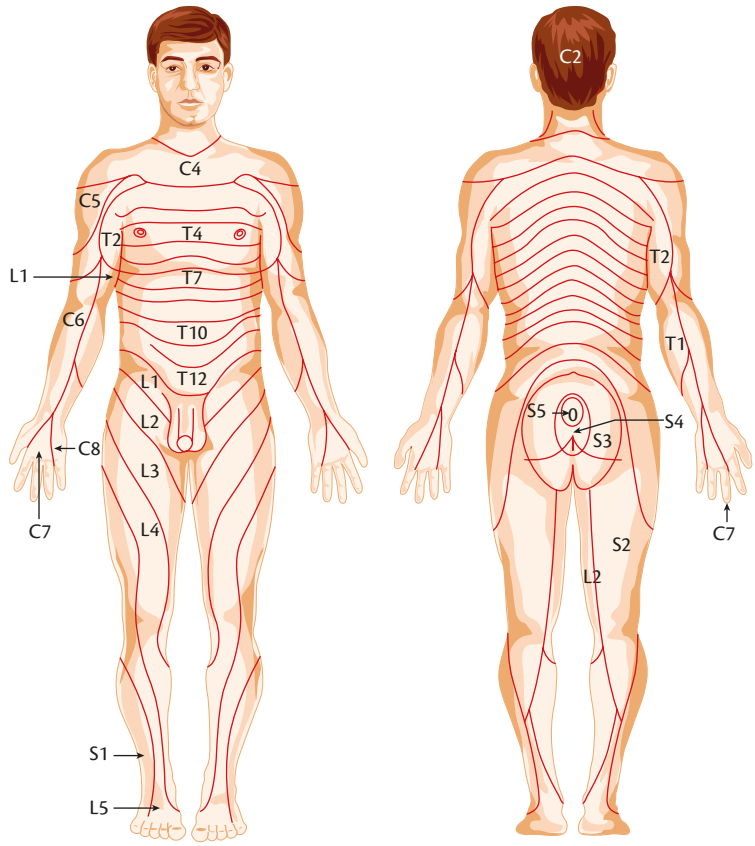
The peripheral nervous system

Nerve fibres can be either myelinated or unmyelinated. Peripheral nerves are myelinated by Schwann cells along their length. Myelinated segments are separated by small gaps (Nodes of Ranvier) [1]. This arrangement permits more efficient salutatory conduction increasing the conduction velocity 5–50 fold [1].

Nerve fibres can be classified in relation to their function. Group A fibres include alpha fibres (Ia and Ib) involved in motor function and proprioception, beta fibres that transmit touch, pressure

and proprioception, gamma fibres that innervate muscle spindles and delta fibres that response to touch, pain, and temperature. Group B fibres are myelinated preganglionic autonomic neurons and Group C are small unmyelinated fibres that can mediate either postganglionic autonomic function, touch sensation or pain [1].

The skin supplied by a single spinal nerve is called a dermatome [2]. The dermatomes of the spinal nerves are reliable (Fig. 220.3), but it is important to note that overlap exists, especially in the thoracic dermatomes [2].



Myotomes

Muscle group	*Nerve supply*	**Reflexes**
Diaphragm	C(3), 4 (5)	
Shoulder abductors	C5	
Elbow flexors	C5, 6	Biceps jerk C5, 6
Supinators/promotors	C6	Supinator jerk C6
Wrist extensors	C6	
Wrist flexors	C7	
Elbow extensors	C7	Triceps jerk C7
Finger extensors	C7	
Finger flexors	C8	
Intrinsic hand muscles	T1	Abdominal reflex T8–12
Hip flexors	L1, 2	
Hip adductors	L2, 3	
Knee extensors	L3, 4	Knee jerk L3, 4
Ankle dorsiflexors	L4, 5	
Toe extensors	L5	
Knee flexors	L4, 5 S1	
Ankle plantar flexors	S1, 2	Ankle jerk S1, 2
Toe flexors	S1, 2	
Anal sphincter	S2, 3, 4	Bulbocavernosus reflex S3, 4 Anal reflex S5 Plantar reflex

Fig. 220.3 Schematic of the dermatomes.

Reproduced from Barnes MP (editor), 'Spinal cord injury and its management'. In: David A. Warrell et al. (eds), *Oxford Textbook of Medicine*, 5th edn, 2014, online: figure 24.13.2.1, with permission from Oxford University Press.

The muscles innervated by a single spinal nerve are called a myotome [1]. In general most muscles are supplied by two adjacent segments of the spinal cord [1].

The upper and lower limb muscles and skin are innervated by the brachial, lumbar, sacral, and coccygeal plexuses [2]. The brachial plexus is formed by the anterior rami (roots) of the C5–T1 nerves [2]. The roots go on to form three trunks, three ventral, and three dorsal divisions followed by three cords before becoming terminal nerves including the musculocutaneous, accessory, radial, median, and ulnar nerves [2]. Several peripheral nerves are given off the roots, trunks and cords (Fig. 220.4).

The lumbar plexus is formed from the anterior rami of the L1–L4 spinal nerves. The L1 and L2 roots form the iliohypogastric nerve, ilio-inguinal, and genitofemoral nerves (Fig. 220.5).

The L2–L4 roots form the lateral cutaneous nerve of the thigh, femoral, and obturator nerves [2]. The sacral and coccygeal plexus are formed from the L4–S5 roots [2]. The major branches include the superior and inferior gluteal nerves, the posterior femoral cutaneous nerve, the sciatic nerve that divides into tibial and peroneal nerves, and the pudendal nerve (Fig. 220.6).

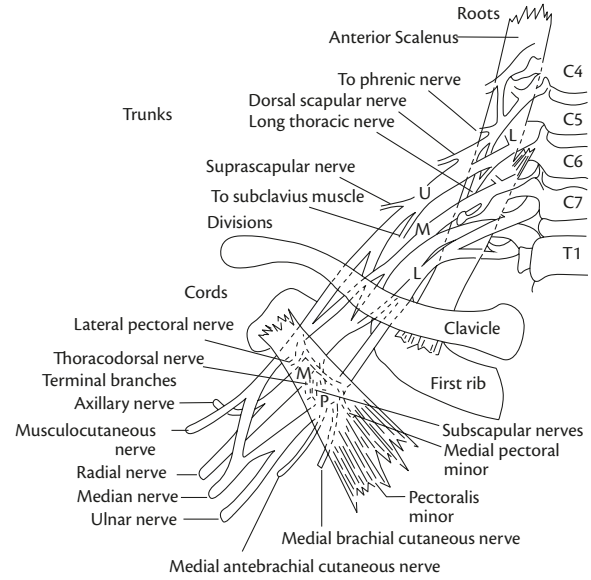


Fig. 220.4 Organization of the brachial plexus as the five cervical roots give rise to three trunks, three anterior, and three posterior divisions, three cords and the terminal branches that give rise to the major nerves of the arm, forearm, and hand.
Reproduced from Giddins G, 'Brachial Plexus Injuries'. In: Bulstrode C et al. (eds), *Oxford Textbook of Trauma and Orthopaedics*, 2nd edn, 2011, figure 12.26, with permission from Oxford University Press.

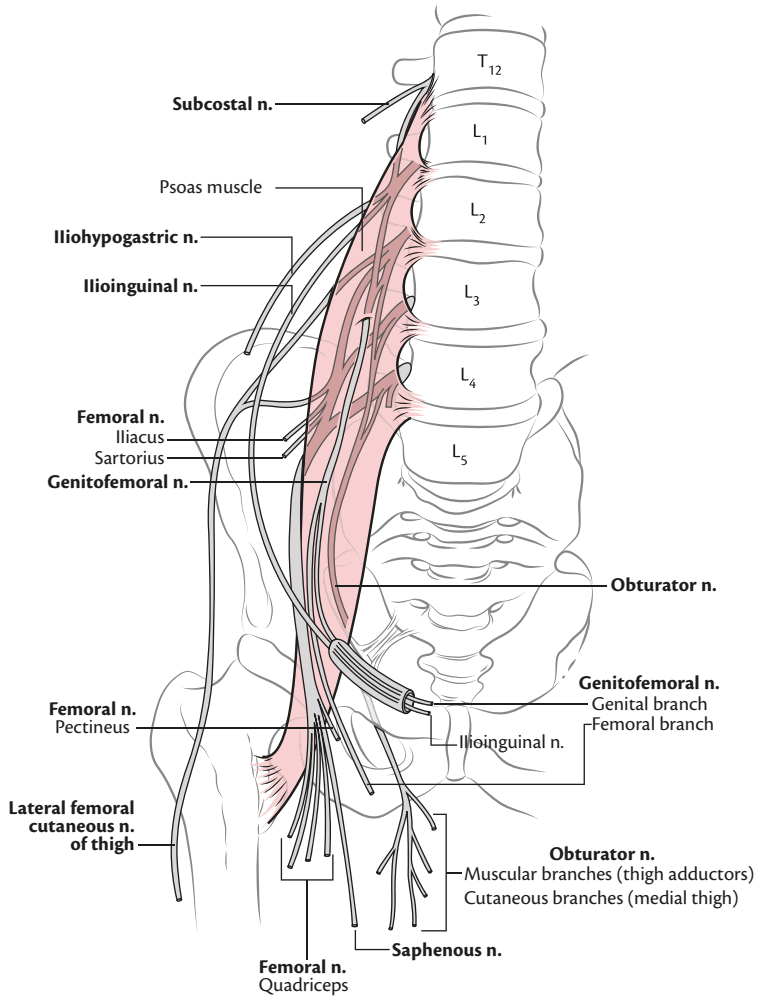


Fig. 220.5 The lumbar plexus.
Reproduced from AA Leis and MP Schenk (editors), *Atlas of Nerve Conduction Studies and Electromyography*, Second Edition, 2012, Figure 24.1, by permission of Oxford University Press, USA.

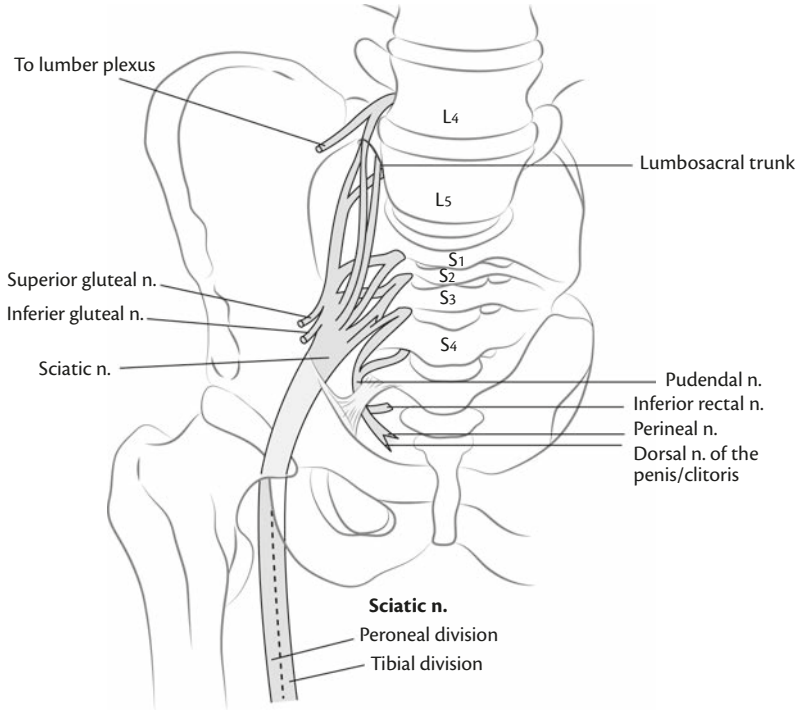


Fig. 220.6 The sacral and coccygeal plexus.
Reproduced from AA Leis and MP Schenk (editor), *Atlas of Nerve Conduction Studies and Electromyography*, Second Edition, 2012, Figure 17.1, by permission of Oxford University Press, USA.

Conclusion

The spinal cord, together with the peripheral nervous system, forms a predictable organized network that allows localization of disease through the distribution of symptoms and signs, both at a gross anatomical level and at the level of specific tracts and nerve fibres.

References

1. Sinnatamby CS. (2011). *Last's Anatomy: Regional and Applied*, 12th edn. London: Elsevier.
2. Moore KL, Agur AMR, and Dalley AF. (2011). *Essential Clinical Anatomy*, 4th edn. Baltimore: Lippincott Williams & Wilkins.

PART 9.2

Neurological monitoring

CHAPTER 221

Electroencephalogram monitoring in the critically ill

Paul M. Vespa

Key points

- Electroencephalography (EEG) monitoring produces a large quantity of data over a long time period and expertise is required for its interpretation.
- EEG monitoring can assist in detecting brain ischaemia and seizures, monitoring depth of sedation, and in improving prognostication.
- The use of cEEG in critically-ill patients with non-traumatic or traumatic brain haemorrhage may be considered the standard of care, given the high incidence of seizures and the marked adverse effects of seizures in this clinical scenario.
- Commercially available software packages that process EEG data can simplify EEG monitoring, but often the raw EEG data must be inspected to ensure accurate interpretation.

Introduction

The critical care of patients with acute neurological injury is frequently dependent on neurological monitoring of the brain. Soon after a brain injury, the brain experiences increased vulnerability to secondary insults. These insults include cytotoxic brain oedema, repeat ischaemia, fever-related injury, and seizures. Monitoring intracranial pressure and cerebral oxygenation have become common in recent years, but ideally the fundamental concept is to monitor brain function. Brain monitoring can detect important changes in brain physiology and function that can be affected by direct medical or surgical intervention. Electroencephalography (EEG) monitoring, conventionally known as continuous EEG monitoring (cEEG), is the predominant monitor of brain function. This chapter considers the fundamentals of cEEG monitoring, and will focus on these points:

- The fundamentals of EEG for the intensivist.
- Seizures detection after haemorrhagic brain injury and coma.
- The pathophysiological response of seizures after brain injury.
- The detection of seizures by visual inspection of the raw EEG and/or processed EEG.
- Treatment of status epilepticus by rapid identification and abolition of seizures using cEEG.
- The use of quantitative EEG to detect brain ischaemia and seizures, to monitor sedation, and to aid prognosis.

The fundamentals of EEG for the intensivist

EEG is a well-established method of monitoring brain electrical activity that is conceptually similar to electrocardiography. The brain has a fundamental rhythm much like the heart's normal sinus rhythm. In contrast to the heart, the brain's rhythm is variable and much faster than the normal heart beat, and usually has a frequency range of 4–20 cycles/second (Hertz). The normal brain rhythm looks much like ventricular fibrillation. The EEG usually speeds up when the patient is more alert, and slows down and has lower amplitude when the patient is more somnolent. When the patient is sedated, there is a lot of low amplitude activity in the 13–30 Hertz range, or beta activity. This beta activity is a sign that the brain is healthy and responding to the sedatives. Sleep activity occurs under normal conditions and the classic sign of sleep is the sleep spindle. In contrast to normal EEG rhythms, a seizure looks like ventricular tachycardia. Fig. 221.1a–e shows the main predominant features of EEG. Fundamentally, an EEG that has symmetry between right and left hemispheres, and is spontaneously variable over time and reactive to stimulation is considered to be normal. Epileptic seizures are repetitive discharges of spikes, which evolve over a short period of time, usually 1–2 minutes. A spike looks much like a paroxysmal atrial or ventricular complex from the ECG with a triphasic appearance (Fig. 221.1e).

Methods for cEEG monitoring in the ICU

cEEG is analogous to continuous ECG monitoring. cEEG is continuously displayed at the bedside, 24 hours per day, for moment-to-moment online observation by physicians and nurses (see Fig. 221.2). A physician trained in the interpretation of EEG reviews the ongoing EEG activity at the bedside at least three times each day and additionally, when requested, the bedside nurse observes suspicious EEG activity. Seizures are detected in one of three ways:

- On-line identification of seizures by the neuro-ICU nurse or neurointensivist.
- By the total power trend seizure detection method.
- By detection during regularly scheduled EEG segment review.

The date and time of the seizure, and the clinical behaviour noted by the bedside nurse or neurointensivist are recorded.

Commercial software packages for automated seizure detection exist. These methods make use of a processed EEG that provides

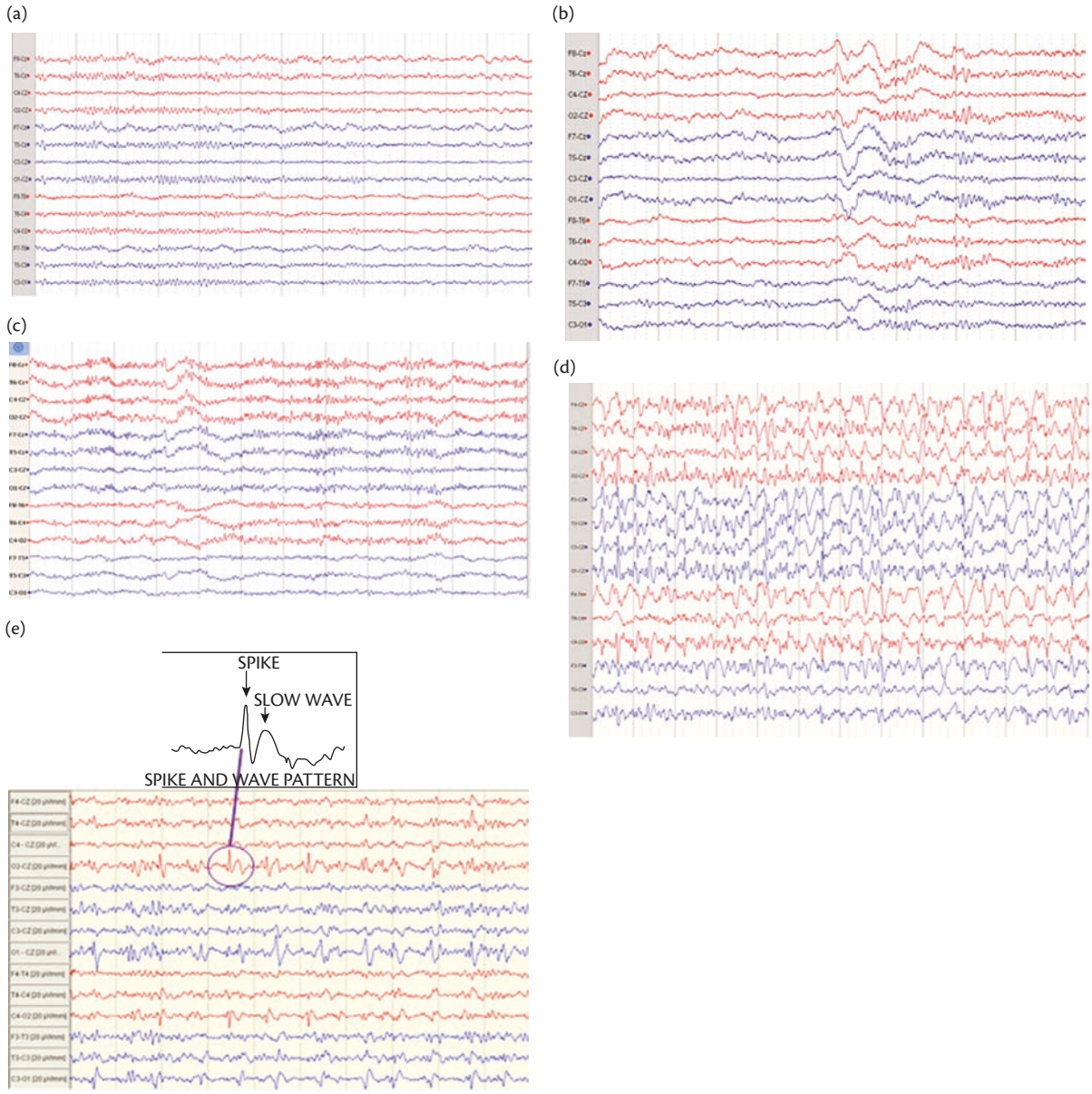


Fig. 221.1 Examples of basic EEG patterns. (a) An example 14-channel EEG segment demonstrating normal alpha rhythm in all electrodes. (b) An example of normal stage II sleep with sleep spindles shown across all electrodes. (c) The typical example of diffuse beta that occurs with deep sedation using propofol. (d) An example of a generalized non-convulsive seizure seen on cEEG. (e) A highlight showing the details of example spike and wave morphology that is seen with seizures. Red lines indicate the right side of the brain and blue lines indicated the left side of the brain.

trends of the waveforms, but most still require human interpretation of the raw EEG.

Seizure detection is based on the inspection of the raw EEG or the processed EEG. The seizure has a spike and wave morphology, which repeats over time and grows in amplitude and/or speed.

Quantitative EEG in the ICU

EEG is very labour intensive because it produces a lot of data that is collected over a long period of time. For most intensive care units (ICUs), there is a need for a summary of the EEG data over time, and a summary for non-experts to understand the current state of the brain with respect to several important questions:

- Is the brain ischaemic?
- Are seizures occurring?
- Is the patient sedated?
- Is the patient neurologically viable?

Quantitative EEG (qEEG) is generically a process to compress the EEG, and display the EEG in a temporal and spatial distribution along a timeline. The basic qEEG parameter is a compressed spectral

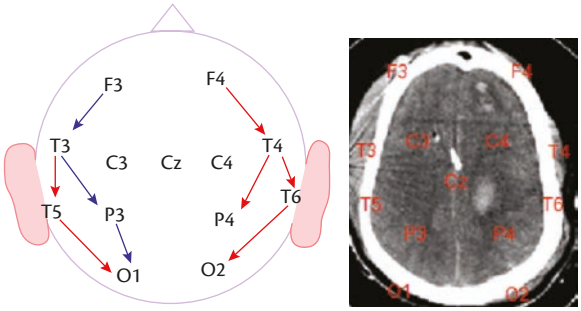


Fig. 221.2 An example of the nomenclature and localization of the electrodes used in ICU continuous EEG monitoring. The left scalp electrodes have odd numbers and the right scalp electrodes have even numbers. An example of a brain CT showing minimal artefact from scalp subdermal needle electrodes.

array (CSA), in which short EEG segments are separated into frequency bins and displayed as a function of the relative amount (or power) of each frequency. The CSA is then displayed in multiple formats by various manufacturers. Fig. 221.3 outlines the basic concept of converting EEG to CSA. In the most basic form, qEEG becomes a single number that represents an overall simplification of the EEG rhythms; this is the method used by the Bispectral Index (BIS) monitor. In the most complex methods, 5 or more qEEG parameters are presented simultaneously in a time series.

Quantitative EEG in brain ischaemia

Classically, the analog EEG becomes abnormal when cerebral blood flow falls below 20–25 cm^3/100 g/min. However, subtler signs of ischaemia at higher blood flows have been seen using raw EEG. These signs include, in order of appearance:

- A loss of fast beta frequencies (12–30 Hz).
- Slowing of background into 5–7 Hz theta frequencies.
- Slowing into the delta range (1–4 Hz).
- Flattening of the EEG with burst-suppression or continuous suppression.

Jordan and Stringer [1] found that hemispheric EEG slowing correlated with moderate to severe reductions in cerebral blood flow as determined by stable Xenon CT cerebral blood flow measurements.

qEEG measures, such as CSA and frequency analysis trending have proven more useful in acute ischaemic disease. CSA has an appeal to the non-neurologist since it requires less expertise to interpret and can convey large amounts of neurophysiological data in a concise manner.

Several studies of continuous or extended EEG monitoring in the acute phases of stroke have been performed. In patients with aneurysmal subarachnoid haemorrhage the ratio of alpha/(theta + delta) activity and alterations in total power were very sensitive to transient ischaemia caused by vasospasm. In patients following stroke, the percentage of alpha and delta activity correlates with reductions in CBF and cerebral metabolic rate for oxygen in the acute and subacute stages of stroke.

The percentage alpha activity trend variability may be a useful measure of the adequacy of blood flow in patients with aneurysmal subarachnoid haemorrhage. In asymptomatic patients with adequate blood flow, a variability (or fluctuation) of the trend is very evident. However, the percentage alpha trend variability decreases acutely with the onset of vasospasm-induced decreases in cerebral blood flow. With treatment and resolution of vasospasm, the percentage alpha trend variability returns to normal (Fig. 221.4). A comparison of the temporal changes in transcranial Doppler (TCD) velocities and the qEEG variables suggest that the increased TCD flow velocity that occurs in vasospasm can be predicted in advance by reductions in percentage alpha variability. Thus, the acute EEG and qEEG provide insightful information that can be integrated with other information to determine the state of cerebral blood flow and metabolism in the acutely-ill neurological patient.

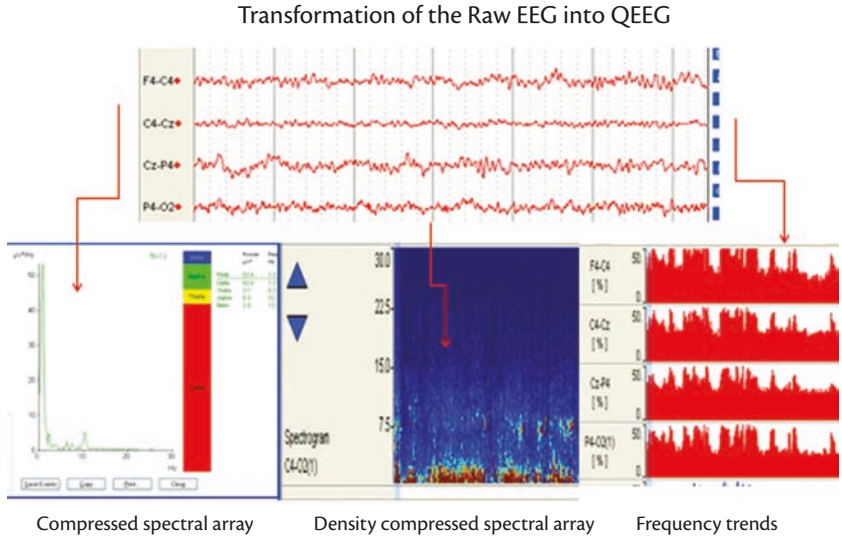


Fig. 221.3 A conceptual montage of images demonstrating how short segments of raw EEG (top) are automatically and periodically transformed using computer algorithms into quantitative EEG displays (bottom). Three potential quantitative displays are shown including: (bottom left) compressed spectral array [with a short duration of data from one electrode displayed as an integral based on frequency]; (bottom middle) compressed density spectral array [with long duration of data displayed as a function of time across the abscissa, frequency domain along the ordinate, and the power of each frequency conveyed as colour, with red indicating the highest power]; (bottom right) Frequency trends [with a single frequency band (alpha bandwidth) displayed as function of time across the abscissa and power across the ordinate.

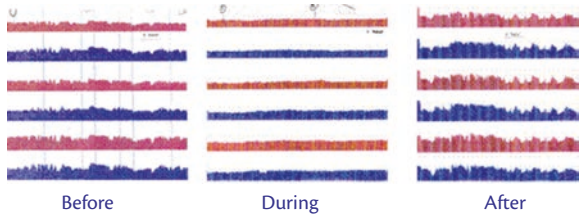


Fig. 221.4 An example of the percent alpha frequency trend changing over time as a function of cerebral vasospasm-related delayed cerebral ischaemia. Each segment shows an 8-hour trend of percent alpha. During spasm (middle) the percent alpha becomes invariant and indicates cerebral ischaemia. After spasm resolves, the percent alpha once again becomes variant (right) similar to baseline (left).

Reprinted from Electroencephalography and Clinical Neurophysiology, Vespa PM et al., 'Early detection of vasospasm after acute subarachnoid hemorrhage using continuous EEG ICU monitoring', 103, 6, pp. 607–615, Copyright 1997, with permission from Elsevier.

Similar findings have been reported by [2] for the alpha–delta ratio. The alpha–delta ratio appeared to be even more sensitive for the detection of delayed cerebral ischaemia.

Detection of seizures using qEEG

Seizures occur with relatively high frequency in comatose ICU patients, with estimates from between 8–12 % of patients with general medical critical illness, and 20–40% of patients with neurocritical illness. Automated seizure detection algorithms have been created to detect seizures, but most of these algorithms do not perform reliably in the ICU setting. Hence, qEEG is often used to enhance the ability to identify and detect seizures. Several qEEG methods have been used to detect seizures. The qEEG trends permit one to determine the timing, duration, repetition rate, and total duration of the seizures. However, each of the qEEG parameters is subject to contamination by artefact from muscle or high frequency non-seizure activity. Hence, it is critical to verify the seizure by examination of the raw EEG waveform. It is unclear which qEEG parameter is best for the detection of seizures. However, what is clear is that within a single subject, seizures usually have a typical morphology on the raw EEG and a typical qEEG appearance. This permits one to operationalize a particular qEEG pattern that can be monitored by the non-expert and treatment can be gauged according to the incidence of that qEEG marker.

Non-convulsive seizures in ICU patients

In an initial study of continuous EEG monitoring in a neuroscience ICU population in 124 patients with ICU admission diagnoses that included stroke, intracerebral haemorrhage, seizures, metabolic coma, brain tumours, and brain trauma, seizures occurred in 35% of the patients during the ICU course. Over 75% demonstrated non-convulsive seizures or non-convulsive status epilepticus. Seizures were not readily clinically diagnosed by obvious motor manifestations and the diagnosis required EEG evaluation. The duration of monitoring was determined by the incidence of epileptiform activity. The impact of the cEEG on clinical decision making was determined using the available EEG information in making the following decisions:

- Initiating or modifying anticonvulsants.
- Obtaining a CT or MRI scan.
- Adjusting cerebral perfusion or mean arterial blood pressure.

Overall, the cEEG was decisive in these decisions in 51% of patients, and made a significant contribution in the remaining 31% of patients. Thus, cEEG monitoring detected abnormal subclinical pathophysiology that could be treated and contributed directly to patient care in a large number (82%) of patients.

The incidence of non-convulsive seizures after traumatic brain injury has been recently established. In a seminal study Vespa et al. [3,4] used cEEG monitoring in patients with moderate and severe traumatic brain injury (GCS 3–12). Monitoring was performed for 7–10 days after injury, beginning at the time of admission to the intensive care unit. Electrographic seizures without clinical signs of convulsions were the most common form of seizure; 22% of 91 patients were found to have seizures, with a majority (57%) demonstrating non-convulsive seizure activity. Most seizures occurred within the initial week after the brain injury and the incidence of seizures was not affected by therapeutic phenytoin levels or by the withdrawal of ethanol, nor by the type of brain injury.

The incidence of seizures after brain ischaemia has relied upon studies of clinical signs of seizure activity. The incidence of clinically-defined seizures after bland ischaemia stroke varies from 5 to 17% The incidence of seizures after stroke increases with large territory ischaemic injury and with cardioembolic stroke. The use of cEEG after ischaemic stroke suggests that the incidence of non-convulsive seizures is much higher than detected in the previous studies, which are based on clinical signs of seizures.

The incidence of seizures after intracerebral haemorrhage has been noted to be higher than after ischaemic stroke. Immediate and early seizures occur in 2.8–18.7% of patients with the status epilepticus occurring in 1.1–2% of patients. In a recent study [5,6] the incidence of seizures detected by cEEG after intracerebral haemorrhage was 28% compared with 6% after ischaemic stroke. Using similar cEEG methods, Claassen [2] detected an 18% incidence rate of seizures in a mixed population of intracerebral haemorrhage, subarachnoid haemorrhage, and ischaemic stroke. Again, most seizures occurred within the first week after injury. Oddo et al. [7] have found a high incidence of seizures in septic patients in general ICUs. Hence, across many ICU populations, seizures are common neurological insults.

Seizures have been seen increasingly after cardiac arrest, especially in the era of more intensive treatment of these patients using therapeutic hypothermia. Once considered a hopeless condition, therapeutic hypothermia is being routinely applied to cardiac arrest patients. Several groups have performed continuous EEG monitoring during and after therapeutic hypothermia. The incidence rate of seizures ranges between 12 and 23% in recent studies and tend to occur during rewarming. Table 221.1 summarizes available studies on the incidence of seizures in selected neurocritical care populations.

Continuous EEG in prognosis

Prognosis remains one of the most significant questions for most comatose patients and methods to determine prognosis, such as brain imaging, neurological examination, and evaluation of serum biomarkers often are insufficient to render meaningful prognosis.

Table 221.1 This table lists available studies on the incidence of seizures in selected neurocritical care populations

Study on ICU cEEG	Number of patients	Seizure incidence (%)	Diagnostic groups
Jordan 1995 [9]	124	35	Coma from variety of diagnoses
Vespa 1999 [3]	94	22	TBI
Vespa 1999b [4]	300	21	TBI, SAH, I-C haemorrhage
Vespa 2003 [6]	63	28	I-C haemorrhage
Claassen (2004) [2]	204	17	SAH
Pandian (2004) [10]	105	42	Coma from variety of diagnoses
Young 2006 [11]	55	20	Coma from variety of diagnoses
Ronne-Engstrom (2006) [12]	70	33	TBI
Claassen (2007) [13]	102	28	I-C haemorrhage
Oddo (2009) [7]	201	22	Sepsis and medical ICU diagnoses
Vespa (1999) [3]	140	23	TBI
Rittenberger (2012) [14]	101	12	Cardiac arrest
Mani (2012) [15]	38	23	Cardiac arrest
Wusthoff (2011) [16]	26	65	Cardiac arrest

TBI, traumatic brain injury; SAH, subarachnoid haemorrhage; I-C haemorrhage, intracranial haemorrhage.

Data from various studies (see references).

EEG has a long track record of being useful for the determination of prognosis. Selected characteristics of raw EEG, such as the background rhythm and Synek scale, spontaneous variability and responsiveness stimulation have been used to assist in prognosis [8], but remain somewhat arbitrary and difficult to use due to a lack in inter-reader reliability and qualitative interpretation. qEEG is more objective, since it uses derived measures, and uses a larger amount of data that has been trended over time. Lack of variability in the CSA of comatose patients is a powerful predictive indicator of persistent unresponsiveness and lack of recovery after traumatic brain injury. More recently, the lack of variability over time of the percent alpha trend (PAV) during the initial 3 days after severe traumatic brain injury was found to have a high predictive value for clinical outcome at 1 month [17] and 6 months [18]. The PAV is very low in those patients who are destined to have a poor outcome, and the lack of improvement in the PAV over a few days also predicts a poor outcome. PAV trends are automatically created by modern EEG software, and can be useful in tracking improvement or lack of improvement in real time. A caveat in using PAV, as well as the other qEEG parameters, is that deep sedation can artificially reduce the variability in the PAV, and thus create a falsely poor PAV. Several other forms of qEEG may also be useful for prognosis.

Use of qEEG for sedation monitoring

qEEG may be used to monitor sedation in the ICU. The most commonly used modality is the BIS [19]. BIS is an algorithm-derived number that roughly indicates the degree of EEG activity when patients are under general anaesthesia. BIS ranges from 0 (brain dead) to 100 (normal brain function) and a value of <60 indicates general anaesthesia, and <30 indicating burst suppression. BIS has been used intra-operatively to monitor the effects of general anaesthesia, and has been specifically designed to detect the effects of inhalational anaesthetics. The application of BIS to ICU monitoring has been more controversial due to the inability of BIS to monitor non-inhalational sedatives and several case reports questioning its reliability in the ICU due to muscle artefact, machine interference, and lack of ability to detect seizures [20].

Apart from sedation monitoring, qEEG has been used to assist in deep sedation and barbiturate-induced coma. The burst suppression index is an example qEEG parameter that can be useful in titrating barbiturates.

Goal-directed treatment of seizures based on cEEG

Patients with seizures after brain haemorrhage or cerebral injury are prone to increased brain oedema, shift and elevated intracranial pressure [5,6]. These events occur during the initial week after injury, which overlaps with the peak incidence of post-traumatic seizures. Several principals of goal directed seizure treatment can be derived from the current literature:

- cEEG should be started immediately upon presentation of the brain injury or haemorrhage.
- Brain haemorrhage patients (traumatic or non-traumatic) have a higher risk than ischaemic stroke patients and should have priority for monitoring if resources are limited.
- Monitoring should continue for at least 5 days.
- The lack of clinical seizure activity is not an indication to avoid cEEG since the most seizures are non-convulsive.
- cEEG is a useful monitor for titration of anti-epileptic medications.

Conclusion

Anticonvulsants are typically quite effective at stopping the seizure activity when used as continuous infusions. However, the goal

for the duration of continuous infusion is not clear and recurrent seizures can occur when the continuous infusion is stopped, even when continued routine anticonvulsants are used. Goal-directed treatment using cEEG as a clinical guide has been reported to be effective in stopping seizures and led to an overall improvement in clinical outcome in a case-controlled cohort study [3,4]. The net effect on patient care was to improvement outcome, while decreasing length of stay and being cost neutral in the process.

References

1. Jordan, KG. (1993). Continuous EEG and evoked potential monitoring in the neuroscience intensive care unit. *Journal of Clinical Neurophysiology*, **10**(4), 445–75.
2. Claassen J, Mayer SA, Kowalski RG, Emerson RG, and Hirsch LJ. (2004). Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology*, **62**(10), 1743–8.
3. Vespa, PM, Nuwer, MR, Nenov, V, et al. (1999). Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous EEG in the intensive care unit. *Journal of Neurosurgery*, **91**, 750–60.
4. Vespa, PM, Nenov V, and Nuwer MR. (1999b). Continuous EEG monitoring in the Intensive Care Unit: Early findings and clinical efficacy. *Journal of Clinical Neurophysiology*, **16**(1), 1–13.
5. Vespa, P, McArthur, D, Glenn, T, et al. (2003). Persistently reduced levels of extracellular glucose early after traumatic brain injury correlate with poor outcome at six months: a microdialysis study. *Journal of Cerebral Blood Flow and Metabolism*, **23**, 865–77.
6. Vespa, P, O'Phelan, K, Mirabelli, J, et al. (2003). Acute seizures after intracerebral hemorrhage: A factor in progressive midline shift and outcome. *Neurology*, **60**, 1441–6.
7. Oddo M, Carrera E, Claassen J, Mayer SA, and Hirsch LJ. (2009). Continuous electroencephalography in the medical intensive care unit. *Critical Care Medicine*, **37**(6), 2051–6.
8. Boccagni C, Bagnato S, Sant Angelo A, Prestandrea C, and Galardi G. (2011). Usefulness of standard EEG in predicting the outcome of patients with disorders of consciousness after anoxic coma. *Journal of Clinical Neurophysiology*, **28**(5), 489–92.
9. Jordan KG. (1995). Neurophysiologic monitoring in the neuroscience intensive care unit. *Neurologic Clinics*, **13**(3), 579–626.
10. Pandian JD, Cascino GD, So EL, Manno E, Fulgham JR. (2004). Digital video-electroencephalographic monitoring in the neurological-neurosurgical intensive care unit: clinical features and outcome. *Archives of Neurology*, **61**(7), 1090–4.
11. Young GB. (2006). Nonconvulsive seizures and electroencephalogram monitoring in the intensive care unit. Advances in Neurology, **97**, 221–7.
12. Ronne-Engstrom E, Winkler T. (2004). Continuous EEG monitoring in patients with traumatic brain injury reveals a high incidence of epileptiform activity. *Acta Neurologica Scandinavica*, **114**(1), 47–53.
13. Claassen J, Jetté N, Chum F, et al. (2007). Electrographic seizures and periodic discharges after intracerebral hemorrhage. *Neurology*, **69**(13), 1356–65.
14. Rittenberger JC, Popescu A, Brenner RP, Guyette FX, and Callaway CW. (2012). Frequency and timing of nonconvulsive status epilepticus in comatose post-cardiac arrest subjects treated with hypothermia. *Neurocritical Care*, **16**(1), 114–22.
15. Mani R, Schmitt SE, Mazer M, Putt ME, Gaieski DF. (2012). The frequency and timing of epileptiform activity on continuous electroencephalogram in comatose post-cardiac arrest syndrome patients treated with therapeutic hypothermia. *Resuscitation*, **83**(7), 840–7. doi: 10.1016/j.resuscitation.2012.02.015. Epub 2012 Feb 23.
16. Wusthoff CJ, Dlugos DJ, Gutierrez-Colina A, et al. (2011). Electrographic seizures during therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy. *Journal of Child Neurology*, **26**(6), 724–8.
17. Vespa, P, Martin, NA, Nenov, V, et al. (2002). Delayed increase in extracellular glycerol with post-traumatic electrographic epileptic activity: support for the theory that seizures induce secondary injury *Acta Neurochirugia*, **81**(Suppl.), 355–7.
18. Hebb MO, McArthur DL, Alger J, et al. (2007). Impaired percent alpha variability on continuous electroencephalography is associated with thalamic injury and predicts poor long-term outcome after human traumatic brain injury. *Journal of Neurotrauma*, **24**(4), 579–90.
19. Klopman MA, Sebel PS. (2011). Cost-effectiveness of bispectral index monitoring. *Current Opinion in Anesthesiology*, **24**(2), 177–81.
20. Duarte LT and Saraiva RA. (2009). When the bispectral index (BIS) can give false results. *Revue Brasilia Anestesiologica*, **59**(1), 99–109.

CHAPTER 222

Cerebral blood flow and perfusion monitoring in the critically ill

Samson Sujit Kumar Gaddam and Claudia S. Robertson

Key points

- Prevention of secondary cerebral ischaemic insults is an important strategy in the management of acute neurological conditions. Monitoring of cerebral perfusion may aid in early identification of ischaemic insults and help in the management.
- Cerebral perfusion pressure (CPP) is a simple way of assessing cerebral perfusion, but in some cases ischaemia can be present even with a normal CPP.
- CBF imaging, either with stable xenon CT or other CT and MRI techniques, can provide quantitative regional cerebral blood flow (CBF) measurement, but only at a single instance in time and are difficult to use in managing critically-ill patients.
- CBF can be measured in the intensive care setting, either directly or indirectly, through measurement of cerebral oxygenation.
- Some of the tools monitor global perfusion and some assess only regional perfusion in a local area of brain surrounding the monitor. With these local monitors, the location of the probe is important in interpretation of the findings.

Introduction

Cerebral pathological conditions such as traumatic brain injury (TBI) and stroke can result in significant morbidity and mortality. The various biochemical cascades that follow primary brain injury lead to secondary brain injury resulting in raised intracranial pressure and decreased cerebral perfusion. Current critical care management of TBI and stroke involves monitoring of cerebral physiological parameters such as cerebral blood flow (CBF) and cerebral oxygenation, which may help in early recognition and treatment of secondary brain injury.

Cerebral blood flow and perfusion

Knowledge of the characteristics of cerebral circulation in normal individuals is pivotal to the understanding of CBF and cerebral metabolism in pathological states. CBF can be represented by one of the following formulas:

$$CBF = CPP/CVR \quad \text{[eqn 1]}$$

$$CBF = (k \times CPP \times d^4)/(8 \times l \times v) \quad \text{[eqn 2]}$$

where CPP is cerebral perfusion pressure, which is equal to mean arterial pressure (MAP) minus intracranial pressure (ICP), CVR is cerebral vascular resistance, k is a constant, d is the diameter of the vessel, l is length of the vessel, and v is blood viscosity. CBF is normally regulated by cerebral metabolic rate and is also affected by CPP and arterial PCO_2. Normal CBF is 55 mL/100 g/min (gray matter = 75–80 mL/100 g/min, white matter = 20–30 mL/100 g/min).

Cerebral metabolism is entirely dependent on the oxidation of glucose and requires a constant supply of oxygen. Cerebral metabolic rate of oxygen ($CMRO_2$) is given by the following formula:

$$CMRO_2 = CBF \times AVDO_2 \quad \text{[eqn 3]}$$

where $AVDO_2$ is the arteriojugular venous difference of oxygen content. $CMRO_2$ is kept constant under most conditions at an average 3.2 mL/100 g/min (1.5 μmol/g/min). In normal states CBF is tightly coupled to $CMRO_2$ and CBF increases or decreases based upon the local metabolic requirements of brain tissue. This coupling is mediated by metabolic variables like PO_2, PCO_2, extracellular pH, adenosine, extracellular potassium ion concentration, and nitric oxide. However, in pathological states such as TBI and stroke, there can be uncoupling of CBF and $CMRO_2$.

Cerebral blood flow and perfusion monitoring

The available monitoring techniques for CBF measure flow directly or indirectly by assessing the relative adequacy of CBF through estimation of cerebral oxygenation. Measurement of CPP is the most widely used method to assess CBF. It involves continuous invasive monitoring of arterial blood pressure and ICP. An increase in ICP or a decrease in MAP can result in reduction in CBF causing ischaemia of the injured brain. The guidelines for management of severe head injury recommend CPP to be maintained at a minimum of 60 mmHg [1]. However, in states of impaired autoregulation such as TBI, cerebral perfusion may be inadequate despite a CPP of 60 mmHg, and other monitoring techniques may be useful to supplement assessment of cerebral perfusion.

Other available methods of measuring CBF, including stable xenon-enhanced computed tomography (CT), single photon emission computed tomography (SPECT), perfusion CT, perfusion

magnetic resonance imaging (MRI), and positron emission tomography (PET) provide intermittent measurements of flow. Although PET provides accurate and valuable quantification of physiological and metabolic parameters like CBF, $CMRO_2$, and oxygen extraction fraction after intravenous ^{15}O-radioisotope administration, cost-effectiveness, radiation-exposure, and the need to transport the patient are major impediments to its clinical usefulness [2]. Perfusion CT uses infusion of iodinated contrast and collection of serial sequences of images using a helical CT scanner. Each image is then subtracted from a baseline image to develop a time-enhancement curve. In addition to providing quantification of both global and regional CBF, it allows determination of vasomotor reactivity. Perfusion-weighted MRI is helpful in identifying ischaemic regions, but it can be time-consuming and challenging to scan critically-ill patients in an MRI suite. SPECT provides semi-quantitative data on CBF by measuring the localization of ^{99m}Tc radioisotope in the brain tissue. Abnormal areas are compared with the contralateral side or the cerebellum, and relative CBF is calculated. It is useful in the management of patients with acute stroke, vasospasm, and occlusive vascular disease. Measurement of both global and regional CBF with stable xenon CT imaging (inhalation of 28–33% xenon) is also feasible, but these techniques provide only intermittent data, are inaccurate in pulmonary disorders, and are not widely available except for research purposes [2,3]. Like PET all imaging studies require transportation of the patient to the imaging suite.

Thermal diffusion flowmetry (TDF) and laser Doppler flow (LDF)

These allow continuous monitoring of CBF at the bedside. These methods are invasive and require placement of a probe on the surface of or within the brain. Attention to the placement of probes in the region of interest is crucial as these devices detect only the changes occurring in the surrounding brain tissue. TDF measures regional blood flow by calculating the temperature difference between a neutral plate and a heated element (two gold disks or two bands). TDF correlates well with stable xenon CT results and has been reported to help in early detection of neurological deterioration [4]. LDF measures erythrocyte flux and then calculates CBF [5]. It has been used in monitoring of patients with ischaemic insults and is also useful in assessing autoregulation. Potential risks of invasive techniques include complications such as bleeding, infection, and displacement of the probe.

Transcranial Doppler (TCD) ultrasonography

This provides a non-invasive means of real time bedside measurement of flow velocity (FV) from the major intracerebral vessels such as the middle cerebral artery (MCA). FV is directly proportional to flow and inversely proportional to cross-sectional area of the vessel, and can be used as an indicator of CBF as long as vessel diameter does not change [6]. Some studies have shown close correlation between changes in MCA flow velocities and stable xenon CT CBF values [7]. However, an increase in FV could be due to a decrease in vessel diameter (such as that which occurs with cerebral arterial vasospasm) or to an increase in CBF (hyperaemia). The MCA to extracranial internal carotid artery flow velocity ratio (known as the Lindegaard ratio or hemispheric index) is used to differentiate between these two conditions [8]. Normal hemispheric index is 1.76 ± 0.1 and values above 3 are suggestive of vasospasm. TCD is also used to assess cerebral autoregulation and confirm brain death [9]. One limitation is that the temporal ultrasonic window that is normally used for TCD study is absent in 5–10% of patients.

Monitoring of CBF alone may not be sufficient in a critical care setting as the relative adequacy of blood flow cannot be determined based on absolute values of CPP or CBF. For example, when CBF is low (25–30 mL/100 g/min), the brain is either hypoperfused or there is a reduced cerebral metabolic requirement. Which of these two conditions exists can be determined by measurement of cerebral oxygenation using techniques such as measurement of jugular venous oxygen saturation ($SjvO_2$) or brain tissue oxygenation ($PbtO_2$).

Global cerebral oxygenation

This can be monitored by insertion of a fibre optic $SjvO_2$ catheter into the jugular vein and positioning the tip of the catheter in the jugular bulb. In normal young males, $SjvO_2$ ranges from 55 to 71% (mean 61.8%). In patients with brain injury, $SjvO_2$ is typically higher than normal and averaged $68.1 \pm 9.7\%$ in large series [10–12]. Current guidelines for the management of TBI recommend maintaining a $SjvO_2$ of at least 50% [1]. There is some controversy over optimal placement of the $SjvO_2$ catheter since jugular venous blood is incompletely mixed. Stocchetti et al. [13] found differences between the values of $SjvO_2$ measured from right and left jugular bulbs. Metz et al. [14] based on their study of bilateral $SjvO_2$ in 22 patients recommended that the catheter should be placed on the dominant side in diffuse injury and on the ipsilateral side when the injury is focal. The potential complications with $SjvO_2$ monitoring include carotid puncture, injury to nerves in the neck, pneumothorax, infection, and venous thrombosis. Although $SjvO_2$ is useful as a measure of global cerebral oxygenation, it cannot identify regional cerebral ischaemia and has low sensitivity. PET studies have shown that approximately 13% of brain tissue must be affected before $SjvO_2$ levels drop below 50% [15].

Local cerebral oxygenation

This can be measured with two techniques, brain tissue PO_2 ($PbtO_2$) and near infrared spectroscopy (NIRS). $PbtO_2$ is measured by a catheter (Clark electrode) placed into the brain tissue. Normal values for $PbtO_2$ are 20–40 mmHg. As the brain tissue oxygenation is measured only in the tissue directly surrounding the tip of the catheter, the placement of the catheter is very important. When the probe is placed in normal brain tissue, the values closely parallel global oxygenation, but when the probe is positioned in injured tissue, the values reflect local oxygenation and can vary substantially from global oxygenation. Current guidelines for the management of TBI recommend treatment of $PbtO_2$ values less than 15mm Hg [1]. Clinical studies have shown increased mortality and morbidity in TBI patients with low $PbtO_2$ [16]. Spiotta et al. [17] found improvement in outcome and mortality with $PbtO_2$-guided therapy when compared with conventional ICP/CPP management in patients with severe TBI.

Near infrared spectroscopy

NIRS is a bedside, real-time transcranial method used for continuous monitoring of local cerebral oxygenation [18]. It measures near infrared light (650–1100 nm) reflected from haemoglobin

molecules based on the oxygenation state and calculates regional oxygen saturation (rSO_2) from the attenuation of the light. The probe is usually placed over the forehead and needs to be in contact with the scalp for optimal reading. NIRS readings are influenced by ambient light, thickness of scalp and bone, presence of blood, and amount of melanin in the skin. It has been shown to be a useful modality in monitoring patients undergoing cardiopulmonary bypass surgery [19], carotid endarterectomy and in cerebral autoregulation assessment. Various studies have evaluated the use of NIRS in patients with brain trauma and subarachnoid haemorrhage. NIRS oxygen saturation (rSO_2) has been shown to correlate well with $SjvO_2$ in some TBI studies. Dunham et al. [20] observed that rSO_2 greater than 75% suggested an adequate CPP and rSO_2 less than 55% suggested an inadequate CPP.

Intracerebral microdialysis

This is used to monitor the metabolic products in brain. Biochemical parameters, such as energy substrates (glucose and pyruvate), metabolic products (lactate), neurotransmitters, glycerol, and potassium can be measured. Elevated lactate/pyruvate ratio is associated with fatal outcome after TBI. Glycerol levels are elevated in severe TBI. Neurotransmitters such as glutamate are elevated following TBI and seizures. As with $PbtO_2$ catheters, microdialysis probes only measure metabolic products in the tissue immediately around the catheter tip, and require knowledge of the position of the catheter for correct interpretation of the findings.

Acknowledgements

We are grateful to Thomas Buell, who helped with the preparation of this chapter. The work was supported by NIH grant #P01-NS38660.

References

1. (2007). Guidelines for the management of severe traumatic brain injury. *Journal of Neurotrauma*, **24**(Suppl. 1), S1–106.
2. Coles JP, Fryer TD, Smielewski P, et al. (2004). Incidence and mechanisms of cerebral ischemia in early clinical head injury. *Journal of Cerebral Blood Flow and Metabolism*, **24**, 202–11.
3. Dagal A and Lam AM. (2011). Cerebral blood flow and the injured brain: how should we monitor and manipulate it? *Current Opinion in Anaesthesiology*, **24**, 131–7.
4. Lee SC, Chen JF, and Lee ST. (2005). Continuous regional cerebral blood flow monitoring in the neurosurgical intensive care unit. *Journal of Clinical Neuroscience*, **12**, 520–3.
5. Bhatia A and Gupta AK. (2007). Neuromonitoring in the intensive care unit. I. Intracranial pressure and cerebral blood flow monitoring. *Intensive Care Medicine*, **33**, 1263–71.
6. Molina CA and Alexandrov AV. (2007). Transcranial ultrasound in acute stroke: from diagnosis to therapy. *Cerebrovascular Diseases*, **24**(Suppl. 1), 1–6.
7. Kofke WA, Brauer P, Policare R, Penthany S, Barker D, and Horton J. (1995). Middle cerebral artery blood flow velocity and stable xenon-enhanced computed tomographic blood flow during balloon test occlusion of the internal carotid artery. *Stroke*, **26**, 1603–6.
8. Lindegaard KF. (1999). The role of transcranial Doppler in the management of patients with subarachnoid haemorrhage—a review. *Acta Neurochirugia*, **72**(Suppl.), 59–71.
9. Sharma D, Souter MJ, Moore AE, and Lam AM. (2011). Clinical experience with transcranial Doppler ultrasonography as a confirmatory test for brain death: a retrospective analysis. *Neurocritical Care*, **14**, 370–6.
10. Gopinath SP, Robertson CS, Contant CF, et al. (1994). Jugular venous desaturation and outcome after head injury. *Journal of Neurology, Neurosurgery and Psychiatry*, **57**, 717–23.
11. Robertson CS, Gopinath SP, Goodman JC, Contant CF, Valadka AB, and Narayan RK. (1995). SjvO2 monitoring in head-injured patients. *Journal of Neurotrauma*, **12**, 891–6.
12. Cormio M, Valadka AB, and Robertson CS. (1999). Elevated jugular venous oxygen saturation after severe head injury. *Journal of Neurosurgery*, **90**, 9–15.
13. Stocchetti N, Paparella A, Bridelli F, Bacchi M, Piazza P, and Zuccoli P. (1994). Cerebral venous oxygen saturation studied with bilateral samples in the internal jugular veins. *Neurosurgery*, **34**, 38–43.
14. Metz C, Holzschuh M, Bein T, et al. (1998). Monitoring of cerebral oxygen metabolism in the jugular bulb: reliability of unilateral measurements in severe head injury. *Journal of Cerebral Blood Flow and Metabolism*, **18**, 332–43.
15. De Georgia MA, and Deogaonkar A. (2005). Multimodal monitoring in the neurological intensive care unit. *Neurologist*, **11**, 45–54.
16. Valadka AB, Gopinath SP, Contant CF, Uzura M, and Robertson CS. (1998). Relationship of brain tissue PO_2 to outcome after severe head injury. *Critical Care Medicine*, **26**, 1576–81.
17. Spiotta AM, Stiefel MF, Gracias VH, et al. (2010). Brain tissue oxygen-directed management and outcome in patients with severe traumatic brain injury. *Journal of Neurosurgery*, **113**, 571–80.
18. Calderon-Arnulphi M, Alaraj A, and Slavin KV. (2009). Near infrared technology in neuroscience: past, present and future. *Neurological Research*, **31**, 605–14.
19. Vohra HA, Modi A, and Ohri SK. (2009). Does use of intra-operative cerebral regional oxygen saturation monitoring during cardiac surgery lead to improved clinical outcomes? *Interactive Cardiovascular and Thoracic Surgery*, **9**, 318–22.
20. Dunham CM, Sosnowski C, Porter JM, Siegal J, and Kohli C. (2002). Correlation of noninvasive cerebral oximetry with cerebral perfusion in the severe head injured patient: a pilot study. *Journal of Trauma*, **52**, 40–6.

CHAPTER 223

Intracranial pressure monitoring in the ICU

Jonathan K. J. Rhodes and Peter J. D. Andrews

Key points

- Intracranial pressure (ICP) monitoring is an established monitoring modality in intensive care unit.
- It can aid prognostication after severe brain injury.
- Measurement of ICP can warn of life-threatening deterioration.
- Control of ICP and management of CPP can help maintain oxygen delivery to the brain.
- Further research into the efficacy of ICP monitoring, including defining treatment thresholds (ICP and CPP) and effectiveness of associated reduction therapies is urgently required.

Monro–Kellie doctrine

Alexander Monro (1733–1817), professor of Anatomy at the University of Edinburgh Medical School, and his former pupil George Kelly of Leith (1758–1829), initiated the doctrine that now bears their names. This states that the sum of the volumes of brain tissue, cerebrospinal fluid (CSF) and intracranial blood is constant. An increase in one should cause a decrease in one or both of the remaining two [1].

This doctrine predicts that in the presence of a space-occupying lesion in or around the brain, such as a haematoma, contusion, swelling around an area of infarction or the presence of diffuse swelling of the brain itself, blood, and CSF volume will reduce, and a pressure rise within the rigid skull will be prevented.

The significance of the Monro–Kellie doctrine is that in practice the volume compensation possible due to blood and CSF redistribution can be extremely limited. Prior to the exhaustion of this compensation an increase in volume results in a very limited increase in intracranial pressure (ICP) and, compliance (Δ volume/Δ pressure) is high. However, once this is exhausted, marked increases in ICP occur after volume changes of only a few cubic centimetres. Compliance is then said to be low (Fig. 223.1).

Normal ICP is position dependent. For a subject in the horizontal position, ICP can be 10–15 mmHg. When the subject is upright it decreases and can have a negative value (–5 mmHg) relative to the foramen of Monro. Following brain injury, swelling may obstruct the normal CSF pathways within and surrounding the brain, preventing even redistribution of pressure within the intracranial compartment. With increasing ICP a pressure gradient can then develop within the skull, causing brain contents to shift or herniate from high to low pressure areas, either within the supporting dura or down through the foramen magnum. This can cause irreversible structural brain damage and is a common cause of brain death. Increased ICP can also compromise cerebral perfusion, leading to ischaemia, further swelling due to oedema, and a cycle of increasing ICP.

In many centres, the measurement and monitoring of intracranial pressure has therefore become an integral part of the early management of patients with acute brain injury. A continuous display of ICP can providing an early warning of evolving pathology, allowing urgent control measures to prevent herniation. The calculation of cerebral perfusion pressure (CPP, calculated as the mean arterial pressure (MAP) minus the ICP) is also fundamental to the maintenance of cerebral blood flow and prevention of secondary ischaemic insults, which can adversely affect outcome.

Techniques for ICP measurement

ICP can be measured by a variety of methods. In 2007, the Brain Trauma Foundation concluded that, 'the ventricular catheter connected to an external strain gauge is the most accurate low-cost and reliable method for monitoring intracranial pressure' [2]. However the economic comparisons of devices, including disposables and bedside monitors, is unlikely to have included the costs associated with placement in an operating room, which is mandatory for ventricular devices. The measurement of ICP through a ventricular catheter coupled via a fluid-filled line to an external strain gauge is analogous to the more familiar transduction of arterial or central venous pressure. Intraventricular catheter systems allow treatment of ICP by draining CSF, sampling of CSF for diagnosis or research, and these systems can be recalibrated after insertion. However, if ventricular blood load is heavy they can become occluded with clot. Furthermore, if the ventricles are effaced or collapsed due to intracranial pathology placement might not be possible.

Microstrain gauge, pneumatic, and fibre optic devices also exist that can be placed either into the ventricular system or brain parenchyma. Parenchymal placement is technically simpler and may be performed by non-surgical specialists, outside the operating room environment. However microstain gauge and fibre optic systems cannot be recalibrated without removal making drift from a zero (atmospheric pressure) baseline not assessable. Another consideration is that of MRI compatibility, as not all available systems are specified MRI safe.

Haematoma formation associated with ICP monitoring is described with an incidence of 11% in one series [3]. However,

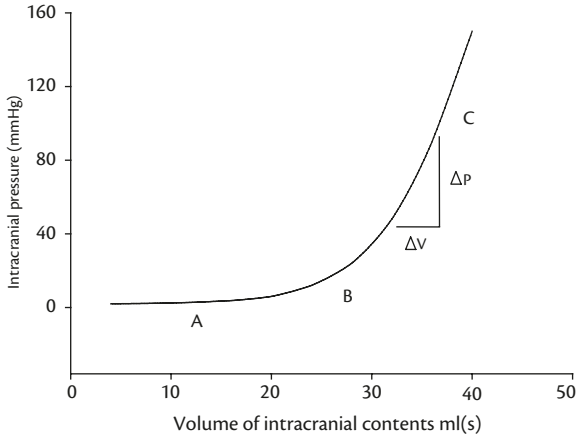


Fig. 223.1 Intracranial pressure–volume relationship. In health, when ICP is normal, an increase in the volume of the intracranial contents can be accommodated without an increase in ICP, region A. However, this accommodation is limited and soon a point of decompensation is reached, point B. Thereafter, further increases in volume result in large increases in ICP, region C. In region A compliance (ΔV/ΔP) is high. In region C compliance is low. The inverse of compliance is elastance (ΔP/ΔV).

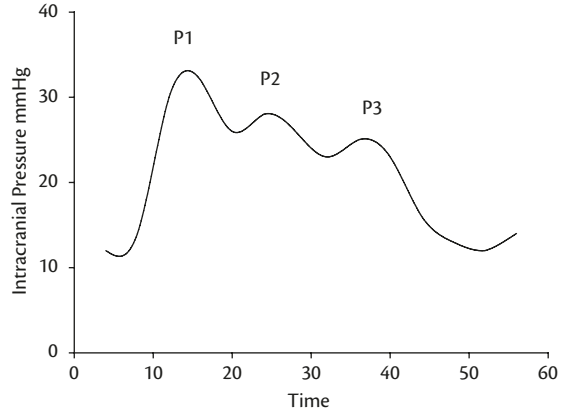


Fig. 223.2 Component parts of an ICP wave. The first (P1) reflects the arterial pressure wave transmitted into the CNS through the choroid plexus. The second peak (P2) is due to mass transport of blood with each cardiac cycle. The final peak is the dicrotic notch and represents the closing of the aortic valve. With reducing intracranial compliance the amplitude of P2 increases to match and then exceed that of P1.

clinically significant bleeding requiring surgical intervention is much less common, with a published incidence of 0.5% [2]. Correction of coagulation defects is an essential prerequisite to the placement of an ICP monitor. The risk of infection should also be considered and thorough asepsis at placement is essential. Culture positive probe tips have been reported in up to 17% of cases [4]. However, clinically significant infection is much rarer, and was only seen in patients with ventricular placement where ventriculitis was a risk [4]. This risk is thought to increase with duration of catheter placement and for intraventricular systems, repeated CSF sampling. The frequency of regular CSF culture for infection surveillance needs to be balanced against the risk of repeated CSF access. In clinical practice, CSF surveillance varies from none to, every 48 hours or daily if infection is suspected.

ICP waves

In addition to the determination of a value for ICP at any single moment, in order to avoid herniation and reduced CBF, the display and analysis of the ICP waveform, and its trends with time can add further valuable information.

The normal ICP wave contains three component parts (Fig. 223.2). As intracranial pressure increases the amplitude of the ICP wave form also increases. With each cardiac cycle there is a transient increase in CBV. When ICP increases and the compliance of the volume–pressure relationship is low, this increase in volume causes an increasingly large pressure change with each left ventricular systole. The amplitude of the ICP wave therefore increases. Ultimately at the upper inflection point of the volume pressure relationship the amplitude of the ICP wave is reduced. At this point ICP approximates to mean arterial pressure (MAP) and so CPP is very low. Further increases in ICP collapse the cerebral arterial bed limiting the increase in blood volume and so amplitude falls [5].

In 1964 Nils Lundberg, using a ventricular cannula attached to an external strain gauge, recorded the changes in ICP with time in non-ventilated patients with chronic pathologies. He also observed that following TBI increases in ICP were associated with clinical deterioration, that ICP recording could be used to rationalize management and he described a series of characteristic waves present in the ICP trends [6]. Lundberg 'A' waves or 'plateau waves' have an amplitude of 50–100mmHg and last 5–20 minutes. The generation of these waves is thought to be due to an exaggerated attempt to maintain CBF in the presence of reduced intracranial compliance or may be due to vasomotor centre instability. A spontaneous reduction in cerebral perfusion pressure will lead to vasodilatation to maintain CBF. The increase in CBV will increase ICP and so lower CPP once more. This cycle continues until vasodilatory capacity is exhausted. If a Cushing's response due to brain stem ischaemia increases MAP or treatment is given to lower ICP, CPP can be restored and the plateau can be terminated. With restoration of CPP cerebral blood flow improves, followed by vasoconstriction, reduced CBV and lowering of ICP and therefore further improvement in CPP (Fig. 223.3). 'B' waves are oscillating waves with an amplitude up to 50 mmHg and a frequency of 0.5–2/min. At low amplitude (<30 mmHg) they are thought to represent physiological cyclical oscillations in CBF due to respiratory cycling altering cardiac output. A fall in cardiac output reduce CBF leading to vasodilatation as part of physiological autoregulation. CBV will increase and ICP will increase. As cardiac output and CBF increase the cycle reverses with vasoconstriction reducing CBV and, hence, ICP again. Thus, CBF is maintained about a mean with small oscillations and corresponding changes in ICP. An alternative explanation is that these oscillations are primarily driven by tissue metabolism regulating cerebral blood flow. Accumulation of metabolic products at a tissue level will increase CBF due to vasodilatation, and so CBV and ICP increase. As the metabolic load is 'washed out' vasoconstriction occurs, and CBF, CBV, and hence ICP decreases. Whatever the exact cause of these waves, in the presence of reduced intracranial compliance the amplitude of the ICP oscillations can be increased, and so they indicate intracranial pathology. Lundberg 'C' waves are also oscillating waves with an amplitude up to <20 mmHg and a frequency of 4–8/min. These waves occur in health and their significance is uncertain [6,7].

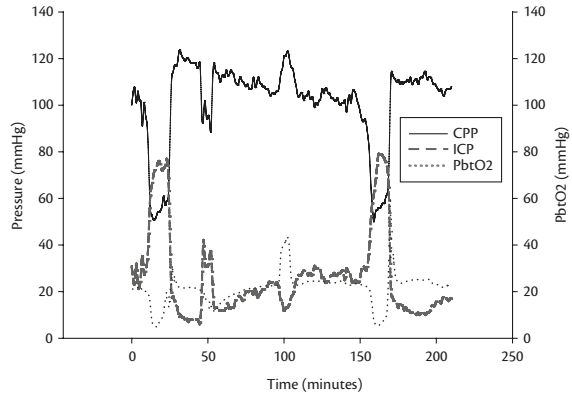


Fig. 223.3 Characteristic Lundberg A waves. Cerebral perfusion pressure (CPP), intracranial pressure (ICP) and brain tissue oxygen tension ($PbtO_2$) are plotted continuously. The large amplitude ICP waves lead to a reduction in CPP. The resulting ischaemia is suggested by the associated fall in $PbtO_2$.

Indications

Determination and continuous measurement of ICP may be useful in a variety of acute brain pathologies. The use of ICP monitoring is incorporated into international guidelines for traumatic brain injury management [2]. In addition, ICP monitoring is employed in severely-ill patients with reduced level of consciousness following subarachnoid haemorrhage (SAH), intracerebral haematoma, ischaemic stroke, meningo-encephalitis, hypoxic brain injury and other conditions associated with diffuse cerebral oedema such as fulminant liver failure.

The use of ICP monitoring or protocol driven management of raised ICP has been associated with improved outcomes after acute brain injury. Therefore, although ICP monitoring cannot be recommended with a high degree of certainty, it is recommended with moderate certainty for those patients following TBI who are likely to be at risk of intracranial hypertension. These are patients whose post resuscitation GCS is 3–8 and who have an abnormal cranial CT scan [2]. In patients with a normal scan the guidelines are less clear. Many of these patients will not suffer raised ICP, but if the patient has two additional adverse features (Age over 40, unilateral/bilateral motor posturing or systolic BP < 90 mmHg) the risk of intracranial hypertension is increased [8] and ICP monitoring is recommended [2]. A minority of patients whose initial cranial CT scan is normal will have evolving lesions, which may not be apparent in the absence of ICP monitoring. In such circumstances follow-up CT scanning should be performed.

Prognostication and intracranial pressure-guided management

ICP measurement can be helpful in determining prognosis. An ICP greater than 20 mmHg, despite interventions in critical care, is predictive of poor outcome following TBI [9]. Furthermore in clinical series interventions that were able to control ICP are associated with improved outcome [10,11].

The rationale for monitoring ICP and maintaining CPP come from observations that uncontrolled ICP can lead to secondary brain damage by reducing CPP and causing herniation. Hypotension is associated with worsened outcome after TBI [9] and secondary injuries are often ischaemic in nature.

Whether treating increased ICP improves outcome in brain-injured patients is an obvious question, and has only been tested in one randomized controlled trial conducted in South America, in which ICP-guided management was not superior to management guided by clinical examination and repeated imaging [12], ICP monitoring was associated with less use of potentially harmful ICP reducing interventions. Supporting data that the control of ICP improves outcome currently comes from observational data or studies using historical controls. Marmarou et al. reported in an observational study of patients in the Traumatic Coma Data bank, when ICP was measured for at least 48 hours after injury, that the proportion of ICP readings greater than 20 mmHg was predictive of poor outcome [9]. Eisenberg and colleagues conducted a trial designed to test the efficacy of barbiturate infusion in controlling ICP resistant to stranded measures. Post hoc analysis of outcome at 1 month found that survival was significantly better in patients in whom ICP could be controlled, in both the treatment and control groups [10]. Similarly, Saul and Ducker published a retrospective analysis of two sequential series of similar patients in which ICP treatment was started at differing thresholds. In the first series ICP treatment was initiated at an ICP >25 mmHg, with mannitol and CSF drainage. In the later series, the lower threshold of 15 mmHg was used, treatments guided by a protocol and escalating through mannitol, CSF drainage, and barbiturate infusion. In the later protocol, there were significantly fewer patients with an ICP >25 mmHg. This was associated with a significant reduction in mortality [11]. The ability to control ICP or the association of better outcome with ICP <20 mmHg could simply reflect less severe pathology or the prognostic relationship between ICP and outcome. Data suggesting ICP monitoring does not improve outcome comes from a more contemporary report. Cremer et al. [13] compared outcomes in severe TBI patients admitted to two different trauma centres. One provided supportive intensive care with therapy guided by clinical signs and serial CT scans. The second centre used an ICP/CPP targeted approach. The probability of favourable outcome was no different in the two centres.

Many of these studies are now quite dated as clinical management is constantly changing. Better availability and resolution of modern CT scanning, driving early surgical intervention, changing sedation regimes, ventilation practices and the development of protocol driven treatment in specialist centres are some of the probable confounders influencing outcomes today. In several of the studies cited, hyperventilation and systemic steroids were standard therapies; these treatments are no longer advocated in the management of TBI [10,11,14]. The Eurotherm3235 trial showed that titrated hypothermia was effective at reducing ICP after TBI when used as the primary stage II intervention, but resulted in a higher mortality and poorer outcomes [15].

Further developments in ICP measurement

Pressure reactivity

Although CPP-guided management of patients with brain injuries is standard practice in many units there is significant uncertainty as to the optimum CPP target. The widely accepted value of a minimum CPP of 60 mmHg is a guideline only [2]. It is based on cohorts of patients who had improved outcomes or better surrogate markers of cerebral perfusion compared with case controls. This guideline may be appropriate for populations of patients, but for individuals there may be considerable variation.

The pressure reactivity index (PRx) is a continuously derived variable, which essentially indicates if cerebrovascular autoregulation is intact or not. Study of PRx suggests that in individual patients there is a CPP at which PRx is optimal and where autoregulation is best preserved. In retrospective analysis deviation of mean CPP from a PRx defined $CPP_{optimal}$ correlated with adverse outcome [16]. Although guidelines suggest that CPP should not be allowed to fall below 60mmHg, for an individual patient, calculated $CPP_{optimal}$ can be considerably higher [2,16], but whether routine use of this technique improves outcome is not currently known.

Brain tissue oxygen monitoring

The management of ICP and CPP aims to maintain cerebral blood flow and, hence, oxygen delivery. Evidence from studies in which brain oxygenation has been measured would suggest that these parameters alone are not sufficient to guarantee this delivery [17]. Brain parenchymal oxygen tension monitoring, in addition to ICP monitoring, is an option in some commercial clinical systems. Oxygen and associated temperature electrodes can be either inserted through the same craniotomy as the ICP monitor or they can be incorporated into a single catheter.

Measurement of parenchymal oxygen can be used to guide patient management. Brain oxygen tension ($PbtO_2$) can be improved by treating raised ICP, optimizing arterial carbon dioxide tensions, correcting anaemia or increasing CPP. Much like PRx, brain oxygen tension can be used to set an individual patient's CPP. It has been demonstrated that below $CPP_{optimal}$, defined by PRx, $PbtO_2$ decreases linearly. Above $CPP_{optimal}$ $PbtO_2$ plateaus, so increasing CPP further does not improve oxygenation [18], these data provide indirect support for the concept of targeting a derived $CPP_{optimal}$.

Conclusion

ICP measurement is an established monitoring modality in ICU and can aid prognostication after acute brain injury. ICP monitoring is recommended in all patients with severe TBI and an abnormal cranial CT scan. The ability to control ICP is associated with improved outcome after TBI. The lessons from TBI studies can also be applied to other acute pathologies of the CNS where ICP can be increased. ICP measurement can warn of impending disaster and allow intervention. Furthermore, maintenance of CPP may help to ensure adequate cerebral oxygen delivery, although this might not be sufficient without measuring brain oxygenation as well. Although a recent trial in two South American countries suggested that ICP-guided management and management guided by clinical examination and repeated imaging produced equivalent outcomes, the external validity and generalizability of these results remains to be confirmed.

References

1. Mokri B. (2001). The Monro–Kellie hypothesis: applications in CSF volume depletion. *Neurology*, **56**(12), 1746–8.
2. The Brain Trauma Foundation (2007). Guidelines for the Management of Severe Traumatic Brian Injury 3rd edition. *Journal of Neurotrauma*, **24**(S1), 1–106.
3. Koskinen LO and Olivecrona M. (2005). Clinical experience with the intraparenchymal intracranial pressure monitoring Codman MicroSensor system. *Neurosurgery*, **56**(4), 693–8.
4. Martinez-Manas RM, Santamarta D, de Campos JM, Ferrer E. (2000). Camino intracranial pressure monitor: prospective study of accuracy and complications. *Journal of Neurology, Neurosurgery, and Psychiatry*, **69**(1), 82–6.
5. Avezaat CJ, van Eijndhoven JH, and Wyper DJ. (1979). Cerebrospinal fluid pulse pressure and intracranial volume-pressure relationships. *Journal of Neurology, Neurosurgery, and Psychiatry*, **42**(8), 687–700.
6. Lundberg N, Troupp H, and Lorin H. (1965). Continuous recording of the ventricular-fluid pressure in patients with severe acute traumatic brain injury. A preliminary report. *Journal of Neurosurgery*, **22**(6), 581–90.
7. Andrews PJ and Citerio G. (2004). Intracranial pressure. Part one: historical overview and basic concepts. *Intensive Care Medicine*, **30**(9), 1730–3.
8. Narayan RK, Kishore PR, Becker DP, et al. (1982). Intracranial pressure: to monitor or not to monitor? A review of our experience with severe head injury. *Journal of Neurosurgery*, **56**(5), 650–9.
9. Marmarou A, Anderson RL, Ward JD, et al. (1991). Impact of ICP instability and hypotension on outcome in patients with severe head trauma. *Journal of Neurosurgery*, **75**(1S), S59–66.
10. Eisenberg HM, Frankowski RF, Contant CF, Marshall LF, and Walker MD. (1988). High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. *Journal of Neurosurgery*, **69**(1), 15–23.
11. Saul TG and Ducker TB. (1982). Effect of intracranial pressure monitoring and aggressive treatment on mortality in severe head injury. *Journal of Neurosurgery*, **56**(4), 498–503.
12. Chesnut RM, Temkin N, Carney N, et al. (2012). A trial of intracranial-pressure monitoring in traumatic brain injury. *New England Journal of Medicine*, **367**(26), 2471–81.
13. Cremer OL, van Dijk GW, van Wensen E, Brekelmans GJ, Moons KG, Leenen LP, Kalkman CJ. (2005). Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. *Critical Care Medicine*, **33**(10), 2207–13.
14. Miller JD, Butterworth JF, Gudeman SK, et al. (1981). Further experience in the management of severe head injury. *Journal of Neurosurgery*, **54**(3), 289–99.
15. Andrews PJ, Sinclair HL, Rodriguez A, Harris BA, et al. (2015). Hypothermia for Intracranial Hypertension after Traumatic Brain Injury (the Eurotherm3235 Trial Collaborators). *New England Journal of Medicine*, 2015 Oct 7. [Epub ahead of print] PMID: 26444221
16. Steiner LA, Czosnyka M, Piechnik SK, et al. (2002). Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Critical Care Medicine*, **30**(4), 733–8.
17. Stiefel MF, Udoetuk JD, Spiotta AM, et al. (2006). Conventional neurocritical care and cerebral oxygenation after traumatic brain injury. *Journal of Neurosurgery*, **105**(4), 568–75.
18. Jaeger M, Dengl M, Meixensberger J, and Schuhmann MU. (2010). Effects of cerebrovascular pressure reactivity-guided optimization of cerebral perfusion pressure on brain tissue oxygenation after traumatic brain injury. *Critical Care Medicine*, **38**(5), 1343–7.

CHAPTER 224

Imaging the central nervous system in the critically ill

Olivier Bodart and Steven Laureys

Key points

- Computed tomography (CT) scan is still preferred to magnetic resonance imaging (MRI) in the acute management of traumatic brain injury (TBI) due to its sensitivity to lesion that requires immediate surgery, its accessibility, and the speed of the acquisition.
- Recent studies show the prognostic value of MRI sequences, such as diffusion tensor imaging (DTI) in coma following TBI or anoxia.
- CT remains the gold standard to detect acute haemorrhage.
- CT and CT angiography are suited to detect acute ischaemic stroke and major arterial occlusions, which is useful to aid the thrombolytic versus interventional therapy. However, MRI is more sensitive in the very first hours and can detect contraindications to IV thrombolysis.
- In traumatic spine injuries CT is used for the evaluation of bony structures and MRI for the evaluation of ligamentous injuries and the spinal cord.

Introduction

Signs and symptoms of central nervous system dysfunctions are frequently seen in the critical care setting, either in patients who are admitted primarily for a brain or spine lesion or for any other reason. There are many conditions that can lead to neurological impairment and it is beyond the scope of the present chapter to detail the imaging characteristics of them all. We will focus on some key primary brain and spines injuries. We will do so by discussing when it is important to obtain neurological imaging, which modality to use, what one can expect to find, and what are the main implications for determining prognosis.

Imaging of the brain

Traumatic brain injury

Patients admitted for a major traumatic brain injury (TBI) require emergency imaging of the head and brain primarily to identify lesions that may require urgent neurosurgery or special monitoring. The technique of choice is usually Computed tomography (CT) however, in cases of **mild** TBI (of which the definition may vary) it is not always necessary. Among the scales developed to avoid excessive use of health resources, the Canadian computed tomography head rule scale is highly sensitive and among the most specific to determine which patients with minor/mild head injury require CT scanning [1]. CT is preferred to magnetic resonance imaging (MRI) in the emergency set-up as it is faster in acquiring the data, more widely available, and more accessible to patients dependent on life-supporting equipment. MRI has the advantage of an absence of radiation for the patient. However, the presence of a pacemaker and/or metallic foreign bodies are contraindications. MRI is increasingly used for the initial assessment of patients with TBI, but it remains to be shown whether the extra findings do change patients' management [2]. CT is highly sensitive to skull fractures and acute intracranial bleeding, especially to lesions that would require immediate surgery, such as epidural or subdural haematomas. When performed with contrast enhancement, it also provides a whole brain and neck angiogram, and is thus able to demonstrate vascular injuries (such as blunt injuries, traumatic dissections, aneurysms, etc.). However, digital subtraction angiography remains the technique of choice for these latter lesions. MRI is more sensitive to lesions of the brainstem and the posterior fossa, and has a better tissue contrast, hence a better spatial resolution. It is thus able to detect more subtle (but still clinically relevant) brain injuries, such as 'diffuse axonal injury' and cortical contusions [3].

Some neuroimaging techniques can provide the caregiver valuable information on the prognosis of their patient. For example, some specific MRI sequences, such as diffusion tensor imaging (DTI), provide prognostic information that is often more accurate than clinical or CT scores [4].

Stroke

Strokes can be classified into two major categories: ischaemic and haemorrhagic. Ischaemic strokes are caused by interruption of the blood supply (caused by thrombosis, arterial embolism, etc.), while haemorrhagic strokes result from rupture of a blood vessel or an abnormal vascular structure. About 87% of strokes are caused by ischaemia and the remainder by haemorrhage. Some haemorrhages can develop inside areas of ischaemia (termed 'haemorrhagic transformation'). Such haemorrhagic strokes are associated with higher mortality rates than ischaemic strokes. In acute cerebrovascular accidents (CVA), neuroimaging is needed in an emergency setting to determine the ischaemic or haemorrhagic nature of the lesion and, hence, to direct the patient's further therapeutic management. Due to the wide availability of a CT scanner in emergency departments, this technique is often performed first in stroke patients. CT is excellent to demonstrate acute haemorrhagic lesions (Fig. 224.1a), whilst

MRI is more sensitive in following the progression of the haemorrhage and in searching for the possible underlying causes. Both techniques may identify complications of haemorrhagic stroke, such as intraventricular haemorrhage, brain oedema, and hydrocephalus. In ischaemic stroke, the sensitivity of the CT scan in the first 6 hours is low. However, some early signs may still be seen, such as loss of gray matter–white matter differentiation, swelling of the circumvolutions, and (less frequently) spontaneous hyperdensity in the middle cerebral artery (Fig. 224.1b). Nonetheless, CT and CT angiography are able to detect acute ischaemic stroke and major arterial occlusions, which is useful in guiding thrombolytic or interventional therapy. In comparison, MRI is far more sensitive in detecting acute ischaemic lesions (Fig. 224.1c); diffusion-weighted imaging (DWI) can show ischaemic impairment (cytotoxic oedema) within 3 minutes of the event. It can also better demonstrate the exact extent of the ischaemic lesion and is able to show smaller lesions, as well differentiate acute ischaemic lesions from old ones (Fig. 224.1d). MRI perfusion imaging can be useful to study penumbra and other zones at risk of lesion extension.

Prognosis in stroke depends of many factors among which the localization and the size of the ischaemic and/or haemorrhagic lesion are assessable by neuroimaging techniques.

Subarachnoid haemorrhage

Patients presenting with excruciating headache, and even more if associated with focal neurological deficit, should be scanned as soon as possible to exclude subarachnoid haemorrhage (SAH). The spontaneous hyperdensity of blood on CT makes it a very sensitive tool for diagnosis of this condition (Fig. 224.1e). Many cases of SAH are related to trauma and up to 85% of the non-traumatic cases are caused by a ruptured aneurysm that must be treated to prevent recurrence. Some MRI sequences such as FLAIR (fluid attenuated inversion recovery) can demonstrate SAH as hyperintensities in sulci or cisterns, but this finding has many other possible diagnoses and is thus less specific than CT. It can, however, be useful in demonstrating an underlying tumour in intraparenchymal bleeding, and is able to detect small SAH after a few days. Vasospasm is a frequent complication of SAH, which can be assessed via transcranial Doppler ultrasonography, MR and CT angiography, and digital subtraction angiography. Risk of clinically significant vasospasm can be estimated using the modified Fischer scale, which stratifies the risk by the appearance of the SAH on the initial CT [5]. CT or MRI can assess hydrocephalus, another possible complication of SAH. Angiography remains the gold standard for detecting even smaller aneurysms, and is one of the therapeutic options for these,

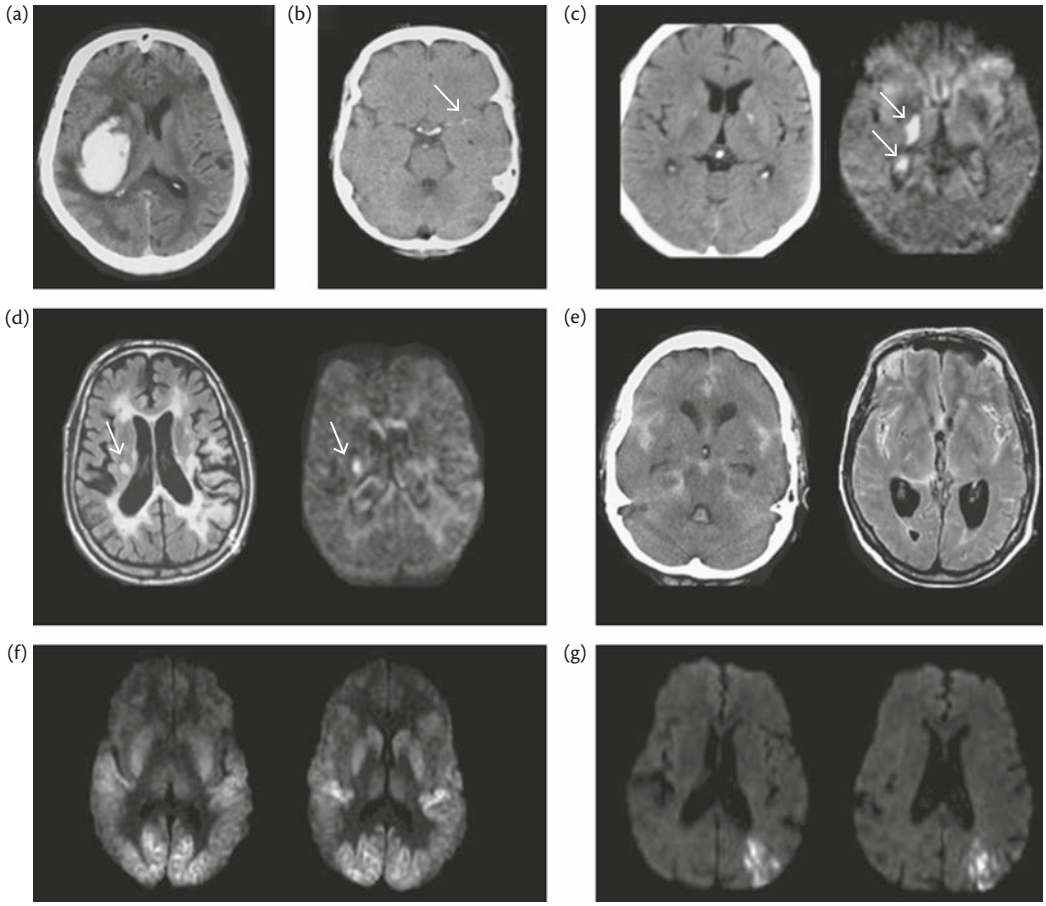


Fig. 224.1 (a) CT scan of acute intracranial haemorrhage. The CT image shows hyperdense acute haemorrhage in the basal nuclei-corona radiata on the right, along with surrounding hypodense oedema. (b) Early hyperdensity on a CT scan of the left middle cerebral artery (indicated by arrow). (c) CT scan (left) and MRI (right) of acute ischaemia. The image on the right shows high sensitivity of MRI DWI in the acute phase of ischaemia (visible as hyperintensity in DWI sequences); the acute ischaemia is not evident on the CT scan (left). (d) DWI sequence is useful to differentiate new ischaemic lesions (arrow—more evident on right image), not easily discernable on a FLAIR image (left image). (e) Acute SAH is better seen on a CT scan (left) than MRI (right). (f) Widespread hyperintensity on DWI in hypoxia (most affected are the cortex and basal nuclei). (g) Boundary zone hyperintensity on DWI in hypoperfusion.

CT, computed tomography; DWI, diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery; SAH, subarachnoid haemorrhage.

depending of their location, size, and other factors. If an aneurysm is suspected, digital suppression angiography should be done as soon as the condition of the patient allows.

Anoxic brain injuries

Following a cardiac arrest or a prolonged hypoxic state (also often encountered in TBI), patients may have significant neurological deficits and a depressed level of consciouness. Neuroimaging techniques can be used, even early, to assess the extent of the anoxic-ischaemic lesions. In the first 2 days, CT may reveal diffuse swelling with consequent effacement of the sulci, ventricles, and cisterns, hypodensities of the cortical and basal ganglia gray matter, and an attenuation of the gray–white matter interface (also termed loss of gray–white differentiation). MRI, for the reasons previously explained (related to the incompatibility of life-supporting equipment and the time required to perform the scan), is often difficult to obtain immediately. When performed early, DWI and FLAIR may show widespread hyperintensities, which classically first affect the basal ganglia and the thalamus, and next the cortex, the subcortical white matter, the cerebellum and the hippocampus (Fig. 224.1f) (while MRI T1 and T2 sequences can be normal or near normal). In the subacute phase, there is usually a resolution of the brain oedema and of the hyperintensities evident on DWI. FLAIR and T2 sequences may show extensive changes in the gray matter and the development of white matter lesions. In case of hypoperfusion (i.e. without blood flow cessation), the lesions tend to be situated in the watershed territories (Fig. 224.1g). In case of a pure hypoxic event, lesions in DWI tend to be restricted to the thalamus and some cortical regions. Prolonged coma (other than caused by sedation) of more than 6 hours is of poor prognosis. The better outcome can be expected in young patients who had a cardiac arrest due to a primary cardiac arrhythmia, and in who the blood flow was restored in less than 6 minutes. Hypoxic events also tend to have a better prognosis. In the acute phase, the presence of bilateral hippocampal hyperintensities in DWI and in FLAIR sequences is a marker of poor prognosis [6], as is diffuse hyperintensities on these sequences [7] or a decrease in fractional anisotropy (a DWI measure reflecting brain water diffusion measured in three directions with a lower number indicating less restricted diffusion due to impaired white matter integrity) in selected regions of the white matter [8].

Other conditions

In a general context, CT should be performed as an emergency in cases of a new focal neurological deficit, persistent altered mental status, or partial-seizure onset for adults above 40 years old. This is especially so in the presence of fever, recent trauma, history of cancer, anticoagulant use, or suspicion of AIDS. MRI should be performed first if a cerebellar, brainstem, or internal auditory canal lesion is suspected. It is also an excellent technique to search for intra- or extra-axial mass lesions. MRI is also very good in diagnosing inflammatory and infectious diseases, such as abscesses, empyema, and encephalitis. It can show the extent of the lesion, and its potential communication with the ventricles, vessels, and sinuses.

Imaging the spine

Traumatic lesions

If spine trauma is suspected, neuroimaging should be performed as soon as possible as urgent surgical realignment and fixation may be necessary. In asymptomatic traumatic patients, imaging of the cervical spine is not necessary if the neurological examination is strictly normal, if the patient is not intoxicated, if there are no complains of cervical pain or midline tenderness, and if there are no other major injuries related to the trauma that might distract the patient [9]. In the emergency department, although the plain radiographies may rule out major cervical spine injuries [10], patients with major trauma should usually undergo whole body CT, as the cervical, thoracic, and lumbar spine can thus be imaged at the same time. CT scanning is highly effective and superior to MRI for studying bone structures. MRI is better to study the soft tissues around the spine and, more importantly, allows a high-resolution study of the spinal cord, which is of paramount importance in cases of compression (especially if caused by intraspinal haematomas, ligament damage, or a prolapsed disc—all conditions in which plain radiography and CT scan can be near-normal). The indications for spine CT scan in the traumatic setting are a history of major trauma, especially in the presence of impaired consciousness, physical signs of spine trauma, a history of distracting mechanism of injury and the presence of neurological signs and symptoms. Spine fractures are often complex and may require surgical stabilization. The extent of spinal cord damage and oedema on MRI is correlated with functional outcome.

Non-traumatic lesions

In the setting of non-traumatic spinal cord lesions, MRI is the most informative imaging technique, as it allows a good evaluation of the spinal cord. It should be performed early, as compressive lesions require urgent surgery. Specific appearance of the lesions on different MRI sequences, potential enhancement, and location will help in differentiating aetiologies, from inflammatory demyelinating and infectious processes to ischaemia and vitamin deficiency. A practical diagnostic work-up algorithm using spinal cord MRI has recently been proposed [11]. The prognosis will mainly be related to the etiology, and in the case of non-traumatic compression of the spinal cord, to the rapidity of the neurosurgical management.

Acknowledgements

The authors thank Carol Di Perri for her precious help and comments. OB is a research fellow and SL is research director at the Fonds National de la Recherche Scientifique de Belgique (FNRS).

References

1. Stiell IG, Wells GA, Vandemheen K, et al. (2001). The Canadian CT Head Rule for patients with minor head injury. *Lancet*, **357**(9266), 1391–6.
2. Manolakaki D, Velmahos GC, Spaniolas K, de Moya M, and Alam HB (2009). Early magnetic resonance imaging is unnecessary in patients with traumatic brain injury. *Journal of Trauma*, **66**(4), 1008–12.
3. Morais DF, Spotti AR, Tognola WA, Gaia FF, and Andrade AF (2008). Clinical application of magnetic resonance in acute traumatic brain injury. *Arquivos de Neuro-Psiquiatria*, **66**(1), 53–8.
4. Galanaud D, Perlbarg V, Gupta R, *et al.* (2012). Assessment of white matter injury and outcome in severe brain trauma: a prospective multicenter cohort. *Anesthesiology*, **117**(6), 1300–10.
5. Frontera JA, Claassen J, Schmidt JM, *et al.* (2006). Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. *Neurosurgery*, **59**(1), 21–7.

6. Greer DM, Scripko PD, Wu O, *et al*. (2013). Hippocampal Magnetic Resonance Imaging Abnormalities in Cardiac Arrest are Associated with Poor Outcome. *Journal of Stroke and Cerebrovascular Disease*, **22**(7), 899–905.
7. Wijman CA, Mlynash M, Caulfield AF, *et al*. (2009). Prognostic value of brain diffusion-weighted imaging after cardiac arrest. *Annals of Neurology*, **65**(4), 394–402.
8. Luyt CE, Galanaud D, Perlbarg V, *et al*. (2012). Diffusion tensor imaging to predict long-term outcome after cardiac arrest: a bicentric pilot study. *Anesthesiology*, **117**(6), 1311–21.
9. Hoffman JR, Mower WR, Wolfson AB, Todd KH, and Zucker MI (2000). Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. National Emergency X-Radiography Utilization Study Group. *New England Journal of Medicine*, **343**(2), 94–9.
10. Richards PJ. (2005). Cervical spine clearance: a review. *Injury*, **36**(2), 248–69.
11. Hodel J, Outteryck O, Jissendi P, Zins M, Leclerc X, and Pruvo JP (2012). MRI of myelitis. *Journal Belge de Radiologie—Belgisch Tijdschrift voor Radiologi*, **95**(4), 270–76.

PART 9.3

Sleep disturbance

CHAPTER 225

Pathophysiology and therapeutic strategy for sleep disturbance in the ICU

Louise Harder and Atul Malhotra

Key points

- Sleep is an essential homeostatic function.
- Sleep disturbance can lead to impaired neurocognitive and cardiometabolic function.
- Sleep apnoea is a common condition which can affect pharmacological and airway management in the ICU.
- Sleep disturbance in the ICU may contribute to delirium.
- Patient ventilator dyssynchrony may contribute to sleep disruption in the intensive care unit.

Introduction

The topic of sleep in the intensive care unit has been receiving increasing attention in recent years, but remains poorly studied. Robust data support the impact of sleep deprivation and sleep fragmentation on various health outcomes in outpatient populations [1]. However, the relevance of these data to critically-ill patients remains unknown. This review summarizes the currently available literature, recognizing that some of the information provided is extrapolated from best available evidence [2].

Sleep is an essential function of the body, which when disrupted has health consequences. Sleep can be disturbed in a variety of ways including insufficient sleep duration (sleep deprivation) and sleep fragmentation, e.g. as seen in obstructive sleep apnoea (OSA) or with repetitive environmental stimuli. Sleep deprivation in outpatients has well established neurocognitive and cardiometabolic sequelae. For example, sleep deprivation is an important risk factor for motor vehicle accidents, memory impairment, and mood disturbances. In addition, rigorous data have defined an important impact of sleep deprivation on glucose tolerance [3]. Physiological studies have also shown impairment in function of other hormones, such as leptin and ghrelin, both hormones which change in a direction that stimulates appetite [4]. As such, epidemiological studies have shown increased incidence of hypertension, myocardial infarction, obesity, and all cause mortality [1]. Thus, one could reasonably hypothesize that inadequate sleep duration could have important biological effects in critically-ill patients.

Sleep disorders

Many sleep disorders have important health effects, but respiratory abnormalities, e.g. OSA are the most relevant for the intensivist. OSA is a very common condition characterized by repetitive collapse of the pharyngeal airway, resulting in sleep fragmentation, recurrent desaturations, and catecholamine surges [5]. The condition is estimated to affect roughly 5% of the USA population and is likely increasing in prevalence due to increasing obesity and the ageing population. OSA has important consequences, including risk of motor vehicle collisions and incident cardiovascular disease. Although randomized trial data are still evolving, nasal continuous positive airway pressure (CPAP) is the treatment of choice as it has been shown to reduce daytime sleepiness and blood pressure, and probably also reduces the risk of motor vehicle collisions and cardiovascular events [6].

Despite the high prevalence, OSA remains underappreciated, with estimates of 80–90% of disease remaining undiagnosed [7]. Given the associated comorbidities of OSA, including diabetes, obesity, and hypertension, patients with OSA are at risk of critical illness and thus knowledge of OSA is important to the intensivist. The following concepts should be emphasized:

- Patients with OSA are at increased risk of peri-operative complications [8], including an increased risk of respiratory failure, prolonged intubation, and delayed discharge. A large study assessing patients undergoing bariatric surgery found that OSA was an independent risk factor for post-operative complications [9]. As patients with OSA are particularly sensitive to hypnotics and analgesics, careful attention to pharmacology is required to avoid hypoventilation and respiratory compromise. At present, the data fall short of showing a definitive reduction in peri-operative risk with CPAP therapy in patients with OSA, although investigative efforts are ongoing in this area.
- Patients with OSA frequently have difficult airways, which can complicate intubation and lead to failure of extubation. Many risk factors for difficult intubation traditionally used by anaesthesiologists (such as Mallampati score, retrognathia, and neck circumference) are also predictive of OSA. As such, experienced anaesthesiologists frequently recognize patients as challenging,

even if a formal diagnosis of OSA has not been made. Following extubation, it is likely that upper airway dysfunction contributes to recurrent respiratory failure. Thus, one mechanism underlying the well-established benefit of non-invasive ventilation post-extubation in high risk patients may be via distending the upper airway by raising its transmural pressure [10].

- Obesity hypoventilation syndrome (OHS) occurs in roughly 10% of patients with OSA. Almost half of patients with OHS present with acute hypercapnic respiratory failure, emphasizing the role of the intensivist in managing such patients. Appropriate initial diagnosis and management followed by long-term non-invasive ventilation or CPAP generally results in good outcomes.
- Sleep apnoea can be important in patients with acute congestive heart failure (CHF). OSA has been observed in more than 50% of patients with acute CHF and treatment with nasal CPAP has been shown to improve left ventricular ejection fraction both in the acute setting and in the longer term [11].
- Patients with OSA are at greater risk of cardiovascular complications particularly during the night with an increased propensity for sudden cardiac death and myocardial infarction during the night time, as compared to the usual 10.00 hours peak seen in patients without OSA [12]. Patients with OSA are also at risk of atrial and ventricular tachyarrhythmias often in temporal association with breathing abnormalities. However, the link of OSA to bradyarrhythmias and complete heart block is more controversial. Data suggest that treatment of OSA can decrease cardiovascular risk, including the risk of arrhythmias. Given that CPAP compliance is quite variable, we recommend that treatment, in addition to CPAP, address cardiac issues directly for optimal patient care.

Sleep fragmentation in the ICU

Although OSA is characterized by sleep fragmentation, its consequences are also probably related to recurrent desaturations and catecholamine surges. As such, sleep fragmentation, which can occur in critically-ill patients, may or may not have similar sequelae to OSA. Indeed, there are a variety of issues underlying sleep disturbances in ICU patients (see Table 225.1).

Studies of sleep in the ICU have documented poor sleep quality characterized by minimal slow wave sleep and rapid eye movement (REM) sleep and recurrent arousals from sleep [13]. However, standard EEG criteria for sleep staging may be hard to implement in the critically ill. For example, sleep spindles (one of the hallmark findings of stage 2 non-REM sleep) can be induced with benzodiazepines. Thus, a distinction between sedation and sleep can be quite challenging. Similarly, delta wave activity is used to define slow wave sleep (or N3 non-REM sleep), but can also be seen in encephalopathy. The discussion of sedation versus sleep becomes quite complex due to these issues around defining accurate stages of sleep. We would emphasize that a sedated patient may not receive the beneficial effects associated with natural sleep. While some data support reduced sleep drive following propofol anaesthesia in sleep-deprived animals, the clinical relevance of these data is unclear [13].

Insights into the sleep versus sedation controversy have been provided through basic neurobiology. The ventrolateral pre-optic area (VLPO) of the hypothalamus is thought to be the critical centre for the control of sleep. Lesions to the VLPO can produce insomnia [14]. Various anaesthetic agents, therefore, can be tested in VLPO-lesioned animals to understand the potential role of sleep pathways in determining the response to medications. For example, dexmedetomidine is thought to work through sleep centres, and thus is considered by some to be inducing pharmacological sleep, rather than sedation. In contrast, other anaesthetic agents probably work through non-specific GABA inhibition of neurons and exert their effects via pathways independent of VLPO. Indeed, some randomized trial data have suggested that dexmedetomidine may improve clinical outcome compared with benzodiazepine infusions, although the role of sleep homeostasis in determining these findings is unknown [15].

Delirium

The importance of delirium in the ICU has recently been emphasized based on data showing an association with increased mortality.

Table 225.1 Causes of sleep disturbance in ICU patients

Factor	Issue	Solution
Excessive noise	Disrupts sleep, particularly with changes in noise levels	Silence unnecessary alarms Minimize conversations, etc., during night time Consider earplugs
Bright light	Disrupts circadian rhythms, suppresses melatonin	Maintain light/dark cycle Consider melatonin supplementation
Reduced total sleep time	May affect metabolic and immune function	Provide adequate dark time Discharge from ICU as soon as possible
REM suppression	May be risk factor for delirium	Unclear
Patient/ventilator asynchrony	Can fragment sleep, increase respiratory efforts/dyspnoea	Careful bedside assessment Provide optimal flow delivery, triggering sensitivity Consider proportional assist ventilation
Air leak during non-invasive ventilation	Can fragment sleep	Optimize interface

The mechanisms underlying delirium are complex, but may relate at least in part to disruption of sleep. Trompeo has shown that severe suppression of REM sleep is associated with increased incidence of delirium [16]. However, as yet, there are no convincing data demonstrating that interventions to improve sleep yield a reduction in delirium in the ICU. Indeed, benzodiazepines are a risk factor for delirium [15], emphasizing the need for alternative medications and non-pharmacological approaches to optimizing sleep. Randomized trials are ongoing to study optimized treatment of delirium and to assess its impact on longer term outcomes, such as neurocognitive performance, sleep, and post-traumatic stress disorder. Such data will be critical to defining the causal pathways in ICU patients.

Mechanical ventilation

Patient–ventilator dyssynchrony can be a source of discomfort and recurrent awakenings. Pleural pressure is thought to be the trigger for arousal from sleep based on observations that individuals wake from sleep at a particular oesophageal pressure threshold, regardless of the respiratory stimulus [17]. Thus, high respiratory drive or patient efforts against high resistance can generate markedly negative pleural pressures, which may generate arousals from sleep. Optimizing ventilator triggering, positive end-expiratory pressure, and inspiratory flow profile can improve synchrony. We have chosen three findings to emphasize:

- A randomized trial has shown improvement in sleep quality with the use of proportional assist ventilation compared with standard pressure support ventilation. The mechanism underlying this observation is unclear, but ostensibly ventilatory support commensurate with patient demands can improve synchrony [18].
- During non-invasive ventilation, air leak has been shown to disrupt sleep. The mechanism underlying this finding may relate to disruption of respiratory pattern or may simply involve facial or oral mechanoreceptors [19].
- Central apnoeas are observed when $PaCO_2$ falls below the so-called chemical apnoea threshold. Improvements in breathing patterns are observed with reductions in pressure support levels or with the addition of dead space. Thus, central apnoeas in patients being assessed for liberation from mechanical ventilation do not necessarily require return to passive mechanical ventilation with full support.

Immune function

Sleep disruption has been shown to affect immune function. Antibody titre responses following influenza vaccine are impaired in people who are sleep deprived as compared to controls. In epidemiological studies, reduced sleep duration is associated with an increased incidence of community acquired pneumonia [20]. One study in which investigators innoculated rhinovirus into healthy volunteers found an increased susceptibility to clinical infection among those who were sleep-deprived compared with controls. Furthermore, some experimental work regarding natural killer cell and T cell function has also shown important deleterious influences of sleep deprivation. At present there is a paucity of data regarding whether sleep disturbance in the ICU can contribute to ventilator associated pneumonia or other nosocomial infections.

Conclusion

Well-established therapies for sleep disorders have shown improved outcomes in the acute setting. Despite widespread recognition of the importance of natural sleep and its disturbance on well-being, there remains a paucity of information regarding the causes, effects, and effective treatment of sleep disorders in critically-ill patients. Basic questions about sleep in the ICU remain. For example, how should sleep be quantified in critically-ill patients? Does sleep disturbance in the ICU yield important consequences on clinical outcomes? Does treating sleep disruption contribute to improved outcomes in patients treated in the ICU? Some existing data support simple sleep-related interventions to improve surrogate outcome measures in critically-ill patients. The impact of interventions to improve sleep on hard clinical outcomes requires further study.

References

1. Ayas NT, White DP, Manson JE, et al. (2003). A prospective study of sleep duration and coronary heart disease in women. *Archives of Internal Medicine*, **163**(2), 205–9.
2. Pisani MA, Friese RS, Gehlbach BK, Schwab RJ, Weinhouse GL, and Jones SF. (2015). Sleep in the intensive care unit. American Journal of Respiratory and Critical Care Medicine, **191**(7), 731–8.
3. Spiegel K Leproult R, and Van Cauter E. (1999) Impact of sleep debt on metabolic and endocrine function. *Lancet*, **23**, 1435–9.
4. Nedeltcheva AV, Kilkus JM, Imperial J, Schoeller DA, and Penev PD. (2010). Insufficient sleep undermines dietary efforts to reduce adiposity. *Annals of Internal Medicine*, **153**(7), 435–41.
5. Malhotra A and Loscalzo J. (2009). Sleep and cardiovascular disease: an overview. *Progress in Cardiovascular Diseases*, **51**(4), 279–84.
6. Marin JM, Carrizo SJ, Vicente E, and Agusti AG. (2005). Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*, **365**(9464), 1046–53.
7. Young T, Peppard P, and Gottlieb D. (2002). The epidemiology of obstructive sleep apnea: a population health perspective. *American Journal of Respiratory and Critical Care Medicine*, **165**, 1217–39.
8. Memtsoudis S, Liu SS, Ma Y, et al. (2011). Perioperative pulmonary outcomes in patients with sleep apnea after noncardiac surgery. *Anesthesia and Analgesia*, **112**(1), 113–21.
9. Flum DR, Belle SH, King WC, et al. (2009). Perioperative safety in the longitudinal assessment of bariatric surgery. *New England Journal of Medicine*, **361**(5), 445–54.
10. Nava S, Gregoretti C, Fanfulla F, et al. (2005). Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. *Critical Care Medicine*, **33**(11), 2465–70.
11. Khayat RN, Abraham WT, Patt B, Pu M, and Jarjoura D. (2009). In-hospital treatment of obstructive sleep apnea during decompensation of heart failure. *Chest*, **136**(4), 991–7.
12. Gami AS, Howard DE, Olson EJ, and Somers VK. (2005). Day-night pattern of sudden death in obstructive sleep apnea. *New England Journal of Medicine*, **352**(12), 1206–14.
13. Weinhouse GL and Schwab RJ. (2006). Sleep in the critically ill patient. *Sleep*, **29**(5), 707–16.
14. Saper CB, Scammell TE, and Lu J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature*, **437**(7063), 1257–63.
15. Pandharipande PP, Pun BT, Herr DL, et al. (2007). Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *Journal of the American Medical Association*, **298**(22), 2644–53.

16. Trompeo AC, Vidi Y, Locane MD, et al. (2011). Sleep disturbances in the critically ill patients: role of delirium and sedative agents. *Minerva Anestesiologica*, **77**(6), 604–12.
17. Gleeson K, Zwillich CW, and White DP. (1990). The influence of increasing ventilatory effort on arousal from sleep. *American Review of Respiratory Disease*, **142**, 295–300.
18. Bosma K, Ferreyra G, Ambrogio C, et al. (2007). Patient–ventilator interaction and sleep in mechanically ventilated patients: pressure support versus proportional assist ventilation. *Critical Care Medicine*, **35**(4), 1048–54.
19. Meyer TJ, Pressman MR, Benditt J, et al. (1997). Air leaking through the mouth during nocturnal nasal ventilation: effect on sleep quality. *Sleep*, **20**(7), 561–9.
20. Patel SR, Malhotra A, Gao X, Hu FB, Neuman MI, and Fawzi WW. (2012). A prospective study of sleep duration and pneumonia risk in women. *Sleep*, **35**(1), 97–101.

PART 9.4

Agitation, confusion, and delirium

CHAPTER 226

Causes and epidemiology of agitation, confusion, and delirium in the ICU

Eduard E. Vasilevskis and E. Wesley Ely

Key points

- Delirium is extremely common in the intensive care unit (ICU), occurring in 60–80% of mechanically-ventilated patients at some point during their ICU stay.
- Hypoactive delirium (without agitation) is far more common that hyperactive delirium (with agitation), and often goes unrecognized unless actively sought with validated delirium measurement instruments.
- The onset of delirium should prompt an investigation into underlying causative and potentially reversible factors. These include medications, untreated pain, and untreated infections.
- Benzodiazepines are a common risk factor predisposing to and prolonging delirium in the ICU. Alternative analgesic and sedative agents should be considered prior to the use of benzodiazepines.
- Early mobility is a process of care that is protective against delirium. Successful mobility protocols include standard safety parameters, begin therapy as early as 24 hours following ICU admission, and include mechanically-ventilated patients.

Introduction

The presence of agitation, confusion, and/or delirium is common in the intensive care unit (ICU), occurring in 60–80% of mechanically-ventilated patients, and 40–60% of non-ventilated patients. Often their presence signifies evidence of acute end organ injury and is precipitated by a variety of underlying aetiologies. The vulnerability of the patient and the severity of the predisposing insult impact both the epidemiology, as well as the causes of agitation, confusion, and delirium.

Definitions

Agitation, confusion, and delirium are separate yet related conditions that are best understood when viewing through the lens of clear definitions as follows:

- **Agitation**: a disorder of excessive psychomotor activity that may include disorientation, pressured speech, labile affect, and potentially dangerous behaviours in the ICU that could lead to removal of vascular access lines, pulling at endotracheal tubes, and ventilator dyssynchrony [1].
- **Confusion**: an abnormality in orientation, memory, and/or thought process. Confusion by itself may be acute or chronic. A confused patient may be agitated, sedated, or have a normal level of consciousness.
- **Delirium**: a form of acute brain dysfunction that is characterized by inattention, cognitive impairment, and alterations in consciousness [2]. Additional, although less common, features of delirium include hallucinations, delusions, and labile affect. Depending upon the level of consciousness, delirium can be either hyperactive (with agitation), hypoactive (with sedation), or mixed [3], with the latter two categories occurring most frequently in the intensive care unit.

The conditions listed above are not mutually exclusive (Fig. 226.1). Agitated patients may or may not be delirious, although all should be formally assessed for the presence of delirium. Alternatively, agitation may be a patient response to pain, anxiety, drug withdrawal, or psychosis. Importantly, delirious patients may not be agitated, with a majority being sedated or only intermittently agitated.

The remainder of this chapter will focus on delirium since it includes a significant proportion of agitated patients, is commonly missed by practitioners when validated measurement instruments are not used (this is particularly true for hypoactive delirium) [4], and is associated with increased health care utilization, and increased risk of both death and long-term cognitive impairment [5,6].

Pathophysiology of delirium

Just as hypotension reflects cardiovascular system dysfunction and decreasing urine output reflects renal system dysfunction, ICU delirium reflects acute dysfunction of the nervous system. Delirium is the end product of a sequence of insults and injury that lead to a common measurable manifestation of end-organ brain injury. Delirium does not have a single aetiology, but rather has multiple different and potentially interacting aetiologies. Recent studies have implicated inflammation [7] and metabolic derangements of neurotransmitters [8] in the development of delirium. Other factors may include abnormalities in cerebral blood flow, endothelial dysfunction, pain, and toxic effects of medications.

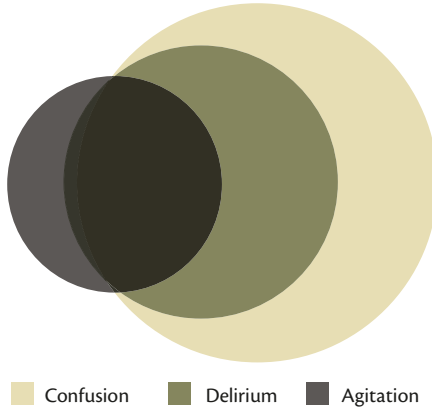


Fig. 226.1 Agitation, confusion, and delirium.

Epidemiology of delirium

Delirium can be assessed in a variety of different ways. The most common method is to report the period prevalence of ICU delirium, which is the frequency at which patients experience at least one day of delirium during their entire ICU stay. When period prevalence is considered, it is estimated that between 60 and 80% [6,9] of mechanically-ventilated, and between 40 and 60% of non-ventilated patients will experience at least one day of delirium during their ICU stay. When one considers only the first 24 hours of ICU admission, the point prevalence is between 20 and 40% [10]. The cumulative incidence of delirium depends upon the inclusion or exclusion of patients identified with delirium in the first 24 hours, and therefore may be equivalent to the period prevalence reduced by 20–40%, respectively.

The epidemiology of ICU delirium is also population dependent, and leads to variable reports of prevalence and incidence. For example, the consideration of coma is an important factor. Coma incidence is mutually exclusive from delirium, and is one of the strongest risk factors for subsequent development of delirium [11]. Studies, therefore, that exclude patients admitted with coma lead to reduced reports of prevalence and incidence of delirium [12]. In addition, studies with a higher proportion of patients with persistent coma (i.e. delirium could not be measured during the patient's entire ICU stay), will likely under-represent the degree of acute brain dysfunction among the studied cohort of patients. Populations with increased burden in other risk-factors (e.g. mechanically-ventilated patients with sepsis), will similarly report increased measures of both prevalence and incidence of delirium [6]. In addition, delirium epidemiology may be less accurate among populations in whom accurate assessments of delirium is difficult (e.g. those with sensory impairment, language barriers, or neurological deficits) or who have clinical features that may also be present among delirious patients (e.g. psychomotor retardation in patients with depression or dementia).

A final consideration of ICU delirium epidemiology includes whether validated screening instruments were used, the instrument selected, and the training received by those using the instrument. Each instrument (e.g. CAM-ICU or ICDSC) has unique test characteristics and minimum training requirements for reliable measurements.

Regardless of the population, it is critical to understand that the prevalence and incidence of hypoactive delirium, or mixed hypo/hyperactive delirium far exceeds that of hyperactive (e.g. agitated) delirium alone [3]. This is why the use of validated instruments for measurement is critical in the ICU, because without such instruments up to 70% of cases of delirium are not recognized [4]. The high false negative clinical diagnosis of delirium is in large part due to the high prevalence of hypoactive delirium.

Causes of delirium

Delirium is a syndrome, and reflects end organ dysfunction that results from a variety of unique and likely interacting pathways. Currently, it is felt that the development of delirium depends upon a combination of host vulnerability, regarded as predisposing factors combined with the severity of a specific insult. A highly vulnerable patient may require a minimal insult, whereas a resilient patient requires a severe insult to precipitate delirium.

Non-modifiable risk factors for ICU delirium

A patient's given vulnerability is described by their predisposing (i.e. non-modifiable) risk factors. These include prior comorbidities, demographic factors, genetic factors, as well as the specific acute illness for which the patient was admitted. Among comorbidities, prior cognitive impairment is among the most important [12,13]. Age is an important demographic factor, although less consistently associated with ICU delirium [14]. Both dementia and age will become increasingly important risk factors as the number of elderly patients and patients with dementia cared for in ICUs grows worldwide. Few genetic factors have been investigated, although apolipoprotein E4 is a genetic marker that has been associated with incident delirium [15]. Finally, the severity of the presenting illness plays an important role in predisposing patients to delirium. A patient that presents with higher severity of illness (e.g. sepsis or coma) is at far greater risk for the development of delirium [11,14]. For example, over 80% of patients that are admitted to the ICU in a comatose state and are discharged alive will at some point transition from a comatose state into a delirious one [6,10].

Modifiable risk factors for ICU delirium

Whereas the predisposing factors are largely non-modifiable, other factors may be more directly influenced by the clinical decision making and processes of care in the ICU. Attention to these factors may potentially prevent or decease the duration of delirium among ICU patients.

The most consistently described risk factor for incident and prolonged delirium is the choice of sedative, and most notably the use of benzodiazepines [9,13,14,16,17]. Importantly, the risk of ICU delirium is dose dependent, with up to 100% of patient that receive daily lorazepam equivalents of 20 mg or more experiencing delirium [14]. Similar relationships have been seen with midazolam. Dexmedetomidine is a newer sedative therapy, that when compared with benzodiazepines, reduces the risk for incident delirium [16,17]. This either supports a beneficial effect of dexmedetomidine, and/or supports the previously described harmful effect of benzodiazepines. There are limited data regarding the

effects of propofol on incident delirium. Opiate medications are another medication class that has been implicated in some investigations, but results have been inconsistent, and may depend upon the patient population studied (e.g. trauma, surgical, or medical) [9,14]. The role of opiates is complicated because under-treatment of pain is recognized as a risk factor for delirium, and should be treated when identified. Antipsychotics, both typical and atypical, have not been shown consistently to be either protective or harmful for incident delirium in the ICU despite their common use for treatment of delirium [18].

Non-pharmacological factors play an equally important role in impacting the risk for ICU delirium. Early mobilization is an important example of a practice that demonstrates great potential in the prevention of delirium, reducing the duration of delirium by a median of 2 days [19]. The mechanism of protection is unclear, but may include reduction of sedative agents by means of scheduled interruption of sedation, cognitive activation during exercise, and direct neuroprotective benefits associated with exercise. Additional non-pharmacological practices that deserve the ongoing attention include the removal of unnecessary lines and catheters [12] and interventions that improve the quantity and quality of sleep in the ICU, such as the use of earplugs [20].

Overall, when approaching a patient with ICU delirium, it is important to first recognize that there is a new acute end organ injury that signifies a new or worsening process. Clinicians may use the mnemonic '**THINK**' to exclude or treat possible underlying causes (see Chapter 227, 'Assessment and Therapeutic Strategy for Agitation, Confusion, and Delirium in the ICU', for an explanation of this). This should lead to a focused physical exam including neurological assessment, laboratory and medication review, and investigation of any underlying infectious or other acute medical condition.

Conclusion

Confusion is a non-specific, and non-diagnostic term to describe a patient with a wide range of symptoms, from memory impairment to disorientation. Agitation embodies an increased level of psychomotor activity and anxious or aggressive behaviour. Many agitated patients may also be delirious, yet they represent a minority of all delirious patients. Both predisposing and precipitating risk factors play important roles in the development of delirium. Cognitive impairment and age are among the most important predisposing risk factors, whereas benzodiazepine use and immobility are common modifiable factors. Recent trials suggest that dexmedetomidine may reduce the risk of delirium when compared to benzodiazepines. Promising non-pharmacological protective factors include early mobilization and sleep protocols. The onset of delirium should prompt the physician to THINK and investigate for the underlying cause(s).

References

1. Cohen IL, Gallagher TJ, Pohlman AS, Dasta JF, Abraham E, and Papadokos PJ. (2002). Management of the agitated intensive care unit patient. *Critical Care Medicine*, **30**(1), S97–123.
2. American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. Washington, DC: American Psychiatric Association.
3. Peterson JF, Pun BT, Dittus RS, et al. (2006). Delirium and its motoric subtypes: a study of 614 critically ill patients. *Journal of the American Geriatric Society*, **54**(3), 479–84.
4. Spronk PE, Riekerk B, Hofhuis J, and Rommes JH. (2009). Occurrence of delirium is severely underestimated in the ICU during daily care. *Intensive Care Medicine*, **35**, 1276–80.
5. Girard TD, Jackson JC, Pandharipande PP, et al. (2010). Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Critical Care Medicine*, **38**(7), 1513–20.
6. Ely EW, Shintani A, Truman B, et al. (2004). Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *Journal of the American Medical Association*, **291**(14), 1753–62.
7. Girard T, Ware L, Bernard G, et al. (2012). Associations of markers of inflammation and coagulation with delirium during critical illness. *Intensive Care Medicine*, **38**, 1965–73.
8. Adams Wilson JR, Morandi A, Girard TD, et al. (2012). The association of the kynurenine pathway of tryptophan metabolism with acute brain dysfunction during critical illness. *Critical Care Medicine*, **40**(3), 835–41.
9. Pisani MA, Murphy TE, Araujo KLB, Slattum P, Van Ness PH, and Inouye SK. (2009). Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. *Critical Care Medicine*, **37**(1), 177–83.
10. McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, and Inouye SK. (2003). Delirium in the intensive care unit: Occurrence and clinical course in older patients. *Journal of the American Geriatric Society*, **51**(5), 591–8.
11. van den Boogaard M, Pickkers P, Slooter AJC, et al. (2012). Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. *British Medical Journal*, **344**, e420.
12. Van Rompaey B, Elseviers M, Schuurmans M, Shortridge-Baggett L, Truijen S, and Bossaert L. (2009). Risk factors for delirium in intensive care patients: a prospective cohort study. *Critical Care*, **13**(3), R77.
13. Pisani MA, Murphy TE, Van Ness PH, Araujo KL, and Inouye SK. (2007). Characteristics associated with delirium in older patients in a medical intensive care unit. *Archives of Internal Medicine*, **167**(15), 1629–34.
14. Pandharipande P, Shintani A, Peterson J, et al. (2006). Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*, **104**(1), 21–6.
15. Ely EW, Girard TD, Shintani AK, et al. (2007). Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients. *Critical Care Medicine*, **35**(1), 112–17.
16. Pandharipande PP, Pun BT, Herr DL, et al. (2007). Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *Journal of the American Medical Association*, **298**(22), 2644–53.
17. Riker RR, Shehabi Y, Bokesch PM, et al. (2009). Dexmedetomidine vs midazolam for sedation of critically ill patients. *Journal of the American Medical Association*, **301**(5), 489–99.
18. Devlin JW and Skrobik Y. (2011). Antipsychotics for the prevention and treatment of delirium in the intensive care unit: What is their role? *Harvard Review of Psychiatry*, **19**(2), 59–67.
19. Schweickert WD, Pohlman MC, Pohlman AS, et al. (2009). Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*, **373**(9678), 1874–82.
20. Van Rompaey B, Elseviers MM, Van Drom W, Fromont V, and Jorens PG. (2012). The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients. *Critical Care*, **16**(3), R73.

CHAPTER 227

Assessment and therapeutic strategy for agitation, confusion, and delirium in the ICU

Michele C. Balas and E. Wesley Ely

Key points

- Without routine monitoring, delirium often goes unrecognized in the critical care setting.
- A number of easily-administered, valid, and reliable agitation/sedation and delirium screening tools are available for use in critically-ill adults.
- The treatment of agitation and delirium in the intensive care unit (ICU) setting begins with prompt recognition and removal of the underlying cause of the disorder.
- Delirium most often occurs as a direct physiological consequence of a new medical condition or substance intoxication, withdrawal, or side effect.
- The role antipsychotic medications play in the prevention and treatment of ICU delirium has yet to be determined. In terms of pharmacological management of ICU delirium, the question is not necessarily what medication to give, but which to discontinue.

Introduction

During their time in an intensive care unit (ICU), critically-ill patients frequently experience fluctuations in their level of consciousness, experience various emotions, such as fear, isolation pain, and anxiety, and display a variety of psychomotor behaviours including both hypo- and hyperactivity. Without routine monitoring using valid and reliable pain, sedation/agitation, and delirium screening tools, it is often impossible for clinicians to determine the exact aetiology of their patient's mental status change or behaviour. The first step in the assessment and management of agitation, confusion, and delirium, therefore, is accurately determining which condition or syndrome the patient is experiencing.

Agitation, confusion, and delirium assessment

Agitation, a psychomotor disturbance characterized by a marked increase in both motor and psychological activities, occurs frequently in ICU patients and is believed to be caused by a number of factors, including pain, the inability to communicate, anxiety, drug withdrawal, and delirium [1]. Confusion is a very general term often used to describe people experiencing problems with coherent thinking. Since confusion is such a non-specific term, we will not refer to it in this chapter. The American Psychiatric Association's *Diagnostic and Statistical Manual*, 5th edn (DSM-5) [2] diagnostic criteria for delirium include:

- **Criterion A**: a disturbance in **attention** (i.e. reduced ability to focus, sustain, or shift attention) and awareness.
- **Criterion B:** the disturbance develops over a short period of time (usually hours to days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of the day.
- **Criterion C:** an additional disturbance in **cognition** (e.g. memory deficit, disorientation, language).
- **Criterion D**: the disturbances in Criteria A and C are not explained better by another pre-existing established or evolving neurocognitive disorder, and do not occur in the context of a severely reduced level of arousal (e.g. coma)
- **Criterion E:** there is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple aetiologies.

The treatment of agitation and delirium in the ICU setting historically involved the administration of high dose, often continuously infused, sedatives and narcotics, the application of physical restraints to prevent patients from harming themselves or others, and as needed (prn) intravenous antipsychotics. Numerous studies conducted over the last 20 years, indicate that this is a potentially harmful management strategy. The current, more patient-centred, focus is to use sedation/agitation and delirium assessment tools and management protocols aimed at achieving 'light' levels of sedation. Beneficial outcomes linked to the use of such protocols in controlled studies include shorter duration of mechanical ventilation, lower mortality rates, more 'on-target' sedation, less pain and agitation, reduced direct drug costs, lower tracheostomy rates, and decreased incidence of ventilator associated pneumonia, with few negative outcomes reported [3].

Sedation/agitation screening tools

A necessary component of protocol-directed sedative administration, and mental status examination in general, is the use of appropriate sedation/agitation rating scales. While a number of these scales have been developed for use with critically-ill patients, the two most widely used include the Richmond Agitation-Sedation Scale (RASS) [4] and the Sedation Agitation Scale (SAS) [5]. The RASS consists of a 10-point scale, with four levels of anxiety or agitation (+1 to +4 with a higher score indicating greater anxiety or agitation), one level to denote a calm and alert state (0), and five levels of sedation (–1 to –5 with a more negative score indicating deeper sedation). The SAS consists of a 7-point scale, with three levels of agitation (5–7 again with a higher score indicating greater agitation), one level to denote a calm and co-operative state (4), and three levels of sedation (3–1 with the lower score indicating deeper sedation). Each tool requires administrators to first observe the patient's behaviour, assess their responsiveness to verbal commands, and if not responsive, to assess their response to a physical stimulus. Both scales are quickly and easily administered, demonstrate good reliability and validity, and have been used with patients in a variety of critical care settings.

ICU delirium screening tools

In addition to disturbances in consciousness and cognition, critically-ill patients experiencing delirium often present with a variety of other signs and symptoms (Box 227.1). This variability in presentation makes accurate diagnosis challenging, particularly in mechanically-ventilated patients who cannot speak. While psychiatric evaluation remains the 'gold standard' for delirium diagnosis, this approach is often impractical in critical care settings due to the large number of patients at risk for developing this syndrome.

To address these issues, the use of standardized delirium screening tools is advised by several international organizations. While a number of tools have been developed for use in mechanically-ventilated and non-ventilated patients in ICU, the two most widely used, easily administered, valid, and reliable tools include the Confusion Assessment Method-ICU (CAM-ICU) [6] and the Intensive Care Delirium Screening Checklist (ICDSC) [7]. The CAM-ICU defines delirium in terms of the four DSM-V diagnostic features. Delirium is deemed present when a patient displays an acute change or fluctuating course of mental status (Feature 1), inattention (Feature 2), and **either** an altered level of consciousness (Feature 3), **or** disorganized thinking (Feature 4). Attention is assessed with either visual or auditory components, including picture recognition or hand squeezing to a series of letters. A current RASS score of anything other than 0 is considered evidence of an altered level of consciousness. Finally, disorganized thinking is assessed by having the patient respond to a series of 4 yes/no questions and performing a simple command. Patients unresponsive to verbal stimulation (i.e. RASS score of –4 or –5) cannot be screened for delirium with the CAM-ICU.

The ICDSC contains eight items based on DSM criteria and features of delirium including altered level of consciousness, inattention, disorientation, hallucination or delusion, psychomotor agitation or retardation, inappropriate mood or speech, sleep/wake cycle disturbance, and symptom fluctuation. The scale is completed based on information collected from an entire 8-hour period or from the previous 24 hours. Each item is scored as either 1 (present) or 0 (absent). A total score of 4 or greater is considered to indicate the presence of delirium.

Box 227.1 Additional manifestations and associated features of delirium

- **Disturbance of consciousness:**
  - Reduced clarity and awareness of environment.
  - Distracted by irrelevant stimuli.
  - Engagement in conversation difficult.
- **Changes in cognition:**
  - Impairment in memory (most commonly recent).
  - Disorientation (usually time or place).
  - Language disturbances (e.g. dysarthria, dysgraphia, rambling or irrelevant speech).
- **Perceptual disturbances** (e.g. hallucinations, illusions, misinterpretations, or delusions).
- **Associated features**:
  - Disturbance in sleep/wake cycle.
  - Disturbed psychomotor behaviour (both hypo- and hyperactivity).
  - Emotional disturbances (e.g. fear, depression, anxiety, irritability, anger, euphoria, or apathy).
  - Situation inappropriate behaviour (e.g. calling out, screaming, or cursing).
  - Non-specific neurological findings (e.g. tremor, myoclonus, asterixis).

Implementation strategies

Without the use of valid and reliable screening tools, ICU nurses and physicians are notoriously poor at detecting delirium, at times missing the diagnosis in 75% of cases [8]. This under-recognition is significant in that it can seriously hamper early treatment and reversal of the underlying cause of delirium. Fortunately, studies, have shown that it is possible to implement delirium screening tools into everyday clinical care [9]. Interprofessional educational strategies that have been used to increase the ICU provider's knowledge of delirium assessment tools include the use on on-line, on-demand education videos, lectures, case-based scenarios, and spot checking by expert raters.

Therapeutic strategies

Identify and remove cause of delirium/agitation

The next step in the assessment and management of agitation and delirium is to determine and promptly remove the underlying cause of the disorder. The ICU team should talk with the patient's family or caregivers to determine the patient's mental status before

they were admitted to the hospital. This is an important step in differentiating delirium from the more chronic cognitive changes associated with dementia. It is important, however, for providers to be cognizant of the fact that delirium can be superimposed on dementia and that persons with dementia who develop delirium are at even greater risk for physical, functional, and cognitive morbidity. The importance of conducting a health history and physical examination in accurately determining the aetiology of delirium cannot be over-emphasized.

Delirium most often occurs as a direct physiological consequence of a new medical condition [2]. This is particularly true for older adults for whom a change in mental status is often the first 'clue' to deterioration in health status. A number of general medical conditions are associated with delirium (Table 227.1). It may be particularly helpful for ICU providers to use the mnemonic 'THINK' (**T**oxic situations and medications, **H**ypo/hyper states, **I**nfection and immobility, **N**on-pharmacological and neurological, and **K**+ (fluid and electrolyte disturbances)) when determining the likely cause of delirium [3] In all patients screening positive for delirium, a focused physical, neurological, and laboratory assessment, to determine if a new medical condition is present, is warranted.

Several illicit and prescription drugs are reported to cause delirium (Box 227.2) [2]. The most common in the ICU setting include benzodiazepines and opioids. Because critically-ill adults are exposed to numerous medications during their normal course of treatment, it is essential for providers to perform a careful medication review. Any medications identified as a potentially cause of delirium should be discontinued as soon as possible.

While it is beyond the scope of this chapter to fully discuss the assessment and management of drug withdrawal, it is important to note that delirium can also occur due to substance withdrawal. Withdrawal symptoms can develop after the cessation of heavy and prolonged alcohol use or in patients with long-term exposure to high-dose opiates or sedatives [2]. Withdrawal symptoms include

Box 227.2 Substances and medications associated with the development of delirium

Substance intoxication

- ***Commonly used in ICU setting***: sedatives, hypnotics, opioids, anxiolytics.
- ***Other***: alcohol, amphetamines and related substances, cannabis, cocaine, hallucinogens, inhalants, phencyclidine, and related substances.

Substance withdrawal

- ***Commonly used in the ICU setting***: sedatives, hypnotics, opioids, anxiolytics.
- ***Other***: alcohol.

Side effect of other medications

- ***Commonly used in the ICU setting***: anaesthetics, analgesics, anti-arrhythmics, anti-asthmatic agents, antibiotics, anticholinergics, anticonvulsants, antihistamines, antihypertensives, antimicrobials, β blockers, clonidine, corticosteroids, digoxin, diuretics, gastrointestinal medications, histamine H_2 receptor antagonists, immunosuppressive agents, other cardiovascular medications, psychotropic medications, particularly those with anticholinergic side effects.
- ***Other***: antidepressants, anti-parkinsonian drugs, antivirals, lithium, dopamine agonists, muscle relaxants, toxins including organophosphate (anticholinesterase), insecticides, carbon monoxide, volatile substances, herbal preparations.

Data from American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), Copyright © 2013 American Psychiatric Association.

Table 227.1 'THINK' acronym for underlying medical conditions associated with delirium

T	**T**oxic situations	Shock, congestive heart failure, myocardial infarction, cardiac arrhythmias, new organ failure (e.g. respiratory, renal, hepatic), severe trauma, temperature dysregulation, post-operative states, neoplasms, history of hypertension*)
	Toxic medications	Deliriogenic medications including benzodiazepines*, hypnotics, opioids*, anxiolytics (see also Box 227.2)
H	'**H**ypo' and '**H**yper' states	Hypoxaemia, hypocarbia, hypercarbia, hypoglycaemia, hypoalbuinaemia, hypothiaminaemia
I	**I**nfection	Infections (e.g. respiratory, urinary tract, septicaemia)
	Immobilization	Bed rest, physical and chemical restraints
N	**N**on-pharmacological reasons	Sensory deprivation (visual and hearing impairment), sensory overload (noise, lighting), social isolation, inability to communicate needs, sleep deprivation
	Neurologic reasons	Pre-existing dementia*, head trauma, ictal and post-ictal states, vascular diseases, such as stroke and hypertensive encephalopathy, Pick's disease, brain tumour, focal lesions, history of alcoholism*
K	**K**+ (potassium)	Potassium and other fluid/electrolyte problems including dehydration, anaemia, endocrinopathy, and acid/base disturbances

*Risk factor identified in previous ICU studies.

Data from American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), Copyright © 2013 American Psychiatric Association; and data from Balas MC et al., 'Critical care nurses' role in implementing the "ABCDE bundle" into practice', *Critical Care Nurse*, 2012, 32(2), p. 34, with permission from the American Association of Critical Care Nurses.

autonomic hyperactivity, increased hand tremor, agitation, anxiety, nausea and vomiting, hallucinations or illusions, and rarely grand mal seizures [2]. Withdrawal symptoms typically develop when blood concentrations of the substance declines sharply after the substance has been discontinued. Symptoms in general can be relieved by either administering the substance from which the patient is withdrawing or the use of another CNS depressant [2]. Finally, in the absence of an obvious cause of delirium, or for patients with focal neurological findings, further testing (e.g. neuroimaging, lumbar puncture) may be warranted.

Utilize non-pharmacological measures

In older, critically-ill patients each day spent delirious in the ICU is associated with a 10% relative decrease in survival time [10], suggesting that reducing the duration of delirium should be an important goal of treatment. There is, unfortunately, a relative dearth of high quality studies examining the effect of non-pharmacological interventions on either the incidence or duration of delirium. A notable exception to this finding is the use of early mobility protocols. A strategy for whole-body rehabilitation, consisting of interruption of sedation and physical and occupational therapy in the

Table 227.2 Non-pharmacological interventions to prevent and manage ICU delirium—the PEACE acronym

Physiological	◆ Routinely monitor patient's vital signs, blood glucose, oxygen saturation, and laboratory profiles (monitor for deviations from baseline) ◆ Consider additional physiologic monitoring if applicable (i.e. telemetry to monitor QTc interval for patients receiving antipsychotic medications) ◆ Attempt to restore physiological and nutritional stability. Prevent and/or correct electrolyte disturbances and dehydration. Identify and treat infections. Consult support services as needed ◆ Consider using one-to-one observation in cases where tube/catheter dislodgement would threaten patient safety
Environmental	◆ Discontinue any unnecessary lines/tubes or equipment. If needed, consider 'camouflaging' them (e.g. abdominal binder for gastrojejunal tubes) ◆ Keep call bell in reach at all times. Use calendars/clocks to assist with orientation. Establish a consistent, structured routine ◆ Keep the environment as calm and quiet as possible with adequate light and limit noise level. Avoid frequent room changes ◆ Provide optimal level of environmental and cognitive stimulation ◆ Use music that has individual significance to help with relaxation
Activities of Daily Living	◆ Attempt to normalize sleep patterns. Use non-pharmacological sleep promotion strategies (e.g. noise reduction, use of low level lighting, avoidance of constant lighting, increase daytime activity). Avoid using diphenhydramine or benzodiazepines for sleep ◆ Provide glasses, hearing aids, or other assistive devices as needed ◆ Favour mobilization/avoid immobilization. Consider implementing early mobilization protocol and evaluation by physical and occupational therapy ◆ Assist with feeding/ADLs as needed. Initiate aspiration, safety, and fall precautions as needed
Communication/ **C**oordination	◆ *With patients:* a. Provide patient with a way of communicating their needs to staff and family (e.g. paper/pencil, communication boards, Passy Muir Valves for tracheostomies) b. Encourage patients to be involved in, and control, as much of their care as possible. Acknowledge patients feelings and fears, and provide reassurance as needed c. Use short, simple sentences; speak slowly and clearly; identify oneself by name and call patient by their preferred name. Repeat questions if needed, allow adequate time for response. Tell patients what you want done, not what not to do. Listen and observe behaviour ◆ *With family:* a. Inform significant other of patient's change in mental status and provide emotional support as needed b. Encourage scheduled visits and involvement of family and friends (for acute change in mental status it may be helpful to call in the family 24/7) ◆ *With staff:* a. Perform 'walking rounds' and discuss mental status exam with off-going care provider b. Notify charge nurse/supervisor of patients experiencing a change in mental status c. Collaborate with clinical nurse specialist and other nurses to formulate individualized plan of care for patient d. Encourage continuity of care providers or primary nurse
Education	◆ Educate staff on hazards of physical restraint use and bedrest ◆ Reinforce fact that delirium or an acute change in mental status in never '**normal**' ◆ Ensure continuity of care, and safe ICU and hospital discharge ◆ Ensure no informed consent is obtained from delirious patients ◆ Educate staff on hazards of polypharmacy

Data from Balas MC et al., 'Management of delirium in critically ill older adults', *Critical Care Nurse*, 2012, **32**(4), pp. 15–26.

earliest days of critical illness was found to be not only safe and well tolerated, but resulted in better functional outcomes at hospital discharge, more ventilator-free days, and a shorter duration of delirium [11].

A bundled approach to managing ICU acquired delirium and weakness through the use of spontaneous **A**wakening and **B**reathing trial **C**oordination, **D**elirium monitoring/management, and **E**arly mobility protocols (ABCDE bundle) has also recently been proposed in the ICU literature [12]. While based on the best available evidence, the effect this bundle has on patient outcomes has yet to be fully determined. One recent, single centre, before after trial found patients treated with the ABCDE bundle spent three more days breathing without mechanical ventilator assistance, had lower mortality rates, and had a near halving of the odds of delirium compared with patients before the bundle became standard of care [13]. It is encouraging, nevertheless, that interdisciplinary, multicomponent non-pharmacological intervention studies in patients hospitalized outside the ICU have proven beneficial [14]. Suggested non-pharmacological interventions that may be helpful in reducing ICU delirium are provided in Table 227.2.

When all else fails, consider pharmacological intervention

Maintaining critically-ill patients at a light level of sedation with non-benzodiazepine medications is associated with a number of favourable outcomes including a lower risk for delirium [15]. There are also data suggesting that critically-ill mechanically-ventilated patients sedated with dexmedetomidine may have a lower prevalence of delirium compared with those sedated with benzodiazepine infusions [16]. Despite their widespread use, however, there is little high quality evidence to support the administration of antipsychotic medications in the prevention and/or treatment of ICU delirium [15].

There have been few studies that have explored the role of antipsychotic medications in the prevention and treatment of delirium in the ICU. The first study of 105 mechanically-ventilated ICU patients found no difference in the number of days spent alive without delirium or coma in patients who were prophylactically treated with haloperidol, ziprasidone, or placebo [17]. In the second study of 36 ICU patients, researchers found that subjects treated with quetiapine compared to placebo experienced a quicker resolution of delirium [18]. In the third study, a similar decrease over time in delirium severity was noted between fixed-dose oral olanzapine and oral haloperidol in patients with delirium [19]. It is important to note that none of these studies identified serious safety concerns with the medications that were studied.

A more recent prospective, placebo-controlled blinded randomized study demonstrated that low dose intravenous haloperidol prophylaxis may reduce the prevalence of delirium in **low acuity** elderly post-operative patients who are admitted to the ICU [20]. In summary, there is little evidence that haloperidol reduces the duration of ICU delirium, there is some evidence suggesting that quetiapine may help reduce the duration of ICU delirium, and the use of antipsychotic medications in certain critically ill populations (e.g. older post-operative patients, adults undergoing cardiac surgery) may be beneficial.

Conclusion

There are several valid, reliable, and easily-administered delirium screening tools applicable for use in the critical care setting. Incorporating these tools into everyday practice will require sustained inter-professional education and a commitment to using the findings of screening to appropriately develop and/or modify patients' care. If delirium is identified, ICU providers should focus their efforts on identifying and promptly treating the underlying physiological or substance-induced causes. Non-pharmacological delirium prevention and treatment strategies, such as early mobilization, appear to be beneficial. While frequently used, the role antipsychotic medications play in the prevention and treatment of ICU delirium is yet to be determined.

References

1. Chevrolet J and Jolliet P. (2007). Clinical review: agitation and delirium in the critically ill—significance and management. *Critical Care*, **11**(3), 214.
2. American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. Washington, DC: American Psychiatric Association.
3. Balas MC, Vasilevskis EE, Burke WJ, et al. (2012). Critical care nurses' role in implementing the 'ABCDE bundle' into practice. *Critical Care Nurse*, **32**(2), 35–8.
4. Sessler CN, Gosnell MS, Grap MJ, et al. (2002). The Richmond Agitation–Sedation Scale: validity and reliability in adult intensive care unit patients. *American Journal of Respiratory and Critical Care Medicine*, **166**(10), 1338–44.
5. Riker RR, Picard JT, and Fraser GL. (1999). Prospective evaluation of the Sedation–Agitation Scale for adult critically ill patients. *Critical Care Medicine*, **27**(7), 1325–9.
6. Ely EW, Inouye SK, Bernard GR, et al. (2001). Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *Journal of the American Medical Association*, **286**(21), 2703–10.
7. Bergeron N, Dubois MJ, Dumont M, Dial S, and Skrobik Y. (2001). Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Medicine*, **27**(5), 859–64.
8. Spronk PE, Riekerk B, Hofhuis J, and Rommes JH. (2009). Occurrence of delirium is severely underestimated in the ICU during daily care. *Intensive Care Medicine*, **35**(7), 1276–80.
9. Pun BT, Gordon SM, Peterson JF, et al. (2005). Large-scale implementation of sedation and delirium monitoring in the intensive care unit: a report from two medical centers. *Critical Care Medicine*, **33**(6), 1199–205.
10. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, and Van Ness P. (2009). Days of delirium are associated with 1-year mortality in an older intensive care unit population. *American Journal of Respiratory and Critical Care Medicine*, **180**(11), 1092–7.
11. Schweickert WD, Pohlman MC, Pohlman AS, et al. (2009). Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*, **373**(9678), 1874–82.
12. Vasilevskis EE, Ely EW, Speroff T, Pun BT, Boehm L, and Dittus RS. (2010). Reducing iatrogenic risks: ICU-acquired delirium and weakness-crossing the quality chasm. *Chest*, **138**(5), 1224–33.
13. Balas MC, Vasilevskis EE, Olsen KM, et al. (2014). Effectiveness and safety of the awakening breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. *Critical Care Medicine*, **42**(5), 1024–36.
14. Inouye SK, Bogardus ST, Charpentier PA, et al. (1999). A multicomponent intervention to prevent delirium in hospitalized older patients. *New England Journal of Medicine*, **340**(9), 669–76.

15. Barr J, Fraser GL, Puntillo K, et al. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical Care Medicine*, **41**(1), 263–306.
16. Pandharipande PP, Pun BT, Herr DL, et al. (2007). Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *Journal of the American Medical Association*, **298**(22), 2644–53.
17. Girard T, Pandharipande P, Carson S, et al. (2010). Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: The MIND randomized, placebo-controlled trial. *Critical Care Medicine*, **38**, 428–37.
18. Devlin JW, Skrobik Y, Riker RR, et al. (2011). Impact of quetiapine on resolution of individual delirium symptoms in critically ill patients with delirium: a post-hoc analysis of a double-blind, randomized, placebo-controlled study. *Critical Care*, **15**(5), R215.
19. Skorbik YK, Bergeron N, Dumont M, and Gottfried SB. (2004). Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Medicine*, **30**(3), 444–49.
20. Wang W, Li H, Wang D, et al. (2011). Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. *Critical Care Medicine*, **40**(3), 731–739.

PART 9.5

The unconscious patient

CHAPTER 228

Causes and diagnosis of unconsciousness

Robert D. Stevens and Joshua Kornbluth

Key points

- Changes in consciousness are seen in a range of physiological and pathological settings, including sleep, anaesthesia, brain lesions, metabolic disturbances, and complex partial or generalized seizures.
- In neurobiological terms, consciousness may be viewed as having an arousal dimension and an awareness dimension phenotypically expressed as the capacity to meaningfully integrate self or environmental stimuli.
- Loss of consciousness is associated with lesions that disrupt neuronal systems in the brainstem and diencephalon which mediate arousal, or thalamocortical, or corticocortical systems which mediate awareness.
- As there are many causes of unconsciousness, a timely and focused history and neurological examination are critical to defining the differential diagnosis.
- Care must be taken to differentiate states of unresponsiveness (e.g. locked-in syndrome) from unconsciousness.

Introduction

In the realm of medicine and biology, consciousness is generally understood as a state in which there are distinct, but interlinked arousal and awareness functions, which are necessary to process and respond to internal or external stimuli. Arousal is the overall level of responsiveness, and is analogous to vigilance or wakefulness. Awareness is the brain's ability to process self or environmental stimuli of different modalities. Isolated loss of a specific domain of awareness, such as hemispatial neglect following a non-dominant parietal lesion, will not impair awareness of other modalities and does not impact overall consciousness. Similarly, patients with receptive aphasia are impaired in their ability to interpret language and may mistakenly be viewed as having a global alteration in consciousness, although the level of awareness in other domains of consciousness may be intact [1]. The threshold for perceiving and responding to stimulus is also variable between individuals and within the same individual, influenced by both intrinsic (i.e. genetic factors, circadian regulation, and biological clocks) and extrinsic (i.e. stimulant or sedative pharmacologic compounds) variables.

The biology of consciousness

Loss of consciousness is a normal part of the sleep–wake cycle. Functional MRI studies in healthy controls have shown patterns of brain hypometabolism during sleep which are comparable with what may be seen in patients with disorders of consciousness. The key difference between sleep and pathological unconsciousness is that sleep is intrinsically reversible with stimulation. The patient with a disorder of consciousness may arouse with stimulation, but quickly returns to their baseline impaired consciousness when stimulation is withdrawn [1]. Pathological unconsciousness can be due to structural lesions or functional disturbances (Box 228.1).

Box 228.1 Differential diagnosis of coma

Primary cerebral disorders

Bilateral or diffuse hemispheric disorders

- Subarachnoid haemorrhage.
- Hypoxic-ischaemic encephalopathy.
- Cerebral venous thrombosis.
- Brain tumour.
- Central nervous system infections.
- Immunological disorders affecting the central nervous system.
- Generalized or complex partial seizures.
- Posterior reversible encephalopathy syndrome.
- Hydrocephalus.

Unilateral hemispheric disorders (with displacement of midline structures)

- Traumatic brain injury (contusions, subdural haematoma, epidural haematoma).
- Large hemispheric ischaemic stroke.
- Primary intracerebral haemorrhage.

Brain stem disorders.

- Central pontine myelinolysis.
- Compression from cerebellar lesions.

Systemic derangements causing coma

- Medication overdose/adverse effects (opioids, benzodiazepines, barbiturates, tricyclic antidepressants, neuroleptics, aspirin, selective serotonin reuptake inhibitors, paracetamol, anticonvulsants).
- Drugs of abuse (opioids, alcohol, methanol, ethylene glycol, amphetamines, cocaine).
- Exposures (carbon monoxide, heavy metals).

Toxic–metabolic

- Hypoxia, hypercapnia.
- Hypothermia.
- Hypoglycaemia, hyperglycaemic crises.
- Hyponatraemia, hypernatraemia.
- Hypercalcaemia.
- Hepatic failure.
- Renal failure.
- Wernicke's encephalopathy.
- Systemic inflammatory response syndrome, severe sepsis.

Endocrine

- Panhypopituitarism.
- Adrenal insufficiency.
- Hypothyroidism; hyperthyroidism.

Adapted with permission from Wolters Kluwer Health and Society of Critical Care Medicine: *Critical Care Medicine*, Stevens RD et al., 'Approach to the comatose patient', **34**(1), pp. 31–41, 2006.

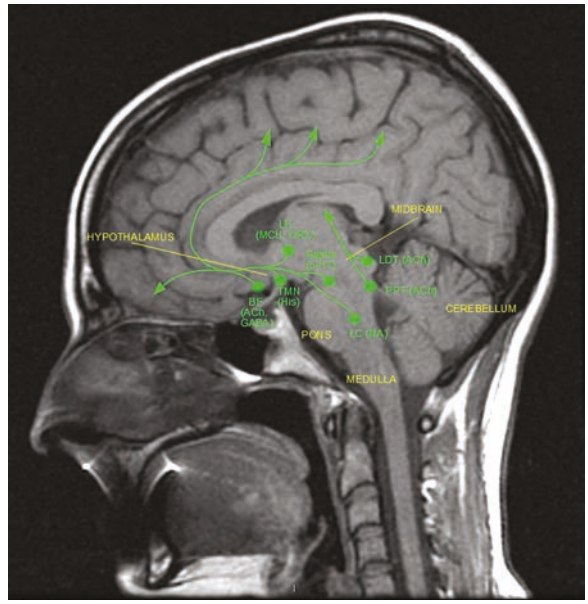


Fig. 228.1 Neuronal systems responsible for arousal.
Key components of the ascending arousal system: The yellow pathway represents major inputs to the reticular nuclei of the thalamus originating from cholinergic (ACh) cell groups in the rostral pons, the pedunculopontine (PPT) and laterodorsal tegmental nuclei (LDT). These inputs facilitate thalamocortical transmission. The pathways demonstrated in red activate the cerebral cortex to make possible the processing of inputs from the thalamus. This arises from neurons in the monoaminergic cell groups, including the tuberomammillary nucleus (TMN) containing histamine (His), the dorsal and median raphe nuclei containing serotonin (5-HT), and the locus coeruleus (LC) containing noradrenaline (NA). This pathway also receives contributions from neurons in the lateral hypothalamus (LH) containing orexin (ORX) or melanin-concentrating hormone (MCH), and from basal forebrain (BF) neurons that contain gamma-aminobutyric acid (GABA) or ACh.

This may be a sustained or protracted process as in severe brain injury (e.g. trauma, stroke) or it may reverse within minutes as with syncope. Pathological unconsciousness may also be a result of a toxic or metabolic encephalopathy due to global cortical dysfunction as is the case with hepatic and septic encephalopathy

Arousal is dependent on the ascending reticular activating system (ARAS), an ensemble of neuronal systems originating the brainstem and projecting to the thalamus, hypothalamus, and basal forebrain. The ARAS is a necessary, but not a sufficient, determinant of conscious awareness, which also depends on the integrated function of brainstem, diencephalic and cortical networks (Fig. 228.1). The ARAS includes neuronal populations located in the tegmentum of the midbrain and the pons. These neurons project to the intralaminar nuclei of the thalamus and basal forebrain, which in turn project via glutamatergic and cholinergic efferents to disseminated cortical destinations. Nuclei in the upper brainstem modulate activity in the basal forebrain, thalamus, striatum, and cortex via norepinephrine, dopamine, and serotonin neurotransmission [2]. The hypothalamus also plays a major role in conscious–unconscious transitions via histaminergic outputs that are implicated in circadian regulation, and via orexin-producing neurons, which regulate arousal by modulating output from brainstem arousal centres [3,4]. Appreciation of a stimulus is not enough for consciousness; there needs to be sufficient motivation for stimuli to enter conscious awareness and be acted upon. Through lesional and functional brain imaging studies it appears that these goal-directed behaviours originate in the medial frontal and anterior cingulate cortices.

Aetiologies of unconsciousness

Aetiologies of pathological unconsciousness may be divided into structural causes and functional or metabolic ones (Box 228.1). The brainstem-diencephalic-cortical substrates of arousal and awareness have redundancy, and therefore discrete focal lesions rarely cause severe or durable derangements in consciousness [5]. Although small brainstem lesions may result in coma, they generally must involve bilateral or paramedian structures [1,6]. Alternatively, consciousness-impairing lesions disrupt communication between structures in the ARAS and their targets, as with bilateral thalamic infarcts in the 'top of the basilar' artery thrombosis. Supratentorial processes that impair consciousness tend to compress or distort diencephalic structures through herniation or excessive midline shift.

Unconsciousness may be the result of a functional derangement of systems necessary for maintaining consciousness. This is commonly associated with derangement of brain oxygen or of glucose delivery or utilization, for instance, as in hypoxia, ischaemia, hypoglycaemia, carbon monoxide, or cyanide toxicity [7]. There may be pathological changes in neuronal or astroglial function due to changes in cellular or extracellular volume, as is the case

with hyponatraemia, hepatic failure, or the dialysis disequilibrium syndrome. There may be changes in neuronal excitability as is the case with seizures, severe electrolyte disturbances, acidaemia and selected drug toxicities.

The degree of neurological impairment determined by a structural lesion or a metabolic derangement is directly linked to the time-course of the underlying disease process. A slowly growing neoplasm may produce minimal symptoms, whereas an acute haemorrhage causing the same degree of anatomical displacement may be neurologically devastating. Similarly, acute fulminant metabolic syndromes tend to produce rapid and severe alterations of consciousness, whereas chronic disorders may present with subtle changes in cognition without altering consciousness until late into the disease course [7,8].

Clinical disorders of consciousness

Classification of disorders of consciousness is made difficult both by the vast differential for these disorders and also by the use of inconsistent or imprecise nomenclature. The terms 'somnolence', lethargy', 'obtundation', 'stupor', and 'coma' are frequently used to characterize clinical phenotypes across the spectrum of impaired consciousness. **Somnolence** refers to a state of drowsiness or near-sleep; this is a normal state prior to sleep, but is pathological if protracted. Another common descriptor is **lethargy**, which denotes a state of extreme fatigue or drowsiness or abnormally prolonged sleep. Plum and Posner define **obtundation** as 'a mild to moderate reduction in alertness, accompanied by a lesser interest in the environment. Such patients have slower psychological responses to stimulation . . . and may be drowsy between bouts of sleep' [1]. **Stupor** is a 'condition of deep sleep or similar behavioural unresponsiveness from which the subject can be aroused only with vigorous and continuous stimulation' [1]. While often used, these terms lack face validity, and may not be meaningfully distinguishable. In clinical practice, it is more helpful to describe the patient's response to a provocative verbal or tactile stimulus [8].

Coma is a state in which both arousal and awareness are severely depressed. Coma is distinguished from transient causes of unconsciousness (syncope) by a duration of at least 1 hour [9]. Coma may resolve to wakefulness or may transition to the **vegetative state** (VS; also referred to as Unresponsive Wakefulness Syndrome) or the **minimally cognitive state** (MCS). As in coma, patients in VS show no evidence of environmental or self-awareness and may have spontaneous or stimulus-induced stereotyped reflexive movements, however they do have cyclic periods of eye opening without visual fixation or pursuit [5,8,10]. MCS is a term reserved for patients with a severe alteration in consciousness who have intermittent, but inconsistent behaviours indicative of self or environmental awareness [9]. VS is characterized by severely depressed function within corticothalamic/corticocortical systems, whereas in MCS there is some residual connectivity within these systems suggesting a greater potential for recovery [11].

Diagnostic approach to the unconscious patient

The first and most important step in assessing unconsciousness is a stepwise neurological examination. Examination of the acutely unconscious patient is necessarily concise and focuses on determining the underlying process, with a primary differentiation into structural versus functional or metabolic aetiologies [8]. On physical examination, particular attention must be paid to the threshold at which a response to stimulus is elicited, an assessment of brainstem function including observation of the breathing pattern, motor responses, and respiratory pattern.

Determining the threshold of responses to stimuli is most commonly achieved with a clinical tool such as the Glasgow Coma Scale (GCS) [12] or the Full Outline of UnResponsiveness (FOUR) score [13], both of which have been extensively validated in patients with coma from a variety of aetiologies (Table 228.1). GCS and FOUR facilitate communication between clinicians and are useful in grading disease severity, yet they also have significant limitations [14]. The assessment of cranial nerve function is critical in that it may have inferential value regarding neighbouring tegmental arousal systems; analysis of respiratory pattern may also help localize the brainstem dysfunction or damage. Extensor or 'decerebrate' posturing is characterized by a stereotypical adduction, extension, and pronation of the upper extremities and extension of the lower extremities, and is indicative of injury to the caudal diencephalon, midbrain, or pons. Flexor or 'decorticate' posturing is manifested by stereotypical flexion and adduction of arms and wrists with extension of lower extremities and is associated with hemispheric or thalamic damage that spares structures at or below the diencephalon [1].

The diagnostic evaluation of the unconscious patient is predicated in the first instance on the search for an aetiological diagnosis. Physiological perturbations such as hypo- or hypertension, bradycardia, respiratory pattern, and hypo- or hyperthermia, should be identified and corrected as they can be both a cause and a consequence of unconsciousness. Tests for hypoglycaemia or electrolyte abnormalities, liver function, renal function, and urine toxicology should be obtained as part of the initial assessment. Complete blood count and coagulation studies should be sent to identify a systemic infectious/inflammatory process or bleeding diathesis. Arterial blood gas should be analysed for hypoxia, hypercarbia, and acidosis. Thyroid function tests and tests of adrenal function should be sent in selected patients. Blood and urine cultures should be sent and a lumbar puncture considered for CSF analysis. Lumbar puncture can rapidly rule out CNS infection or subarachnoid haemorrhage. Brain imaging should be reviewed prior to lumbar puncture in order to assess for mass lesions, which might precipitate brain herniation.

Patients with an acute loss of consciousness whose aetiology is not immediately identified should be evaluated with computed tomography (CT). CT identifies intracranial haemorrhage, hydrocephalus, brain oedema, and compartmental shift, and may suggest stroke, abscess, or tumour [8]. Patients with persisting unexplained coma and/or absent or equivocal CT findings should be evaluated with magnetic resonance imaging (MRI). MRI is more sensitive than CT in identifying posterior fossa lesions, diffuse axonal injury, subtle changes associated with metabolic, septic, autoimmune, or infectious processes.

Patients with unexplained coma should also be evaluated with an electroencephalogram (EEG) to identify non-convulsive seizures or status epilepticus (NCSE). EEG monitoring can reveal NCSE in up to 19% of critically-ill patients being evaluated for a decreased level of consciousness [15]. EEG may also be helpful

Table 228.1 Comparison of the GCS and the FOUR score

Scale	Scoring	Advantages	Limitations
GCS	**Total score from 3 (poor) to 15 (good)** *Eye opening* 4 = Spontaneous 3 = To speech 2 = To pain 1 = None *Best verbal response* 5 = Orientated 4 = Confused conversation 3 = Inappropriate words 2 = Incomprehensible sounds 1 = None *Best motor response* 6 = Obeys commands 5 = Localizes to pain 4 = Withdrawal (normal flexion) 3 = Abnormal flexion (decorticate) 2 = Extension (decerebrate) 1 = None	Widely implemented Easy to learn Rapidly assessed	Prognostic value heavily weighted to motor sub-score No direct assessment of the brainstem Unable to identify a locked-in syndrome
FOUR	**Total score 0 (poor) to 16 (good)** *Eye response* 4 = Eyelids open or opened, tracking, or blinking to command 3 = Eyelids open, but not tracking 2 = Eyelids closed but open to loud voice 1 = Eyelids closed, but open to pain 0 = Eyelids remain closed with pain *Motor response* 4 = Thumbs-up, fist, or peace sign 3 = Localizing to pain 2 = Flexion response to pain 1 = Extension response to pain 0 = No response to pain or generalized myoclonus status *Brainstem reflexes* 4 = Pupil and corneal reflexes present 3 = One pupil wide and fixed 2 = Pupil or corneal reflexes absent 1 = Pupil and corneal reflexes absent 0 = Absent pupil, corneal, and cough reflex *Respiration* 4 = Not intubated, regular breathing pattern 3 = Not intubated, Cheyne–Stokes breathing pattern 2 = Not intubated, irregular breathing 1 = Breathes above ventilator rate 0 = Breathes at ventilator rate or apnoea	Adapted for testing responsiveness in intubated/aphasic/aphonic patients Evaluates aspects of brainstem function Able to identify patients with locked-in syndrome	Not widely implemented More complicated than the GCS, possibly more difficult to learn

Glasgow Coma Scale: reprinted from *The Lancet*, **304**(7872), Teasdale G and Jennett B, 'Assessment of coma and impaired consciousness: a practical scale', pp. 81–4, copyright 1974, with permission from Elsevier. FOUR score: reproduced from Wijdicks EFM et al., 'Validation of a new coma scale: the FOUR score', *Annals of Neurology*, **58**, pp. 585–93, copyright 2005, with permission from John Wiley and Sons Ltd.

in revealing characteristic patterns associated with metabolic or hepatic encephalopathy (e.g. triphasic waves) [7], herpes simplex encephalitis (temporal focus showing periodic lateralized epileptiform discharges or non-ictal sharp wave activity) [16].

Differential diagnosis of unconsciousness

The most important syndrome to be differentiated from coma is the locked-in syndrome (LIS). This results from de-efferentation with preservation of systems necessary for arousal and awareness. The classic lesion causing LIS is injury to the ventral pons just caudal to the third cranial nerve nuclei, resulting in total loss of corticospinal tract/motor function except vertical eye movements and blinking [1]. This may occur secondary to ischaemic stroke, haemorrhage or trauma. Severe neuromuscular disorders such as Guillain–Barré syndrome, botulism, and critical illness neuropathy can engender a state of de-efferentation akin to the LIS. Recently, a subset of patients has been identified who clinically appear to be in VS or MCS, but who retain elements of responsiveness when evaluated with functional MRI or EEG [17–19]; these subjects have evidence of higher-level cortical integration, which is not detectable by bedside neurologic examination—they are 'functionally locked-in' [20].

Coma must also be distinguished from **brain death**, which is the irreversible loss of all brain function, characterized clinically by the absence of consciousness, brainstem reflexes, respiratory drive and motor responses. This assessment is performed only after confounding variables are excluded. **Akinetic mutism** is a condition that may also mimic coma. This is a state of wakefulness in which patients do not move (akinesis) or speak (mutism) and do not appear to be able to respond to stimuli. This usually results from bilateral damage to the anterior cingulate gyrus, dorsal or central thalamus, basal forebrain, or midbrain [1,5,8]. **Catatonia** is psychiatric condition associated with schizophrenia, bipolar disorder, and depression. It manifests with open eyes and the apparent inability to move or purposeless activity not influenced by external stimuli. In the hyperactive subtype these patients appear agitated though this behaviour is not purpose-directed and is poorly responsive to intervention. This condition can be differentiated from coma by EEG and typically resolves with a benzodiazepine challenge.

References

1. Posner J, Saper C, Schiff N, and Plum F. (2007). *Plum and Posner's Diagnosis of Stupor and Coma*, 4th edn. New York: Oxford University Press.
2. Parvizi J and Damasio A. (2001). Consciousness and the brainstem. *Cognition*, **79**(1–2), 135–60.
3. Mignot E, Taheri S, and Nishino S. (2002). Sleeping with the hypothalamus: emerging therapeutic targets for sleep disorders. *Nature Neuroscience*, **5**(Suppl.), 1071–5.
4. Saper CB, Scammell TE, and Lu J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature*, **437**(7063), 1257–63.
5. Goldfine AM and Schiff ND. (2011). Consciousness: its neurobiology and the major classes of impairment. *Neurology Clinic*, **29**(4), 723–37.
6. Parvizi J and Damasio AR. (2003). Neuroanatomical correlates of brainstem coma. *Brain*, **126**(Pt 7), 1524–36.
7. Angel MJ and Young GB. (2011). Metabolic encephalopathies. *Neurology Clinic*, **29**(4), 837–82.
8. Stevens RD and Bhardwaj A. (2006). Approach to the comatose patient. *Critical Care Medicine*, **34**(1), 31–41.
9. Giacino JT, Ashwal S, Childs N, et al. (2002). The minimally conscious state: definition and diagnostic criteria. *Neurology*, **58**(3), 349–53.
10. Multi-Society Task Force on PVS (1994). Medical aspects of the persistent vegetative state. *New England Journal of Medicine*, **330**(21), 1499–508.
11. Schiff ND, Ribary U, Moreno DR, et al. (2002). Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. *Brain*, **125**(6), 1210–34.
12. Teasdale G and Jennett B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet*, **2**(7872), 81–4.
13. Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, and McClelland RL. (2005). Validation of a new coma scale: the FOUR score. *Annals of Neurology*, **58**(4), 585–93.
14. Kornbluth J and Bhardwaj A. (2011). Evaluation of coma: a critical appraisal of popular scoring systems. *Neurocritical Care*, **14**(1), 134–43.
15. Claassen J, Mayer SA, Kowalski RG, Emerson RG, and Hirsch LJ. (2004). Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology*, **62**(10), 1743–8.
16. Steiner I, Budka H, Chaudhuri A, et al. (2010). Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. *European Journal of Neurology*, **17**(8), 999–e57.
17. Cruse D, Chennu S, Chatelle C, et al. (2011). Bedside detection of awareness in the vegetative state: a cohort study. *Lancet*, **378**(9809), 2088–94.
18. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, and Pickard JD. (2006). Detecting awareness in the vegetative state. *Science*, **313**(5792), 1402.
19. Monti MM, Vanhaudenhuyse A, Coleman MR, et al. (2010). Willful modulation of brain activity in disorders of consciousness. *New England Journal of Medicine*, **362**(7), 579–89.
20. Bruno MA, Vanhaudenhuyse A, Thibaut A, Moonen G, and Laureys S. (2011). From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. *Journal of Neurology*, **258**(7), 1373–84.

CHAPTER 229

Management of unconsciousness in the ICU

Joshua Kornbluth and Robert D. Stevens

Key points

- Management of the unconscious patient centres on the search and treatment of the underlying cause, which may be structural or metabolic.
- Circulatory status, airway, and ventilation must be evaluated and stabilized in all cases both to prevent secondary brain injury, and to allow pursuit of diagnostic and therapeutic interventions targeted to the cause of unconsciousness.
- Physical examination may fail to identify ongoing neurological dysfunction and injury, hence selective evaluation and monitoring with non-invasive and invasive methods should be considered.
- In patients with severe TBI, current guidelines recommend ICP monitoring if GCS <9 and if there is an abnormal head CT.
- The prognosis depends on the aetiology, and should integrate available clinical and ancillary evaluations.

Introduction

The management of the unconscious patient centres on an efficient search for causative mechanisms, particularly those that can be halted or reversed by timely intervention. This task is made challenging by the non-specific nature of clinical signs and the large differential diagnosis for the causes of unconsciousness. Concurrent with the diagnostic evaluation, physiological imbalances likely to exacerbate brain dysfunction or damage must be rapidly identified and corrected. Lastly, prognostication and optimizing chances of recovery are equally important aspects of management.

Initial approach

Loss of consciousness results from either structural brain lesions or from toxic/metabolic disturbance. The initial management priority is to assess and stabilize cardiovascular, airway, and ventilatory status. Endotracheal intubation and mechanical ventilation is recommended unless the underlying aetiology of acute unconsciousness can be immediately identified and reversed. Systemic arterial hypertension, especially with associated bradycardia, should arouse concern for intracranial hypertension, yet it may also be the principal aetiological factor, as in intracerebral haemorrhage (ICH) or posterior reversible encephalopathy syndrome. For unconscious patients with traumatic brain injury (TBI) or those in whom trauma cannot be ruled out, the neck should be immobilized until stability of the cervical spine is confirmed clinically (i.e. after return of consciousness) or by imaging. For an overview of management of the acutely unconscious patient refer to Fig. 229.1 [1].

Physical examination

Physical examination must be directed and succinct. Assessment of coma centres on detailed evaluation of brainstem function and motor responses [2]. Different scoring systems exist to estimate the level of wakefulness. Best known are the Glasgow Coma Scale (GCS) based on an assessment of motor, verbal and eye responses, and the Full Outline of UnResponsiveness (FOUR), which incorporates cranial nerve reflexes and breathing patterns [3]. The remainder of the physical examination should evaluate for diagnostic signs: examination of the head and neck (e.g. meningismus), the extremities (e.g. Kernig's or Brudzinski's signs) the optic fundi (e.g. subhyaloid or vitreous haemorrhage in subarachnoid haemorrhage), and the skin (e.g. purpuric lesions in meningococcal meningitis).

Metabolic coma

Metabolic disturbances can cause dramatic alterations in consciousness (Table 229.1). Hence initial assessment should include measurement of core body temperature, serum glucose, and electrolyte concentrations, and a urine or serum toxicology screen. Additionally, the clinician should consider empiric thiamine and specific pharmacological antagonists, such as naloxone, where appropriate.

Seizure activity is identified in patients with rhythmic, repetitive, twitching or jerking movements of the head, face, eyes, or limbs, which resolves with administration of an intravenous benzodiazepine. A substantial proportion of unconscious critically-ill patients may have non-convulsive seizures or status epilepticus (StE NCSE), which may only be identified with an EEG [4].

Patients with suspected meningitis or encephalitis must be treated with appropriate empiric antimicrobial therapy. Loss of consciousness may also supervene in a subset of patients with a remote, non-neurological source of infection. Sepsis-associated

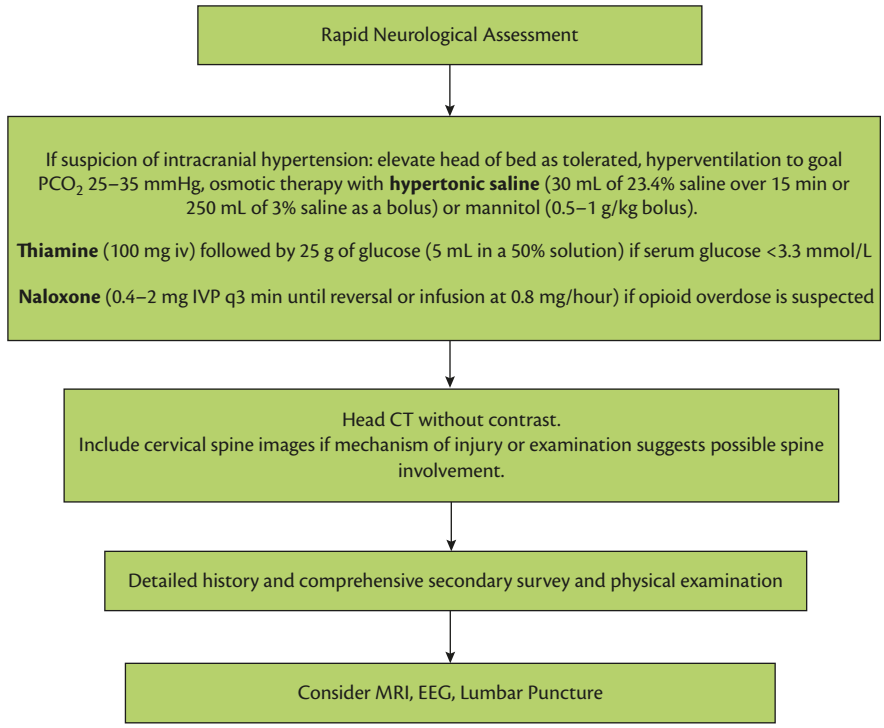


Fig. 229.1 Algorithm for management of the acutely unconscious patient.

IVP, intravenous push.

Adapted with permission from Wolters Kluwer Health and and Society of Critical Care Medicine: *Critical Care Medicine*, Stevens RD, 'Approach to the comatose patient', **34**(1), pp. 31–41, 2006.

Table 229.1 Common causes of toxic-metabolic encephalopathy

Aetiology	Diagnostic studies	Management options or principles
Sepsis-associated encephalopathy	Infectious source identification, exclude meningoencephalitis	Antimicrobial therapy, source control
Hepatic encephalopathy	Liver function tests, serum ammonia, head computerized tomogram	If acute, treatment of cerebral oedema and intracranial hypertension. Consider N-acetyl cysteine Both acute and chronic, agents to decrease ammonia (i.e. lactulose, rifaximin)
Hyponatraemia	Serum and urine sodium concentration; serum and urine osmolalities	Rate of correction depends on chronicity of hyponatraemia; in general increase the serum sodium concentration by 4–6 mmol/L and by less than 9 mmol/L in any 24-hour period and less than 18 mmol/L in any 48-hour period
Hypernatraemia	Serum and urine sodium concentration; serum and urine osmolalities	Correct severe hypernatraemia by 1 to 2 mmol/L/hour to avoid cerebral oedema
Uraemic encephalopathy	Serum creatinine and urea	Renal replacement therapy
Hypoglycaemia	Serum glucose	Bolus iv 25–50mg glucose
Wernicke's encephalopathy	Classic triad of confusion, ataxia and ophthalmoplegia High index of suspicion, especially in nutritionally deficient populations (chronic alcoholics, advanced cancer, bariatric surgery)	Intravenous thiamine repletion
Hypoxic-ischaemic encephalopathy	Electoencaphalogram (EEG), somatosensory-evoked potentials (SSEPs), magnetic resonance imaging (MRI)	Therapeutic hypothermia
Toxidrome	Identification of toxic ingestion	Activated charcoal if recent oral intake and to disrupt hepatoenteric recirculation Antidotes/antagonists if available

is managed with source identification and control, antimicrobial therapy, and rigorous supportive measures.

Structural coma

When the cause of acute unconsciousness cannot be identified and reversed within the first minutes, the patient should undergo endotracheal intubation and a computed tomography (CT) of the head obtained immediately. Structural abnormalities associated with loss of consciousness include lesions in the arousal systems located in the rostral brainstem and diencephalon, unilateral hemispheric lesions with sufficient mass effect to affect the arousal systems, or lesions involving bilateral cerebral hemispheres [2]. In cases when a structural cause is not identified or well characterized with CT, brain MRI should be considered, in particular if acute cerebral ischaemia or infarction is a diagnostic consideration.

Loss of consciousness is a presenting sign in acute transtentorial herniation [2,5], and there is a correlation between the degree of lateral displacement of midline structures and the severity of alteration of consciousness [6]. The time-course during which midline structures are displaced will determine the likelihood and degree of alteration of consciousness (Fig. 229.2). Evidence of acute clinical herniation and/or increased intracranial pressure (ICP) (e.g. hypertension, bradycardia, apnoea) should be managed with hyperosmolar therapy, hyperventilation, and sedation to control brain oedema and cerebral blood volume, while surgical decompression options are explored [7]. For an overview of this approach refer to Fig. 229.3. If acute obstructive hydrocephalus is identified, emergent placement of an intraventricular catheter is indicated.

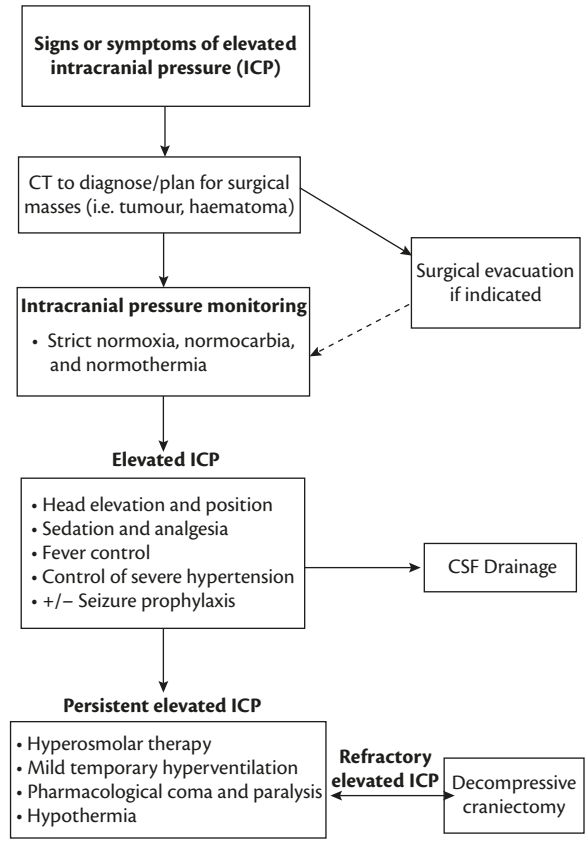


Fig. 229.3 Diagnosis and treatment of intracranial hypertension.
Adapted from *Neurologic Clinics*, Rangel-Castilla L et al., 'Management of intracranial hypertension', **26**(2), pp. 521–41, Copyright 2008, with permission from Elsevier.

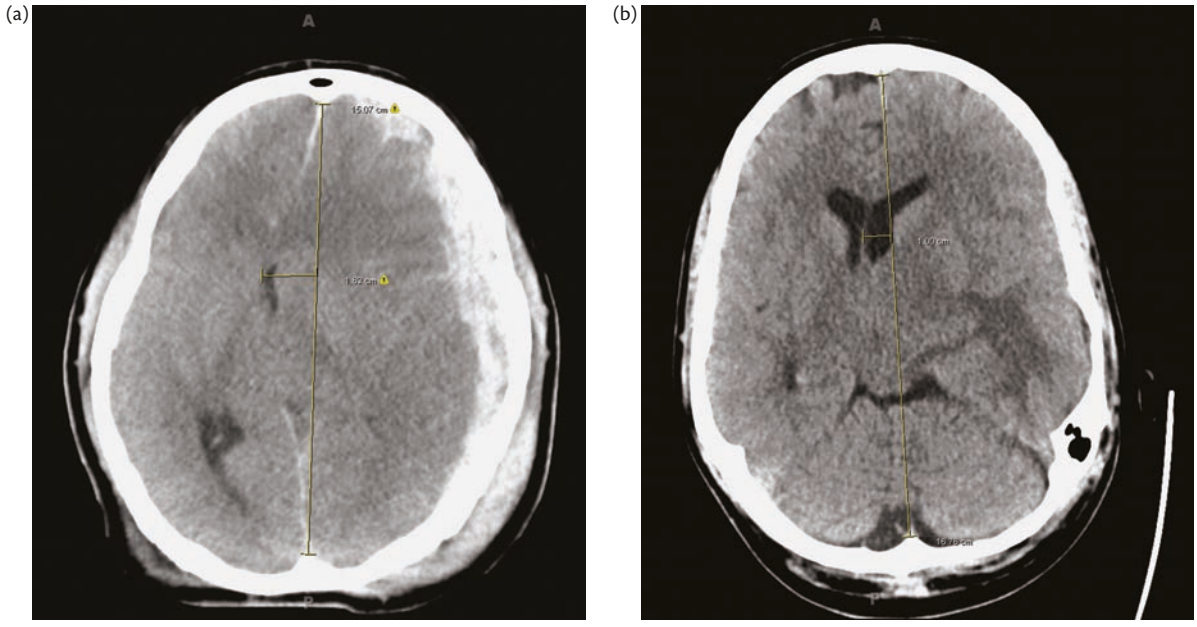


Fig. 229.2 (a) Non-contrast head CT of a 58-year-old patient with an acute left-sided subdural haematoma with resultant 1.8 cm of midline shift at the septum pellucidum—this patient had a GCS of 3. (b) Non-contrast head CT of a 67-year-old patient with a left-sided glioma with 1 cm of midline shift at the septum pellucidum—this patient had a GCS of 15.

Role of neuromonitoring

In patients with severe brain injury, perturbations in brain physiology and metabolism may not be apparent on physical examination, hence the need for neurophysiological monitoring. Continuous electroencephalography, somatosensory-evoked potentials (SSEP) and brainstem auditory-evoked responses are valuable electrodiagnostic modalities, which have established roles in the diagnosis and prognosis of unconscious patients. Other commonly used methods are ICP monitoring, cerebral microdialysis, and brain tissue oxygen monitoring.

Continuous EEG (cEEG) is indicated in unconscious patients to identify non-convulsive seizures or status epilepticus, and to monitor response to anti-epileptic drug therapy. Continuous EEG monitoring is also useful in pharmacologically-induced coma for treatment of refractory intracranial hypertension where burst-suppression is the goal. Selected patterns on EEG (e.g. burst suppression, lack of stimulus-evoked background reactivity) have significance in patients with anoxic-ischemic encephalopathy following cardiac arrest [8]. Non-convulsive seizures or (NCSE) may occur in up to 19% of patients after SAH, 21% of patients after ICHm, 11% after ischaemic stroke, 18% of patients after TBI, and as many as 35% of patients following cardiac arrest [9].

In patients with severe TBI, current guidelines recommend ICP monitoring if GCS <9 and if there is an abnormal head CT [10]. Increased ICP may cause permanent injury, both by direct effect of pressure on brain structures with subsequent herniation and by cerebral infarction via global or regional reductions in cerebral perfusion pressure (e.g. posterior cerebral artery occlusion resulting from transtentorial herniation). The role of routine ICP monitoring in other clinical settings is less well studied however a recent international multidisciplinary consensus conference recommended that ICP and CPP should be monitored in patients at risk for ICP elevation based on clinical and/or imaging features, and to guide medical and surgical interventions [11]. Cerebral oxygenation may be measured globally via sampling of jugular bulb oximetry whereas regional oxygenation may be assessed via an invasive probe that measures brain tissue oxygen tension (PbO_2). Evidence indicates that low values of PbO_2 are associated with adverse TBI outcome [12] and that decreased PbO_2 may occur independently of ICP changes [13]. Cerebral microdialysis allows near real-time monitoring of dynamic changes in brain neurochemistry, which can be influenced through physiological or metabolic intervention. Microdialysis-derived markers of cerebral metabolic distress, including elevated brain interstitial lactate-pyruvate ratio and low glucose, are independently associated with long-term neurological recovery after TBI [14].

Prognosis

In patients with acute loss of consciousness, prognosis is dependent on the underlying aetiology. Hypoglycaemic coma, for instance, will have an excellent prognosis if rapidly recognized and reversed. The most common aetiologies of coma are hypoxic/ischaemic injury following cardiac arrest and severe TBI, each of which carries a significant risk of death or long-term disability [2]. In both settings, prognosis relies on features of the neurological examination, anatomical and physiological changes identified with neuroimaging, abnormalities detected with electrodiagnostic methods, as well as physiological and biochemical imbalances at both the brain and systemic level.

In patients with severe TBI, prognostic scoring systems derived from multivariable models are able to discriminate between favourable and unfavourable 6-month outcomes, and have been validated both internally and externally [15,16]. Both IMPACT and CRASH scores include age, pupillary responses, motor responses, pattern of injury on head CT, and non-neurological perturbations, such as hypoxia, hypotension, and extracranial injuries [15,16]; notwithstanding, these systems do not have sufficient accuracy to determine prognosis for individual patients.

Following cardiac arrest, neurologic prognosis is determined on the basis of physical findings and selected electrophysiological markers [17]. Specific variables associated with adverse outcome include absent pupillary or corneal reflexes at 72 hours, absent or extensor motor responses at 72 hours, myoclonic status epilepticus, burst suppression on EEG, and bilaterally absent cortical signals on SSEP testing. Improved outcome observed in cardiac arrest patients treated with therapeutic hypothermia has prompted a re-evaluation of neurological prognostication, with recent studies demonstrating that selected clinical signs, such as the absence or abnormality of motor responses, have lost specificity as outcome predictors [9,18].

Recovery

Although early and intensive physical and occupational therapy have been linked to improved outcome in critically-ill patients [19], the rehabilitation of patients with persisting unconsciousness presents many inherent challenges. Studies conducted in unconscious patients following TBI indicate that pharmacological promotion of arousal may be associated with better short-term functional recovery, an effect that was recently demonstrated in a multicentre randomized controlled trial of amantadine [20]. Most of the data supporting the use of these drugs is in the subacute and chronic phase of recovery, potential benefits in the acute period need further study.

References

1. Stevens RD and Bhardwaj A. (2006). Approach to the comatose patient. *Critical Care Medicine*, **34**(1), 31–41.
2. Posner J, Saper C, Schiff N, and Plum F. (2007). *Plum and Posner's Diagnosis of Stupor and Coma*, 4th edn. Oxford: Oxford University Press.
3. Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, and McClelland RL. (2005). Validation of a new coma scale: the FOUR score. *Annals of Neurology*, **58**(4), 585–93.
4. Oddo M, Carrera E, Claassen J, Mayer SA, and Hirsch LJ. (2009). Continuous electroencephalography in the medical intensive care unit. *Critical Care Medicine*, **37**(6), 2051–6.
5. Koenig MA, Bryan M, Lewin JL, 3rd, Mirski MA, Geocadin RG, and Stevens RD. (2008). Reversal of transtentorial herniation with hypertonic saline. *Neurology*, **70**(13), 1023–9.
6. Ropper AH. (1986). Lateral displacement of the brain and level of consciousness in patients with an acute hemispheral mass. *New England Journal of Medicine*, **314**(15), 953–8.
7. Stevens, R.D., Shoykhet, M., and Cadena, R. (2015). Emergency neurological life support: intracranial hypertension and herniation. *Neurocritical Care*, **23**(Suppl. 2), 76–82.
8. Rossetti AO, Oddo M, Logroscino G, and Kaplan PW. (2010). Prognostication after cardiac arrest and hypothermia: a prospective study. *Annals of Neurology*, **67**(3), 301–7.

9. Friedman D, Claassen J, and Hirsch LJ. (2009). Continuous electroencephalogram monitoring in the intensive care unit. *Anesthesia and Analgesia*, **109**(2), 506–23.
10. Brain Trauma Foundation AAoNS, Congress of Neurological Surgeons (2007). Guidelines for the management of severe traumatic brain injury. *Journal of Neurotrauma*, **24**(Suppl. 1), S1–106.
11. LeRoux P, Menon DK, Citerio G, et al. (2014). Consensus summary statement of the international multidisciplinary consensus conference on multimodality monitoring in neurocritical care: a statement for healthcare professionals from the neurocritical care society and the european society of intensive care medicine. *Intensive Care Medicine*, **40**(9), 1189–209.
12. Maloney-Wilensky E, Gracias V, Itkin A, et al. (2009). Brain tissue oxygen and outcome after severe traumatic brain injury: a systematic review. *Critical Care Medicine*, **37**(6), 2057–63.
13. Chang JJ, Youn TS, Benson D, et al. (2009). Physiologic and functional outcome correlates of brain tissue hypoxia in traumatic brain injury. *Critical Care Medicine*, **37**(1), 283–90.
14. Timofeev I, Carpenter KL, Nortje J, et al. (2011). Cerebral extracellular chemistry and outcome following traumatic brain injury: a microdialysis study of 223 patients. *Brain*, **134**(Pt 2), 484–94.
15. Steyerberg EW, Mushkudiani N, Perel P, et al. (2008). Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Medicine*, **5**(8), e165; discussion.
16. Collaborators MCT, Perel P, Arango M, et al. (2008). Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *British Medical Journal*, **336**(7641), 425–9.
17. Greer DM, Yang J, Scripko PD, et al. (2012). Clinical examination for outcome prediction in nontraumatic coma. *Critical Care Medicine*, **40**(4), 1150–6.
18. Bouwes A, Robillard LB, Binnekade JM, et al. (2012). The influence of rewarming after therapeutic hypothermia on outcome after cardiac arrest. *Resuscitation*, **83**(8), 996–1000.
19. Schweickert WD, Pohlman MC, Pohlman AS, et al. (2009). Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*, **373**(9678), 1874–82.
20. Giacino JT, Whyte J, Bagiella E, et al. (2012). Placebo-controlled trial of amantadine for severe traumatic brain injury. *New England Journal of Medicine*, **366**(9), 819–26.

CHAPTER 230

Non-pharmacological neuroprotection in the ICU

Niklas Nielsen and David B. Seder

Key points

- After control of the primary process causing acute neurological injury, further control of secondary injury pathways can be achieved by manipulating brain temperature, and achieving biochemical and metabolic homeostasis.
- Surgical techniques are routinely used to remove blood or trapped cerebrospinal fluid, control mass effect, or repair unstable vascular abnormalities.
- Therapeutic temperature management to a defined target can be achieved and maintained using cold fluids, ice packs, body surface cooling pads, and surface and intravascular devices with servo (feedback) mechanisms.
- Successful temperature management requires attentive surveillance, and control of shivering and other potential complications such as bleeding, infection, cardiac arrhythmias, and electrolyte and metabolic disturbances.
- Extremes of oxygenation and ventilation are associated with worse long-term functional outcomes, and should be avoided.

Principles of neuroprotection

Following respiratory and haemodynamic stabilization, neuroprotection rests on two main principles. First, the rapid diagnosis and management of the primary brain injury: restore the spontaneous circulation in cardiac arrest, secure the bleeding aneurysm with surgery or coiling, and remove the acute thrombus in stroke. Secondly, the prevention of further secondary injury and cellular injurious processes facilitate a milieu of healing and repair by optimization of physiological and metabolic parameters. Table 230.1 describes general haemodynamic and metabolic causes of secondary injury that may exacerbate most or all types of neurological injury. This chapter outlines a clinical approach to managing neurological injury, focusing on non-pharmacological strategies.

Specific non-pharmacological therapies to decrease secondary neurological injury

Decompressive surgery

The routine use of decompressive hemi-craniectomy in stroke is supported by the pooled result of three small randomized clinical trials. In patients aged less than 60 suffering from large volume cerebral infarction due to carotid terminus or middle cerebral artery (MCA) occlusion, surgical decompression reduced mortality and improved overall neurological outcomes compared with best medical management alone [1]. The timing of hemi-craniectomy in stroke is likely to be crucial—performed too early, it may be done unnecessarily in a small number of patients, who would otherwise make a good recovery with medical therapy alone. Performed too late, the patient may suffer harm due to increased intracranial pressure (ICP), herniation, and its associated injuries. One trial suggested benefit primarily in patients whose surgery was less than 48 hours after stroke onset [2], which suggests that such patients require close monitoring, frequent brain imaging, and a predetermined plan in place in the event that oedema progresses to the point of needing surgery. With increasing brain swelling, small changes in intracranial volume result in large changes in ICP; understanding this relationship reinforces the need for constant observation and a predetermined management plan (Fig. 230.1). In European guidelines, decompressive craniectomy within 48 hours after symptom onset is recommended (Class 1, level A) in patients 60 years or younger with evolving malignant MCA infarction [3].

The appropriate use of surgical decompression is less clear in traumatic brain injury (TBI). One large trial randomizing patients with severe traumatic brain injury (TBI) and elevated ICP to early bifrontal decompressive craniectomy or best medical management showed no benefit with surgery [4]. Further trials are ongoing and pending those trial results, decompressive surgery remains a frequently used salvage therapy when the cranial vault can no longer contain its contents [5].

Targeted temperature management

In many clinical settings including, stroke, and following cardiac arrest and TBI, fever may be a marker of injury severity, a cause of secondary neurological injury, or both. Fever is associated with worse outcomes, which has led to the concept of therapeutic thermoregulation. Deliberate lowering the body and brain temperature to a level below the hypothalamic thermostat set point has been used for neuroprotection for decades. This intervention has traditionally been termed **induced** or **therapeutic** hypothermia, but recently **targeted temperature management** (TTM) was suggested to cover all dimensions where temperature is regulated with the goal of improving patients' outcomes [6].

Temperature management is used to protect organs during the ischaemia period before transplantation, during neurosurgery for

Table 230.1 General causes of secondary brain injury

Aetiology	Pathophysiology	Prevention/management
Hypotension	Inadequate cerebral perfusion pressure (CPP) Ischaemia and infarction	Maintenance of adequate blood pressure Optimize vascular tone Optimize intravascular volume
Hypoxia	Exacerbation of ischaemic injury	Interventions aimed at increasing O_2 delivery
Hyperoxia	Exacerbation of reperfusion injury, vasoconstriction	Normalize PaO_2
Hyperventilation	Arteriolar constriction decreases cerebral blood flow, increases volume of ischaemic tissue	Ventilate to normal pH and $PaCO_2$
Hypoglycaemia	Ischaemic injury	Target arterial or venous blood glucose levels >6 mmol/L
Hyperglycaemia	Increases oxidative damage	Target arterial or venous blood glucose levels <10 mmol/L
Increased intracranial pressure and brain oedema	Increases/potentiates ischaemia, may lead to brain herniation	Elevate head of bed Avoid jugular compression Manage discomfort and anxiety Optimize volume status Optimize plasma oncotic pressure Osmotherapy, cerebral perfusion pressure optimization, hypothermia, metabolic suppression, decompressive surgery
Fever	Increases inflammation, intracranial pressure, apoptosis, cellular metabolic activity, excitotoxicity	Infection control Antipyretics Targeted temperature management
Hyperperfusion	Loss of cerebral autoregulation	Antihypertensives

aneurysmal clipping, and has been a mainstay for protecting neurological function during cardiac surgery with induced circulatory standstill. In these examples, hypothermia is induced before the ischaemic event and is often maintained through reperfusion. When TTM is used in critical care the ischaemic event and even often reperfusion from the ischaemia have already taken place, and temperature management is used in an attempt to prevent further reperfusion injury and other secondary damage. Experimental animal studies indicate beneficial effect of hypothermia in both global and focal ischaemia models at various temperatures, ranging from very mild hypothermia of 35°C to deeper levels. The exact mechanism of the protective action of temperature modulation is not fully understood, but experiments have shown that hypothermia decreases the cerebral metabolic rate of oxygen and affects cell death pathways, such as excitotoxicity, apoptosis, inflammation, calcium homeostasis, gene expression and free radical production. Inducing hypothermia also decreases elevated ICP [7,8].

Clinically targeted temperature management is recommended in many guidelines for the treatment of patients resuscitated after cardiac arrest and in in hypoxic ischemic encephalopathy in neonates [9]. Other areas of potential use are spinal cord injury, traumatic brain injury, hepatic encephalopathy with cerebral oedema, and stroke, but these indications lack proof of efficacy.

Clinical trials indicate improved survival and neurological outcome when a target temperature of 32–34°C is employed for 12–24 hours in comatose adult patients with return of circulation after suffering

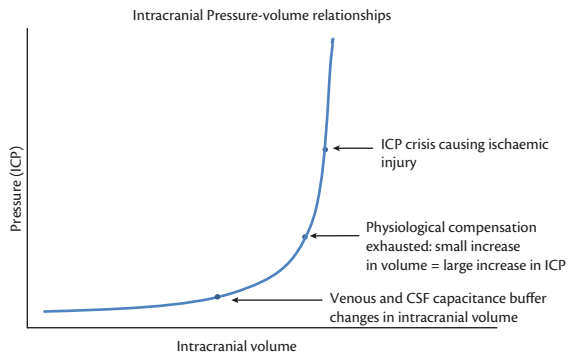


Fig. 230.1 Intracranial pressure–volume relationships. Initially displacement and reduction in the intracranial volumes of cerebrospinal fluid (CSF) and venous blood acts as a compensatory mechanism and ICP does not increase dramatically. Once this compensatory mechanism is exhausted the ICP increases exponentially.

out-of-hospital cardiac arrest from a shockable rhythm. During the last decade, this intervention has been widely implemented around the world. Clinical practice has also extended to cardiac arrests with other initial rhythms, and following in-hospital cardiac arrest. The population that might benefit most from targeted temperature management is not yet defined [6,10]. Moreover, the optimal depth, duration and timing of targeted temperature management are unknown. Since lower temperatures are associated with higher rates of infection, sepsis, coagulopathy, arrhythmias, and metabolic and electrolyte disturbances, and because the neuroprotective activity of hypothermia probably varies among indications, a tailored approach to the optimal use in an individual patient awaits further research. It is also unknown if targeting normothermia and preventing fever might be as effective as inducing hypothermia in a general population. Large trials in stroke, cardiac arrest and TBI are ongoing [11].

Targeted temperature management is divided in three phases: induction to the desired temperature, maintenance of the target temperature, and rewarming. Rapid infusion of cold crystalloid fluids and externally placed cooling pads can be used for induction of hypothermia. Intravascular or external servo-controlled temperature management systems are convenient means for inducing and maintaining hypothermia. At the end of the cooling period, the body temperature is gradually returned to normothermia at a controlled rate of up to 0.5°C/hour. Again, the optimal rate of rewarming is not known, but uncontrolled rewarming may result in rapid increase in temperature and rebound fever. Rewarming is a period in which ICP, seizures, and hypotension may cause secondary injury, and close monitoring is important. Continued fever control after the intervention period or even continued targeted temperature management to hypothermic levels could be considered if the underlying physiology is unresolved [7].

Ventriculostomy and cerebrospinal fluid (CSF) drainage

Patients with acute, obstructive hydrocephalus require urgent decompression by external ventricular drainage. When no functional intracranial mass lesion is present, and hydrocephalus is communicating in nature, lumbar drainage is a reasonable alternative. The choroid plexus produces 15–20 mL cerebrospinal fluid/hour in a normal adult. As a result, obstruction rapidly results in increased ICP and progressive obtundation. Standard therapy is placement of a ventricular catheter through a small frontal burrhole to drain cerebrospinal fluid (CSF). Ventricular drainage catheters have a high infection rate, and must be placed and handled using sterile and aseptic technique. Prophylactic antibiotics at the time of insertion or the routine use of antibiotic-coated or impregnated catheters may be reasonable practices to reduce infection risk, dependent on the local microbial environment [12].

Ventriculostomy is also used to monitor ICP, and CSF drainage to relieve pressure when the ICP is elevated. Although the exact level of intracranial pressure causing harm is unknown, most experts agree on treatment of ICP when it exceeds 20 mmHg and maintenance of cerebral perfusion pressure (CPP) >60 mmHg for adult patients [13,14].

Evacuation of blood

Animal models suggest blood is inherently inflammatory and probably harmful in the brain, ventricles, and subarachnoid space. In aneurysmal subarachnoid haemorrhage, the volume of subarachnoid blood is associated with the subsequent development of vasospasm [15], and lumbar drainage accelerates clearance of blood from the subarachnoid space and decreases delayed neurological deficits. Preliminary work in intraventricular haemorrhage shows benefit to an aggressive strategy of intraventricular clot removal, and a large randomized trial comparing intraventricular tissue plasminogen activator administration with placebo is currently underway.

Bedside care

To facilitate venous drainage from the skull jugular venous return should not be constricted—optimize head/neck position and avoid venous obstruction from tight endotracheal or tracheostomy ties, or from cervical spine collars. The effect of elevating the head of the bed to optimize ICP varies from patient to patient, and should be guided by volume status, and ICP and CPP monitoring.

Physiological homeostasis

Oxygenation

Hypoxia is a potent and well-established cause of secondary brain injury. The impact of hyperoxia is more controversial. Increased oxygenation levels are associated with the formation of reactive oxygen species and lipid peroxidation of neuronal cell membranes. When high fractions of oxygen are administered at normo- or hyperbaric conditions cerebral vessels constrict, with potential to worsen ischemia, and hyperoxia may provoke seizures related to increased cerebral excitation. There may also be adverse consequences for the respiratory system. Hyperoxia may, on the other hand, increase oxygen delivery, improve the cerebral metabolic rate of oxygen by improving mitochondrial function, and may be anti-inflammatory. The higher tension of oxygen may also help diffusion over swollen endothelium and decrease oedema formation associated with the primary injury. Animal experimental data are conflicting, and support both benefit and harm from hyperoxia. In clinical studies on stroke, hyperbaric oxygen does not seem to be beneficial, and several studies indicate worse outcomes with hyperoxia following resuscitation from cardiac arrest. Current data suggest there is no proven benefit of hyperoxia as an intervention in acute treatment of neurological injuries, and potential harm must be considered. Best current evidence suggests oxygen should be titrated to arterial normoxia as soon as initial resuscitation is accomplished [16].

Ventilation

Changes in blood carbon dioxide tension ($PaCO_2$) have profound effects on cerebral blood flow. Cerebral blood flow decreases due to arterial vasoconstriction when ventilation is increased and $PaCO_2$ falls. Vasoconstriction due to hypocapnia leads to decreased oxygen delivery in the already injured brain, with global or focal ischaemia, and may further increase neurological damage. Conversely, hypercapnia leads to cerebral vasodilation and may increase oedema and ICP. For patients with controlled ventilation and neurological injury, most evidence points in the direction of avoiding both hypo- and hypercapnia, and thus aim for normocapnia [17]. Therapeutic hyperventilation still has a role in the acute treatment of increased ICP with concomitant neurological deterioration, while awaiting more definitive treatments like haematoma evacuation, drainage,

or decompressive craniectomy [14]. For patients treated with hypothermia, it is even more important to pay close attention to ventilation and $PaCO_2$, since hypothermia will lower body CO_2 production and simultaneously increase gas solubility, sometimes leading to accidental hypocapnia and worsened ischaemia.

Blood gas analysis is also affected by body temperature. There are two approaches for blood gas presentation—gas tensions corrected for actual body temperature (pH-stat), and gas tensions not corrected for body temperature and thus analysed at 37°C (alpha-stat). Whether to use alpha- or pH-stat for blood gas analysis during hypothermia is open to debate, but it is important that the clinician is familiar with the differences of the two approaches [18].

Glycaemic control

Sustained hyperglycaemia is common in all forms of acute neurological injury and is associated with worse outcomes. In experimental models of stroke, TBI, and global ischaemia, hyperglycaemia increases neurological injury. There are few data to corroborate these causal relationships in humans, and it may be that hyperglycaemia results from the stress response seen with more severe injury.

Hypoglycaemic episodes lead to energy substrate deficiency in the injured brain, and are clearly associated with harm. The concept of 'tight glycaemic control' will lead to more hypoglycaemic episodes and may therefore be particularly problematic in patients with neurologically injuries. Most recommendations today, both for focal and global ischaemia, advocate a blood glucose concentration between 6 and 10 mmol/L after brain injury, and avoiding wide variations in blood glucose concentration [19,20].

Conclusion

Halting the primary injurious processes, preventing secondary brain injury, and restoring metabolic, haemodynamic, and biochemical homeostasis to allow healing are critical functions of the intensivist in treating neurological disease.

References

1. Vahedi K, Hofmeijer J, Juettler E, et al. (2007). Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet: Neurology*, **6**(3), 215–22.
2. Hofmeijer J, Kappelle LJ, Algra A, et al. (2009). Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. *Lancet: Neurology*, **8**(4), 326–33.
3. European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee, Ringleb PA, et al. (2008). Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovascular Diseases*, **25**(5), 457–507.
4. Cooper DJ, Rosenfeld JV, Murray L, et al. (2011). Decompressive craniectomy in diffuse traumatic brain injury. *New England Journal of Medicine*, **364**(16), 1493–502.
5. Albanese J, Leone M, Alliez JR, et al. (2003). Decompressive craniectomy for severe traumatic brain injury: Evaluation of the effects at one year. *Critical Care Medicine*, **31**(10), 2535–8.
6. Nunnally ME, Jaeschke R, Bellingan GJ, et al. (2011). Targeted temperature management in critical care: a report and recommendations from five professional societies. *Critical Care Medicine*, **39**(5), 1113–25.
7. Polderman KH. (2008). Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet*, **371**(9628), 1955–69.
8. Yenari MA and Han HS. (2012). Neuroprotective mechanisms of hypothermia in brain ischaemia. *Nature Reviews Neuroscience*, **13**(4), 267–78.
9. Hazinski MF, Nolan JP, Billi JE, et al. (2010). Part 1: Executive summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*, **122**(16 Suppl. 2), S250–75.
10. Nielsen N, Friberg H, Gluud C, et al. (2011). Hypothermia after cardiac arrest should be further evaluated—a systematic review of randomised trials with meta-analysis and trial sequential analysis. *International Journal of Cardiology*, **151**(3), 333–41.
11. Nielsen N, Wetterslev J, al-Subaie N, et al. (2012). Target temperature management after out-of-hospital cardiac arrest—a randomized, parallel-group, assessor-blinded clinical trial—rationale and design. *American Heart Journal*, **163**(4), 541–8.
12. Sonabend AM, Korenfeld Y, Crisman C, et al. (2011). Prevention of ventriculostomy-related infections with prophylactic antibiotics and antibiotic-coated external ventricular drains: a systematic review. *Neurosurgery*, **68**(4), 996–1005.
13. Grande PO. (2011). The Lund concept for the treatment of patients with severe traumatic brain injury. *Journal of Neurosurgical Anesthesiology*, **23**(4), 358–62.
14. Brain Trauma Foundation, American Association of Neurological Surgeons, and Congress of Neurological Surgeons. (2007). Guidelines for the management of severe traumatic brain injury. *Journal of Neurotrauma*, **24**(Suppl. 1), S1–106.
15. Claassen J, Bernardini GL, Kreiter K, et al. (2001). Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the Fisher scale revisited. *Stroke*, **32**(9), 2012–20.
16. Diringer MN. (2008). Hyperoxia: good or bad for the injured brain? *Current Opinion in Critical Care*, **14**(2), 167–71.
17. Curley G, Kavanagh BP, and Laffey JG. (2010). Hypocapnia and the injured brain: more harm than benefit. *Critical Care Medicine*, **38**(5), 1348–59.
18. Pynnonen L, Falkenbach P, Kamarainen A, et al. (2011). Therapeutic hypothermia after cardiac arrest—cerebral perfusion and metabolism during upper and lower threshold normocapnia. *Resuscitation*, **82**(9), 1174–9.
19. Egi M, Finfer S, and Bellomo R. (2011). Glycemic control in the ICU. *Chest*, **140**(1), 212–20.
20. Oddo M, Schmidt JM, Mayer SA, et al. (2008). Glucose control after severe brain injury. *Current Opinion in Clinical Nutrition and Metabolic Care*, **11**(2), 134–9.

PART 9.6

Seizures

CHAPTER 231

Pathophysiology and causes of seizures

Thomas P. Bleck

Key points

- Several mechanisms linked to critical illness can lead to seizures.
- Seizures may be the primary reason for admission to the ICU, for example, for the treatment of status epilepticus, or occur secondary to another critical illness.
- Failure to remove glutamate and potassium from the extracellular space occurs in cerebral trauma, hypoxia, ischaemia, and hypoglycaemia.
- Loss of normal neuronal inhibition occurs during withdrawal from alcohol and other hypnosedative agents, or in the presence of GABA antagonists, such as penicillin or imipenem.
- Conditions such as cerebral trauma, haemorrhage, abscesses, and neoplasms produce physical distortions of the adjacent neurons, astrocytes, and the extracellular space. Although acute metabolic disturbances can produce seizures, an underlying structural lesion must always be considered and excluded.

Introduction

Seizures result from imbalances between excitation and inhibition, and between neuronal synchrony and dyssynchrony [1]. Current models of human seizures implicate the cerebral cortex in the genesis of seizures, although thalamic mechanisms (particularly the thalamic reticular formation) are involved in the synchronization of cortical neurons. These same systems are involved in the maintenance of consciousness and in sleep–wake cycling [2]. Often, the precipitants of a seizure at a particular time in the critical care setting are pharmacological, even in the patient with a predisposition to seizures. Others may reflect normal physiological rhythms; for example, sleep stage transitions are typically times of increased cortical and thalamocortical neuronal synchrony.

A clear distinction should be drawn between seizures, which are events occurring to the patient, and epilepsy, which is a chronic condition characterized by the tendency to have repeated seizures as a consequence of a central nervous system disorder. In the critical care unit, the majority of patients experiencing seizures do not have pre-existing epilepsy, and their chances of developing epilepsy in the future are usually more dependent on the cause of their seizures than on the number or intensity of seizures they experience. Because of other deleterious neuronal and systemic effects of seizures, however, their rapid diagnosis and suppression during a period of critical illness is almost always necessary [3].

The major excitatory neurotransmitters in the cerebral cortex are excitatory amino acids, particularly glutamate. These transmitters control a variety of ion channels and second messenger systems, some of which are linked to the production of nitric oxide. The ion channels gated during excitation allow the entry of sodium, which depolarizes the post-synaptic neuron, and calcium, which can trigger both intracellular metabolic processes and the transcription of a variety of gene products. During normal brain function, these processes are required for learning, memory, and other functions.

The line dividing normal neuronal physiology from the excessively rapid, hypersynchronous depolarizations, which characterize a seizure is quite narrow, and appears to depend upon several mechanisms that can be deranged by critical illnesses. Failure to remove glutamate and potassium from the extracellular space, functions performed predominantly by astrocytes, occurs in trauma, hypoxia, ischaemia, and hypoglycaemia. Loss of normal inhibition, which is provided in the cortex primarily by gamma-aminobutyric acid (GABA), and to a lesser extent, glycine, occurs during withdrawal from alcohol and other hypnosedative agents, or in the presence of GABA antagonists, such as penicillin or imipenem. The deleterious effect of the ICU environment on sleep–wake cycling alters thalamocortical rhythmicity, but its contribution to seizures is only beginning to be studied.

The reader will recognize that many of these mechanisms are common to other conditions, such as stroke and trauma, for which the patient may require critical care. In the future, one hopes that a more direct approach to correcting these mechanisms will improve the outcome of these patients. At present, the mainstay of therapy is the pharmacological effect to interfere with the processes that trigger or maintain seizures, particularly by employing GABA agonists (e.g. benzodiazepines), or agents that interfere with sustained high-frequency repetitive firing (e.g. phenytoin). While the currently available agents are relatively effective in this role, they all have significant adverse effects, and do not interfere with the process of epileptogenesis.

Many of the central problems regarding epileptogenesis remain to be solved, but the process involves several steps that are relevant to the intensivist. Focal cerebral cortical disorders, whether or not accompanied by seizures in their acute stages, may lay the foundation for later epilepsy. Conditions such as cerebral trauma, haemorrhages, abscesses, and neoplasms, all produce physical distortions

of the adjacent neurons, astrocytes, and the extracellular space. Deposition of iron in the cortex from the breakdown of haemoglobin appears particularly epileptogenic. The timely diagnosis and management of these conditions may prevent later epilepsy or lessen its severity.

Aetiology

In critical care, seizures may either be the patient's primary condition (because of status epilepticus), or develop as a complication of another illness. The physician must determine rapidly if a treatable aetiology is present. The patient suffering a single seizure, or a few discrete seizures, in the setting of a critical illness may not require antiseizure therapy, but this decision depends on the aetiology of the seizure and the confounding effects of other illnesses. The patient presenting in status epilepticus requires aggressive treatment, unless an underlying condition renders, such intervention pointless.

Discrete seizures

Seizures occurring during another critical illness usually represent a central nervous system manifestation of a systemic disorder. In our prospective study of neurological complications of critical medical illnesses, seizures were the second most common problem encountered and were almost as frequent as metabolic encephalopathy [4]. The most frequent causes were cerebrovascular disease, central nervous system infections, metabolic encephalopathies, neoplasms, hypoglycaemia, and osmolar disorders (including non-ketotic hyperglycaemia). At the Mayo Clinic, Wijdicks and Sharbrough retrospectively analysed seizures occurring in intensive care units (ICUs), finding that drug withdrawal was the commonest aetiology of seizures in their patients [5]. Box 231.1 summarizes common causes of seizures in ICU patients.

Iatrogenic precipitants of seizures should be rapidly detected and the cause removed, if possible, instead of treating the patient only with antiseizure agents. Seizures occurring because of the abrupt withdrawal of GABA agonists (e.g. hypnosedatives, such as barbiturates and benzodiazepines) are managed by using a drug of the same class, followed by a very slowly decreasing dose to prevent recurrence of withdrawal seizures. The actual agent selected may be different than that from which the patient is withdrawing; the choice depends on the other circumstances of the patient. Alcohol withdrawal seizures constitute a special type of hypnosedative withdrawal, because several neurochemical systems are involved in addition to GABA, and other withdrawal phenomena may be anticipated once seizures begin [6]. Although seizures due to alcohol withdrawal, and other hypnosedative agents, are usually thought to be primarily generalized, a substantial minority of alcohol withdrawal seizures have focal components [7]. These localized cortical disturbances probably reflect pre-existing areas of cortical hyperexcitability, as might follow remote head trauma, which are rendered more excitable by the loss of inhibition.

Acute metabolic disturbances commonly produce seizures in ICUs, but one must consider that seizures may be symptoms of structural disorders that are made manifest by metabolic disorders. Generalized convulsions are typical of metabolic disturbances, but two common exceptions are seizures due to non-ketotic hyperglycaemia or hypoglycaemia, which often have focal components [8].

Box 231.1 Common aetiologies of seizures in critically-ill patients

Anoxic encephalopathy (must be distinguished from myoclonic activity)

Central nervous system infections

- Brain abscess.
- Encephalitis.
- Meningitis.
- Subdural empyema.

Cerebrovascular disorders

- Central nervous system vasculitis.
- Cortical vein thrombosis.
- Intracerebral haemorrhage:
  - Ischaemic stroke.
  - Lupus cerebritis.
- Subarachnoid haemorrhage.
- Thrombotic thrombocytopenic purpura.

Drug intoxication

- Antibiotics with proconvulsant effects—high-dose penicillins in patients with renal failure:
  - Third and fourth generation cephalosporins.
  - Imipenem/cilastatin in patients with renal failure or damaged blood–brain barrier.
  - Function.
- Cocaine and other central stimulants.
- Dopamine antagonists.
- Meperidine metabolites (e.g. normeperidine).
- Theophylline: tramadol.
- Tricyclic antidepressants.

Drug withdrawal

- Alcohol withdrawal.
- Hypnosedative drug withdrawal (primarily benzodiazepines and barbiturates).
- Withdrawal of other anticonvulsants in patients with a history of seizures or a seizure: diathesis.

Head trauma

Metabolic encephalopathies

- Acute severe hyposmolality (e.g. water intoxication): hepatic failure (seizures are rare).
- Renal failure.
- Acute renal failure:
  - Drug or metabolite intoxication.
  - Hypertensive encephalopathy.

- Chronic renal failure:
  - Drug or metabolite intoxication.
  - Dialysis dementia.

Neoplasms

- Primary.
- Metastatic.

Acute hypo-osmolar states (that is, those developing over hours) frequently present with generalized convulsions, as well as evidence of increased intracranial pressure. Hypo-osmolar states developing over days are rarely associated with seizures; these patients more commonly present with weakness or confusion without seizures or loss of consciousness. Hypocalcaemia is frequently listed as a cause of seizures in children and adults, but it is rarely the sole cause of convulsions beyond the neonatal period and must not be used as an excuse to avoid investigation for other aetiologies, especially structural lesions (Bleck, 1991) [9]. The same is true of hypomagnesaemia.

Systemic infections may produce non-convulsive seizures that are difficult to detect in patients being sedated for mechanical ventilation [10,11].

Many drugs commonly used in intensive care are potentially epileptogenic, especially in patients with renal or hepatic dysfunction. One important example is the development of non-convulsive seizures in patients treated with cefepime [12].

Autoimmune and paraneoplastic disorders causing seizures often result in intensive care admissions for patients because of the need for airway control and mechanical ventilation [13].

Status epilepticus

When status epilepticus develops in a critically-ill patient, the aetiologies are the same as those of discrete seizures. Status epilepticus, especially in patients with systemic disorders affecting the central nervous system, may not manifest as convulsions and should be considered in any case of prolonged change in mental status [14]. For those patients admitted to ICUs primarily because of status epilepticus, the most frequent causes in recent series are alcohol or antiseizure drug withdrawal, anoxia, head trauma, central nervous system infection, acute metabolic disturbances, and tumours [15–17].

Non-convulsive status epilepticus is now recognized to be relatively common among critically-ill patients with impaired consciousness [18]. This is often overlooked in patients for whom another aetiology of altered awareness is present [19]. Non-convulsive status epilepticus may be present in up to 30% of patients being treated with therapeutic hypothermia after cardiac arrest; the value of various antiseizure treatments remains to be established, but the outcome of such treatment in some cases is dramatic [20].

References

1. Fountain NB and Lothman EW (1995). Pathophysiology of status epilepticus. *Journal of Clinical Neurophysiology*, **12**, 326–42.
2. Bleck TP. (1997). Levels of consciousness and attention. In: Goetz CG and Pappert EJ (eds), *Textbook of Clinical Neurology*, pp. 2–29. Philadelphia: W. B. Saunders Co.
3. Ford G and Bleck TP (1997). Seizures in the intensive care unit. In: Parrillo JE (ed.), *Current Therapy in Critical Care Medicine*, 3rd edn, pp. 318–23. Toronto: B.C. Decker.
4. Bleck TP, Smith MC, Pierre-Louis JC, Jares JJ, Murray J, and Hansen CA. (1993). Neurologic complications of critical medical illnesses. *Critical Care Medicine*, **21**, 98–103.
5. Wijdicks EF and Sharbrough FW (1993). New-onset seizures in critically ill patients. *Neurology*, **43**(5), 1042–4.
6. Schuchardt V and Bourke DL. (1994). Alcoholic delirium and other withdrawal syndromes. In: Hacke W, Hanley D, Einhäupl K, Bleck TP, and Diringer M (eds), *Neurocritical Care*, pp 835–39. Berlin: Springer.
7. Alldredge BK and Lowenstein DH (1993). Status epilepticus related to alcohol abuse. *Epilepsia*, **34**(6), 1033–7.
8. Harden CL, Rosenbaum DH, and Daras M (1991). Hyperglycemia presenting with occipital seizures. *Epilepsia*, **32**, 215–20.
9. Bleck TP (1991). Convulsive disorders. *Clinical Neuropharmacology*, **14**(3), 191–8.
10. Glaser CA, Winter K, DuBray K, et al. (2012). A population-based study of neurologic manifestations of severe influenza A (H1N1) pdm09 in California. *Clinics in Infectious Diseases*, **55**, 514–20.
11. Kirkham FJ, Wade AM, McElduff F, et al. (2012). Seizures in 204 comatose children: incidence and outcome. *Intensive Care Medicine*, **38**, 853–62.
12. Smith NL, Freebairn RC, Park MA, Wallis SC, Roberts JA, and Lipman J (2012). Therapeutic drug monitoring when using cefepime in continuous renal replacement therapy: seizures associated with cefepime. *Critical Care and Resuscitation*, **14**, 312–15.
13. Bleck TP. (2010). Less common etiologies of status epilepticus. *Epilepsy Currents*, **10**, 31–3.
14. Garrett W, Chang CWJ, and Bleck TP. (1996). Nonconvulsive status epilepticus in thrombotic thrombocytopenic purpura. *Annals of Neurology*, **39**, 245–6.
15. DeLorenzo RJ, Pellock JM, Towne AR, and Boggs JG. (1995). Epidemiology of status epilepticus. *Journal of Clinical Neurophysiology*, **12**, 316–25.
16. Lowenstein D and Alldredge B (1993). Status epilepticus in an urban hospital in the 1980s. *Neurology*, **43**, 483–8.
17. Hussain N, Appleton R, and Thorburn K (2007). Aetiology, course and outcome of children admitted to paediatric intensive care with convulsive status epilepticus: a retrospective 5-year review. *Seizure*, **16**, 305–12.
18. Bleck T. (2012). Status epilepticus and the use of continuous electroencephalographic monitoring in the intensive care unit. *Continuum*, **18**, 560–78.
19. Lanzino G, D'Urso PI, Suarez J, and the Participants in the International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage (2011). Seizures and anticonvulsants after aneurysmal subarachnoid hemorrhage. *Neurocritical Care*, **15**, 247–56.
20. Hovland A. Nielsen EW, Klüver J, and Salvesen R (2006). EEG should be performed during hypothermia. *Resuscitation*, **68**, 143–6.

CHAPTER 232

Assessment and management of seizures in the critically ill

Thomas P. Bleck

Key points

- Seizures may be difficult to detect in critically-ill patients who are sedated and/or paralysed with neuromuscular blocking agents. An urgent electroencephalogram should be obtained when seizures are suspected.
- Unless the cause is known, investigations may include an urgent computed tomography or magnetic resonance imaging (if this is logistically possible) and a lumbar puncture if central nervous system infection is suspected.
- Status epilepticus is continuous or recurrent seizure activity lasting five or more minutes without an intervening recovery period.
- Most seizures are self-limiting and stop after 1–2 minutes. Seizures that continue for more than 5 minutes should be treated.
- General supportive measures include attention to airway, breathing, and circulation (ABCs) and the exclusion of hypoglycaemia. Drug treatment is commonly with parenteral benzodiazepines; propofol and barbiturates are alternatives.

Introduction

Patients with seizures enter the intensive care environment either as a complication of another critical illness or for the management of status epilepticus. The diagnostic studies required vary with the presentation, and must often wait for the institution of emergent therapies, such as antibiotics in cases of suspected bacterial meningitis and antiseizure treatment for status epilepticus.

Discrete seizures

Recognition of a generalized seizure is straightforward in previously alert patients not receiving neuromuscular junction blocking agents, but such patients are less common in intensive care practice than in other areas. Partial (focal) seizures that do not secondarily generalize are also difficult to detect in these patients. The intensive care unit (ICU) staff must maintain a high index of suspicion for the development of seizures in such patients, and maintain a correspondingly low threshold to obtain neurological consultation and electroencephalographic studies. Box 232.1 presents some guidelines for the recognition of seizures in the ICU. One should strive to make a definitive diagnosis of the aetiology of altered alertness, even if that diagnosis is

Box 232.1 Recognizing seizures in critically-ill patients

- Make a positive diagnosis of the aetiology of altered awareness.
- In patients receiving neuromuscular junction blockade, evidence of sympathetic over-activity (e.g. pupillary dilation, hypertension, tachycardia) may reflect seizure activity, as well as pain or inadequate sedation. Only EEG monitoring can reliably distinguish between these possibilities.
- In patients with intact neuromuscular transmission, observe for a prolonged post-ictal state after a recognized seizure; facial myoclonus; unexplained fluctuations in the level of consciousness; and nystagmoid eye movements.
- In most situations, neuromuscular blocking agents can be discontinued transiently to assess the patient's neurological examination without harming the patient. If this cannot be done, one should consider intermittent (or continuous) EEG monitoring for patients receiving proconvulsant agents (e.g. imipenem/cilastatin) even in the absence of autonomic signs suggesting seizures.
- Hypnosedative agents may diminish the motor manifestations of seizures or status epilepticus without attenuating the electrical activity or preventing the consequent neuronal damage. Thus, one should either lower the dose of these drugs occasionally to assess the patient's neurologic status, or obtain intermittent (or continuous) EEG monitoring.
- Although elevations in serum prolactin and ACTH levels commonly accompany seizures, many common disorders and treatments in ICU patients may produce similar elevations (e.g. neuroleptic agents, which are also proconvulsant). Furthermore, this neuroendocrine response fatigues with frequent seizures. Thus, studies of these substances are often unreliable markers of seizure activity in ICU patients.
- Decerebrate (extensor) posturing and opisthotonic posturing are occasionally seen in ICU patients, and may be confused with seizure activity. If they cannot be distinguished on clinical grounds, an EEG should be obtained. Short-acting neuromuscular junction blockade may be necessary (e.g. vecuronium (0.1 mg/kg), with appropriate ventilatory and airway management). Succinylcholine should usually be avoided in this setting to avoid the possible precipitation of severe hyperkalaemia.

metabolic encephalopathy, to prevent missing the possibility of such remediable disorders as seizures or status epilepticus [1].

When a seizure is suspected, an electroencephalogram (EEG) should be obtained urgently. This is of special importance when a patient does not return to baseline mental status, which suggests progression to non-convulsive status epilepticus [2,3]. Most patients will need a brain imaging study in this setting, since a majority of critical care patients with new onset seizures have structural intracranial lesions [4]. Although magnetic resonance imaging is usually the study of choice in patients with new onset seizures, critically-ill patients may not be able to undergo this procedure for logistical reasons. Computed tomographic scanning remains a useful alternative. The need for other studies, such as lumbar puncture for cerebrospinal fluid analysis, depends on the likely diagnostic possibilities. If bacterial meningitis is suspected at any stage, appropriate antibiotic therapy should be instituted without waiting to obtain a lumbar puncture [5].

Classifying the seizure according to the International Classification of Epileptic Seizures [6] aids in the aetiological diagnosis, and often has therapeutic implications (see Boxes 232.1 and 232.2).

Status epilepticus

The usual definition of status epilepticus involves continuous or recurrent seizure activity without recovery; 5 minutes is now considered an operational definition of status [7]. The average duration of monitored single seizures is 62 seconds [8], and since most seizures end spontaneously within 4 minutes, one should consider treatment for status epilepticus after about 5 minutes.

Status epilepticus is easily diagnosed when the patient suffers prolonged convulsions or has numerous partial seizures without intervening recovering normal alertness. More challenge arises when status epilepticus occurs without obvious motor manifestations, especially if the patient has other reasons for unresponsiveness. In such circumstances, careful observation for small clonic movements (e.g. twitches of the corner of the eye) may suggest the diagnosis. Other neurologic symptoms such as aphasia may be signs of status epilepticus [9]. About 20% of status epilepticus is non-convulsive [10]. The EEG appearance of different forms and durations of status epilepticus is quite variable [11,12].

Management

Discrete seizures

The first concern in caring for any patient experiencing a seizure is to protect the patient from harm to the extent that this is possible. This is usually a straightforward task in the general hospital patient (e.g. preventing aspiration, removing sharp objects from the patient's vicinity), but assumes a new level of complexity in ICU patients who are critically dependent on devices whose connection to the patient is of limited or no flexibility (e.g. intra-aortic balloon pumps, high-frequency oscillatory ventilators). In such circumstances, immediate neuromuscular junction blockade may be necessary. If neuromuscular blockade is not immediately necessary the patient should be observed for seizure classification and possible intervention to maintain the airway and ensure adequate ventilation. When emergent therapy is indicated, the physician should proceed. In most cases, efforts should be made to make an aetiological diagnosis expeditiously, and institute treatment for the underlying cause if possible.

Box 232.2 Classification of epileptic seizures

Partial seizures (seizures beginning locally)

Simple partial seizures (consciousness not impaired)

- With motor symptoms.
- With somatosensory or special sensory symptoms.
- With autonomic symptoms.
- With psychic symptoms.

Complex partial seizures (with impairment of consciousness)

- Beginning as simple partial seizures and progressing to impairment of con-sciousness:
  - Without automatisms.
  - With automatisms.
- With impairment of consciousness at onset:
  - Without automatisms.
  - With automatisms.

Partial seizures (simple or complex), secondarily generalized

Generalized seizures (bilaterally symmetric, without localized onset)

Absence seizures

- True absence ('petit mal').
- Atypical absence.

Myoclonic seizures

Clonic seizures

Tonic seizures

Tonic-clonic seizures ('grand mal')

Atonic seizures

Unclassified seizures

Reproduced from 'Commission on classification and terminology of the International League Against Epilepsy (1981) Proposal for revised clinical and electroencephalographic classification of epileptic seizures', *Epilepsia*, **22**(4), pp. 489–501, copyright 1981, with permission from John Wiley and Sons Ltd.

Whether to administer antiseizure drugs after one seizure in a critically-ill patient is often a complex decision. The causes of the patient's seizure may be unknown or may be difficult to reverse. Another seizure may pose substantial risk to a patient with tenuous cardiopulmonary function, which may be sufficiently great that medications are justified after one seizure. In this circumstance, two treatment modalities are currently available. Our centre employs a long-acting benzodiazepine (e.g. lorazepam, or clonazepam), unless contraindicated by its effect on the patient's level of alertness. Acceptable alternative include levetiracetam, lacosamide, valproate, phenytoin, or fosphenytoin.

The choice of a maintenance antiseizure medication for those who remain at risk for further seizures is beyond the scope of this chapter. However, the physicians caring for the patient in the ICU

should realize that subsequent physicians may continue that initial agent for months or years, and should communicate the bases for their decision for later reconsideration.

Status epilepticus

Attention to basic life support issues (airway, breathing, and circulation) are central to the management of generalized convulsive status epilepticus. While the rapid termination of this condition is often the best way to deal with airway problems, emergent endotracheal intubation may be necessary for the patient unable to ventilate adequately, or if treatment to terminate status epilepticus causes respiratory depression. If laryngoscopic intubation is required in a patient with suspected intracranial hypertension, premedicate the patient with lignocaine, thiopentone, propofol, or etomidate to blunt the increase in ICP associated with laryngoscopy.

Therapy for status epilepticus was exhaustively reviewed in a recent guideline to which the interested reader is referred [13]. A study of the prehospital treatment of status epilepticus suggests that the rapidity of effective treatment is extremely important in the termination of the condition [14].

During the first 30–60 minutes of status epilepticus most patients are hypertensive; after this, blood pressure usually declines to normal or hypotensive values. Many drugs used to terminate status epilepticus can induce hypotension, so the clinician should always be ready to support the circulation with fluids and vasopressors.

Since hypoglycaemia may be associated with status epilepticus, either as an aetiology or as a consequence of prolonged seizure activity with autonomic failure, the blood glucose should be rapidly determined. Since the techniques employed for bedside determination lose accuracy outside the normal range, 'borderline' hypoglycaemic values should be treated (together with thiamine administration). Non-ketotic hyperglycaemia frequently presents with epilepsia partialis continua, which does not typically respond to antiseizure agents, but which usually remits with rehydration and control of the blood sugar.

Therapy for status epilepticus involves three principles:

- Terminating the condition.
- Preventing its recurrence.
- Managing its complications.

The US Department of Veterans Affairs study of status epilepticus compared four treatment regimens for generalized convulsive status epilepticus (lorazepam, diazepam followed by phenytoin, phenytoin alone, and phenobarbital alone). This study showed that lorazepam (0.1 mg/kg), terminated 63% of generalized convulsive status epilepticus episodes [15]. In another important result, about 20% of patients remained in electrical status epilepticus after their clinical seizure activity stopped. This reinforces the clinical suspicion of non-convulsive status epilepticus in patients who do not begin to wake within 15–20 minutes after the apparent termination of their seizures.

Recommended lorazepam doses vary from 0.05 to 0.2 mg/kg (up to 8 mg in adults), administered at a rate of 0.04 mg/kg/min. Increasing the dose above 8 mg does not appear to improve the response rate. If this drug fails, phenytoin is frequently chosen as a second-line agent. However, the aggregate response rate to all second-line drugs in the DVA study was about 9%, and to third-line drugs, 3% [16]. This suggests that additional conventional treatments have limited utility after the first choice fails.

At this juncture, the patient is refractory to standard therapy and one might use one of the 'definitive' treatments. These more aggressive treatments should be given in ICUs, since the patient requires ventilatory support and frequently needs haemodynamic support. EEG monitoring is also necessary, since these drugs typically abolish clinical evidence of seizure activity before achieving electroencephalographic control.

My practice is to use either midazolam or propofol at this juncture. Midazolam therapy starts with a loading dose of 0.2 mg/kg and an initial maintenance dose of 0.2 mg/kg/hour [17,18]. The maintenance dose is titrated to produce clinical and electroencephalographic suppression of seizures, rather than a burst-suppression EEG pattern. This agent is effective in over 70% of cases of refractory status pooled from three centres, but produces substantial tachyphylaxis. When the infusion rate reaches 2.0 mg/kg/hour, arbitrary change to another drug is recommended, usually propofol or pentobarbitone. This is often required in those situations in which the patient has a prolonged stimulus for epileptogenesis, such as encephalitis. Typical doses for propofol in status epilepticus range from 2 to 15 mg/kg/hour; we also use a loading dose of 2 mg/kg. Prolonged infusion of high dose propofol should be avoided because of the risk of inducing potentially fatal propofol infusion syndrome.

Recommendations for pentobarbitone loading doses vary from 5 to 12 mg/kg, with maintenance doses beginning at about 1 mg/kg/hour. An EEG goal of burst-suppression is traditional, but since there is no clear evidence to support this, I now choose seizure suppression instead [19]. A pentobarbitone dose adequate to produce burst-suppression or a completely flat EEG background is often necessary to suppress all seizures, and there are several examples of seizures arising from a background of this pattern. Thus, continuous EEG monitoring is required; intermittent sampling of the EEG to insure that this pattern is present is not adequate to be certain that no seizures are occurring [20]. The extent to which occasional seizures produce further brain damage in this setting is unknown.

Adverse effects of pentobarbitone include hypotension (from both venodilation and diminished myocardial contractility), immune suppression, poikilothermia, interference with the clearance of pulmonary secretions, and loss of gastrointestinal motility. Total parenteral nutrition may be required because of an ileus. Pulmonary embolism prophylaxis is necessary and gastric mucosal protection is advisable.

The optimal duration of these therapies is uncertain. To prevent recurrence of refractory status epilepticus, we typically institute a regimen of high-dose phenobarbital (aiming for a phenobarbital serum concentration of 50–100 μg/mL or higher) before withdrawing the agent being used for definitive control of status epilepticus. These choices are modified based on the patient's history. This withdrawal of therapy is attempted once or twice daily, and requires both EEG and clinical absence of seizures to be considered successful.

Many other agents have been reported to be useful in terminating status epilepticus, but none have been demonstrated to be superior to those discussed herein. Ancillary treatments, such as hypothermia and electroconvulsive therapy have been described, and are sometimes employed when drug therapy is not working or not tolerated. Surgical resection of a seizure focus, subpial transection, and the use of vagal nerve stimulators have also been employed.

Complications of status epilepticus include neuronal damage, rhabdomyolysis, hyperthermia, and cerebral oedema. The only

current approach to neuronal damage is to prevent it by rapid termination of status epilepticus, but excitatory amino acid antagonists are one of a number of promising neuroprotective treatments currently under study. Rhabdomyolysis from sustained muscular over-activity may be sufficient to produce renal damage. It may be preventable if treated early with volume expansion and alkalinization with sodium bicarbonate. Hyperthermia usually resolves after status epilepticus is controlled, but may contribute to neuronal damage prior to this point. External cooling is usually sufficient to control it once status epilepticus is terminated. Cerebral oedema due to status epilepticus is vasogenic in experimental models, and may be managed with steroids and mannitol in the rare case in which it produces symptoms. However, if marked oedema is present, the treating clinicians should consider the likelihood that both status epilepticus and the oedema reflect an underlying pathologic process.

References

1. Bleck TP (1993). Why isn't this patient awake? *Journal of Intensive Care Medicine*, **8**, 155–6.
2. Fagan KJ and Lee SI (1990). Prolonged confusion following convulsions due to generalized nonconvulsive status epilepticus. *Neurology*, **40**, 1689–94.
3. Bassin S and Bleck TP. (2011). Seizures in the critically ill. In: Vincent J-L, Abraham E, Moore FA, Kohanek P, and Fink M (eds), *Textbook of Critical Care*, 6th edn, pp. 203–11. New York: Elsevier/Saunders.
4. Bleck, T. P. (1995). Seizures in the critically ill. Critical Care Medicine: Principles of Diagnosis and Management. Chicago: Mosby-Year Book, 1217–1233.
5. Chang CWJ and Bleck TP. (1995). Status epilepticus. *Neurology Clinic*, **13**, 529–48.
6. Commission on classification and terminology of the International League Against Epilepsy (1981). Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*, **22**, 489–501.
7. Lowenstein DH, Bleck T, and Macdonald RL (1999). It's time to revise the definition of status epilepticus. *Epilepsia*, **40**, 120–2.
8. Theodore WH, Porter RJ, Albert P, et al. (1994). The secondarily generalized tonic-clonic seizure: a videotape analysis. *Neurology*, **44**, 1403–7.
9. Manford M, Fuller GN, and Wade JP. (1995). 'Silent diabetes': non-ketotic hyperglycaemia presenting as aphasic status epilepticus. *Journal of Neurology, Neurosurgery, and Psychiatry*, **59**, 99–100.
10. Krumholz A, Sung GY, Fisher RS, Barry E, Bergey GK, and Grattan LM (1995). Complex partial status epilepticus accompanied by serious morbidity and mortality. *Neurology*, **45**, 1499–504.
11. Treiman DM. (1995). Electroclinical Features of Status Epilepticus. *Journal of Clinical Neurophysiology*, **12**, 343–62.
12. Drislane FW and Schomer DL. (1994). Clinical implications of generalized electrographic status epilepticus. *Epilepsy Research*, **19**(2), 111–21.
13. Brophy G, Bell R, Claassen J, et al. (2012) Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. *Neurocritical Care*, **17**, 3–23.
14. Silbergleit R, Durkalski V, Lowenstein D, et al. (2012). Intramuscular versus intravenous therapy for prehospital status epilepticus. *New England Journal of Medicine*, **366**, 591–600.
15. Treiman DM, Meyers PD, Walton NY, et al. (1998). A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *New England Journal of Medicine*, **339**(12), 792–8.
16. Bleck TP. (2006). Critical care of the patient in status epilepticus. In: Wasterlain C and Treiman D (eds), *Status Epilepticus*, pp. 607–13. Boston: MIT Press.
17. Kumar A and Bleck TP. (1992) Intravenous midazolam for the treatment of refractory status epilepticus. *Critical Care Medicine*, **20**, 483–8.
18. Parent JM and Lowenstein DH. (1994). Treatment of refractory generalized status epilepticus with continuous infusion of midazolam. *Neurology*, **44**, 1837–40.
19. Bleck TP. (1992). High-dose pentobarbital treatment of refractory status epilepticus: a meta-analysis of published studies. *Epilepsia*, **33**, 5.
20. Bleck T. (2012). Status epilepticus and the use of continuous electroencephalographic monitoring in the intensive care unit. *Continuum*, **18**, 560–78.

PART 9.7

Intracranial hypertension

CHAPTER 233

Causes and management of intracranial hypertension

Nino Stocchetti and Andrew I. R. Maas

Key points

- Intracranial hypertension damages the brain.
- Intracranial pressure increases when a pathological process causes the total volume inside the cranial cavity to increase above a threshold limit.
- Acute hydrocephalus in subarachnoid haemorrhage worsens the neurological presentation. Cerebrospinal fluid should be drained before considering limiting active treatment.
- Decompression after malignant cerebral hemispheric infarction reduces ICP, but does not guarantee a better outcome.
- The most frequent cause of acute neurological worsening in a patient with a shunt system is dysfunction of the system itself.

Introduction

The pathophysiology of raised intracranial pressure (ICP), with particular reference to traumatic brain injury is covered in other chapters of this textbook. Values of ICP exceeding 15 mmHg are considered pathological in adults, and critical thresholds for treatment are generally set at 20 mmHg. Intracranial hypertension (HICP) is deleterious to the brain in two ways—by causing tissue distortion and herniation, and by causing low cerebral perfusion pressure (CPP). CPP is calculated as the difference between mean arterial blood pressure (MAP) and ICP: (CPP = MAP – ICP). A CPP lower than 60 mmHg is considered pathological in adults, because it may cause critical reductions of cerebral blood flow (CBF).

ICP is a function of intracranial volume. As a rule of thumb, the intracranial volume remains constant as expressed in the Monroe-Kellie doctrine:

$$V_{brain} + V_{blood} + V_{cerebrospinal\ fluid(CSF)} = \text{Constant} \qquad \text{[eqn 1]}$$

When the volume of one component in the intracranial cavity increases, and cannot be compensated for by a corresponding decrease in the volume of another component (for instance, by a displacement of CSF into the spinal space), ICP increases. Typically, the relationship between intracranial volume and pressure is not linear and shows three components. When additional volume enters the space, initially ICP remains relatively constant; when further volume is added, ICP starts rising. Finally, even a moderate addition of extra volume causes a sharp ICP increase.

The exponential volume–pressure relation has strong clinical implications, because ICP can decompensate rapidly, reaching dangerous, or even fatal levels after a time of apparently unremarkable fluctuations.

This chapter focuses on HICP in patients with four different pathologies:

- Subarachnoid haemorrhage (SAH).
- Spontaneous intraparenchymal haemorrhage.
- Malignant cerebral hemispheric infarction.
- Acute hydrocephalus.

Intracranial hypertension in SAH

Causes

Rupture of an intracranial aneurysm, the most frequent cause of subarachnoid haemorrhage, causes a massive increase in ICP. Bleeding occurs at high pressure (roughly equivalent to arterial pressure) and the patient (when fortunate enough to preserve consciousness and speech) complains of symptoms of acute intracranial hypertension, such as severe headache and vomiting.

In an experimental SAH model in rats, ICP rose to 55 mmHg in the first few minutes of bleeding. Despite a concomitant MAP increase, CPP fell to 19 mmHg, and local cortical blood flow declined to 22% of baseline [1]. Direct ICP measurement in humans during aneurysmal bleeding is, obviously, rare. In one patient who was undergoing ICP monitoring during aneurysm coiling, an episode of bleeding seen at angiography was accompanied by an immediate increase in ICP to 80 mmHg (personal observation).

Increased ICP is common during treatment in the ICU after SAH. In a series of 433 SAH admitted to ICU after surgical aneurysm repair, HICP was recorded in more than 50% of patients [2].

Several mechanisms may be responsible for an increase in ICP following SAH, but three are especially relevant—disturbances of the CSF circulation, global cerebral damage, and delayed ischaemic deficits. Disturbances of the CSF circulation, with impaired reabsorption and acute hydrocephalus, are common after SAH, more often in the acute phase, but in a minority of cases resulting in chronic hydrocephalus. Acute hydrocephalus may deeply affect the neurological presentation after SAH, placement of a ventricular catheter with external drainage of CSF is indicated before considering limitation of active treatment [3]. Despite concerns that early ventriculostomy might increase the risk of rebleeding, this risk

appears extremely low in expert hands, especially if over- drainage of CSF is avoided [4].

Although aneurysm rupture is a focal event, with blood extravasation and often haematoma formation around the site of bleeding, SAH causes diffuse damage to the brain, which is not limited to the location of the aneurysm or any accompanying haematoma. This damage, probably occurs at the time of aneurysm's rupture, impairs cerebral metabolism, and may induce cerebral oedema in the first days [5], with subsequent HICP.

Further ischaemia may develop after the first days/week. These delayed ischaemic deficits are often related to cerebral arterial vasospasm [6], but may also occur in the absence of overt vasospasm. Other mechanisms, including spreading depression, have been implicated [7]. When delayed ischaemia impairs the ionic pumps, intracellular water accumulates, and ICP may increase.

It is unclear if ICP is an independent predictor of worse outcome or more a marker of brain damage. Some studies report prognostic effects [8], but others in which ICP was entered in a multivariable model, do not [2].

Treatment

There are no studies proving that ICP monitoring or ICP-guided interventions improve outcome after SAH. However, HICP is a severe and treatable complication of SAH. Increased ICP is associated with severe disturbances of cerebral metabolism and oxygenation, further aggravating pre-existing cerebral damage. When microdialysis has been used in patients with HICP after SAH, signals of brain energy crisis have been detected [8]. For these reasons, ICP should be monitored in patients with high-grade SAH. An external ventricular drain is the recommended monitoring tool, offering both ICP measurement and CSF drainage. Drainage is the first reasonable treatment of increased ICP after SAH. It should be done cautiously, avoiding acute pressure gradients, particularly when the aneurysm is not yet secured. Special attention has to be paid to CPP, which is essential to prevent, or limit, further ischaemia. Mannitol was effective in lowering ICP and improving cerebral metabolism when used in 12 comatose SAH patients [9]. Agents capable of reducing ICP at the expense of MAP (such as sedatives or barbiturates) should only be used if arterial pressure and CPP are kept adequate.

Intracranial hypertension in spontaneous intraparenchymal haematoma

Causes

Intracerebral (I-C) haemorrhage is caused by the rupture of an intracranial vessel, usually in the basal ganglia. It is often a complication of systemic arterial hypertension or anticoagulant therapy. The amount of blood can vary, from asymptomatic microbleeds to large haematomas. Small bleeds can be relatively compensated by CSF displacement, while large haemorrhages (larger than 100 mL) may cause a severe increase in ICP at the moment of bleeding. The formation of an intracranial haematoma is a dynamic process, with expansion during the first day, due to further blood accumulation, and due to water accumulation in the parenchyma surrounding the haematoma [10]. Various mechanisms contribute to oedema formation, together with glutamate release, causing cytotoxic oedema, mediators such as oxygen-free radicals, complement factors and TNFα may increase permeability and lead to vasogenic oedema [11]. Tissue and vascular compression by the haematoma, further worsened by oedema, can cause hypoperfusion in areas not primarily affected by haemorrhage. However, the degree of cerebral blood flow (CBF) compromise around the haematoma is controversial, and ischaemia has not been confirmed in CBF studies. However, autoregulation is disrupted or lost, and after I-C haemorrhage the brain is especially vulnerable to reduction of arterial pressure and CPP. Several studies have demonstrated a close association between lesions demonstrated with magnetic resonance imaging (MRI) and low arterial pressure [12]. The crucial role of CPP in I-C haemorrhage has been confirmed using multimodal monitoring. CPP below 80 mmHg was associated with a greater risk of brain hypoxia and, to a lesser degree, with metabolic crisis [13]. Clinical seizures may occur in 9–13% of cases, and are detected more frequently with continuous EEG monitoring. Seizures may cause, or worsen, HICP [11].

Treatment

There are no studies proving that ICP monitoring or ICP-guided interventions, improve outcome following I-C haemorrhage. Management of increased ICP, however, seems a reasonable clinical target for reducing secondary brain damage and improving outcome [11]. Surgical removal of the haematoma aims to reduce the mass effect and ICP. Management of intraventricular haemorrhage can prevent hydrocephalus and improve ICP. Prevention and treatment of seizures may also help control ICP.

Osmotic agents have been used with contradictory results. In two randomised trials osmotic therapy did not improve CBF and outcome, while in a recent study a continuous infusion of hypertonic saline in 26 patients reduced the number of HICP episodes, compared with a control group, with potential outcome benefits, at the cost of hypernatraemia [14].

Intracranial hypertension in malignant hemispheric infarction

Causes

Massive hemispheric infarction follows acute obstruction of the middle cerebral artery (MCA), usually of embolic origin, with catastrophic effects. Complete ischaemia in the MCA territory is followed by oedema, which may involve a large portion of the hemisphere. When measured by MRI with diffusion-weighted imaging, volumes up to 300 mL have been recorded [15]. Following this, ICP increases and brain herniation is a frequent cause of death. The risk for such 'malignant' hemispheric infarction with secondary deterioration due to ICP is greatest in younger patients in who the lack of cerebral atrophy reduces intracranial compliance.

There is no effective medical treatment for this life-threatening event, and surgical decompression has been attempted in order to relieve ICP, preserve the unaffected brain, and improve outcome.

Despite the predominant role of ICP in this pathology, the benefits of ICP monitoring are unclear. Very few cases with accurate ICP measurement are reported in the literature. In 19 cases studied before surgical decompression with intraparenchymal probes, there was no correlation between the estimated volume of the infarct, on average 241 mL, and ICP. More concerning, pupillary abnormalities and severe brainstem compression were present in some patients despite normal ICP values [16].

Treatment

Osmotic agents have been used in order to control HICP after cerebral infarction. Two small series showed that mannitol does not alter midline shift, but can improve the neurological condition, acting preferentially on the non-infarcted, still perfused brain [17].

Surgical decompression may be a more effective treatment. Decompression lowers ICP, prevents herniation and decreases mortality after cerebral infarction. The big issue is that by reducing mortality it may increase the number of survivors with severe disability. In selected young patients, early decompression has been attempted with acceptable rates of disability [15]. Data from relatively small series in young patients have been pooled emphasizing the importance of three factors—age, early intervention, and infarct location. Older patients have consistently poorer outcome, regardless of treatment, so that recent trials have been restricted to patients in their fifties. Early intervention is crucial. Acceptable results, with reduced mortality and increased rate of favourable outcome compared with controls, can be achieved only when decompression is performed in the first 48 hours after stroke [18]. Finally, an infarct in the dominant, rather than in the non-dominant hemisphere may affect outcome differently. All these issues require further investigation [19].

Intracranial hypertension and hydrocephalus

Causes

Hydrocephalus is defined as an abnormal accumulation of CSF within the brain. The dynamics of CSF flow have been termed 'the third circulation' [20]. This term was coined from the realization that the CSF should not be regarded as simply a watery cushion for the brain, but rather as a dynamic and circulating medium with biological functions. These include functions as 'lymph' of the brain, and as transporter for mediators and neurotransmitters. The CSF is formed in the brain ventricles by secretion from the choroid plexus and by drainage of the extracellular fluid from the brain into the ventricular compartments. The production of CSF is, on average, 0.35 mL/min (approximately 500 mL/day); with a volume of approximately 150 mL, the CSF is almost completely refreshed 4–5 times per day. CSF flow is therefore relatively high and any disturbance in the triad of production, flow, and reabsorption can cause an abnormal accumulation of CSF within the brain, leading to HICP.

In general, three main causes of hydrocephalus may be differentiated:

- **Overproduction**: this concerns a relatively rare cause, resulting from a tumour of the choroid plexus, predominantly occurring in the paediatric population.
- **Obstruction of flow**: obstruction commonly occurs at narrow passages, such as at the level of the foramen of Monroe in the third ventricle, the aqueduct or in the fourth ventricle (infratentorial compartment).
- **Impaired reabsorption**: normally CSF is resorbed through the granulations of Pacchioni into the superior sagittal sinus. Any 'clogging' of these granulations, such as may occur following an infection or bleeding into the CSF space (e.g. following intraventricular or subarachnoid haemorrhage) can result in impaired reabsorption. Often, both a partial obstruction to flow and impaired reabsorption may contribute to the onset of symptoms.

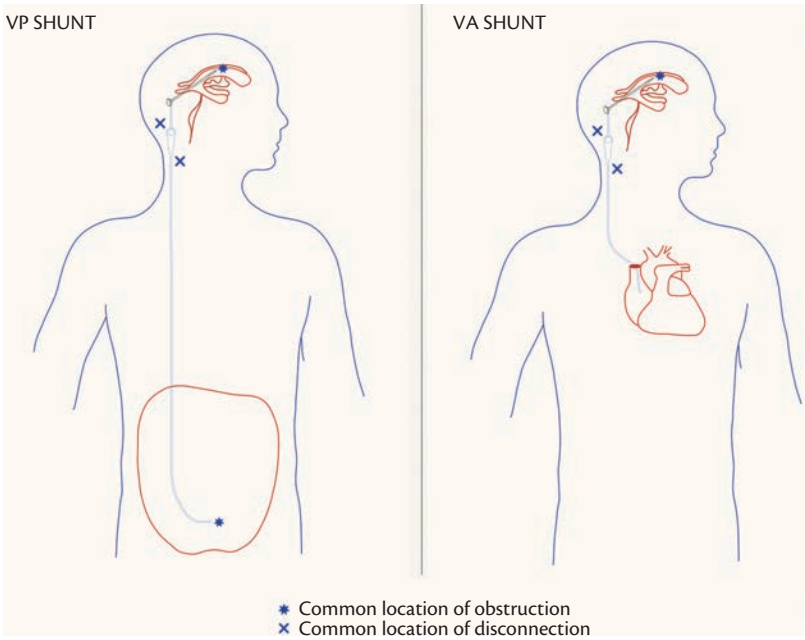


Fig. 233.1 A CSF shunt system consists of a ventricular catheter connected by a valve to the distal catheter draining CSF either to the abdominal cavity or to the right atrium of the heart. Disconnections commonly occur at the distal or proximal connections of the valve. Obstruction may occur at the level of the ventricular catheter (in-growth of choroid plexus into catheter) or in case of a ventriculoperitoneal shunt at the end of the distal peritoneal catheter. Frequently a low grade infection of the shunt system is the cause of the obstruction as the momentum covers the infection focus. A ventriculo-atrial shunt only functions adequately if the cardiac catheter is located within the right atrium (generally below the level of the 5th thoracic vertebra on chest X-ray).

Table 233.1 Diagnostic work-up of shunt dysfunction

Diagnostic test/examination	To detect
Radiographic examination of shunt system	
X-ray skull	Disconnection Check valve setting (in case of programmable valve)
X-ray abdomen* (for V-P shunt)	Intraperitoneal location
X-ray chest (for ventriculo-atrial shunt)	Position in right atrium
CT brain	Enlarged ventricles
Puncture of ventricular reservoir (if present) or valve with	
Pressure measurement	High ICP
Can CF be withdrawn?	Obstruction ventricular catheter
Send CSF to laboratory for: ◆ CSF culture. ◆ Cell count. ◆ Glucose/protein.	Infection

*Mark abdominal incision with metal object to locate entry into abdominal cavity.

Symptoms may develop gradually over time or acutely. Here, we focus on an acute onset of symptoms, which may occur with an obstruction of CSF flow, in the presence reduced intracranial compliance or because of an acute dysfunction of a CSF shunt. A CSF shunt is a valved internal drainage system, which diverts CSF either to the abdominal cavity (ventriculoperitoneal shunt) or via the jugular vein to the heart (ventriculo-atrial shunt). Dysfunction of the shunt system may be caused by a disconnection of one of the components of the drainage system or by obstruction of the ventricular or distal catheter. Disconnection commonly occurs proximal or distal to the valve, which is required to regulate flow and pressure whilst preventing backflow (Fig. 233.1). Presenting symptoms may include headache and vomiting followed by a decrease in the level of consciousness (Table 233.1). Emergency treatment is then life saving.

Treatment

Treatment of HICP due to hydrocephalus is relatively simple and consists of drainage of CSF. In the presence of an obstruction, CSF drainage should never be performed by lumbar puncture. Ventricular drainage is indicated. In acute situations a temporary solution is to insert a ventricular catheter to drain CSF externally. Drainage can be performed at a set pressure level (e.g. 15 mmHg) or be determined by the volume of CSF drained dependent on the indication for CSF drainage. When the indication is CSF leakage, the volume of CSF drained is important and drainage should be adjusted to a set volume. When the indication is intracranial hypertension drainage should be at a set pressure level. If the opening pressure is high, it is better to initially set the level at which CSF is drained high and then to slowly decrease it over the next 24 hours. The major risk of external CSF drainage is infection with infection rates of 2–10%. Strict sterile conditions should be maintained for every drain related procedure, but the routine use of extended antibiotic prophylaxis is not recommended. Periprocedural short duration prophylaxis may be considered an option. The infection rate increases with the duration of external CSF drainage. Routine catheter changes are however not recommended. The incidence of colonization of catheters may be decreased with the use of silver- or antibiotic-coated catheters, but the clinical benefit of these catheters in terms of reducing infections has not been definitively proven.

Temporary external drainage is indicated in emergency situations or in situations where the CSF obstruction may be resolved (e.g. surgery for a posterior fossa tumour). Definitive treatment of hydrocephalus can consist of either a third ventriculostomy (opening of the floor of the third ventricle into the basal cisterns) or an internal shunt procedure in which the CSF is most commonly diverted to the peritoneal cavity.

References

1. Westermaier T, Jauss A, Eriskat J, Kunze E, and Roosen K. (2009). Time-course of cerebral perfusion and tissue oxygenation in the first 6 h after experimental subarachnoid hemorrhage in rats. *Journal of Cerebral Blood Flow and Metabolism*, **29**(4), 771–9.
2. Heuer GG, Smith MJ, Elliott JP, Winn HR, and LeRoux PD. (2004). Relationship between intracranial pressure and other clinical variables in patients with aneurysmal subarachnoid hemorrhage. *Journal of Neurosurgery*, **101**(3), 408–16.
3. Gigante P, Hwang BY, Appelboom G, Kellner CP, Kellner MA, and Connolly ES. (2010). External ventricular drainage following aneurysmal subarachnoid haemorrhage. *British Journal Neurosurgery*, **24**(6), 625–32.
4. Hellingman CA, van den Bergh WM, Beijer IS, et al. (2007). Risk of rebleeding after treatment of acute hydrocephalus in patients with aneurysmal subarachnoid hemorrhage. *Stroke*, **38**(1), 96–9.
5. Helbok R, Ko SB, Schmidt JM, et al. (2011). Global cerebral edema and brain metabolism after subarachnoid hemorrhage. *Stroke*, **42**(6), 1534–9.
6. Crowley RW, Medel R, Dumont AS, et al. (2011). Angiographic vasospasm is strongly correlated with cerebral infarction after subarachnoid hemorrhage. *Stroke*, **42**(4), 919–23.
7. Strong AJ and Macdonald RL. (2012). Cortical spreading ischemia in the absence of proximal vasospasm after aneurysmal subarachnoid hemorrhage: evidence for a dual mechanism of delayed cerebral ischemia. *Journal of Cerebral Blood Flow and Metabolism*, **32**(2), 201–2.
8. Nagel A, Graetz D, Schink T, et al. (2009). Relevance of intracranial hypertension for cerebral metabolism in aneurysmal subarachnoid hemorrhage. Clinical article. *Journal of Neurosurgery*, **111**(1), 94–101.
9. Helbok R, Kurtz P, Schmidt JM, et al. (2011). Effect of mannitol on brain metabolism and tissue oxygenation in severe haemorrhagic stroke. *Journal of Neurology, Neurosurgery, and Psychiatry*, **82**(4), 378–83.
10. Keep RF, Hua Y, and Xi G. (2012). Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. *Lancet: Neurology*, **11**(8), 720–31.
11. Qureshi AI, Mendelow AD, and Hanley DF. (2009). Intracerebral haemorrhage. *Lancet*, **373**(9675), 1632–44.
12. Prabhakaran S, and Naidech AM. (2012). Ischemic brain injury after intracerebral hemorrhage: a critical review. *Stroke*, **43**(8), 2258–63.
13. Ko SB, Choi HA, Parikh G, et al. (2011). Multimodality monitoring for cerebral perfusion pressure optimization in comatose patients with intracerebral hemorrhage. *Stroke*, **42**(11), 3087–92.
14. Wagner I, Hauer EM, Staykov D, et al. (2011). Effects of continuous hypertonic saline infusion on perihemorrhagic edema evolution. *Stroke*, **42**, 1540–5.
15. Vahedi K, Vicaut E, Mateo J, et al. (2007). Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). *Stroke*, **38**(9), 2506–17.

16. Poca MA, Benejam B, Sahuquillo J, et al. (2010). Monitoring intracranial pressure in patients with malignant middle cerebral artery infarction: is it useful? *Journal of Neurosurgery*, **112**(3), 648–57.
17. Videen TO, Zazulia AR, Manno EM, et al. (2001). Mannitol bolus preferentially shrinks non-infarcted brain in patients with ischemic stroke. *Neurology*, **57**(11), 2120–2.
18. Vahedi K, Hofmeijer J, Juettler E, et al. (2007). Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet: Neurology*, **6**(3), 215–22.
19. Molina CA and Selim MH. (2011). Decompressive hemicraniectomy in elderly patients with malignant hemispheric infarction: open questions remain beyond DESTINY. *Stroke*, **42**(3), 847–8.
20. Milhorat TH. (1975). The third circulation revisited. *Journal of Neurosurgery*, **42**, 628–45.

PART 9.8

Stroke

CHAPTER 234

Epidemiology of stroke

Candice Delcourt and Craig Anderson

Key points

- Approximately 20 million strokes occur in the world each year; stroke is the second most common cause of death resulting in 6 million deaths worldwide each year, 30% of survivors have permanent disability.
- Hypertension is the most important modifiable risk factor.
- Stroke has other major consequences in terms of residual physical disability, depression, dementia, epilepsy, and carer burden.
- Ischaemic strokes are more common than haemorrhagic strokes, and account for between 60 and 90% of strokes depending on the population.
- As with other forms of vascular disease, management of lifestyle-related risk factors offers the best approach to reducing the global burden of stroke.

Introduction

Worldwide, approximately 20 million strokes occur each year and over one-quarter of these are fatal. This makes stroke the second most common cause of death after ischaemic heart disease and responsible for about 6 million deaths (almost 10% of all deaths) annually [1]. Among survivors, at least 30% will have permanent disability, so stroke is also the fifth leading cause of premature life lost due to disability as defined by the metric 'disability-adjusted life years' (DALYs) [2]. Stroke also has consequences that extend beyond physical disability to that of depression (in about 30%), dementia (10%), and epilepsy (5%). Moreover, as stroke is often a manifestation of generalized vascular disease, around 20% of survivors experience either further stroke or serious vascular event within a few years of the index event [3]. There are also the considerable direct costs of care for patients with acute stroke, estimated to be about 2–4% of all the costs of healthcare, worldwide [4]. Finally, there are the indirect economic costs associated with lost productivity and the out-of-pocket expenses for families. The grief and suffering imposed by stroke are difficult to quantify, but are clearly enormous. With ongoing demographic changes, including the ageing and urbanization of populations, together with the persistence of highly prevalent risk factors related to adverse lifestyles, the global burden of disease related to stroke is predicted to increase substantially by 2030. Ischaemic stroke contributes the greatest share of the impact of stroke. It has a rate of approximately 1 in 1000 person-years, and accounts for between 60% of all strokes in Asia and 90% in Western 'white' populations.

Definition of stroke and transient ischaemic attack

Despite significant advances being made in diagnostic technology and the management of stroke in recent decades, the diagnosis remains largely clinical. For the last 40 years stroke has been defined by the World Health Organization (WHO) as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function with symptoms lasting 24 hours or longer (or leading to death), with no apparent cause other than vascular origin' [5]. Where the symptoms (and signs) resolve within 24 hours, the syndrome has traditionally been defined as transient ischaemic attack (TIA). However, this arbitrary time-based definition was established before the widespread availability of brain imaging (computerized tomography (CT) or magnetic resonance imaging (MRI)) and use of early treatment to recanalize an occluded cerebral artery. Patients with TIAs commonly have ischaemic lesions on brain imaging [6] and these carry the same prognosis for death, permanent disability, and recurrent stroke as that of a minor ('completed') ischaemic stroke [7,8]. For epidemiological purposes, the old definition of TIA is likely to remain, but for clinical management, the presence of an ischaemic lesion in association with an acute stroke syndrome should be considered an ischaemic stroke and patients managed accordingly.

Prediction of ischaemic stroke following TIA

A simple assessment called the ABCD^2 score, is calculated according to a 7-point scale that sums each patient's score on 5 risk factors: **A**ge ≥ 60 (1 point) versus < 60 years old (0 point), **B**lood pressure (BP) systolic ≥140 or diastolic ≥90 mmHg(1 point)), **C**linical features unilateral paresis (2 points), speech disturbance(1 point)), **D**uration of symptoms >60 minutes (2 points), 10–59 minutes (1 point) and <10 minutes (0 point), and **D**iabetes (1 point). This score can be used to identify patients at high risk of ischaemic stroke in the first days after TIA [9,10]: the higher the score, the higher the prediction. Rapid assessment of the internal carotid artery by CT or MRI angiography, or duplex ultrasonography, will allow the detection of an 'unstable' (i.e. irregular or ulcerated plaque) or high grade (>70%) stenosis that should be treated early to prevent the occurrence of a major stroke in an otherwise well patient.

Classification systems for ischaemic stroke

Ischaemic stroke can result from a heterogeneous range of disorders that are not necessarily related to atherosclerosis, have different manifestations of occurrence and patterns of outcome, and may require different management. Broadly speaking, ischaemic stroke,

which accounts for about 80% of stroke in 'white Caucasian' populations (other ethnic groups have a greater proportion of haemorrhagic strokes), can occur via the following principle mechanisms (with proportional frequencies) as applied in clinical research as the TOAST (Trial of ORD 10172 in Acute Stroke Treatment) criteria [11]:

- **Cardio-embolism (20–30%)**: secondary to atrial fibrillation (AF), valvular heart disease or from infectious endocarditis.
- **Large vessel atherosclerosis (20–30%)**: in situ atheromatous occlusion of intracerebral arteries (more common in Oriental Asian patients), or artery-to-artery embolism from carotid stenosis or plaques in the arch of the aorta.
- **Small vessel disease (10–20%)**: lacunar disease.
- **Arterial dissection (3–5%)**: mostly extra-cranial carotid or vertebral arteries
- **Rare forms (1–5%)**: includes secondary to recreational drug use (e.g. cocaine and amphetamines, which can also cause haemorrhagic strokes), haematological (e.g. polycythaemia), arteritis (e.g. temporal arteritis), metabolic (e.g. Fabry disease), cerebrovasoconstrictor syndrome, or many other disorders.
- **Unknown or undetermined cause ('cryptogenic') (5–10%).**

A popular classification of ischaemic stroke that uses only clinical symptoms and signs was derived from the Oxfordshire Community Stroke Project (OCSP) [12]. The OCSP syndromic classification system is based upon the extent of cerebral involvement and is a simple grading system of severity and prognosis covering total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), lacunar infarcts (LACI), and posterior circulation infarcts (POCI).

Haemorrhagic stroke

Parenchymal intracerebral (I-C) haemorrhage account for 10–40% of strokes around the world, but most of those affected live in developing countries where hypertension is common. I-C haemorrhage is the least treatable form of stroke, and carries a high risk of death and residual disability, 30-day mortality is 30–55%, with half of these deaths occurring within the first few days. I-C haemorrhage arises from the brain parenchyma, but can extend into the ventricular system and subarachnoid, subdural, or extradural spaces.

I-C haemorrhage is difficult to differentiate from ischaemic stroke at the bedside, but certain features raise suspicion of the diagnosis. Rapidly progressive neurological signs and symptoms, associated headache, vomiting and seizures, and a reduced level of consciousness that is disproportionate to any focal deficit (i.e. paresis), all suggest mass effect from an underlying haematoma. Neck stiffness indicates that blood has breached the subarachnoid space, generally via the ventricular system, which can produce chemical meningitis and/or hydrocephalus. The most reliable way to diagnosis I-C haemorrhage is a non-contrast computed tomographic (NCCT) brain scan.

Most I-C haemorrhage, approximately 80%, occur secondary to disease of small (<3 mm) penetrating arteries from chronically-elevated blood pressure (BP). I-C haemorrhage typically occurs in deeper locations of the brain, such as the putamen, thalamus, pons, and cerebellum. Another, increasingly recognized cause of I-C haemorrhage, is cerebral amyloid angiopathy, which is due to the deposition of amyloid β-peptide in small and middle size vessels. This is presumed to 'destabilizes' surrounding architecture to produce I-C haemorrhage.

Subarachnoid haemorrhage

The other form of haemorrhagic stroke is subarachnoid haemorrhage (SAH), most often due to spontaneous rupture of an intracranial aneurysm. It accounts for about 5% of strokes, but leads to a similar loss of productive life years as cerebral infarction. In Western countries, SAH has an annual incidence of 8–10 per 100,000, a 30-day case fatality of up to 45%, and leaves many survivors with varying degrees of physical disability and psychosocial problems.

Rates and risk factors

Stroke incidence varies between different countries and regions, and over time. Among recent (1990 onwards) population-based studies that have used standardized definitions and case ascertainment procedures, the age-standardized rates (per 100,000 person-years) of stroke have varied from 58 in France to 314 in Finland. Between 1970–1979 and 2000–2008, there has been a 42% decrease in age-adjusted rates in high-income countries, but a more than doubling of rates in low- and middle-income countries. Stroke mortality also varies between populations; age-standardized mortality is higher in Eastern Europe and low- and middle-income countries than elsewhere. In Asia, where the burden of stroke is particularly high, death from stroke is proportionally greater than that from myocardial infarction, a pattern that is the reverse of that seen in Western countries, and probably due to a greater proportion of strokes being due to I-C haemorrhage [13].

While age-standardized stroke incidence and mortality appears to have declined in high-income countries [14,15], the absolute number of people experiencing strokes, and mortality and dependency from stroke, will continue to increase [16], due to the ageing of populations and where the highest stroke rates occur. As a result, stroke is predicted to remain the second most common cause of death worldwide, accounting for an estimated 7.8 million deaths annually by 2030 [1,2].

Stroke is associated with a number of identified modifiable and non-modifiable risk factors; 90% of the population-attributable risk of stroke can be explained by 10 factors (hypertension, physical inactivity, abdominal obesity, ratio of apolipoprotein B to A1, smoking, diet, cardiac causes, diabetes mellitus, psychosocial stress or depression, and excessive alcohol intake) [17]. Elevated BP (defined as systolic >115 mmHg) is the most important modifiable risk factor, estimated to account for at least half of all strokes, with about half of this burden due to 'hypertension' defined as systolic BP >140 mmHg and/or diastolic BP >90 mmHg [18].

Elevated BP is a major determinant of initial (primary) and recurrent (secondary) ischaemic stroke. Observational studies demonstrate a strong and near continuous relationship between the risk of stroke and usual level of BP [19]. The association exists for both systolic and diastolic BP and continues among those with average or below average BP, with no threshold identified below which the risk of stroke does not decrease. The association becomes attenuated with increasing age although remains strongly positive for all age groups. A 10 mmHg lower usual systolic BP is associated with 40–50% lower risk of stroke among those under 60 years of age, but a 20–30% lower risk among those over 70 years. The association is consistent in men and women, non-Asian and Asian populations, and for both fatal and non-fatal strokes, but it appears steeper for I-C haemorrhage than for ischaemic stroke. Finally, disturbances of the normal diurnal

variation in BP, including absence of nocturnal drop ('non-dipping') and wide fluctuations, particularly excessive early morning acceleration in the peak ('morning surge'), are especially associated with strokes and other manifestations of cerebrovascular disease [9].

Other major risk factors include AF, extracranial carotid artery atherosclerosis, diabetes mellitus, cigarette smoking, and hyperlipidaemia.

In-hospital strokes

In-hospital strokes are not uncommon due to the increasing number of operations being performed on older patients, including those with known and asymptomatic co-morbid vascular disease. The major contributing procedures are in cardiothoracic surgery including coronary artery bypass grafting where risk of stroke may be as high as 5% overall, and 10% in those ≥75 years. For valvular cardiac surgery the risk may be as high as 10–15%. The management of anticoagulation in patients with AF is complex—it is not uncommon for peri-operative strokes to occur in patients who have had their anticoagulation stopped to reduce bleeding risk. The annual risk of stroke in the setting of AF varies from less than 1% in younger healthy adults with otherwise normal cardiac structure and function, to more than 10% according to the presence of one or more clinical characteristics such as congestive cardiac failure, hypertension, older age (≥75 years), diabetes mellitus, and a history of previous stroke or TIA. All 'high risk' patients should be considered for 'bridging therapy' with low molecular weight heparin prior to surgery and full anticoagulation recommenced as soon as possible (preferably within 48 hours) after surgery to lower the considerable risk of stroke. For most patients this carries an acceptable small increase in the risk of peri-operative bleeding, which can generally be managed. The risk of cardioembolic stroke in the context of peri-operative AF appears dependent on a variety of factors including the degree of cardiac enlargement, particularly of the atria (and propensity for clots to develop through stasis of blood in the atrial appendices), degree of transient hypercoagulability from the trauma of surgery, and the peri-operative development of a low cardiac output syndrome [20].

Conclusion

Stroke constitutes a major proportion of the global burden of disease, and causes premature death and disability across all ages. However, stroke is an eminently preventable and treatable disease. While the best opportunity for reducing the burden of stroke across the community is widespread implementation of broad-based prevention strategies, measures that increase awareness of the symptoms and timely use of diagnostic and treatment strategies can also provide benefits to patients, families, and society.

References

1. Strong K, Mathers C, and Bonita R. (2007). Preventing stroke: saving lives around the world. *Lancet: Neurology*, **6**, 182–7.
2. Lopez A, Mathers C, Ezzati M, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367;1747–57.
3. Hankey G, Jamrozik K, Broadhurst R, et al. (2002). Long-term disability after first-ever stroke and related prognostic factors in the Perth Community Stroke Study, 1989–1990. *Stroke*, **33**, 1034–40.
4. Donnan G, Fisher M, Macleod M, and Davis S. (2008). Stroke. *Lancet*, **371**, 1612–23.
5. World Health Organization Task Force on Stroke and Other Cerebrovascular Disorders. (1989). Stroke1989: recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke*, **20**, 1407–31.
6. Easton J, Saver J, Albers G, et al. (2009). Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. *Stroke*, **40**, 2276–93.
7. Johnston SC, Gress DR, Browner WS, and Sidney S. (2000). Short-term prognosis after emergency department diagnosis of TIA. *Journal of the American Medical Association*, **284**, 2901–6.
8. Coull AJ and Rothwell PM (2004). Underestimation of the early risk of recurrent stroke: evidence of the need for a standard definition. *Stroke*, **35**, 1925–9.
9. Rothwell PM, Giles MF, Flossmann E, et al. (2005). A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet*, **366**, 29–36.
10. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. (2007). Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*, **367**, 283–92.
11. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, and Heuschmann PU. (2001). Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke*, **32**, 2735–40.
12. Bamford J, Sandercock P, Dennis M, Burn J, and Warlow C. (1991). Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet*, **337**, 1521–6.
13. Wei JW, Arima A, Huang Y, et al. (2010). Variation in the frequency of intracerebral haemorrhage and ischaemic stroke in China: a national, multi-centre, hospital register study. *Cerebrovascular Disease*, **29**, 321–7.
14. Anderson C, Carter K, Hackett M, et al.(2005). Trends in stroke incidence in Auckland, New Zealand, during 1981 to 2003. *Stroke*, **36**, 2087–93.
15. Islam MDS, Anderson CS, Hankey GJ, et al. (2008). Trends in incidence and outcome of stroke in Perth, Western Australia during 1989 to 2001: the Perth Community Stroke Study. *Stroke*, **39**, 776–82.
16. Tobias M, Cheung J, Carter K, Feigin V, and Anderson CS. (2007). Stroke surveillance: population-based estimates and projections for New Zealand. *Australia and New Zealand Journal of Public Health*, **31**, 520–5.
17. O'Donnell M, Xavier D, Liu L, et al. (2010). Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*, **376**, 112–23.
18. Lawes C, Vander Hoorn S, and Rodgers A. (2008). Global burden of blood-pressure-related disease, 2001. *Lancet*, **371**, 1513–18.
19. Asia Pacific Cohort Studies Collaboration. (2003). Blood pressure and cardiovascular disease in the Asia Pacific region. *Journal of Hypertension*, **21**, 707–16.
20. Hogue CW, Murphy SF, Schechtman KB, and Davila-Roman VG. (1999). Risk factors for early or delayed stroke after cardiac surgery. *Circulation*, **100**, 642–7.

CHAPTER 235

Diagnosis and assessment of stroke

Candice Delcourt and Craig Anderson

Key points

- Approximately 20 million strokes occur in the world each year, making it the second most common cause of death resulting in 6 million stroke deaths worldwide each.
- Nearly half of stroke survivors have permanent disability.
- Stroke also has major consequences in terms of residual physical disability, depression, dementia, epilepsy, and carer burden.
- Diagnosis and assessment are essentially clinical and confirmed by CT or MRI scanning.
- Prognostication is difficult in the early phase of haemorrhagic stroke, and in ischaemic stroke is affected by the availability and timely use of treatments to recanalize the occluded vessel.

Diagnostic assessment and investigations

There are a wide range of simple structured diagnostic algorithms for the diagnosis of stroke intended to be used by paramedics and triage nurses. In Australia and many other countries, the most common tool in use is FAST:

- **Face**: unilateral facial weakness.
- **Arm**: arm weakness.
- **Speech**: speech disturbance.
- **Time**: known time of onset (and time to call the emergency number).

Diagnostic algorithms allow paramedical staff to rapidly recognize symptoms of stroke, assess eligibility for thrombolysis, and transport to a suitable hospital for treatment [1]. Effective delivery of acute stroke treatments involves efficient links in the chain, with will trained paramedical staff inserting a suitable intravenous access line, providing advanced notification to the emergency department, where there are responsive systems of triage, diagnostic assessment and management [2]. Such systems provide short door-to-imaging and door-to-needle times to allow rapid and probably safer use, and improved outcomes for thrombolytic therapy.

Following admission to the emergency department, all patients with a suspected stroke should have a non-contrast computed tomographic (NCCT) scan, or where available magnetic resonance imaging (MRI), of the brain, routine blood tests (blood count including platelet count, serum glucose, prothrombin time, and international normalized ratio (INR) electrolytes, urea, and creatinine), and an electrocardiogram. With rapid advances being made in brain imaging, the extra- and intracranial vessels (CT angiogram, MR angiogram) and the ischaemic penumbra (CT perfusion, MRI) can be readily visualized. However, these tests should not delay the use of thrombolysis in eligible patients with ischaemic stroke, but are useful in identifying those patients who are unlikely to respond to thrombolysis (massive infarct with dead tissue, large proximal vessel clot occlusion) or endovascular stent (clot) retrieval treatment. There is now good evidence that a second attempt at opening a brain vessel using intra-arterial thrombolysis or specific devices can restore brain function in a potentially salvageable area [3].

The ischaemic penumbra can be mapped using CT perfusion. The penumbra is the area where there is decreased cerebral blood flow (CBF) and increased mean contrast transit time without decreased cerebral blood volume.

In specialized centres, MRI diffusion-perfusion will be used. The diffusion abnormality identifies the core irreversibly injured tissue, while the perfusion abnormality identifies the tissue at risk of eventual infarction.

A period of up to 72 hours of electrocardiogram (ECG) monitoring is useful for the detection of intermittent or poorly-controlled atrial fibrillation (AF), which is an important cause of intracardiac thrombus formation and cardio-embolic stroke. If negative, ambulatory cardiac monitoring for several days, possibly longer with an implantable loop recorder, for patients with a cryptogenic ischemic stroke or transient ischaemic attack (TIA) is recommended. Transthoracic echocardiography is often performed, but rarely useful in altering patient management unless there is a high index of suspicion of an underlying cardiac abnormality (e.g. mural thrombus in a patient with recent myocardial infarction, established coronary artery disease, or poor left ventricular function). Transoesophageal echography is recommended to examine for underlying aortic atheroma, valvular disease (e.g. myxoma, endocarditis) or patent foramen ovale (PFO) in a young patient without a clear cause for cardio-embolic ischaemic stroke. The role of PFO is controversial. PFOs are very common in the general population and the risk of stroke is very small. When a stroke or transient ischaemic attack (TIA) occurs, it is most often small and in the context of a triggering event, such as prolonged air travel or exercise with a valsalva manoeuvre, that allows a small venous thrombus to cross through the PFO into the arterial circulation and block a cerebral vessel. However, more importantly, the risk of recurrent stroke in among those with known PFO is also very

small. Unless the shunt is particularly large (determined by the degree of shunt and enlargement of the left atria), treatment with aspirin is adequate for the prevention of thromboembolism. If the shunt is large, anticoagulation with warfarin is a sensible alternative. Closure of the PFO through use of an endovascular device is an alternative treatment; it requires a skilled proceduralist and carries small risks in particular of AF. Where angiography is less readily available, Transcranial Doppler ultrasound (TCD) can be undertaken to visualize intracranial artery stenosis, collaterals and the haemodynamic change related to a neck vessel stenosis.

Cerebral autoregulation and ischaemic cerebral injury

As the brain has high-energy requirements and is unable to store nutrients, it is totally dependent on having a secure blood supply. Cerebral autoregulation aims to ensure there is an adequate cerebral blood flow (CBF) (50 mL/100 g/min) within a tightly-regulated range despite changes in blood pressure (BP) and cardiac output in relation to posture and activity. When the lower limit of CBF is reached (<10 mL/min/100 g), cerebral ischaemia and neuronal death occur unless blood flow is rapidly restored. Following the occlusion of a cerebral artery that occurs in an acute ischaemic stroke (and TIA), there is immediate hypoxic injury and rapidly occurring death of neurons within a central core. However, there is a more delayed death in a region called the 'ischaemic penumbra', which is protected by virtue of being located in the watershed boundary of the lesion where some blood flow is maintained from collateral vessels. The size and reversibility of the ischaemic penumbra varies widely, although it is related to the extent of involvement of vascular territory in the brain. Outcome depends on rapid recanalization of the occluded vessel, either by natural means or through thrombolytic therapy or endovascular mechanical intervention. It also depends on the availability of a collateral blood supply. Unfortunately, the presence of collateral blood vessels and their response to injury is probably predetermined, and cannot be easily measured at the time of presentation of acute ischaemic stroke and is difficult to modify.

Prognostic predictors: ischaemic stroke

The chance of surviving an ischaemic stroke is a complex function of the brain lesion *per se* and of many other co-morbid and complicating factors. The size and location of the cerebral lesion have an impact on the immediate prognosis, while vascular and co-existing (cardiac) disease and complicating disorders, such as bronchopneumonia, urosepsis, and thromboembolism, all determine whether a patient will survive the first few weeks after onset. Cardiovascular disease also influences long-term survival. Although studies have emphasized the adverse effect that increasing age has on survival after stroke, this relationship is more complex and more related to the presence of other variables that are more common in older people. The presence of pre-morbid disability is particularly important, which underscores the importance of obtaining this information when making decisions about interventions and the prolonged use of supportive care.

The prognosis in terms of general recovery after ischaemic stroke can be assessed in terms of the following variables:

- **Severity of the initial neurological deficit**: including the degree of ataxia and paralysis will determine the speed and ultimate degree of recovery in physical function.
- **Speed of recovery of neurological deficit**: the rapid return of function in the first week is a good prognostic sign.
- **Attention, awareness and cognitive insight are important**: as rehabilitation involves re-learning and participation. Fatigue, poor memory, and lack of insight are major barriers to successful recovery.
- **A supportive spouse or personal carer**: can offset the degree of residual disability and determine whether a patient is able to return home or will require long-term residential care.

Recovery of physical function is most rapid in the first weeks after ischaemic stroke, and tends to plateau by 3–6 months.

Prognostic predictors: haemorrhagic stroke

As it is difficult to reliably predict clinical outcome in the early phase of intracerebral (I-C) haemorrhage, and evidence indicates that 'do-not-resuscitate' or 'withdrawal of care' orders are independent predictors of early mortality. A policy of 'active' care should be applied to patients with I-C haemorrhage upon admission to hospital unless there are extenuating circumstances. A period of acute care allows time for a patient's critical condition to stabilize, and to assess the effects of potential complicating factors, such as early seizure(s), dehydration, and sudden internal 'barotrauma' of the I-C haemorrhage on the brain. It also allows time for counselling and discussion with family members regarding ongoing management in the context of their various cultural, religious, and personal beliefs, including those known or assumed of the patient.

I-C haemorrhage is a dynamic illness, where expansion or 'growth' of the haematoma occurs in most patients. Substantial expansion is conventionally defined as a >33% relative or >12.5 mL absolute growth in the first 24 hours, which is what can be detected visually on a CT scan, occurs in at least one-third of patients within several hours of onset. Both the volume of haematoma on initial CT and the extent of growth are major determinants of outcome. Volumes greater than 30 mL invariably result in early death from neuronal trauma and mass effect, while patients with smaller haematomas may survive the initial event, but remain at risk of succumbing to the complications of residual disability or a recurrent event.

Conclusion

Stroke constitutes a major proportion of the global burden of disease, and causes premature death and disability across all ages. Diagnosis and assessment are essentially clinical and confirmed by CT or MRI. Prognostication is difficult in the early phase of I-C haemorrhage, and in ischaemic stroke is affected by the availability and timely use of treatments to recanalize the occluded vessel.

References

1. Bray JE, Coughlan K, Barger B, and Bladin C. (2010). Paramedic diagnosis of stroke: examining long-term use of the Melbourne Ambulance Stroke Screen (MASS) in the field. *Stroke*, **41**, 1363–6.
2. Park S and Schwamm LH. (2008). Organizing regional stroke systems of care. *Current Opinion in Neurology*, **21**, 43–55.
3. Prabhakaran S, Ruff I, and Bernstein RA (2015). Acute stroke intervention: a systematic review. *Journal of the American Medical Association*, **313**, 1451–62.

CHAPTER 236

Management of ischaemic stroke

Sully Xiomara Fuentes Patarroyo and Craig Anderson

Key points

- The diagnosis of acute ischaemic stroke is based on establishing a clear history of an abrupt onset of neurological symptoms and signs.
- Reperfusion therapy with thrombolysis using intravenous recombinant tissue plasminogen activator should be used routinely in all patients with acute ischaemic stroke within 4.5 hours of onset who have no bleeding risk.
- Endovascular stent (clot) retrieval therapy should be used in patients with documented proximal clot occlusion who are able to access appropriate specialist centres within several hours of onset.
- Patients should be actively monitored following thrombolysis.
- Secondary prevention includes blood pressure (BP) lowering, antiplatelet, or anticoagulation according to cardiothrombotic risk, cholesterol lowering, and selected use of carotid revascularization.

Introduction

Ischaemic stroke accounts for approximately 80% of all strokes worldwide. As the therapeutic time window to rescue the brain from ischaemic injury is extremely short (only a few hours at most) [1], effective management requires good systems of communication and a responsive expert team to ensure rapid diagnosis, and safe and effective delivery of acute treatment. Indeed, two of the most important therapeutic advances in stroke medicine are arguably the recognition that well-coordinated multidisciplinary care (not specifically hyperacute care) in the form of stroke care units [2], can significantly improve the chances of recovery from stroke, and that brain function can be preserved and satisfactory outcomes achieved through the use of reperfusion therapy, until recently limited to thrombolytic therapy but now open to mechanical stent (clot) retrieval treatment [3], to recanalize an occluded vessel and reperfuse the 'at risk' area of the brain, defined as the ischaemic penumbra [4]. Other aspects of management include the prevention of complications of the neurological disability [5], timely rehabilitation, realistic recovery goal setting, and prevention of recurrent stroke and other vascular events.

Diagnosis and acute treatment

Approach to the patient

The diagnosis of acute stroke is based on establishing a clear history of an abrupt onset of 'negative' (i.e. loss of function) neurological symptoms and signs. A brief yet accurate examination focused on detecting neurological deficit(s) is all that is required to identify both the presence and severity of an underlying stroke. The most popular structured scoring system, the National Institutes of Health stroke scale (NIHSS), enables a standardized and reproducible assessment of any neurological deficit, and it is highly predictive of short- and medium-term functional outcome. The NIHSS takes a person about 2 hours to become fully trained and accredited via an online method (see http://www.americanheart.org), and experienced users can streamline their assessment to under 2 minutes. The NIHSS is much more sensitive to neurological impairment than traditional measures, such as the Glasgow Coma Scale (GCS), which was developed for patients with traumatic brain injury.

Paresis ('weakness') or plegia ('complete loss of power') is the most common manifestation of stroke, but it is non-specific and can be attributed to a lesion anywhere along the corticospinal tract. Other features to indicate the lesion has a large size and more indicative of large vessel(s) occlusion in the brain include hemianopia, aphasia, and right gaze deviation and/or visual neglect. Although lacunar strokes are common in older people with hypertension (due to occlusion of small perforating vessels in the basal ganglia, thalamus, internal capsule, or brainstem), they are not be associated with any visual field, language or visuospatial deficit. Symptoms in the posterior circulation include vertigo, ataxia, or diplopia.

Rapid assessment and treatment

There is now compelling evidence from multiple randomized trials to support the routine use of thrombolysis with intravenous recombinant tissue plasminogen activator (rtPA) at a standard dose of 0.9 mg/kg (10% bolus, 90% infusion over 60 minutes, maximum dose 90 mg) in patients with acute ischaemic stroke within 4.5 hours of onset who are otherwise well and have no major contraindications to bleeding [1,4]. The earlier the administration of rtPA, the better the outcome, but the downside is risk of bleeding, the most serious being major symptomatic intracerebral haemorrhage (sICH), which occurs in about 5% of patients in experienced centres. This risk is generally deemed acceptable by most clinicians, patients and families. If a patient cannot give a reliable history, then the onset of the stroke must be taken from the time they were last seen well. This can be particularly difficult when the patient's symptoms are present on waking from sleep (so-called 'wake-up stroke'), in which case the onset time must be taken from when patient was last known to be well prior to going to sleep.

Modern brain imaging, such as computed tomographic (CT) perfusion or magnetic resonance imaging (MRI), can allow detailed assessment of the location and size of ischaemic tissue that

is both 'at risk' (i.e. the penumbra) and probably irreversible (i.e. infarction). However, such imaging is not always readily accessible and the extra time required for processing and measurement of the images delays use of rtPA and its potential benefit. CT or MRI angiography (CTA, MRA) is useful in identifying the location of the blocked cerebral vessel, especially when it is proximal, as indicated by the patient having a neurological deficit and a 'dense artery sign' on the non-contrast CT (NCCT). Due to the large clot burden, such patients are less likely to respond to rtPA and may benefit from mechanical clot retrieval [3,6]. Again, however, obtaining a CTA should not unduly delay treating the patient, due to the injection of contrast (and risk of nephrotoxicity if there is impaired renal function) and the need to obtain direct involvement of a radiologist in the procedure. Thus, a plain NCCT, which takes less than 5 minutes, is all that is required to establish the diagnosis of ischaemic stroke, and the absence of haemorrhage or any secondary structural lesion, to allow rapid treatment with rtPA.

Acute treatment options

Thrombolysis

The 'time is brain' motto is critical—assessment, diagnosis, and treatment needs to comply with an internationally accepted 'door to needle' performance time measure of less than 60 minutes. While there is a long list of potential contraindications to thrombolysis that can be seen in regulatory documents and guidelines, in practice the aim is to ensure that the risks of bleeding are not excessive, and there are no major comorbid medical conditions that may complicate the diagnostic work-up and outcome. Patients who are anticoagulated with warfarin should have their International Normalized Ratio (INR) returned to a near normal level (<1.8) before giving rtPA to avoid an excessive risk of bleeding. There is controversy as to the management of minor strokes (e.g. isolated aphasia or paresis; NIHSS <6). As they have been excluded from most clinical trials because of their good prognosis, greater potential for being a stroke mimic (i.e. migraine, post-seizure, functional, or metabolic disturbance), so rtPA may not provide a net benefit and pose an unnecessary risk. However, a case can be made for giving rtPA to such patients as at least 30% will progress due to an unstable lesion or cerebral blood flow, and the risk of sICH is low as the underlying deficit is small. There is less controversy over the avoidance of rtPA in patients with large strokes (i.e. NIHSS >24; drowsy and obtunded; deficit involving >1/3 of the middle cerebral artery territory) because they have a high risk of sICH and low likelihood of having any underlying reversible ischaemic tissue.

Mechanical clot retrieval

Interventional neuroradiology (INvR) by means intra-arterial thrombolysis (often with the catheter tip dislodging the clot) or more often use of mechanical clot retrieval (of which there are an increasingly wide range of devices/stents) are associated with higher rates of recanalization in comparison with intravenous rt-PA alone, particularly for large proximal clots (i.e. terminal internal carotid artery, proximal anterior or middle cerebral arteries). Recently, substantial evidence of efficacy has been obtained from several randomized trials indicating improved recanalization translates into improved clinical outcome limits the application of the treatment in practice [3]. Moreover, as INvR is a highly skilled, resource-intensive discipline, and the devices are expensive, effects are underway to assess the most appropriate organization of regional systems of care around INvR.

Hemicraniectomy

Malignant middle cerebral artery (MCA) infarction is the term used to describe rapid neurological deterioration from cerebral oedema with transtentorial herniation and brainstem compression [6]. It is most often seen within the first 24–48 hours of ischaemic stroke in younger people (<60 years) as older people are somewhat protected as brain atrophy allows room for expansion of cerebral oedema. It can be predicted from the initial CT by presence of early ischaemic changes of >50% of the MCA territory [7]. No medical therapy has proven to be effective for cerebral oedema, thrombolysis does not reduce the risk of developing malignant MCA infarction, and the prognosis is poor with a mortality rate up to 80%. Decompressive hemicraniectomy, involving resection of a large bone flap to relieve intracranial pressure, has been shown to be a life-saving procedure and improve neurological outcome. It should be considered in all younger patients with large MCA infarction and progressive neurological deterioration over 48 hours after onset. Such cases require early notification to a neurosurgeon to ensure appropriate timing (i.e. before the patient has fixed dilated pupils!) and reinforcement to involved clinicians and family members that the procedure results in most patients being left with degree of disability, but not necessarily requiring residential care.

Aspirin

The use of standard dose (100–300 mg) aspirin with 48 hours of the onset of ischaemic stroke has been shown to improve the chance of surviving free of disability at 6 months [8]. However, the treatment only has a modest effect, does not appear to be time-dependent, and may work more through the prevention of early recurrence of ischaemic stroke, rather than any improvement in the ischaemic deficit. It should be avoided for 24 hours in patients given rtPA (earlier use of antithrombotic agents increases the risk of sICH).

Neurological and physiological monitoring

Immediate period after reperfusion therapy

For at least 24–48 hours after admission to hospital, and particularly following thrombolysis or clot retrieval, patients should be cared for in a monitored facility, either in an intensive care unit or high dependency area of a stroke unit. The most appropriate location is dependent on the severity of the patient's status and availability of resources. Trained nursing (and medical) staff should undertake frequent monitoring and be able to take an appropriate action according to prespecified protocol(s). The most serious early complication of thrombolysis/clot retrieval is sICH, which should be suspected in anyone with sudden deterioration in neurological status, headache, nausea, vomiting, or elevation in blood pressure. An immediate NCCT will differentiate intracerebral (I-C) haemorrhage from cerebral oedema, the patient's coagulation and haematological parameters should be checked, and any residual effect of rtPA can be corrected by administration of 6–8 units of cryoprecipitate (containing clotting Factor VIII) and 6–8 units of platelets. Surgical evacuation of the I-C haemorrhage may be possible following treatment with platelets and cryoprecipitate, although the rapidity of

neurological deterioration is such that prognosis is grave, irrespective of any treatment. All invasive interventions must be balanced against the risk of bleeding:

- Invasive and in-dwelling catheters should be avoided at least an hour post-rtPA (if indicated, consider insertion prior to administration of rt-PA).
- Nasogastric tube, venipuncture, and arterial puncture for 24 hours post thrombolysis.
- Brushing teeth for 36 hours post-thrombolysis (mouth swabs should be used instead).

Blood pressure

Over two-thirds of patients are hypertensive at the time of an acute ischaemic stroke [9] and the higher the BP, the worse outcome [10]. However, in the absence of randomized evidence, there is uncertainty regarding the optimal management of high BP in this setting, particularly as aggressive BP reduction may reduce cerebral blood flow and aggravate ischaemia. Current guidelines, based on expert consensus opinion, recommend that antihypertensive medications be withheld unless the BP exceeds 220/120 mmHg except for those patients considered for rt-PA, where the BP should be lowered to ≤185/110 mmHg and kept at this level thereafter. Whether some drugs should be used preferentially is unknown.

Bed rest, and control of glucose and temperature

Patients should rest in bed for 24 hours after rt-PA, as a precaution against sICH. Cardiac rhythm should be monitored for up to 72 hours. Guidelines recommend monitoring temperature, oxygen saturation, respiratory rate, heart rate, and neurological status every 15 minutes for the first 2 hours, then every 30 minutes for 6 hours, then hourly for 16 hours (a total of 24 hours), and 6-hourly (i.e. four times daily) thereafter. Given the high prevalence of diabetes mellitus among patients with ischaemic stroke, all patients should have a screening blood glucose concentration on admission, and for those with known diabetes or high baseline levels, have glucose monitored 4-hourly for at least the first 24 hours. Although there is no randomized evidence, fever ≥38°C should be treated as should a blood glucose level of >10 mmol/L. As many patients present dehydrated, hydration should be maintained, and most effectively through the intravenous route as dysphagia is common.

Early complications of ischaemic stroke

Thromboembolism

Patients with acute stroke have an increased risk deep venous thrombosis and pulmonary embolism. This risk is higher in patients with severe neurological deficit, older age, and prolonged immobilization. Measures to reduce the risk include early mobilization, aspirin, and the use of external compression devices. The administration of subcutaneous low-dose unfractionated heparin or low-molecular weight heparin is recommended in patients with prolonged immobilizaton (>72 hours) to avoid an early excess risk of sICH; delayed for >24 hours after thrombolysis. External compression is useful in those patients that cannot tolerate an antithrombotic agent. The potential benefit of anticoagulation should be weighed against the small risk of haemorrhagic transformation of the cerebral infarction and of other bleeding complications.

Aspiration pneumonia

Aspiration pneumonia is a common and serious complication after acute stroke, conferring a three-fold increase in mortality [11]. Decrease level of consciousness, immobility, and dysphagia are risks factors with the latter being the most significant. Swallowing assessment by a speech therapist or a trained nurse is recommended for all patients, with the avoidance of food or fluids according to the degree of dysphagia. Care is required in the use of a nasogastric tube for feeding, as the regurgitation of the fluids/feeds can lead to aspiration. There is no evidence that prophylactic use of antibiotics is beneficial.

Seizures

Seizures occur in about 5% of the patients with an ischaemic stroke, but there is no data to support the use prophylactic anti-epilepsy drugs. If seizures occur, lamotrigine and gabapentine may be preferential because they do not interact with anticoagulants or antiplatelet agents [12].

Other complications

Other common complications of acute ischaemic stroke include:

- **Delirium**: causes agitation and distress, and the risk of falls and other injury.
- **Disturbance of sleep**: via multiple potential mechanisms, including sleep fragmentation due external stimuli.
- **Alteration:** in circadian rhythm, medications, either pre-morbid or stroke-related obstructive or central sleep apnoea.

Secondary prevention

Blood pressure lowering

Elevated BP is the single most important reversible risk factor for both first-ever and recurrent (secondary) stroke or TIA. Randomized evidence indicates that lowering BP can produce very large beneficial effects [13]; even a modest (e.g. 8/4 mmHg) average reduction can be associated with a 20–25% reduction in the risk of recurrent stroke and other serious vascular events, even in people with average or below-average levels of BP. The degree of BP lowering is far more important than the particular agent [14]. BP lowering can safely be commenced when the patient is medically stable (i.e. when mobilizing), and modified according to tolerability in the use multiple agents.

Antiplatelet therapy

Antiplatelet therapy (i.e. aspirin, clopidogril, combination low-dose aspirin and dipyridamole) is an essential strategy for the secondary prevention of ischaemic stroke, as well as for other cardiovascular events. While antiplatelet therapy confers a small absolute increase in the risk of I-C haemorrhage and major extracranial haemorrhage, the overall benefits outweigh the bleeding risks among high-risk patients.

Anticoagulation

Anticoagulation with warfarin or the new oral anticoagulants (NOACs) is highly effective at preventing strokes in patients with atrial fibrillation (AF), particularly in the elderly who are at highest

risk. Meta-analyses of trials show that adjusted-dose warfarin (target INR of 2.5) reduces the risk of stroke by about two-thirds, whereas aspirin only reduces the risk by about one-fifth [15], and the excess risks of I-C haemorrhage and major extracranial haemorrhage are small (about 1–2% and <0.3% per year, respectively). Since patients with AF and a history of ischaemic stroke/TIA have a risk of recurrent stroke of >12% per year, the absolute benefit is substantial. NOACs agents, such as the oral direct thrombin inhibitor dabigatran, offer comparable efficacy to warfarin with lower bleeding rates, and they avoid the need for the monitoring INR. However, the anticoagulant effect can only be reversed by dialysis and so the risk of bleeding complications has yet to be quantified.

Cholesterol lowering therapy

Randomized trials indicate that reducing total and low-density lipoprotein (LDL) cholesterol with HMG-CoA reductase inhibitors (statins) significantly reduces the risks of major vascular events, including stroke, across a wide range of lipid levels in patient populations at varying risk of vascular disease [16].

Carotid revascularization

Patients with high degrees (>70%) of carotid stenosis are at elevated risk of ipsilateral ischaemic stroke, most commonly in the first few days after a stroke or TIA. Randomized trials have established the benefits of carotid endarterectomy in such patients with acceptable perioperative risk (2–5%) [17]. The benefits of surgery decrease with time, emphasizing the need for rapid assessment and treatment of such patients. Percutaneous transluminal carotid artery stenting avoids the need for hospital admission and general anaesthesia, but several major randomized trials indicate that it is not superior to surgical endarterectomy [18].

Conclusion

Stroke is a common neurological emergency that requires rapid assessment and treatment, as the opportunities for recovery diminish rapidly with time. A NCCT of the brain can confirm underlying ischaemia and exclude haemorrhage or malignancy. New multimodal imaging (e.g. CT perfusion) offer considerable advantages in defining the location and extent of ischaemia, and assist decision making regarding use of treatments, such as mechanical clot retrieval, provided significant delays in the initiation of treatment can be avoided. Good outcomes are possible with an active approach to patient care, including the use of treatments that target cerebral reperfusion, early recognition, and avoidance of complications, and the initiation of rehabilitation and proven secondary prevention measures such as anti-platelet therapy, BP, and cholesterol lowering.

References

1. Hacke WG, Donnan G, Fieschi C, et al. (2004). Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*, **363**, 768–74.
2. Stroke Unit Trialists' Collaboration (2007). Organised inpatients (stroke unit) care for stroke. *Cochrane Database of Systematic Reviews* 4: CD000197.
3. Prabhakaran S, Ruff I, and Bernstein RA (2015). Acute stroke intervention: a systematic review. *Journal of the American Medical Association*, **313**, 1451–62.
4. Wardlaw JM, Murray V, Berge E, et al. (2012). Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet*, **379**, 2364–72.
5. Balami JS, Chen RL, Grunwald IQ, and Buchan AM. (2011). Neurological complications of acute ischaemic stroke. *Lancet: Neurology*, **10**, 357–71.
6. Mendonça N, Rodriguez-Luna D, Rubiera M, et al. (2012). Predictors of tissue-type plasminogen activator nonresponders according to location of vessel occlusion. *Stroke*, **43**, 417–21.
7. Hofmeijer J, Juettler E, Vicaut E, et al. (2007). Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet: Neurology*, **6**, 215–22.
8. Hofmeijer J, Algra A, Kappelle LJ, et al. (2008). Predictors of life-threatening brain edema in middle cerebral artery infarction. *Cerebrovascular Diseases*, **25**, 176–84.
9. Antithrombotic Trialists' Collaboration (2002). Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *British Medical Journal*, **324**, 71–86.
10. Qureshi AI, Ezzeddine MA, Nasar A, et al. (2007). Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *American Journal of Emergency Medicine*, **1**, 32–8.
11. Qureshi AI. (2008). Acute hypertensive response in patients with stroke: pathophysiology and management. *Circulation*, **118**, 6–187.
12. Katzan IL, Cebul RD, Husak SH, et al. (2003). The effect of pneumonia on mortality among patients hospitalized for acute stroke. *Neurology*, **60**:620–5.
13. Ryvlin P. (2006). Optimizing therapy of seizures in specific clinical situations: are the exceptions the rule? *Neurology*, **67**(12 Suppl. 4), S1–2.
14. Lawes CML, Bennett DA, Feigin VL, and Rodgers A. (2004). Blood pressure and stroke: an overview of published reviews. *Stroke*, **35**, 1024–33.
15. Blood Pressure Lowering Treatment Trialists' Collaboration (2003). Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*, **362**, 1527–35.
16. Hart RG, Pearce LA, and Agullar MI. (2007). Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of Internal Medicine*, **146**, 857–67.
17. Amarenco P, Labreuche J, Lavallée P, and Touboul PJ. (2004). Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke*, **35**, 2902–9.
18. Rothwell PM, Eliziw M, Gutnikov SA, et al. (2003). Pooled analysis of individual patient data from randomised controlled trials of endarterctomy for symptomatic carotid stenosis. *Lancet*, **361**, 107–16.
19. Carotid Stenting Trialists' Collaboration (2011). Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet*, **376**, 1062–73.

CHAPTER 237

Management of parenchymal haemorrhage

Candice Delcourt and Craig Anderson

Key points

- Spontaneous parenchymal intracerebral (I-C) haemorrhage affects several million people in the world each year and carries a high 30-day mortality.
- High blood pressure (BP) is both a causal and prognostic factor for ICH.
- Lowering systolic BP to a target of <140 mmHg within 6 hours after I-C haemorrhage results in better neurological recovery without increasing mortality or harm.
- The role of surgery remains controversial, with no clear evidence that it improves survival and functional recovery.
- Most patients with I-C haemorrhage should receive initial active treatment, with supportive care and rehabilitation among early survivors.

Introduction

Parenchymal intracerebral (I-C) haemorrhage affects several million people in the world annually [1], most of whom reside in developing countries where hypertension and other cardiovascular risk factors are highly prevalent. I-C haemorrhage is the least treatable form of stroke and carries a 30-day mortality of 30–55%, with half of these deaths occurring within the first few days [2]. I-C haemorrhage arises in brain parenchyma but can extend into the ventricular system and subarachnoid, subdural, or extradural spaces. Until recently, there has been no proven medical treatment, and the role of surgery remains controversial. Management is largely supportive and aimed at reducing further brain injury and preventing complications.

Clinical presentation

I-C haemorrhage is difficult to differentiate from ischaemic stroke at the bedside, but certain features raise suspicion of the diagnosis. Progressive neurological signs and symptoms, headache, vomiting, seizures, and a reduced level of consciousness disproportionate to focal deficits (i.e. paresis), all suggest mass effect from an underlying haematoma. Neck stiffness suggests chemical meningitis from blood in the subarachnoid space via the ventricular system. I-C haemorrhage is reliably diagnosed on an early computed tomographic (CT) brain scan.

Aetiological factors and pathophysiology of brain injury

I-C haemorrhage is a dynamic illness and haematoma 'growth' occurs in most patients. Substantial expansion is defined as >33% relative or >12.5 mL absolute growth in the first 24 hours. This can be detected visually on CT and occurs in at least one-third of patients within hours of onset. Both initial haematoma volume and growth are major determinants of outcome. Volumes greater than 30 mL invariably result in early death, while patients with smaller haematomas may survive the initial event but remain at risk of succumbing to the complications of residual disability or a recurrent event [3]. The impact of the haematoma also depends on the degree of perihaematoma oedema and secondary inflammation from thrombin and iron released during haematoma breakdown. If the haematoma stabilizes, and physical disruption is mild to moderate in size and remote from vital structures, the prognosis can be remarkably good.

High BP is both a causal factor for I-C haemorrhage and also a manifestation of large haematomas due to mass effect within the skull. The larger the haematoma, the greater the likelihood of expansion and rebleeding. Perihaematoma oedema develops immediately after I-C haemorrhage from pressure-induced extravasation of serum into brain tissue, rapidly increases over the first 48 hours, and peaks towards the end of the second week. The size of perihaematoma oedema and increases in intracranial pressure are directly related to haematoma size [4]. Although standard brain imaging gives the appearance of an 'ischaemic' halo around haematomas, advanced imaging indicates this is fluid, rather than ischaemia, despite a small reduction in blood flow from the mass effect [5].

Approximately 80% of I-C haemorrhage occur secondary to disease of small (<3 mm) penetrating arteries from chronically-elevated BP, and typically occur in deep brain areas, such as putamen, thalamus, pons, and cerebellum. Cerebral amyloid angiopathy is an increasingly recognized cause of I-C haemorrhage, and is due to deposition of amyloid β-peptide in small- and medium-size vessels. Hypertension is more common in deep I-C haemorrhage than in superficial cortical I-C haemorrhage. I-C haemorrhage in cerebral amyloid angiopathy is usually in association with elevated BP, antithrombotic agents, or trauma. Clinically silent microhaemorrhages (or microbleeds), with residual haemosiderin seen on magnetic resonance imaging (MRI), are typical of amyloid angiopathy. With an ageing population and greater use of warfarin for prevention of cardio-embolic stroke associated with atrial fibrillation, I-C

haemorrhage related to anti-coagulation is increasing and accounts for 10–20% of I-C haemorrhage cases in some centres. The natural history of warfarin-related I-C haemorrhage is for slower, but more protracted haematoma growth than in 'hypertension-related' I-C haemorrhage. Newer anticoagulants reduce I-C haemorrhage risk compared with warfarin, but are harder to reverse if I-C haemorrhage does occur.

Investigations

Non-contrast brain CT is the most appropriate initial investigation for I-C haemorrhage. It will confirm the presence of acute haemorrhage, but is less useful in establishing any underlying cause. CT or MRI angiography is the next step in diagnosing a vascular anomaly (present in 0.1–4.0% of the general population [6]) including arteriovenous malformations (AVM), angiomas, cavernomas, and intracranial aneurysms [7]. A secondary cause of an I-C haemorrhage should be suspected in the presence of subarachnoid haemorrhage, an irregular 'non-circular' shape to the haematoma, perihaematoma oedema disproportionate to haematoma volume, atypical deep or superficial location with associated mass, and in younger patients without a history of hypertension, drug use, or other predisposing factors. MRI gradient echo sequence (T2) is most sensitive for detection of microhaemorrhages. Recently, attention has focused on the 'spot sign'; extravasation of contrast producing a spot or blush within or at the edge of the haematoma. It signifies ongoing bleeding and predicts haematoma growth and poor outcome [8]. Conventional cerebral angiography is needed in cases where there is a high likelihood of a vascular anomaly and interventional treatment is being considered.

Management

General considerations

It is difficult to reliably predict clinical outcome in the early phase of ICH, and evidence indicates that 'do-not-resuscitate' or 'withdrawal of care' orders are independent predictors of early mortality [9]. Patients with I-C haemorrhage at should be treated actively unless there are extenuating circumstances. A period of acute care allows time for a patient's condition to stabilize and for assessment of the effects of complicating factors, such as seizures, dehydration, and brain 'barotrauma' from the I-C haemorrhage. It also allows time for counselling and discussion with family members about management in the context of the patients, and their cultural, religious, and personal beliefs. Patients should receive monitored care, either in an intensive care unit or high dependency section of an acute stroke unit. Inevitably, a sizable component of the management of I-C haemorrhage relates to managing severe neurological disability and providing palliative care.

Early intensive blood pressure control

Elevated BP is common after I-C haemorrhage and strongly associated with poor outcome. A series of pilot, and subsequent larger, clinical trials have demonstrated the feasibility, safety and efficacy of intensive BP lowering in I-C haemorrhage [1,10–12].

The largest clinical trial in I-C haemorrhage, the main phase Intensive Blood Pressure Lowering in Acute Cerebral Haemorrhage Trial (INTERACT2), resolved much of the uncertainty regarding management of elevated BP following I-C haemorrhage. Within 6 hours of I-C haemorrhage, 2839 patients were randomly assigned to intensive (target systolic BP of <140 mmHg within 1 hour) or guideline-recommended (target systolic BP <180 mmHg) BP lowering treatment. The primary outcome of death and major disability was reduced by intensive BP lowering, but fell just short of statistical significance (odds ratio 0.87; 95% confidence interval (CI), 0.75–1.01; $p = 0.06$). However, patients assigned to intensive BP lowering had significantly better functional recovery (modified Rankin scale: odds ratio for greater disability, 0.87; 95% CI 0.77 to 1.00; $p = 0.04$) and better physical and mental health-related quality of life (EQ-5D scale). The intensive treatment was shown to be safe, with no difference in mortality (12.0%) or serious adverse events between the groups.

While more data would strengthen these results, it seems reasonable, on the basis of INTERACT2, that early BP control (to 140 mmHg systolic BP target) in patients with I-C haemorrhage will improve their chance of functional recovery.

Surgery

Despite being part of clinical practice for several decades and having undergone evaluation in multiple randomized trials, the role of surgical decompression of I-C haemorrhage remains controversial, dominated by clinical judgment and variably applied. The totality of evidence indicates surgery is 'on average' beneficial [13]. The problem, however, is in applying this evidence to individuals. Does the chance of net benefit in reversing the neurological deficit overcome the potential for harm associated with cortical incision, general anaesthesia, potential rebleeding and infection? The pivotal Surgical Treatment of Intracerebral Haemorrhage (STICH) trial [14] showed no difference between early versus delayed surgery for supratentorial I-C haemorrhage, but meta-analysis of all trials indicates the greatest potential benefit of surgery is early (within 8 hours) and before patients enter coma [15]. However, the follow-up STICH II [16] trial, targeting conscious patients with isolated superficial cortical I-C haemorrhage also failed to demonstrate improved outcome, although there were non-significant trends in favour of early surgery in poor prognosis patients. Minimally-invasive surgical techniques with burrhole catheter-insertion and instillation of a thrombolytic for haematoma drainage are an attractive, but less widely available option [17].

Although there have been no randomized trials in posterior fossa I-C haemorrhage with brainstem compromise, surgical decompression is generally regarded as a standard treatment. Similarly, symptomatic obstructive hydrocephalus requires temporary or permanent drainage. There is no evidence that intracranial pressure monitoring improves outcome in patients with cerebral oedema.

Fluids

Isotonic fluid (0.9% saline) at 1 mL/kg/hour is standard intravenous replacement for patients with I-C haemorrhage. The use of hypertonic saline (2 or 3% sodium) at 1 mL/kg/hour is an alternative to normal saline in patients with perihaematoma oedema with mass effect.

Seizures

Seizures are common (5%) in acute I-C haemorrhage. Subtle or non-convulsive seizures may manifest as coma or a fluctuating conscious level disproportionate to haematoma size. There may be subtle twitches over the face, trunk or limbs. Seizures may be detected by intermittent or continuous electroencephalogram (EEG) monitoring, but this is complicated by sedation, movement

artefact and changes due to brain injury. Prophylactic antiepileptic drugs are not recommended. Seizures can be treated with IV phenytoin (loading dose of 20 mg/kg) or levetiracetam (500 mg qds) or a variety of oral anti-epileptic drugs.

Fever and hyperglycaemia

Fever (temperature >38°C) and extreme hyperglycaemia should be treated, but not aggressively, as multiple observational studies indicate that this is associated with poor outcome. Current recommendations are to target a blood glucose concentration of 6–10 mmol/L.

Deep venous thrombosis prophylaxis

In immobile patients early (≥1 day) use of low dose subcutaneous unfractionated or low molecular weight heparin or pneumatic calf compression [18] reduces the risk of venous thromboembolism with little risk of further I-C haemorrhage or other bleeding.

Cerebral oedema and raised intracranial pressure

Intracranial pressure can be reduced by nursing the patient in a head-up position (>30°). Patients should be sedated and mechanically-ventilated if agitated, at risk of aspiration, or if hypoxic. Although randomized evidence is lacking, monitoring of intracranial pressure and high level supportive care should be considered in patients with coma, significant mass effect from the haematoma, intraventricular blood or hydrocephalus [19]. Measures designed to lower intracranial pressure include: 20% mannitol (1.0–1.5 g/kg) by rapid infusion, although this is complicated by its gradual diffusion from the vascular compartment into the brain, causing rebound of intracranial pressure; boluses of 23.4% saline solution (0.5–2.0 mL/kg) and moderate hyperventilation. Hypotension can be managed with fluid resuscitation where appropriate and with vasopressors. Corticosteroids have not been shown to be beneficial, and may cause hyperglycaemia and dehydration. Barbiturates may be neuroprotective by blocking free-radical production and decreasing cerebral metabolic oxygen consumption, and hypothermia (to 32–34°C) may also be neuroprotective and reduce cerebral oedema.

Anticoagulant-associated I-C haemorrhage

While randomized evidence is lacking, standard practice is administer vitamin K to reverse the effects of anticoagulation (international normalized ratio (INR) <1.4) in the hope of arresting further bleeding in patients treated with warfarin or other vitamin K antagonists. As vitamin K takes several hours for an effect, a more rapid reversal of anticoagulation is obtained with unactivated prothrombin-complex concentrate (PCC), which consists of the vitamin K-dependent coagulation factors (II, VII, IX, and X). PCC can normalize the INR within 30 minutes of infusion, but it is costly (between US $1000 and $2000). A cheaper and equally effective option is fresh frozen plasma (FFP). However, FFP exposes the patient to transfusion risks including febrile, allergic, and anaphylactic reactions and volume overload, as well as delays associated with checking blood group compatibility, thawing, and the time for normalization of the INR. Currently, there are no antidotes to the new anticoagulants (dabigatran, rivaroxaban, and apixaban); activated charcoal might be given if the most recent dose was less than 2 hours prior. Rapid reversal of dabigatran requires dialysis over several hours. Blood products can be tried on an individual basis, otherwise the effects take 24–36 hours to clear.

Recombinant-activated factor VII (rFVIIa)

Despite strongly positive results in a proof-of-concept phase IIb trial, the pivotal Factor Seven for Acute Hemorrhagic Stroke Trial [20] of the use of recombinant Factor VIIa (80 μg/kg) administered within 4 hours of I-C haemorrhage onset, failed to demonstrate any improvement in outcome despite attenuating haematoma growth by approximately 4 mL at 24 hours. Moreover, those assigned to rFVIIa had an increased risk of venous and arterial thromboembolic complications, including ischaemic stroke and myocardial ischaemia. While there is interest in a more focused approach to using rFVIIa, such as in young patients with a low prevalence of underlying atherosclerosis and those at highest risk of ongoing bleeding (spot-sign positive), the routine use of rFVIIa is not supported.

Conclusion

I-C haemorrhage is a significant public health problem with an increasing burden of disease, particularly in developing countries. Apart from early control of elevated BP, there are no proven therapeutic options. Treatment is, therefore, based on good supportive care, active monitoring by trained staff in a suitable facility, and early detection and management of complications. This is largely on the basis of empirical guidelines in the absence of randomized controlled trials. Once patients are stable, early rehabilitation will reduce the risk of further complications, and promote recovery and return to everyday activities.

References

1. Qureshi AI and Palesch YY. (2011). Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II: design, methods, and rationale. *Neurocritical Care*, **15**(3), 559–76.
2. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, and Klijn CJ. (2010). Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet: Neurology*, **9**(2), 167–76.
3. Broderick JP, Brott TG, Duldner JE, Tomsick T, and Huster G. (1993). Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke*, **24**(7), 987–93.
4. Anderson CS, Huang Y, Arima H, et al. (2010). Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). *Stroke*, **41**(2), 307–12.
5. Butcher KS, Baird T, MacGregor L, Desmond P, Tress B, and Davis S. (2004). Perihematomal edema in primary intracerebral hemorrhage is plasma derived. *Stroke*, **35**(8), 1879–85.
6. el-Gohary EG, Tomita T, Gutierrez FA, and McLone DG. (1987). Angiographically occult vascular malformations in childhood. *Neurosurgery*, **20**(5), 759–66.
7. Kidwell CS, Chalela JA, Saver JL, et al. (2004). Comparison of MRI and CT for detection of acute intracerebral hemorrhage. *Journal of the American Medical Association*, **292**(15), 1823–30.
8. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, et al. (2012). Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. *Lancet: Neurology*, **11**(4), 307–14.
9. Zahuranec DB, Morgenstern LB, Sanchez BN, Resnicow K, White DB, and Hemphill JC, 3rd (2010). Do-not-resuscitate orders and predictive models after intracerebral hemorrhage. *Neurology*, **75**(7), 626–33.
10. Anderson CS, Huang Y, Wang JG, et al. (2008). Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet: Neurology*, **7**(5), 391–9.

11. Qureshi AI, Palesch YY, Martin R, et al. (2010). Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage: results from the antihypertensive treatment of acute cerebral hemorrhage study. *Archives of Neurology*, **67**(5), 570–6.
12. Anderson CS, Heeley E, Huang Y, et al. (2013). Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *New England Journal of Medicine*, **368**(25), 2355–65.
13. Prasad K, Mendelow AD, and Gregson B. (2008). Surgery for primary supratentorial intracerebral haemorrhage. *Cochrane Database of Systematic Reviews*, 4, CD000200.
14. Mendelow AD, Gregson BA, Fernandes HM, et al. (2005). Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet*, **365**(9457), 387–97.
15. Gregson BA, Broderick JP, Auer LM, et al. (2012). Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral hemorrhage. *Stroke*, **43**(6), 1496–504.
16. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, and Mitchell PM. (2013). Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet*, **382**(9890), 397–408.
17. Zhou X, Chen J, Li Q, et al. (2012). Minimally invasive surgery for spontaneous supratentorial intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *Stroke*, **43**(11), 2923–30.
18. Dennis M, Sandercock P, Reid J, Graham C, Forbes J, and Murray G. (2013). Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet*, **382**(9891), 516–24.
19. Morgenstern LB, Hemphill JC, 3rd, Anderson C, et al. (2010). Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, **41**(9), 2108–29.
20. Mayer SA, Brun NC, Begtrup K, et al. (2008). Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *New England Journal of Medicine*, **358**(20), 2127–37.

PART 9.9

Non-traumatic subarachnoid haemorrhage

CHAPTER 238

Epidemiology, diagnosis, and assessment on non-traumatic subarachnoid haemorrhage

Chethan P. Venkatasubba Rao and Jose Ignacio Suarez

Key points

- Non-traumatic subarachnoid haemorrhage (ntSAH) is a neurological emergency.
- The incidence of ntSAH varies greatly around the world.
- Peak incidence occurs around the age of 55 years and women are affected more commonly than men.
- Diagnosis is based on clinical presentation with severe headache and confirmed by cranial CT scan or examination of the cerebrospinal fluid.
- A ruptured cerebral aneurysm is the cause on 80% of cases and should be sought using either CT angiography or digital subtraction angiography.

Introduction

Non-traumatic subarachnoid haemorrhage (ntSAH) is a devastating neurological emergency in which there is extravasation of blood in to the cerebrospinal fluid (CSF) containing spaces of the central nervous system. Being a disease affecting a younger age group, ntSAH has the same impact on loss of productive years as acute ischemic stroke and haemorrhagic stroke [1]. The diagnosis and management continues to challenge neurologists, neurosurgeons, radiologists, interventionalists, and intensivists.

Epidemiology

ntSAH typically affects both males and females in their third to seventh decades of life, and the incidence increases with age with a peak in the sixth decade [2,3]. The incidence also is widely varied globally being as low as 2.0 per 100,000 population in Chinese population and as high as 24.7 in Finnish, and 25.2 in Japanese population (Table 238.1). The gender distribution of the disease also varies with males comprising less than a third of the cohort in the UK Oxfordshire community stroke project, and more than two-thirds in a study in Qatar. Its overall global incidence observing 45,821,896 patient years, when adjusted to age, sex, and diagnostic modality (CT scan) is approximated to be 9 per 100,000 populations. Women appear to be more affected than men by a factor of 1.24 (CI 1.09–1.42). This gender preference appears to be age dependent with men being more predominant in groups younger than 45 years and women in groups older than 45 years of age [2]. African Americans are twice as likely (2.1 (1.3–3.6)) to be affected by ntSAH as compared to Caucasians [4] and the increased risk in African Americans is present in all age groups but appears to be more evident for population younger than 65 years [5].

There is some evidence that the incidence of ntSAH is slightly decreasing. In their analysis evaluating epidemiological reports spanning over 45 years, de Rooij et al. [2] reported that the incidence of ntSAH is reducing annually by 0.6%. One of the main causes was thought to be the increasing use of imaging with head CT scan, which can possibly reduce the incidence of ntSAH, by 1% for every percentage point of patients scanned in the cohort. This was more evident for studies done prior to 1990 where the CT scans were used less consistently. For studies post-1990, the adjusted incidence was stable for individual centres [6]. Overall, the annual incidence of ntSAH appears to be reducing modestly in comparison to other types of strokes (0.6 versus 2% per annum respectively) [7]. This indicates the importance of genetic and other unknown factors that are probably different from the conventional cardio/cerebrovascular risk factors, which cause ntSAH.

Rates of ntSAH-associated mortality oscillate depending on whether the aetiology is aneurysmal or other causes. The mortality associated with aneurysmal ntSAH is approximated to be 40–50% with the majority occurring early in the course of the disease [8,9]. About 10–15% of deaths are estimated to occur prior to hospitalization [10], and about two-thirds occur in the first 48 hours with recurrent bleeding being the leading cause [11]. With advances in care there has been a gradual reduction in mortality. The mortality trends in the hospitalized patients in the United States between 1993 and 2003 show a 20% relative reduction (absolute 6% reduction from 30 to 24%). This improved mortality was more so in larger hospitals and in teaching centres [12]. A similar study assessing nationwide hospital deaths related to aneurysmal ntSAH between 1997 and 2006, estimated that the odds of better survival was 1.22 (1.13–1.32) in 2006 compared with 1997 (absolute rates 27 and 24%, respectively). Female sex (OR 1.02), increasing age (OR 1.02 per year of age) and multiple comorbidities (OR 1.44) were associated with increases in-hospital mortality [13]. In contrast, non-aneurysmal ntSAH (diffuse) carry a mortality of around 7.8% with a majority of patients returning to independent living [14].

Table 238.1 Worldwide incidence of non-traumatic subarachnoid haemorrhage

Country	Incidence of non-traumatic subarachnoid haemorrhage/100,000 population/year (95% CI)	Years studied	Men (%)	Reference
Australia and New Zealand	8.1 (7.4–9.0)	1995–1998	38	The ACROSS group Stroke 2000 (1)
Chile	4.9 (4–5.7)	2000–2003	42	Alvarez et al. JNNP 2010 (2)
China- Beijing	2.0 (1.4–2.6)	1984–1993	48	Ingall et al. Stroke 2000 (3)
Finland	24.7 (23.2–24.6)	1983–1985	53	Sarti et.al. Stroke 1991 (4)
Greece	7.9 (5.9–10.4)	2001–2005	55	Vadikolias et al. Int J stroke 2009 (5)
Japan	25.2 (20.7–29.6)	1977–1991	45	Morikawa et al., Stroke 2000 (6)
Norway	10.3 (9–11.8)	1984–2007	33	Sandvei et al. Neurology 2011 (7)
Qatar	2.69	1983–1988	66	Nogueira et.al. Acta Neurochir (Wein) 1992 (8)
UK	10	1981–1986	27	Bamford et.al. JNNP 1990 (9)
USA- Manhattan	9.1 (6.2–12)	1993–1996	33	Sacco et al. Am.J. Epidemiology (8) 1992 (10)

Data from the following references: (1) 'Epidemiology of aneurysmal subarachnoid hemorrhage in Australia and New Zealand: incidence and case fatality from the Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS)', *Stroke*, 2000, **31**(8), pp. 1843–50. (2) Alvarez G, et al., 'Incidence of subarachnoid haemorrhage in the Aconcagua Valley, Chile: a community-based, prospective surveillance project', *Journal of Neurology, Neurosurgery, and Psychiatry*, 2010, **81**(7), pp. 778–82. (3) Ingall T, et al., 'A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study', *Stroke*, 2000, **31**(5), pp. 1054–61. (4) Sarti C, et al., 'Epidemiology of subarachnoid hemorrhage in Finland from 1983 to 1985', *Stroke*, 1991, **22**(7), pp. 848–853. (5) Vadikolias K et al., 'Incidence and case fatality of subarachnoid haemorrhage in Northern Greece: the Evros Registry of Subarachnoid Haemorrhage', *International Journal of Stroke*, 2009, **4**(5), pp. 322–7. (6) Morikawa Y et al., 'Trends in stroke incidence and acute case fatality in a Japanese rural area: the Oyabe study', *Stroke*, 2000, **31**(7), pp. 1583–7. (7) Sandvei, M.S., et al., Incidence and mortality of aneurysmal subarachnoid hemorrhage in two Norwegian cohorts, 1984–2007. *Neurology*, 2011. **77**(20): p. 1833–9. (8) GJ., N., Spontaneous subarachnoid haemorrhage and ruptured aneurysms in the Middle East. A myth revisited. *Acta Neurochir* (Wien), 1992. **114**(1–2): p. 20–25. (9) Bamford, J., et al., A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project—1981–86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*, 1990. **53**(1): p. 16–22. (10) Sacco, R.L., et al., Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. *Am J Epidemiol*, 1998. **147**(3): p. 259–68.

Clinical Features

NtSAH should be always on the differential diagnosis in those patients presenting with headaches of nuchal and suboccipital origin, of sudden onset and high severity (often described as the worst headache ever,) and associated with photophobia, nausea, vomiting, or loss of consciousness [15]. Focal deficits may include third nerve paralysis with ipsilateral mydriasis seen in posterior communicating artery aneurysms, bilateral lower extremity weakness seen in anterior communicating artery aneurysms, hemispheric symptoms involving motor, sensory language, visuospatial dysfunction seen in the middle cerebral artery aneurysms, nystagmus, and ataxia seen in posterior circulation aneurysms. Sixth nerve involvement can be an indication of posterior circulation aneurysms or a false localizing sign of an elevated intracranial pressure (ICP). The presence of subhyaloid haemorrhages in retina, called Terson's syndrome, indicates the rapidity of raise in the ICP, and often a poor prognostic sign. About 1 in 10 patients with a severe headache and normal neurological examination have ntSAH while one in four patients have ntSAH if they have abnormal neurological signs on examination. About half of the patients present initially with a warning or sentinel bleed.

The diagnosis of ntSAH can be evasive with as much as a third to half of the patients initially misdiagnosed with a tension headache or a migraine headaches. Variable characteristics of headaches have been noticed in patients with ntSAH and this, in part, contributes to misdiagnosis. However, adherence to the international headache society's classification system will help physicians to diagnose ntSAH.

Many objective measures have been developed to assess the clinical severity of ntSAH, of which the World Federation of Neurological Surgeons (WFNS) and the Hunt and Hess scales are most widely used [15]. Both the scales incorporate level of consciousness, and presence or absence of focal deficits, and have been demonstrated to be predictive of clinical outcomes (Table 238.2). However, the WFNS scale has gained more popularity lately and has been the preferred scale in contemporary clinical trials.

Aetiology

Ruptured intracranial aneurysms account for 80% of ntSAH [15]. The risk of rupture increases with increasing aneurysm size, with the risk lowest in aneurysms less than 7 mm in diameter. Causative genetic factors isolated to date implicate candidate genes coding for connective tissue proteins [16]. One in 10 patients with adult polycystic kidney disease have intracranial aneurysms and a familial pattern of aneurysms increases the risk of rupture to 5–7-fold, while modifiable risk factors such as uncontrolled hypertension, smoking, and excessive alcohol consumption doubles the risk [17]. Other uncommon causes of non-aneurysmal ntSAH are noted in Box 238.1.

Assessment

The diagnosis of ntSAH is classically described as the presence of blood in the subarachnoid spaces on a cranial CT Scan, the presence of a bloody CSF (>2000 RBCs/mm^3) or the presence of xanthochromic CSF in the presence of an intracranial or

Table 238.2 Clinical and radiographic measures of subarachnoid hemorrhage and the associated mortality

Score	World Federation of Neurological Societies (W)	Hunt and Hess (H)	Fischer grade (F)	Mortality*
0	Unruptured aneurysm	Unruptured aneurysm	—	1.3% (W and H)
1	GCS 15, no motor deficits	Asymptomatic, mild headache, slight nuchal rigidity	No blood detected	4.9% (W): 1.4% (H): 0% (F)
2	GCS 14–13, no motor deficits	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy	Diffuse blood with vertical layers <1 mm thickness	9.3% (W): 5.4% (H): 0% (F)
3	GCS 14–13, with motor deficits	Drowsiness/confusion, mild focal neurological deficit	Localized clots or vertical layers > 1mm thickness	20% (W): 18.8% (H): 57% (F)
4	12–7 with or without motor deficits	Stupor, moderate-severe hemiparesis	IVH or I-C haemorrhage	33.3% (W): 41.9% (H): 57% (F)
5	6–3 with or without motor deficits	Coma, decerebrate posturing	—	76.5% (W): 76.9% (H)

SAH, subarachnoid haemorrhage; IVH, intraventricular haemorrhage; I-C haemorrhage, intracerebral (parenchymal) haemorrhage.

World Federation of Neurological Societies score: reproduced from *Journal of Neurology, Neurosurgery, and Psychiatry*, Teasdale GM et al., 'A universal subarachnoid hemorrhage scale: a report of a committee of the World Federation of Neurological Societies', **51**(11), p. 1457, copyright 1988, with permission from BMJ Publishing Ltd. Hunt and Hess score: reproduced from Hunt WE and Hess RM, 'Surgical risk as related to time of intervention in the repair of intracranial aneurisms', *Journal of Neurosurgery*, **28**(1), pp. 14–20, copyright 1968, with permission from the American Association of Neurological Surgeons. Fischer grade: reproduced from Fischer MC, et al., 'Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning', *Neurosurgery*, 1980, **6**(1), pp. 1–9, with permission from Wolters Kluwer Health.

Data from Oshiro EM et al., *Neurosurgery*, 1997, 41, 1, pp. 140–147; and Broderick JP et al., *Stroke*, 1994, 25, pp. 1342–1347.

Box 238.1 Non-aneurysmal causes of subarachnoid haemorrhage

Inflammatory

- Primary angiitis of the central nervous system.
- Systemic lupus erythematosus.
- Polyarteritis nodosa.
- Churg–Strauss syndrome.
- Wegener's granulomatosis.

Infective

- Mycotic aneurysms.
- Borreliosis.

Arterial and venous disorders

- Arteriovenous malformation.
- Sinus thrombosis.
- Dural arteriovenous fistulae of the brain and the spinal cord.
- Cavernous angioma of the brain and the spinal cord.
- Arterial dissection.
- Moyamoya disease.

Others

- Sickle cell disease.
- Anticoagulant and antiplatelet agents.
- Cocaine abuse.
- Intracranial and spinal metastases.
- **Intracranial and spinal tumours**: pituitary apoplexy, acoustic neuroma, glioma, angiolipoma, schwannoma, cervical meningioma, etc.

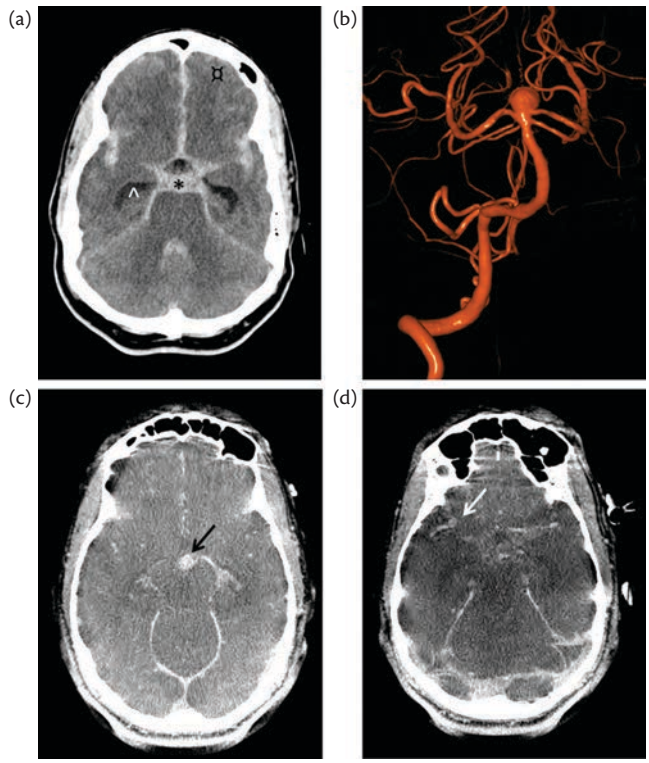


Fig. 238.1 (a) Non-contrast CT head of a patient with ntSAH demonstrating: * hyperdense blood in the subarachnoid space; ^ hydrocephalus in the temporal horns; and ¤, cerebral oedema. (b) 3D cerebral angiogram of the same patient showing a basilar tip aneurysm. DynaCT of the same patient showing the basilar artery aneurysm (c) and a right middle cerebral artery aneurysm (d).

spinal arteriovenous malformation or aneurysm [18]. All patients with suspected ntSAH should be screened with a cranial CT scan. The characteristic imaging feature is hyperdense extravasated blood (Fig. 238.1a). Other features that can be seen include

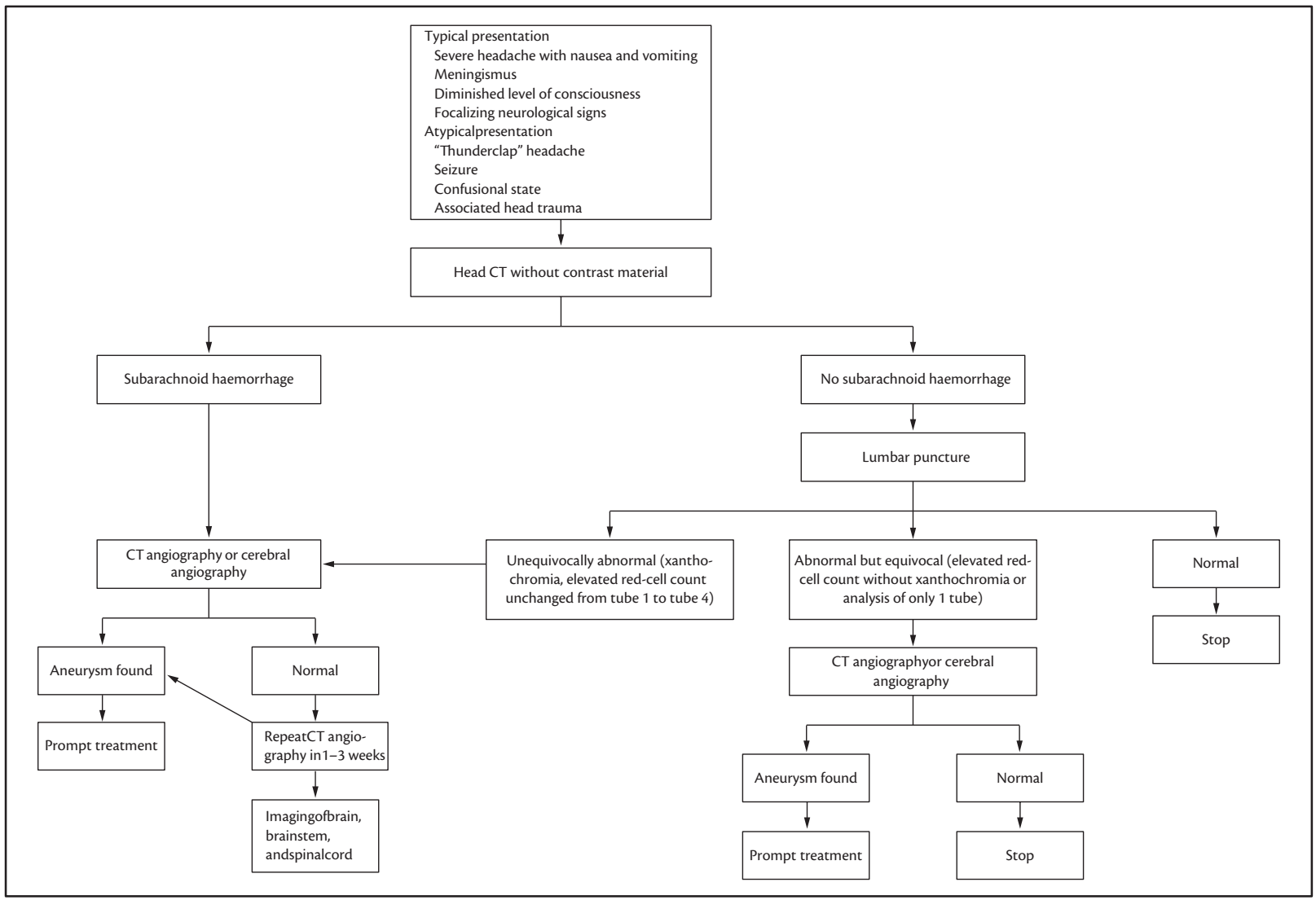


Fig. 238.2 Diagnostic algorithm for ntSAH.

From *New England Journal of Medicine*, Suarez J, et al., 'Aneurysmal Subarachnoid Hemorrhage', **354**, pp. 387–96. Copyright © 2006 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

intraparenchymal haemorrhages, intraventricular haemorrhage, hydrocephalus, and cerebral oedema. Fischer's score and modified Fischer's score, which require CT scans can be helpful in predicting the risk of vasospasm or delayed cerebral ischaemia, and clinical outcomes (Table 238.2). The sensitivity of CT is variable, 100% within 12 hours, 93% within 24 hours and less than 50% 7 days after symptom onset [15]. However, if the CT is negative, and the clinical suspicion is strong, a lumbar puncture should be performed. A decision algorithm for the diagnosis of ntSAH is depicted in Fig. 238.2. Once the diagnosis is established, the patient needs to be evaluated urgently for the presence of an intracranial aneurysm through a cranial CT angiogram or a conventional cerebral digital subtraction angiogram. Although conventional cerebral angiography has been advocated for identifying aneurysms, multidetector row CT angiograms have been shown to have comparable sensitivity and specificity [19]. A careful evaluation of the complete cerebrovascular tree is warranted as up to 15% of patients have multiple aneurysms (Fig. 238.1). The introduction of DynaCT angiogram offers added advantages to conventional angiograms in detecting smaller aneurysms which can be missed otherwise and provides additional structural details, which helps in selecting the operative or endovascular treatment.

Conclusion

ntSAH is a critical neurological emergency, with a wide varied distribution and evasive presentations. The most common cause of ntSAH is a ruptured intracranial aneurysm, and the treating physician should be aware of the pitfalls and the limitations of variable tests used to arrive at the diagnosis.

References

1. Johnston SC, Selvin S, and Gress DR. (1998). The burden, trends, and demographics of mortality from subarachnoid hemorrhage. *Neurology*, **50**(5), 1413–18.
2. de Rooij NK, Linn FH, van der Plas JA, Algra A, and Rinkel GJ. (2007). Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *Journal of Neurology, Neurosurgery, and Psychiatry*, **78**(12), 1365–72.
3. Ingall T, Asplund K, Mähönen M, and Bonita R. (2000). A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. *Stroke*, **31**(5), 1054–61.
4. Broderick JP, Brott T, Tomsick T, Huster G, and Miller R. (1992). The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. *New England Journal of Medicine*, **326**(11), 733–36.
5. Kissela B, Schneider A, Kleindorfer D, et al. (2004). Stroke in a biracial population: the excess burden of stroke among blacks. *Stroke*, **35**(2), 426–31.
6. Linn FH, Rinkel GJ, Algra A, and van Gijn J. (1996). Incidence of subarachnoid hemorrhage: role of region, year, and rate of computed tomography: a meta-analysis. *Stroke*, **27**(4), 625–9.
7. Pajunen P, Pääkkönen R, Hämäläinen H, et al. (2005). Trends in fatal and nonfatal strokes among persons aged 35 to > or =85 years during 1991–2002 in Finland. *Stroke*, **36**(2), 244–8.
8. Bederson JB, Connolly ES Jr, Batjer HH, et al. (2009). Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*, **40**(3), 994–1025.
9. van Gijn J, Kerr RS, and Rinkel GJ. (2007). Subarachnoid haemorrhage. *Lancet*, **369**, 306–18.
10. Huang J and van Gelder JM. The probability of sudden death from rupture of intracranial aneurysms: a meta-analysis. *Neurosurgery*, **51**(5), 1101–5; discussion 1105–7.
11. Brott TG, Duldner JE, Tomsick T, and Leach A. (1994). Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. *Stroke*, **25**(7), 1342–7.
12. Andaluz N and Zuccarello M. (2008). Recent trends in the treatment of cerebral aneurysms: analysis of a nationwide inpatient database. *Journal of Neurosurgery*, **108**(6), 1163–9.
13. Ovbiagele B. (2010). Nationwide trends in in-hospital mortality among patients with stroke. *Stroke*, **41**(8), 1748–54.
14. Hui FK, Tumialán LM, Tanaka T, Cawley CM, Zhang YJ. (2009). Clinical differences between angiographically negative, diffuse subarachnoid hemorrhage and perimesencephalic subarachnoid hemorrhage. *Neurocritical Care*, **11**(1), 64–70.
15. Suarez JI, Tarr RW, and Selman WR. (2006). Aneurysmal subarachnoid hemorrhage. *New England Journal of Medicine*, **354**(4), 387–96.
16. Headache Classification Committee of the International Headache Society (1988). Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia*, **8**(Suppl. 7), 1–96.
17. Feigin VL, Rinkel GJ, Lawes CM, et al. (2005). Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke*, **36**(12), 2773–80.
18. Asplund K, Tuomilehto J, Stegmayr B, Wester PO, and Tunstall-Pedoe H. (1988). Diagnostic criteria and quality control of the registration of stroke events in the MONICA project. *Acta Medica Scandinavica*, **728**(Suppl.), 26–39.
19. Jayaraman MV, Mayo-Smith WW, Tung GA, et al. (2004). Detection of intracranial aneurysms: multi-detector row CT angiography compared with DSA. *Radiology*, **230**(2), 510–18.

CHAPTER 239

Management of non-traumatic subarachnoid haemorrhage in the critically ill

Chethan P. Venkatasubba Rao and Jose Ignacio Suarez

Key points

- ntSAH is associated with high morbidity and mortality. 10% of patients die before obtaining medical attention and 25% die within the first 24 hours of the ictus.
- Immediate management goals are to prevent rebleeding, treat hydrocephalus, and secure the aneurysm.
- Delayed neurological deficits occur due to delayed cerebral ischaemia, seizures, fever, and electrolyte abnormalities.
- Complications following ntSAH can affect most organ systems and include myocardial dysfunction, pulmonary injury, sepsis, and fluid and electrolyte abnormalities.
- Due to the complexity of management, patients with ntSAH should be treated in a critical care environment by a collaborative team of neurosurgeons, neuroradiologists, neurologists, and intensivists.

Introduction

Non-traumatic subarachnoid haemorrhage (ntSAH) is a complex disease affecting multiple systems and the hospital course of affected patients can be variable. This chapter delineates the principles of management of patients in hyperacute (first 24–48 hours), acute (2–7 days), and immediate (7–21 days) phases of ntSAH. Specific complications unique to SAH patients are detailed [1,2].

Hyperacute phase of ntSAH

ntSAH is associated with high morbidity and mortality; 10% of patients die before obtaining medical attention and 25% die within the first 24 hours of the ictus [3]. The causes of early deaths are either rebleeding or hydrocephalus causing fatal increase in the intracranial pressure (ICP). The admission records of all patients with ntSAH should document the time of symptom onset, the World Federation of Neurosurgeons Scale (WFNS), and modified Fischer's scales. All patients with ntSAH should be treated with the fundamentals of critical care: circulation, airway and breathing (CAB) followed by the management of ICP and prevention of rebleeding. Table 239.1 presents a summary of the most common management issues in patients with ntSAH.

ICP and hydrocephalus

Hydrocephalus that develops in the acute phase of subarachnoid haemorrhage can cause significant morbidity or death by an increase in ICP. Immediate management should include placement of an external ventricular drain (EVD). Limited evidence indicates that this may cause an increase in re-bleeding, but the risks of not treating are far more severe [2]. The management of ICP should be based on the general principles outlined in the subsequent sections and in Table 239.1 to keep it less than 20 cmH_2O while maintaining a cerebral perfusion pressure (CPP) of 60–80 mmHg.

$$\text{CPP} = \text{mean arterial pressure}\left(\text{MAP}\right) - \text{ICP}. \qquad \text{[eqn 1]}$$

Seizures

Seizures, which occur in about 20% of the ntSAH patients, can also cause an increase in ICP. The risk is higher in patients over 65 years old, surgically repaired aneurysms and a thick subarachnoid clot or intraparenchymal haemorrhage. Routine use of anticonvulsants is not advocated due to adverse outcomes associated with their use. However, elderly individuals undergoing surgical treatment for an aneurysm repair with a thicker subarachnoid clot can be provided a short term (3–7 days) prophylaxis of anticonvulsants.

Prevention of aneurysm rebleeding

One of the predominant causes of early mortality is rebleeding [3]. Historically, this occurred in about 4% of patients within the first 24 hours and 1–2% per day over the next 14 days. Overall risk is 50% within the first 6 months and 3% yearly following that. The two most important modifiable risk factors for rebleeding are incomplete treatment of the aneurysms and delayed treatment. Current recommendation is that the aneurysm is treated as early as possible and within 24–48 hours of symptom onset as mentioned in the treatment of aneurysm section ('Treatment of Ruptured Cerebral Aneurysm') [1,2]. General measures to reduce rebleeding include controlling MAP to <110 mmHg, adequate pain control and sedation, limiting activity, and cautious drainage of cerebrospinal fluid.

Antifibrinolytics, such as Epsilon amino-caproic acid (EACA) and tranexamic acid (TXA) have been studied in preventing aneurismal rebleeding. However, due to the delay in the initiation of the antifibrinolytic and the increase in the duration of use

Table 239.1 Common neurological and non-neurological complications associated with aneurismal subarachnoid haemorrhage and their management

Complications	Management	Complications related to treatment
Hyperacute phase (24–48 hours from ictus)		
Hydrocephalus	External ventricular drain (EVD) placement	◆ Small chance of re-rupture of the aneurysm ◆ Parenchymal damage related to the placement of EVD
Elevated intracranial pressure (ICP)	◆ EVD placement ◆ Mannitol and hypertonic saline ◆ Control of seizures	◆ See EVD as above ◆ Mannitol and hypertonic saline: nephrotoxicity ◆ See seizures below
Seizures	Anti-epileptic drugs (AED) (use as prophylaxis for only 3 days)	◆ Somnolence ◆ Pharmacological toxicity of the AED
Aneurysm re-rupture	◆ Early treatment ◆ Surgical clipping	◆ Complications related to anaesthesia administration ◆ Parenchymal damage related to surgery ◆ Intra-operative rupture ◆ Bleeding in to subdural, epidural, subgaleal spaces ◆ Infections
	Endovascular coiling (please note that it is recommended that an EVD be placed before the angiogram is performed)	◆ Complications related to anaesthesia administration ◆ Access site haemorrhage ◆ Dissection of the vessels catheterized ◆ Intra-operative rupture of the aneurysm ◆ Residual aneurysm
	Antifibrinolytics (tranexamic acid, Epsilon amino caproic acid (EACA))	◆ Deep vein thrombosis ◆ Pulmonary embolism ◆ Myocardial infarction
	Hypertension management	Cerebral hypoperfusion if the ICP is high
Early phase (2–7 days)		
Delayed neurological deficits: delayed cerebral ischaemia (DCI)	Prophylaxis with nimodipine	◆ Hypotension ◆ Constipation ◆ Ileus, etc
Delayed neurological deficits: vasospasm (VSP)	Hypertension, normovolaemia (Triple H)	◆ Congestive cardiac failure ◆ Pulmonary oedema
Delayed neurological deficits: elevated ICP	See ICP above	
Delayed neurological deficits: seizures	See seizure management above	
Delayed neurological deficits: fevers	◆ Acetaminophen and ibuprofen ◆ Surface cooling devices ◆ Catheter-based cooling devices ◆ Evaluation of infective source and treatment with antibiotics	◆ Liver dysfunction (acetaminophen) and gastritis (ibuprofen) ◆ Skin breakdown ◆ Complications associated with catheter placement
Immediate phase (7–21 days)		
Cardiac complications: troponinaemia	Conservative management if not associated with ST segment changes	
Cardiac complications: ST–T segment changes	Conservative management if not associated with an elevating troponinaemia and other ECG changes suggestive of ischaemia	
Cardiac complications: neurogenic stunned myocardium (severe cases- Takotsubo cardiomyopathy)	Supportive care	

(*continued*)

Table 239.1 Continued

Complications	Management	Complications related to treatment
Cardiac complications: deep venous thrombosis	◆ Inferior vena cava filter ◆ Anticoagulation (left to the discretion of the treating physician and surgeon)	
Pulmonary complications: neurogenic pulmonary oedema	Diuretics	
Pulmonary complications: pneumonia	Appropriate antibiotics	
Pulmonary complications: pulmonary embolism	◆ Inferior vena cava filter ◆ Anticoagulation (left to the discretion of the treating physician and surgeon)	Anticoagulation related parenchymal or systemic bleeding
Metabolic complications: ◆ Hyponatraemia ◆ Cerebral salt wasting	◆ Hypertonic saline ◆ Vasopressin antagonist (VSPA)	◆ Hyperchloraemic acidosis ◆ Higher cost of care with VSPA
Metabolic complications: hyperglycaemia	Insulin for moderate control of hyperglycaemia	Hypoglycaemia
Gastrointestinal complications: stress ulcers	Prophylaxis with proton pump inhibitors, H2 blockers or sucralphate	

(post-securing of the aneurysm), the benefits from prevention of rebleeding seem to be offset by the increase in the risk of delayed cerebral ischaemia (DCI) and other thrombotic complications.

The current recommendations form the neurocritical care society strongly advocates the early securing of the aneurysm. However, the use of very short-term antifibrinolytics may be beneficial to the patients, but convincing data are not available as yet [2].

Treatment of ruptured cerebral aneurysm

The options for securing a ruptured aneurysm are endovascular treatment (coiling) or surgical repair. Many factors, such as the anatomy of the aneurysm, age of the patient, accompanying medical risks and the availability of expertise at the site of treatment determine the treatment modality. The international subarachnoid aneurysm trial ISAT-demonstrated that patients who had ruptured cerebral aneurysms treatable by either method were more likely to be alive and independent in 1 year if treated by endovascular coiling [4]. This study is criticized for selecting patients with better grade of aneurysms and enrolling only 24% of the screened patients and, hence, a newer trial enrolling patients with wide range of SAH severity, ISAT-2 is underway. Endovascular techniques employ a variety of coils and at times may include the deployment of stents to treat aneurysms with wider neck (Fig. 239.1). Stent-assisted treatment of aneurysms may require the use of dual antiplatelet agents (aspirin and clopidogrel), which carry the risk of haemorrhagic complications with ventricular drains and other surgical procedures.

Acute phase of SAH

The hospital course of ntSAH patients can include multi-organ dysfunction, which needs careful monitoring, prevention, and treatment. Complications that can arise are classified according to the organ systems in Table 239.1.

Differences between and importance of DCI and vasospasm

About 30% of all patients with SAH develop DCI within 2 weeks of a ntSAH. Typically, they present as a change in mentation or focal deficits akin to stroke. Vasospasm (VSP) is defined as a narrowing in the intracerebral arteries as a result of endothelial swelling, vasoconstriction, remodelling of the media, or subendothelial fibrosis. VSP is directly related to the clinical deterioration due to DCI, cerebral infarction, poor outcome, and mortality after ntSAH. Patients with ntSAH can have DCI in the absence of VSP and VSP without DCI. However, due to the close association between the DCI and VSP, the absence of a reliable examination in comatose patients and direct association of the VSP with cerebral infarctions, there is a tendency to interchange the usage of the terms. DCI, defined as a new onset focal neurological deficit or change in the level of consciousness with radiological evidence (CT or MRI) of cerebral infarction, is an independent predictor of death or severe disability.

Monitoring of DCI

Traditionally, DCI has been monitored by clinical examination, which becomes challenging in a comatose patient. Non-invasive monitors such as transcranial Doppler ultrasound (TCD), electroencephalogram (EEG), and near-infrared spectroscopy (NIRS) have been used to assess cerebral dysfunction and perfusion, respectively. TCD has become the widely-accepted screening tool for VSP and elevated velocities and Lindegaard ratio (ratio of the velocity of middle cerebral artery to that of the ipsilateral extracranial internal carotid artery) greater than 6 is a good predictor of VSP.

Invasive monitors such as brain-tissue oxygenation probes ($PtiO_2$), cerebral microdialysis (CMD), and thermodilution methods have been used to determine cerebral perfusion in real time. Although the initial results for these monitors are promising,

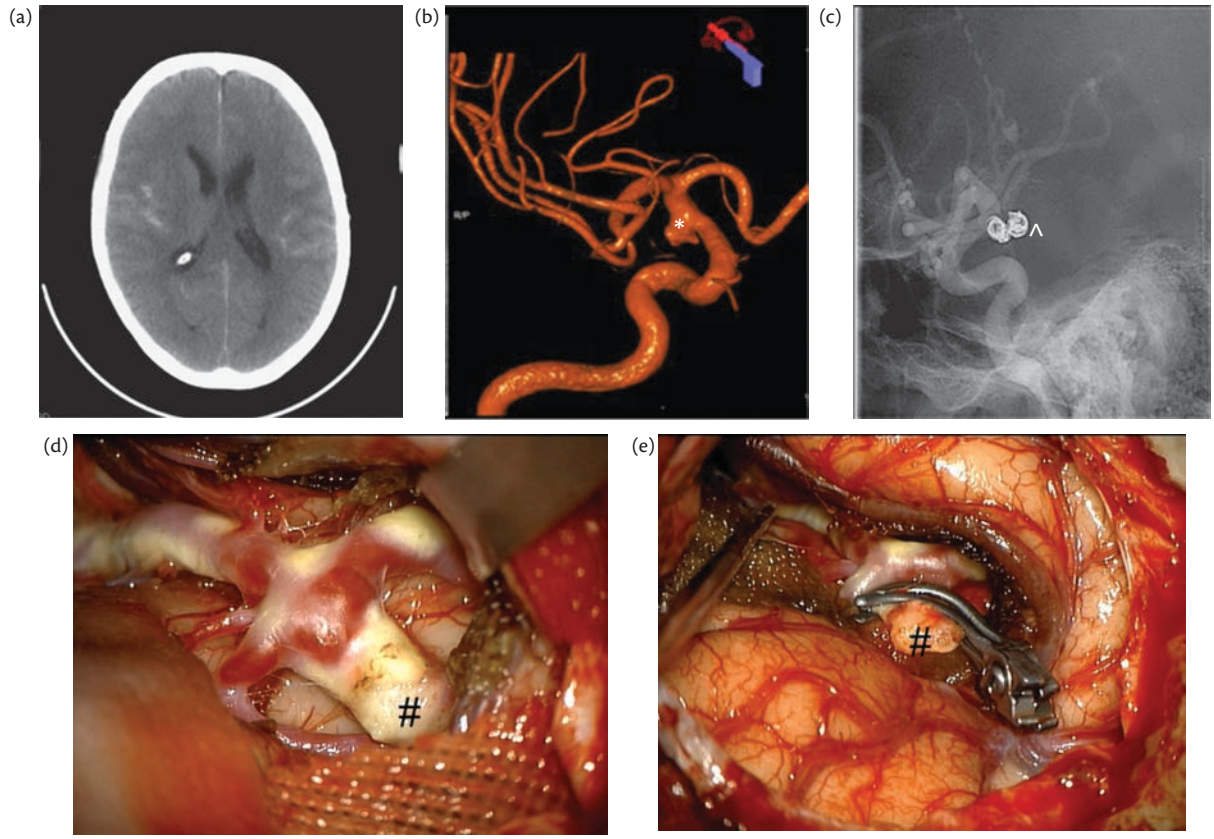


Fig. 239.1 Treatment of aneurysms. (a) Non-contrast CT scan of a 67-year-old female presenting with subarachnoid haemorrhage. (b) 3D reconstruction of a digital subtraction angiogram demonstrating the right middle cerebral artery (MCA) bifurcation aneurysm (*) in the same patient. (c) Digital subtraction angiogram demonstrating the endovascular coiling of the same aneurysm (^). (d) Right MCA bifurcation aneurysm (#) during surgical treatment in a different patient presenting with subarachnoid haemorrhage. (e) Right MCA aneurysm post-placement of an aneurysm clip during the surgery.
Figure 239.1(d) and (e) are courtesy of Dr Edward A.M. Duckworth, Asst. Prof of Neurosurgery, Baylor College of Medicine, Houston, TX.

further investigations are needed to determine their role in daily clinical practice

How to treat DCI and VSP?

The treatment of VSP and resulting DCI has traditionally been through non-invasive and invasive measures. Neuroprotective agents such as nimodipine started prophylactically is the standard of care and augmenting blood pressure, volume, and cardiac output known as the triple-H therapy (hypertension, hypervolaemia, and haemodilution) are the available means of treating DCI.

Non-invasive measures

Neuroprotection

Nimodipine has been extensively studied as a neuroprotector in SAH and administration of 60 mg every 4 hours for the first 21 days is currently the standard of care. Important to note is that there is no effect of nimodipine on VSP, but DCI seems to improve, underscoring the importance of alternative pathways causing DCI. Other neuroprotective agents that have been investigated are the statins and magnesium. Current evidence does not support the routine use of statins but patients treated with a statin prior to the ntSAH should continue the treatment. Recently, MASH-2, a randomized control trial evaluating the routine use of 2 g of magnesium sulphate daily for 2 weeks in ntSAH patients failed to show any improvement in clinical outcomes and routine use of magnesium is not recommended [5].

Haemodynamic augmentation

VSP reduces the cross-sectional area arteries producing an increased resistance to flow, which reduces the flow rate by the fourth power of the radius. Accordingly, induced hypertension, hypervolaemia, and haemodilution have been traditionally used. Augmenting blood pressure can be challenging, as the response to increased pressure can be unpredictable in the absence of cerebral autoregulation. However, experimental and clinical data has shown that norepinephrine causes a more predictable increase in cerebral perfusion pressure (CPP) than dobutamine. Dopamine can increase CPP, while milrinone may not affect the CPP as much, but may cause a temporary improvement in the vessel wall diameter.

Augmentation of blood pressures in the presence of an unruptured aneurysm increases the chances of re-rupture, offers little to no risk if the aneurysm has been secured. To summarize, induced hypertension offers the most efficient increase in the CPP, but is not without side effects (such as pulmonary oedema and myocardial

dysfunction). In case of failure of these therapies, invasive measures can be used.

When to use triggers for invasive measures?

A multidisciplinary panel has recently defined intervention for VSP through a diagnostic and therapeutic cerebral angiogram in the same setting [6]. In low risk patients, the presence of a focal deficit that cannot be explained by other factors, an elevated TCD velocities and/or Lindegaard ratio should prompt a confirmatory evaluation. In poor grade ntSAH patients, the exam is difficult to obtain and invasive monitors such a $PtiO_2$, MCD monitors, can determine the need for intervention. Similarly, the cessation of the measures should be de-escalated in a gradual manner with carefully set goals assessed frequently.

What and how effective are the invasive measures?

Around 70% of all ntSAH patients have angiographic VSP between 5 and 14 days after symptom onset, of which 15–20% result in ischaemia or can be fatal. Prophylactic angioplasty of asymptomatic VSP within 48 hours of ictus has not been shown to improve clinical outcomes, but has demonstrated a reduction in the need for symptomatic treatment. Use of angioplasty in early symptomatic patients helps in improving the vascular diameter, as well as the neurological deficits. Agents that have been used as an intra-arterial adjunct to treat VSP with varying and conflicting results include verapamil, papavarine, and nicardipine. Associated complications, such as ischaemia caused by the cerebral arterial catheterization, as well as vessel rupture should be weighed against clinical benefit. Hence, interventional management of VSP should be attempted when medical therapy fails or is harmful.

Delayed neurological deficits

Delayed neurological deficits (DND) are defined as focal deficits that arise after SAH following initial stabilization that are not due to rebleeding. Some of the common causes of DND include DCI, hydrocephalus, cerebral oedema, fevers, seizures, and electrolyte abnormalities. All these underlying conditions need to be investigated and addressed immediately.

Cardiac complications

Increased serum troponin has been reported in up to 68 % of all the patients with ntSAH [7]. Left ventricular regional wall motion abnormalities (RWMA) are noted variably from as low as 9% to as high as 76% and global hypokinesis is seen in 10–15% of all the ntSAH patients [7]. Cardiac abnormalities after ntSAH (e.g. RWMA, elevated troponin I and B-type natriuretic peptide levels, Q waves, ST segment depression, and abnormal T waves) have shown to be associated with death, poor outcome, and DCI [7]. One of the hypotheses is an excessive sympathetic drive causing sub-endocardial myonecrosis, which could be regional or, when global, can result in Takotsubo's cardiomyopathy. Cardiac arrhythmias (atrial fibrillation/flutter, ventricular tachycardia, ventricular fibrillation) are seen in a third of all ntSAH patients; 5–8% can be fatal.

The management of these complications are focused on the primary pathology. When necessary, dobutamine can be used to augment cardiac output, which in turn can increase CBF. Beta blockers can be used to improve recovery from myocardial injury, and may improve clinical outcomes. No specific data are available regarding the treatment of cardiac arrhythmias.

Pulmonary complications

Pulmonary complications are relatively frequent after ntSAH and include pulmonary oedema, neurogenic pulmonary oedema (NPE), acute respiratory distress syndrome (ARDS), and pulmonary embolism (PE). In a case series of 650 patients with ntSAH, acute lung injury, was seen in 27% of patients. Pulmonary oedema has been reported to occur in 8–23% of patients. Due to the retrospective nature of the studies, it is difficult to determine the true incidence of neurogenic pulmonary oedema; however, there appears to be an association between NPE and the clinical grade of ntSAH, increased serum troponin and increased mortality. ARDS, on the other hand, is sparsely reported and ranges between 4 and 18% in several retrospective studies. Pulmonary oedema, pneumonia, aspiration, and sepsis are frequent causes of ARDS.

The management of pulmonary complications should be directed towards the inciting pathology. As there is a tendency to treat ntSAH patients with hypervolaemia, volume correction should be instituted upon recognition of pulmonary oedema. Goal-directed therapy for euvolaemia using pulmonary catheter-guided haemodynamic management has been shown to reduce the incidence of pulmonary oedema from 14 to 6%.Triple H therapy used to treat VSP in the setting of a left ventricular systolic and diastolic dysfunction (seen in 87% of ntSAH patients in a case series), can produce pulmonary oedema.

Metabolic derangements

Hyponatraemia

Hyponatraemia is the most common electrolyte abnormality, which occurs in 50% of ntSAH patients. It is also shown to be associated with cerebral infarctions and typically precedes VSP. Cerebral salt wasting (CSW) is associated with hypovolaemia and is probably the most common cause, while SIADH is associated with modest hypervolaemia. Despite these associations, hyponatraemia is not an independent marker for poor prognosis. To complicate matters, both conditions can co-exist in ntSAH.

Fludrocortisone and hydrocortisone have been used in randomized trials to treat hyponatraemia secondary to CSW. Vasopressin antagonists and hypertonic saline are also successfully used to treat hyponatraemia associated with euvolaemia/hypervolaemia and hypovolaemia respectively. Determination of volume status can be very challenging in these patients and the readers should refer to Wolf et al., and Gress et al. for further details [8,9].

Hyperglycaemia

Elevated glucose levels (>220 mg/dL; 12 mmol/L) are associated with increased infection rates in ntSAH patients. Intensive glycaemic control (80–120 mg/dL) has been associated with hypoglycaemic episodes, VSP, and poor outcomes. Currently, moderate glycaemic control is suggested for patients with ntSAH.

A comprehensive list of other complications is summarized in Table 239.1.

Conclusion

Multiple complications affecting many organ systems frequently complicate the hospital course of patients affected by ntSAH. Such patients are best cared for in a critical care environment by a specialist team, and intensivists should anticipate and institute appropriate measures for prevention and treatment as necessary. When

possible, the highest grade of evidence should be adhered and, when available, clinical trial enrolments should be encouraged.

References

1. Diringer MN, Bleck TP, Claude Hemphill J, 3rd, et al. (2011). Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. *Neurocritical Care*, **15**(2), 211–40.
2. Connolly ES, Jr, Rabinstein AA, Carhuapoma JR, et al. (2012). Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, **43**(6), 1711–37.
3. Broderick JP, Brott TG, Duldner JE, Tomsick T, and Leach A. (1994). Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. *Stroke*, **25**(7), 1342–7.
4. Molyneux AJ, Kerr RS, Yu LM, et al. (2005). International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet*, **366**(9488), 809–17.
5. Dorhout Mees SM, Algra A, et al. (2012). Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. *Lancet*, **380**(9836), 44–9.
6. Stocchetti N and participants in the International Multi-Disciplinary Consensus Conference on the Critical Care Management of Subarachnoid H (2011). Triggers for aggressive interventions in subarachnoid hemorrhage. *Neurocritical Care*, **15**(2), 324–8.
7. van der Bilt IA, Hasan D, Vandertop WP, et al. (2009). Impact of cardiac complications on outcome after aneurysmal subarachnoid hemorrhage: a meta-analysis. *Neurology*, **72**(7), 635–42.
8. Wolf S and participants in the International Multi-Disciplinary Consensus Conference on the Critical Care Management of Subarachnoid H. (2011). Routine management of volume status after aneurysmal subarachnoid hemorrhage. *Neurocritical Care*, **15**(2), 275–80.
9. Gress DR, and participants in the International Multi-Disciplinary Consensus Conference on the Critical Care Management of Subarachnoid H. (2011). Monitoring of volume status after subarachnoid hemorrhage. *Neurocritical Care*, **15**(2), 270–4.

PART 9.10

Meningitis and encephalitis

CHAPTER 240

Epidemiology, diagnosis, and assessment of meningitis and encephalitis

Simon Nadel and Johnny Canlas

Key points

- Acute brain infections are relatively rare.
- The presentation may have classical features, but a high index of suspicion is required to make a rapid diagnosis, and start appropriate therapy.
- Diagnostic tests are sensitive and specific, but therapy must often be empirical until diagnostic test results are available and treatment can be tailored accordingly.
- As a general principle, early effective treatment is essential to improve outcomes.
- Effective vaccines are becoming increasingly available for the most common CNS infections, but enhanced surveillance is vital to understand changing epidemiology in view of vaccination and antimicrobial pressure.

Introduction

Despite advances in antimicrobial and other adjunctive therapies, infections affecting the central nervous system (CNS) have a varied and unpredictable outcome often with a high morbidity and mortality. Although the spectrum between meningitis and encephalitis is wide, it is important to understand the pathophysiological processes, which take place that lead to meningitis and encephalitis. **Meningitis** is an inflammation of the pia and arachnoid meninges that surround the brain and spinal cord. Due to the occurrence of epidemics, worldwide acute bacterial meningitis is the most common form of serious intracranial infection. **Encephalitis** is an inflammation of the brain parenchyma. It is a relatively rare disease, which often presents as diffuse or focal neurological dysfunction.

Epidemiology

The worldwide incidence of acute bacterial meningitis (ABM) is difficult to ascertain because of wide variation in surveillance, together with underreporting from many developing nations. In the developed world, the incidence is 5 per 100,000 of the population per year. During pandemic meningococcal meningitis, in sub-Saharan Africa, attack rates may exceed 100–800 cases per 100,000 population per year, with the highest attack rates being as high as 1 in 100. Over 75% of all cases of bacterial meningitis occur in children under 5 years of age. Death or handicap may occur in up to 50% of patients depending on age, causative organism and clinical status at presentation [1].

For acute encephalitis, the annual incidence in Western and tropical countries is 7.4 and 6.3 cases per 100,000 population, respectively [2]. Encephalitis can occur following any infective process, the more common organisms include mycoplasma pneumonia, herpes simplex virus (HSV), the enteroviruses, adenoviruses, influenza viruses, and Japanese B virus. HSV encephalitis is the most common cause of sporadic, non-epidemic encephalitis in children and adults in Western countries, and it is usually caused by HSV-1. Disease may present with a variety of syndromes, which vary from the more benign to catastrophic CNS involvement and post-infectious encephalopathies.

In acute bacterial meningitis, the most likely causative organism is age-dependent. In industrialized nations, the incidence of neonatal meningitis is approximately 0.3 per 1000 live births. In developing countries, the incidence is as high as 6.1 per 1000 live births [1]. In neonates under 1 month of age, most of the causative organisms are acquired from the maternal genital tract during labour. Pathogens include **group B Streptococci** (GBStr), *Escherichia coli* and other coliforms, *Listeria monocytogenes*, and other colonic and genitourinary bacteria. Most cases in Europe are due to GBStr and *E. coli*, which together now account for at least two-thirds of all deaths from neonatal meningitis. In older children and adults, *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis*, are responsible for over 90% of cases. Most children with ABM acquire the infection via haematogenous spread.

The epidemiology of ABM has changed dramatically in the last two decades with the introduction of new, highly effective vaccines. Prior to the introduction of the conjugate polysaccharide vaccine against Hib, Hib was the most common cause of ABM worldwide. The estimated global incidence of Hib meningitis for the year 2000 was 31 cases per 100,000 children younger than 5 years, with a case fatality rate of 43% in unimmunized populations. The incidence varies significantly between different regions, from 46 per 100,000 in Africa to 16 per 100,000 in Europe [1].

Currently, *Neisseria meningitidis* and *Streptococcus pneumoniae* are the most common causes of ABM in children. Invasive

meningococcal disease is endemic globally, and most cases are caused by five of the 13 meningococcal serogroups: A, B, C, Y, and W135. The majority of disease in Europe, South and Central America, and Australasia is caused by serogroup B and C organisms. The serogroup B polysaccharide capsule is not immunogenic in humans, and a number of protein-based vaccines against serogroup B disease are in development [3]. The peak incidence of meningococcal disease occurs in children aged 6 months to 2 years, with a second smaller peak at 15–19 years. The annual incidence of meningococcal disease across Europe is 2–89 per 100,000 in children under 1 year and 1–27 per 100,000 in 1-4 year olds [1].

In 2010, there were over 100,000 cases of pneumococcal meningitis in children worldwide, with a peak incidence in children under 2 years of age. Incidence was highest in Africa at 38 cases per 100,000, and lowest in Europe at six cases per 100,000 in children under 5 years of age. These data were gathered prior to widespread use of the 7-valent pneumococcal conjugate vaccine (PCV 7) [4].

In parts of the world where routine immunization has decreased the incidence of ABM caused by these common pathogens other organisms are gaining importance. In 2007, 13% of ABM across all ages in the UK was caused by *Mycobacterium tuberculosis* [5].

The exact incidence of tuberculous meningitis is difficult to ascertain because of difficulties with diagnosis and under-reporting, especially in the developing world. The WHO estimates that approximately one-third of the world population is infected with tuberculosis. The incidence is increasing in developed countries due to immigration and increasing prevalence of HIV infection. In the UK there was a 91.9% increase in the incidence of tuberculous meningitis from 1999 to 2006. In areas where tuberculosis is highly prevalent, meningitis occurs commonly in children aged under 4 years, while in low prevalence areas, most patients with tuberculous meningitis are adults.

Table 240.1 lists the causes of bacterial meningitis according to age and underlying conditions. (**Note**: *Mycobacterium tuberculosis* can cause meningitis at any age.)

The microbial epidemiology of meningitis is also changing in older children and adults in whom nosocomial meningitis accounts for an increasing proportion of infections. Many of these are associated with recent neurosurgical intervention or trauma. In such cases, *Pseudomonas aeruginosa*, enterococci, *Staphylococcus aureus*, and the coagulase-negative staphylococci are the most common causative organisms.

Table 240.1 Causes of acute bacterial meningitis according to age and underlying condition

Age	Organism
0–1 month (neonate)	*Streptococcus agalactiae* (Group B Streptococcus)
	Enteric bacilli (e.g. *Escherichia coli, Klebsiella pneumoniae, Proteus* spp.)
	Listeria monocytogenes
>1–3 months	*Streptococcus agalactiae* (Group B Streptococcus)
	Gram-negative Enteric bacilli (e.g. *Escherichia coli, Klebsiella pneumoniae, Proteus* spp.), *Listeria monocytogenes, Streptococcus pneumonia, Neisseria meningitides, Haemophilus influenzae* type b
>3 months–5 years	*Streptococcus pneumoniae, Neisseria meningitides, Haemophilus influenzae* type b
>5 years–50 years	Streptococcus pneumoniae
	Neisseria meningitidis
>50 years	Streptococcus pneumoniae
	Neisseria meningitidis
	Listeria monocytogenes
	Gram-negative bacilli
Immunocompromised (any age)	*Listeria monocytogenes, Streptococcus pneumoniae, Neisseria meningitides, Haemophilus influenzae* type b, Gram-negative enteric bacilli, *Salmonella* spp., *Pseudomonas aeruginosa*
Post-neurosurgery, post-skull trauma, and cerebrospinal fluid shunt	*Streptococcus pneumoniae, Neisseria meningitides, Haemophilus influenzae* type b, *Staphyloccus aureus*, Coagulase-negative staphylococcus, Gram-negative Enteric bacilli, *Streptococcus pyogenes*, Enterococci

Pathophysiology

Meningitis

Infection cannot occur until colonization of the host has taken place, usually in the upper respiratory tract. Infecting pathogens usually reach the cerebrospinal fluid (CSF) by haematogenous spread following colonization of the skin, the mucosal surface of the nasopharynx, respiratory, or gastrointestinal tract [6]. The organisms are then transported to the brain and translocate across the endothelial cells of the blood–brain barrier (BBB) in order to reach the CSF. Once in the CSF, bacterial products such as peptidoglycan, techoic acid, and endotoxin, stimulate the production of pro-inflammatory cytokines, such as tumour necrosis factor—alpha (TNF-α), interleukins 1 beta and 6, (IL-1β, IL-6), and other mediators (e.g. nitric oxide (NO), reactive oxygen species), leading to influx of leucocytes into the subarachnoid space. This inflammatory response is designed to inhibit bacterial proliferation, but acute inflammation in this confined space leads to pathological effects on brain function and structural brain damage due to oedema, thrombosis, and direct neurotoxicity.

Inflammatory mediators cause an increase in BBB permeability, leakage of plasma proteins into the CSF, further contributing to the development of cerebral oedema and subsequent neuronal damage. The damaged cerebral endothelial cells lead to vasospasm and thrombosis resulting in abnormal cerebral vascular autoregulation and a reduction in cerebral perfusion, and therefore further neuronal damage

Mucosal invasion and penetration occurs in those individuals where local mucosal immunity fails to contain bacterial proliferation, due to local factors such as colonization by virulent organisms and prior viral infection altering barrier function. The spleen plays a vital role in removing non-opsonized material from the circulation, particularly in non-immune individuals who do not have specific antibodies. Individuals who lack a functional spleen (i.e. sickle-cell disease, congenital asplenia, etc.) are at high risk of serious invasive infection, including meningitis, from encapsulated organisms. Other factors such as immunoglobulin, complement factors and inherent host immunity are important determinants of bacterial invasion.

Encephalitis

Viruses spread to the CNS via haematogenous or neuronal routes [7]. Haematogenous spread is more common and leads to an alteration in the BBB, as seen in arthropod-borne viral infections. In acute viral encephalitis, capillary and endothelial inflammation of cortical vessels is seen and this takes place within the gray matter or at the gray-white junction. Viruses also move into the CNS via intraneuronal routes, for example, the herpes viruses. Other data suggest the olfactory tract a route of access. On reaching the brain, the virus either lies dormant, or replication can take place intraneuronally, or can lead to cell-to-cell or extracellular spread. Encephalitis due to *Mycoplasma pneumoniae* may occur following direct bacterial invasion of the brain parenchyma, or due to auto-immune or thromboembolic phenomena [8].

Clinical features

Meningitis

Classically, patients with bacterial meningitis present with headache, fever, photophobia, vomiting, neck stiffness, and alteration of mental status. These signs and symptoms will be present at some stage in 85% of patients [9]. In infants and young children, the signs may be non-specific and fever may occasionally be absent. Where a child has fever with an altered level of consciousness, meningitis must be high in the differential diagnosis. Similarly, the elderly may be afebrile, but confused or obtunded, without the classical signs of meningitis. Other clinical findings may include cranial nerve palsy (particularly nerves III, IV, VI, and VII), focal neurological signs (10–20% of cases) and seizures (up to 30% of cases). Papilloedema is rare (about 1% of cases). With disease progression, signs of raised intracranial pressure (ICP), such as coma, hypertension, bradycardia, and altered respiratory status with focal brain involvement become more likely.

There appear to be two main patterns of clinical presentation of community-acquired meningitis. The first is a prolonged history of non-specific symptoms including lethargy, fever, and myalgias progressing over days and lasting up to a week. The second presentation is an acute fulminating course, with manifestations of both systemic sepsis and meningitis. This is frequently associated with severe cerebral oedema and raised ICP leading to brain herniation and brainstem compression. Depending on the aetiology, cutaneous manifestations may be seen. Approximately 50% of patients with meningococcal meningitis and the majority of patients with meningococcal septicaemia, will have a petechial or purpuric rash [9]. Seizures are common in bacterial meningitis, occurring in 20–30% of patients during the early stages of the illness. Generalized seizures are not associated with a worse outcome. However, focal seizures are likely to be associated with persistent neurological sequelae, as are focal neurological signs and cranial nerve palsies.

Encephalitis

The classic features of acute encephalitis are fever and headache, together with an altered level of consciousness. These may follow a prodrome of myalgia, lethargy, and other non-specific symptoms. Other findings may include neuropsychological disturbance, such as disorientation, confusion, hallucinations, and behavioural disturbances, focal neurological signs, and seizures. The clinical signs and symptoms represent disease progression and specific areas of brain involvement, which may be due to the action of the specific microbe (e.g. HSV has a predilection for the temporal lobes).

Diagnosis

Meningitis

Definitive diagnosis of bacterial meningitis requires isolation of the pathogen from cerebrospinal fluid (CSF). If, for clinical reasons, obtaining CSF is not possible, a clinical diagnosis of meningitis can be made by the finding of clinical signs of meningeal irritation (neck stiffness, positive Kernig's, or Brudzinski's sign), together with positive blood culture, latex agglutination test for bacterial polysaccharide in blood or urine, or positive polymerase chain reaction for

Box 240.1 Proposed criteria for diagnosing acute bacterial meningitis

Bacterial meningitis in children and infants >8 weeks old

Definite bacterial meningitis

- Compatible clinical syndrome:
  - *All ages*: fever (present in 94%).
  - *1–5 months*: irritability (present in 85%).
  - *6–11 months*: impaired consciousness (present in 79%).
  - *>12 months*: vomiting (present in 82%), neck rigidity (present in 78%).
- Plus one of:
  - Positive culture of CSF.
  - Positive CSF Gram stain.
  - Positive bacterial antigen/PCR.

Probable bacterial meningitis

- Compatible clinical syndrome.
- Plus positive blood culture/PCR.
- Plus one of the following CSF changes:
  - >100 leucocytes (neutrophils).
  - glucose CSF/serum ratio < 0.5.
  - protein >1 g/L.

Possible bacterial meningitis

- Compatible clinical syndrome.
- Plus one of the following CSF changes:
  - >100 leucocytes (neutrophils).
  - glucose CSF/serum ratio < 0.5.
  - protein >1 g/L.
- Plus negative cultures or antigen for bacteria, viral, fungal, or mycobacteria.

Neonatal meningitis <8 weeks old

- Compatible clinical syndrome.
- Plus abnormal CSF consistent with bacterial infection or one of:
  - Isolation of likely pathogenic organism from CSF.
  - Positive bacterial antigen/PCR.

bacterial DNA in blood or CSF. Definitions of CNS infection have been proposed and for the meningitis are divided into definitive, probable, or possible bacterial meningitis (Box 240.1) [9].

Purulent meningitis is associated with intracranial hypertension. Performing a lumbar puncture in the presence of intracranial hypertension may cause cerebral herniation. However, brainstem or tentorial herniation may occur even in the absence of lumbar puncture (approximately 5% of cases). Taking an accurate history, with appropriate recognition of the early systemic and neurological signs of meningitis and raised ICP allows an informed decision about whether a lumbar puncture can be performed safely. If signs of raised ICP are present, it is not safe to perform a lumbar puncture, even in the presence of normal brain imaging. Lumbar puncture is contraindicated in the following situations—a significant respiratory and/or haemodynamic compromise, presence of a bleeding diathesis, focal neurological signs, and a fluctuating or significantly reduced level of consciousness (GCS ≤ 8). If there will be a delay in performing lumbar puncture due to concerns about clinical status, it is important to start appropriate antimicrobial therapy as soon as possible. Table 240.2 shows the typical CSF findings in the differentiation between different types of meningitis.

There are several indications for obtaining radiological imaging of the brain in a child with suspected or confirmed meningitis. The main indication for cranial imaging is when the diagnosis is uncertain or to detect other possible intracranial pathology. It is important to bear in mind that normal imaging does not indicate normal intracranial pressure or that it is safe to do a lumbar puncture. If imaging shows evidence of raised ICP, lumbar puncture should not be performed. While CT is widely available and very useful for rapid assessment of hydrocephalus, mass lesions, haemorrhage, or cerebral oedema, MRI will detect more subtle findings. However, non-contrast CT and MRI can be normal in early meningitis [9].

The differential diagnosis for a child presenting with fever and signs of intracranial infection is large and, in addition, the complications of CNS infection include intracranial hypertension, and the presence of a space-occupying lesion. Where brain imaging was undertaken in children admitted with an acute febrile encephalopathy, in the absence of focal neurological signs, imaging played little part in the clinical management [10]. In children with meningitis who have undergone brain imaging using CT, where scans had abnormal findings, the abnormalities included subdural effusion, focal infarction, mild ventricular widening, contrast-enhancing basal meninges, cerebral oedema, and widening of the basal cisterns. Focal infarction and pus in the basal cisterns were associated with long-term neurological sequelae; transient dilatation of the subarachnoid space is a relatively common finding, not necessarily associated with long-term sequelae [11]. Performing imaging for prognostication appears to be of benefit.

Up to 50% of children with meningitis receive oral antibiotics before a definitive diagnosis is made. This treatment often leads to delay in presentation to hospital and may cause diagnostic confusion. CSF may be rapidly sterilized, although cellular and biochemical changes will persist. The only bacterium whose growth is likely to be significantly affected following oral antibiotic administration is meningococcus and this is thought to be due to the high sensitivity of the organism to low concentrations of antibiotics. It is essential that blood and CSF is sent for PCR and bacterial antigen detection, as these will not usually be affected by low CSF antibiotic concentrations following oral administration. Bacterial meningitis is likely in those with abnormal CSF parameters who have a significant raised white blood cell (WBC) count and/or C-reactive protein (CRP). A normal CRP and WBC count, however, do not rule out bacterial meningitis. If bacterial meningitis is suspected clinically and lumbar puncture has not been performed, children should be managed as such regardless of blood results [9].

Encephalitis

When searching for an infecting pathogen, it is important to establish certain epidemiological features including time of year, travel, and contacts. For example, in temperate climates, enteroviral infections are predominant during late summer and early winter [12]. As long as there are no contraindications, lumbar puncture is essential. Typical findings include pleocytosis (mononuclear cells predominate) with an increase in CSF protein. Some patients (3–5%) may have normal CSF and, under these circumstances, the diagnosis is made using assays to detect viral antigens or nucleic acids, as viral

Table 240.2 Cerebrospinal fluid findings in different types of meningitis

Condition	Leucocytes/mm^3	Glucose mmol/l	Protein g/l	Specific tests
Bacterial meningitis	100–500 (sometimes thousands) polymorphs	<60% of simultaneous blood glucose	>0.4	Gram stain, rapid antigen screen/PCR positive
Tuberculous meningitis	25–100 lymphocytes/monocytes predominate	<2.2 May be normal in early stages	Progressive increase to very high	Acid-fast organism on smear/PCR/culture
Viral meningitis	25–500 usually lymphocytes. Often polymorphs in first 24 hours	Usually normal	Mild increase <1	Viral culture, PCR
Fungal meningitis	0–500 lymphocytes	Mildly reduced/normal in early stages	Moderate increase	Fungal culture India ink, cryptococcal antigen
Partially treated bacterial meningitis	100–5000 polymorphonuclear cells/lymphocytes (50/50%)	Low/mildly reduced	Mild to moderate increase	Cultures negative, rapid antigen, and Gram stain positive/PCR
Parameningeal infection	Up to 100s variable mononuclear and polymorphonuclear cells	Normal/mildly reduced	Mild to moderate increase	CSF culture usually negative, cerebral imaging

PCR, polymerase chain reaction.

culture is of limited use. Cerebral imaging is a valuable tool and MRI changes may be present early on the disease. Characteristic changes may be present on an electroencephalogram (EEG) for example, the periodic high-voltage spike wave activity seen coming from the temporal lobes and slow-wave complexes at 2–3-second internals are seen in HSV infection [13].

Conclusion

Acute brain infections are relatively rare. The presentation may have classical features in some patients, but a high index of suspicion is required to make a rapid diagnosis and start appropriate therapy. Diagnostic tests are sensitive and specific, but therapy must often be empirical, at least initially, until more specific diagnostic test results are available and treatment can be tailored accordingly. As a general principle, early effective treatment is essential to improve outcomes. Recognition and appropriate interventions to treat complications are vital. Effective vaccines are becoming increasingly available for the most common CNS infections, but enhanced surveillance is vital to understand changing epidemiology in view of vaccination and antimicrobial pressure.

References

1. Agrawal S and Nadel S. (2011). Acute bacterial meningitis in infants and children. epidemiology and management. *Pediatric Drugs*, **13**, 385–400.
2. Jmor F, Emsley HC, Fischer M, Solomon T, and Lewthwaite P. (2008). The incidence of acute encephalitis syndrome in Western industrialised and tropical countries. *Virology Journal*, **5**, 134.
3. Nadel S. (2012). Prospects for eradication of meningococcal disease. *Archives of Diseases of Childhood*, **97**, 993–8.
4. O'Brien KL, Wolfson LJ, Watt JP, et al. (2009). Burden of disease caused by Streptococcus pneumonia in children younger than 5 years: global estimates. *Lancet*, **374**, 893–902.
5. Health Protection Agency. NOIDS final MIDI report for 2009 (online). Available at: URL: http://webarchive.nationalarchives.gov.uk/20110318112419/http://hpa.nhs.uk/web/hpawebfile/hpaweb_c/1281952671504 (Acessed 2015 Oct 31).
6. Koedel U, Klein M, and Pfister HW. (2010). New understandings on the pathophysiology of bacterial meningitis. *Current Opinion in Infectious Diseases*, **23**, 217–23.
7. Johnson RT. (1987). The pathogenesis of acute viral encephalitis and postinfectious encephalitis. *Journal of Infectious Diseases*, **155**, 359–64.
8. Bitnun A, Ford-Jones E, Blaser S, and Richardson S. (2003). *Mycoplasma pneumoniae* encephalitis. *Seminars in Pediatric Infectious Diseases*, **14**, 96–107.
9. National Institute for Health and Clinical Excellence. (2010). Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. (Clinical guideline 102.) 2010. www.nice.org.uk/CG102.
10. Nadel S, Joarder R, Gibson M, et al. (1999). Emergency cranial computed tomography in the management of acute febrile encephalopathy in children. *Journal of Accident and Emergency Medicine*, **16**, 403–6.
11. Cabral DA, Flodmark O, Farrell K, and Speert DP. (1987). Prospective study of computed tomography in acute bacterial meningitis. *Journal of Pediatrics*, **111**, 201–5.
12. Sawyer MH. (2002). Enterovirus infections: diagnosis and treatment. *Seminars in Pediatric Infectious Diseases*, **13**, 40–7.
13. Ch'ien LT, Boehm RM, Robinson H, Liu C, and Frenkel LD. (1977). Characteristic early electroencephalographic changes in herpes simplex encephalitis. *Archives of Neurology*, **34**, 361–4.

CHAPTER 241

Management of meningitis and encephalitis in the critically ill

Simon Nadel and Johnny Canlas

Key points

- Management of CNS infections requires specific antimicrobial agents, plus supportive treatment targeted at intracranial hypertension and other life-threatening complications.
- It is important that the need for management in an intensive care setting is considered early in the illness.
- Antibiotic resistance amongst the most common organisms causing bacterial meningitis is becoming more common and antibiotic therapy should be adjusted accordingly.
- Anti-inflammatory treatment, such as steroids should be started as soon as possible in patients with proven acute bacterial meningitis.
- In the future, effective vaccines should be available against all the common causes of bacterial meningitis and encephalitis, including *Neisseria meningitidis* serogroup b.

Introduction

The management of CNS infections requires specific antimicrobial agents to eradicate the infection and supportive treatment targeted at reducing raised intracranial pressure with neuroprotective strategies. Advances in the understanding of the pathophysiology of central nervous system infection have led clinicians to use anti-inflammatory agents in the treatment of bacterial meningitis. Some patients may require tracheal intubation and mechanical ventilatory support for the treatment of increased intracranial pressure, seizures, coma, shock, acidosis, and respiratory depression. This chapter will review the management of meningitis and encephalitis. It will necessarily concentrate on acute bacterial meningitis, as patients with this disease will tend to be more severely ill and are more likely to require intensive care management.

Management

Meningitis

Antimicrobial therapy

The initial management of suspected acute bacterial meningitis depends on early recognition, rapid diagnostic evaluation, and urgent introduction of antimicrobial and adjunctive therapy [1]. Antimicrobial therapy should not be delayed by imaging studies in the case of patients with focal neurological signs or papilloedema. Even if lumbar puncture is delayed, the CSF findings will still be important for diagnosis after the start of antimicrobial therapy, and a microbiological aetiology may be obtained by antigen detection or PCR. The longer the delay before starting appropriate antimicrobial therapy, the more likely that the disease will cause sequelae or be fatal. The current recommendation is to commence appropriate antimicrobial treatment for acute bacterial meningitis within 30 minutes of presentation. In cases of suspected meningococcal disease (i.e. presence of a purpuric or petechial rash), antibiotic therapy with parenteral benzylpenicillin is recommended before admission to hospital. In the absence of a rash, prehospital antibiotic treatment is not recommended unless there is a delay in transfer to hospital [2].

Empirical antibiotic therapy should be commenced based on the most likely causative organism for the individual patient, taking into account the patient's age, vaccination status, immune competence, and local patterns of antimicrobial resistance. In developed countries, most authorities recommend a third generation cephalosporin, such as ceftriaxone or cefotaxime, which have excellent CSF penetration and are active against most pathogens causing acute bacterial meningitis. Ceftriaxone should be avoided in infants who are jaundiced, hypo-albuminaemic, acidotic or born prematurely, as it may exacerbate hyperbilirubinaemia. In addition, it should not be administered at the same time as calcium-containing infusions as this may potentially precipitate cardiopulmonary adverse events [3]. *Listeria monocytogenes*, more common in infants <3 months and adults >50 years, is not sensitive to the cephalosporins. Therefore, the addition of a penicillin (e.g. amoxicillin or ampicillin) is recommended.

In the case of patients who are immunosuppressed, following surgery or where CSF leak is suspected, antimicrobial therapy should be broadened to include other Gram-negative organisms, the staphylococci, any possible opportunistic organisms, or *Mycobacterium tuberculosis*. In the post-neurosurgical patient, initial therapy must cover the Gram-negative organisms, including coliforms, *P. aeruginosa*, the skin flora, as well as community-acquired organisms. Broad antimicrobial coverage is essential in these patients. For example, vancomycin and ceftazidime, possibly in combination with an aminoglycoside. Table 241.1 summarizes the empiric choice of antibiotic for meningitis according to age and underlying condition [1].

There are now increasing reports of high-level cephalosporin resistance, conferring resistance of *S. pneumoniae* to the third generation cephalosporins. Factors reported to increase the likelihood

Table 241.1 Empiric choice of antibiotic for meningitis according to age and underlying condition

Age	Empiric choice of antibiotic (intravenous)
0–3 months[a,b,c]	**Broad spectrum cephalosporin and ampicillin:** ◆ Cefotaxime 100 mg/kg 8-hourly; or ◆ Ceftriaxone 80 mg/kg 12-hourly; plus ◆ Ampicillin or amoxicillin 100 mg/kg 8-hourly
>3 months–50 years[b,c]	**Broad spectrum cephalosporin:** ◆ Cefotaxime 100 mg/kg 8-hourly (adult 2 g 8-hourly); or ◆ Ceftriaxone 80 mg/kg 12-hourly (adult 2 g 12-hourly)
>50y[b,c]	**Broad spectrum cephalosporin and ampicillin:** ◆ Cefotaxime 100 mg/kg 8-hourly (adult 2 g 8-hourly) ◆ Ceftriaxone 80 mg/kg 12-hourly (adult 2 g 12-hourly) ◆ Ampicillin or amoxicillin 100 mg/kg 8-hourly (adult 2 g 4-hourly)
Immunocompromised host[c]	**Ceftazidime and ampicillin or amoxicillin:** ◆ Ceftazidime 50 mg/kg 8-hourly (adult 2 g 8-hourly) ◆ Ampicillin *or* amoxicillin 100 mg/kg 8-hourly (adult 2 g 4-hourly)
Post-neurosurgery, post-skull trauma, cerebrospinal fluid shunt	**Ceftazidime and vancomycin:** ◆ Ceftazidime 50 mg/kg 8-hourly (adult 2 g 8-hourly) ◆ Vancomycin 15 mg/kg 6-hourly (adult 2 g/24 hours)

[a]In neonates, in particular preterm neonates, drug dosages may have to be adjusted.

[b]Vancomycin 15 mg/kg 6-hourly (max. 2 g/24 hours, for resistant *Streptococcus pneumoniae*).

[c]If cephalosporin-resistant pneumococci are suspected add vancomycin as in b above.

Max., maximum.

Data from Agrawal S and Nadel S, 'Acute Bacterial Meningitis in Infants and Children. Epidemiology and Management', *Pediatric Drugs*, 2011, **13**(6), pp. 385–400.

Table 241.2 Recommended antibiotic therapy for specific pathogens

Organism	Antibiotic (intravenous)
Neisseria meningitidis	**Broad spectrum cephalosporin:** ◆ Cefotaxime 100 mg/kg 8-hourly (adult 2 g 8-hourly) ◆ Ceftriaxone 80 mg/kg 12-hourly (adult 2 g 12-hourly) ◆ Benzylpenicillin (depending on sensitivity: 300,000 units/kg/day; max. 24 million units/24 hours)
Streptococcus pneumoniae	**Broad spectrum cephalosporin and vancomycin:** ◆ Cefotaxime 100 mg/kg 8-hourly (adult 2 g 8-hourly) ◆ Ceftriaxone 80 mg/kg 12-hourly (adult 2 g 12-hourly) ◆ Vancomycin 15 mg/kg 6-hourly (max. 2 g/24 hours)
Haemophilus influenzae	**Broad spectrum cephalosporin:** ◆ Cefotaxime 100 mg/kg 8-hourly (adult 2 g 8-hourly) ◆ Ceftriaxone 80 mg/kg 12-hourly (adult 2 g 12-hourly)
Listeria monocytogenes	**Ampicillin and gentamicin (synergistic activity):** ◆ Ampicillin 100 mg/kg 8-hourly (adult 2 g 4-hourly) ◆ Gentamicin 7.0 mg/kg 24-hourly (check levels)
Streptococcus agalactiae	**Ampicillin and gentamicin (synergistic activity):** ◆ Ampicillin 100 mg/kg 8-hourly (adult 2 g 4-hourly) ◆ Gentamicin 5–7 mg/kg 24-hourly (depending on gestational age and level)

Max., maximum.

Data from Agrawal S and Nadel S, 'Acute Bacterial Meningitis in Infants and Children. Epidemiology and Management', *Pediatric Drugs*, 2011, **13**(6), pp. 385–400.

of infection with a resistant strain include patient's age (<10 or >50 years), immunosuppression, prolonged hospital stay, children in day care settings, infection by serotypes 14 and 23, and frequent or prophylactic use of antibiotics.

When *S. pneumoniae* meningitis is strongly suspected, vancomycin may be included in empirical therapy until the antimicrobial susceptibility of the isolate has been determined. Vancomycin penetrates the CSF adequately in the presence of meningeal inflammation and the combination of vancomycin and a third generation cephalosporin may be synergistic for meningitis caused by a high-level penicillin-resistant *S. pneumoniae* [1,2].

At present there are no data to suggest that quinolones or extended-spectrum macrolides are beneficial for the empiric therapy of bacterial meningitis. However, early studies with the carbapenem meropenem look promising as single agent therapy for a wide range of pathogens that cause bacterial meningitis. The recommended antibiotics and dosages for the treatment of ABM caused by specific organisms are outlined in Table 241.2.

The duration of antimicrobial therapy is dependent on the age and immune status of the patient, the aetiological agent, and the clinical course or development of complications. There is no universally accepted standard. As little as 7 days of therapy or shorter is appropriate for uncomplicated meningococcal meningitis. For meningitis due to *H. influenzae*, 10 days is the accepted duration, while for pneumococcal meningitis it is 14 days. Meningitis due to *L. monocytogenes* should be treated for 14 days, extending to 21 days in the immunocompromised host. Neonatal Gram-negative meningitis should be treated for at least 21 days following CSF sterilization. For meningitis due to *Streptococcus agalactiae*, at least 14 days treatment is recommended, depending on the clinical course.

The duration of therapy may need to be extended as a result of complications, such as the development of brain abscess or subdural empyema, prolonged fever, or the development of nosocomial superinfection. In such cases, the duration of therapy should

be individualized. Current recommendations in the UK are summarized in Table 241.3.

Anti-inflammatory treatment

Despite effective antimicrobial therapy, neurological morbidity and mortality remains a major consequence of acute bacterial meningitis (ABM). This is partly due to the damaging process within the brain that is mediated by activation of host inflammatory pathways, triggered by the release of endotoxin and other bacterial constituents. This is often accentuated by the use of powerful bactericidal antibiotics, and this has led to the hypothesis that injury to the brain may be reduced by the use of anti-inflammatory treatment.

The role of adjunctive corticosteroids in ABM has been widely studied in the last three decades. Initial trials showed a clear benefit from dexamethasone, with decrease in neurologic sequalae, particularly nerve deafness [4].

In 2007, a Cochrane analysis published a review of 20 randomized clinical trials on the safety and efficacy of corticosteroid use in ABM. According to this analysis, adjuvant corticosteroids were associated with lower case fatality rates, lower rates of severe hearing loss, and fewer long-term neurological sequelae. In children, the beneficial effects of corticosteroid use were less convincing, although there was a trend towards reduced hearing loss and short-term neurological sequelae in non-Hib meningitis, with the effect statistically significant in high-income countries compared with low-income countries. Subgroup analysis suggested that the case fatality rate was reduced by adjuvant steroids in patients with pneumococcal meningitis and that hearing loss was reduced in patients with Hib meningitis [5].

In the absence of any potentially significant harmful effects, dexamethasone is recommended for use in children with confirmed or suspected ABM above 3 months of age in the UK [2] and above 6 months of age in the US [6]. The recommended dosage is 0.6 mg/kg/day in four divided doses for 4 days, commencing prior to or simultaneously with the first dose of antibiotic, or within 4 hours of antibiotic administration.

In adults, the evidence for use of steroids in ABM is less convincing. However, in severe ABM, there are theoretical grounds for using steroids at the same recommended dosage as previously mentioned, without evidence of a worse outcome. The benefit of dexamethasone appears to be greatest if it is administered early in the course of the illness, preferably prior to antibiotic administration. There have been few side effects documented in patients receiving dexamethasone. In particular, there have been no reports of delayed CSF sterilization or treatment failure, although gastrointestinal bleeding has been observed in a small proportion of patients. However, the early reports of a beneficial effect of dexamethasone in bacterial meningitis should be interpreted with caution. There are no good data on the use of adjunctive steroid therapy in neonatal, post-neurosurgical or traumatic meningitis.

Supportive care

Antibiotic administration is only one component of the overall management of patients with meningitis. Neurological derangement often co-exists with circulatory insufficiency, impaired respiration, metabolic derangement, and convulsions. Measures to detect and correct any co-existing physiological derangement are probably important in improving the prognosis.

Neuroprotective strategies

All patients with bacterial meningitis are likely to have raised ICP as part of their disease process. Signs of raised ICP include altered level of consciousness, altered pupillary responses, hyper- or hypotension, reduction in resting pulse rate, altered respiratory pattern, and focal neurological signs. Papilloedema is a late sign. Patients with raised ICP due to bacterial meningitis and other intracranial infections should be assessed for airway, breathing, and circulation. The management is generally as for other causes of intracranial hypertension.

Table 241.3 Current UK guidelines for empirical and specific therapy in bacterial meningitis in children

Age group	Empirical therapy	Specific therapy
>3 months	**Ceftriaxone or cefotaxime:** ◆ +/– vancomycin ◆ 7 days for *N. meningitides* ◆ 10 days for *Hib* ◆ 14 days for *S. pneumonia*	Ceftriaxone
<3 months	Cefotaxime + amoxicillin/ampicillin	
GBS	≥14 days cefotaxime or penicillin or ampicillin + gentamicin	
Gram-negative organisms	21 days cefotaxime or ceftriaxone or meropenem +/– gentamicin	
Listeria monocytogenes	◆ 21 days amoxicillin/ampicillin + gentamicin for first 7 days ◆ +/– vancomycin	
Unconfirmed	◆ ≥14 days amoxicillin/ampicillin + cefotaxime ◆ Consider Aciclovir	

GBS, for Group B Streptococci.

Data from National Institute for Health and Clinical Excellence. Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. (Clinical guideline 102) 2010. www.nice.org.uk/CG102.

Fluid management

Fluid therapy should be guided by clinical assessment of hydration status. Over 50% of children with ABM have hyponatraemia at presentation, often attributed to increased secretion of antidiuretic hormone (ADH), and this may be a marker of severe disease contributing to cerebral swelling. By restricting intravenous fluid administration in the presence of SIADH, the risk of developing cerebral oedema is likely to be diminished.

In general, enteral fluids or feeds should be used where appropriate, and isotonic fluid when intravenous therapy is required. In developing world settings with high mortality and where children present late, full maintenance fluid therapy was associated with reduced spasticity, seizures, and chronic severe neurological sequelae [7].

Sedation and control of convulsions

Seizures occur within 48 hours of presentation in 20–30% of patients with bacterial meningitis. Seizures are especially dangerous in patients with raised ICP, as they result in increased metabolic demands, an increase in cerebral blood flow and may precipitate a further increase in ICP. Convulsions may be difficult to detect in patients who are treated with neuromuscular blocking agents for artificial ventilation. In such patients electrical monitoring should be used to detect seizure activity. The use of anticonvulsant treatment in non-ventilated patients may precipitate respiratory arrest and careful observation of respiration and ventilation could be undertaken during the treatment of seizures. Short- acting benzodiazepines can be used to control acute seizures, and standard anti-epileptic agents for longer term control.

Encephalitis

It may not always be possible to isolate the organism that causes encephalitis. In such circumstances, it is prudent to commence treatment with broad-spectrum antimicrobials and to cover the more likely causative agents. There are some specific therapies available for specific organisms as described in the following sections. Appropriate supportive intensive care may be required including the use of neuroprotective strategies. Newer antiviral agents are continually being identified and may be useful in the future treatment of specific encephalitides. Where organisms which cause encephalitis are endemic, such as Japanese B virus, vaccination programmes are very effective in reducing prevalence of disease.

Mycoplasma pneumoniae encephalitis

In patients with *Mycoplasma pneumoniae* encephalitis, a temporal clinical improvement has been reported in children treated with antibiotics. On the other hand some children recover without antimicrobials [8]. It is not clear whether encephalitis due to M. pneumoniae is an acute-infectious process or a post-infectious/auto-immune process. However, it is probably prudent to treat suspected or confirmed *M. pneumoniae* encephalitis with antimicrobials with activity against mycoplasma. Macrolides are considered the antibiotic of choice despite their poor penetrance of the blood brain barrier. Azithromycin has been found to achieve a high concentration in brain tissue [9].

Herpes simplex encephalitis

Aciclovir is the treatment of choice in *Herpes simplex* encephalitis. The current standard of care for adults and children over the age of 12 months is intravenous aciclovir at a dose of 500 mg/m^2 every 8 hours for 21 days. In infants <12 months, the recommended dose is 20 mg/kg every 8 hours for 21 days. Shorter duration of treatment increases the risk of relapse. Neonatal HSV infection may require a longer duration of therapy. With this regimen, mortality from neonatal HSV encephalitis has fallen to 5%. 40% of survivors develop normally. Outcome is dependent upon age of patient, level of consciousness at presentation, duration of encephalitis, and viral load. If presenting Glasgow Coma Score (GCS) <7, outcome is universally poor. Where treatment was instituted less than four days following the onset of symptoms, the survival at eighteen months increased from 72% to 92% [10].

Other viral encephalitides (enterovirus, rabies virus, arthropod-borne virus)

The enteroviruses include polioviruses, Coxsackie viruses, and echoviruses. They are known to cause both encephalitis and aseptic meningitis, and the management for these cases is supportive. Rabies virus encephalitis is virtually always fatal. It can be prevented by appropriate immunization even when exposure has occurred [11]. The management is generally supportive. Encephalitis due to arthropod-borne viruses is very common worldwide. There are no specific therapies for these apart from supportive care of organ failure.

Enterovirus 71 encephalitis

Enterovirus 71 (EV71) causes major outbreaks of hand, foot, and mouth disease (HFMD), most frequently affecting children. Although present throughout the world, the largest outbreaks of disease have been seen in the Asia–Pacific region and neurological manifestations range from aseptic meningitis to acute flaccid paralysis and brainstem encephalitis.

Brainstem encephalitis, especially affecting the medulla and associated with cardiopulmonary dysfunction has become the most notable feature in EV71 epidemics in Asia. Children typically present with a brief febrile illness and mild neurological signs, which may progress to myoclonic jerks, after which they develop signs of tachycardia, poor perfusion, and tachypnoea that rapidly develop into acute, intractable cardiac dysfunction, and fulminant pulmonary oedema or haemorrhage.

Post-mortem examination and MRI studies of children with EV71 brainstem encephalitis showed extensive inflammation of gray matter of the spinal cord and the whole medulla oblongata.

Treatment of complications

Complications of CNS infections vary according to the aetiological agent, duration of symptoms prior to initiation of appropriate therapy, and the age and immune status of the patient. Early complications are seizures, haemodynamic instability, SIADH, or other dysregulation of the hypothalamic-pituitary axis (such as diabetes insipidus), an acute increase in ICP, profound shock, and DIC. Neonates with any form of bacterial meningitis are likely to develop shock and DIC. Children may suffer severe and permanent neurological sequelae, or mild subtle behavioural disturbance. The most common complication of bacterial meningitis is sensorineural hearing loss.

Focal neurological signs including hemiplegia and quadriplegia may develop in the early stages of meningitis, but are more common in the later stages. Vasculitis and thrombosis may explain these clinical findings. Awareness of other conditions that require acute

Table 241.4 Risk of sequalae from bacterial meningitis in adults and children globally

	Risk after:		
	S. pneumonia (%)	*Hib (%)*	*N. meningitidis (%)*
Hearing	7.5	3.2	2.6
Motor deficit	5.8	2.2	1.0
Behavioural problems	4.6	2.1	0.6
Cognitive difficulties	4.2	1.1	1.6
Epilepsy	2.5	1.5	0.5
Visual disturbances	1.1	0.5	1.5
At least one sequelae	34.7	14.5	9.5
Multiple impairments	5.7	2.6	1.3

neurosurgical intervention is necessary. These include the development of subdural empyema, brain abscess, and acute hydrocephalus. Subdural effusions are more common after *Haemophilus influenzae* meningitis, but can occur with any organism. They usually resolve spontaneously, but the presence of significant and persistent neurological symptoms including seizures, paresis, raised ICP, and development of empyema are indications for drainage. Cerebral abscess must also be considered in any child who deteriorates neurologically, usually following the acute phase of bacterial meningitis, and is often accompanied by persistent fever. Table 241.4 is a summary of risk sequelae from bacterial meningitis worldwide [12].

Conclusion

The successful introduction of vaccines against encapsulated organisms that cause bacterial meningitis has significantly reduced the incidence in developed countries, but there is still a substantial burden of disease in developing countries. Molecular diagnostics are being increasingly used in the diagnosis of non-bacterial encephalitides. Clinical trials on vaccines against *Neisseria meningitidis* serogroup B and newer antimicrobial agents against resistant pneumococcal strains and other viral pathogens are underway. However, there remains limited information on optimum duration of antimicrobial therapy, indications for corticosteroid treatment and optimum fluid therapy. Clinical trials to evaluate best therapies, optimal duration of treatment, adjunctive therapies, neuroprotective agents and new vaccines are urgently needed.

References

1. Agrawal S and Nadel S. (2011). Acute bacterial meningitis in infants and children. epidemiology and management. *Pediatric Drugs*, **13**, 385–400.
2. National Institute for Health and Clinical Excellence. (2010). Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care, Clinical guideline 102. London: NICE. Available at: www.nice.org.uk/CG102.
3. Bradley JS, Wassel RT, Lee L, and Nambiar S. (2009). Intravenous ceftriaxone and calcium in the neonate: assessing the risk for cardiopulmonary adverse events. *Pediatrics*, **123**, e609–13.
4. Lebel MH, Freij RJ, Syrogiannopoulos GA, et al. (1988). Dexamethasone therapy for bacterial meningitis: Results of two double-blind, placebo-controlled trials. *New England Journal of Medicine*, **319**, 964–71.
5. Brouwer MC, McIntyre P, de Gans J, Prasad K, and van de Beek D. (2010). Corticosteroids for acute bacterial meningitis. *Cochrane Database of Systematic Reviews*, **9**, CD004405.
6. American Academy of Pediatrics (2009). Pneumococcal infections. In: Pickering LK (ed.) *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th edn, pp. 524–35. Elk Grove Village (IL): American Academy of Pediatrics.
7. Duke T, Mokela D, Frank D, et al. (2002). Management of meningitis in children with oral fluid restriction or intravenous fluid at maintenance volumes: a randomised trial. *Annals of Tropical Paediatrics*, **22**, 145–57.
8. Lin WC, Lee PI, Lu CY, et al. (2002). Mycoplasma pneumoniae encephalitis in childhood. *Journal of Microbiology, Immunology, and Infection*, **35**, 173–8.
9. Jaruratanasirikul S, Hortiwakul R, Tantisarasart T, et al. (1996). Distribution of azithromycin into brain tissue, cerebrospinal fluid and aqueous humor of the eye. *Antimicrobial Agents and Chemotherapy*, **40**, 825–6.
10. Kimberlin DW. (2005). Herpes simplex virus infections in neonates and early childhood. *Seminars in Pediatric Infectious Diseases*, **16**, 271–81.
11. Moran GJ, Talan DA, Mower W, et al. (2000). Appropriateness of rabies post-exposure prophylaxis treatment for animal exposures. Emergency ID Net Study Group. *Journal of the American Medical Association*, **284**, 1000–7.
12. Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, and Rudan I. (2010). Global and regional risk of disabling sequalae from bacterial meningitis: a systematic review and meta analysis. *Lancet: Infectious Diseases*, **10**, 317–28.

PART 9.11

Non-traumatic spinal injury

CHAPTER 242

Pathophysiology, causes, and management of non-traumatic spinal injury

Oliver Flower and Matthew Mac Partlin

Key points

- Non-traumatic spinal cord injury is at least as common as traumatic spinal cord injury and its incidence increases with age.
- Non-traumatic spinal cord injury has a wide spectrum of aetiologies with varying pathophysiology.
- A high index of suspicion must be present to avoid delayed diagnosis and treatment.
- Management of non-traumatic spinal cord injury focuses on diagnosing and treating the precipitating cause, supportive management, and preventing complications.
- The outcomes of non-traumatic spinal cord injury are similar to those of traumatic spinal cord injury.

Introduction

Non-traumatic spinal cord injury (NTSCI) is the myelopathy caused by a host of conditions other than trauma. While NTSCI shares many clinical and pathological features with traumatic spinal cord injury (TSCI), it has a separate epidemiology and pathophysiology, and its own distinct management elements, largely related to the precipitating causes. Like TSCI, NTSCI has enduring consequences for the individual, their families, and society.

Epidemiology

The incidence of NTSCI equals that of TSCI (10–83/million population/year) [1,2], and in some regions exceeds TSCI [3]. Unlike TSCI, the incidence increases with age, predominantly affecting those between 30 and 60, unlike the male preponderance seen in TSCI [3,4].

Causes

A diverse range of aetiologies may cause NTSCI. The most common causes described in case series in developed countries are degenerative disc disease, canal stenosis, tumours, vascular diseases and inflammatory conditions [5,6]. The International Spinal Cord Society (ISCoS) have compiled a validated and comprehensive classification system, which refers to aetiology by cause, time frame of onset, and whether there was an iatrogenic component to the injury [7]. The aetiologies are summarized in Table 242.1. Other time-critical diagnoses should be considered with the presentation of acute non-traumatic paraplegia or tetraplegia, such as intracranial vascular or space-occupying lesions, peripheral neuropathies including Guillain–Barré syndrome, disorders of the neuromuscular junction, myopathies, toxidromes, and metabolic disorders, such as hypoglycaemia.

Pathophysiology

Anatomy

The adult spinal cord is approximately 46 cm long and ends around the L1 vertebral level. It is therefore shorter than the length of the vertebral column and spinal cord segmental levels (innervation of myotomes and dermatomes) do not correspond to vertebral levels; for example, the L4 spinal cord segment is at approximately the T11 vertebral level.

The vascular supply to the spinal cord is via the vertebral arteries, which form the single anterior and two posterior spinal arteries. These, in turn, are supplied by segmental radicular arteries that are small branches of the cervical, thoracic and lumbar vessels. The largest of the radicular arteries is the artery of Adamkiewicz, often given off from the T10 level, but varying in position from T7 to L4 [8].

Pathology

Spinal cord injury is usually considered in terms of primary and secondary mechanisms [9]. Traumatic spinal cord injury usually consists of a primary compression or contusion or penetration injury followed by secondary injury (often aggravated by hypoxia and hypoperfusion). The primary injury mechanisms in NTSCI include:

- **Compression/contusion**: e.g. disc prolapse, tumour, extradural abscess.
- **Inflammation**: e.g. infection, transverse myelitis, multiple sclerosis (MSc), radiation.
- **Ischaemia**: e.g. aortic dissection, thromboembolic events.
- **Intracellular defects**: e.g. metabolic defects, genetic disorders, congenital disorders.

Table 242.1 Classification of the aetiology of NTSCI (condensed)

Acquired abnormalities	Vertebral column degenerative disorders	◆ Disc prolapse ◆ Ligamentum flavum hypertrophy ◆ Ossification of the posterior longitudinal ligament ◆ Spinal osteophytosis ◆ Spondylolisthesis ◆ Spondylosis ◆ Spinal stenosis
	Metabolic disorders	◆ Deficiency (B12, folate, copper, Vit D) ◆ Osteoporosis ◆ Paget's disease ◆ Osteomalacia
	Vascular disorders	◆ Haemorrhage (epidural or elsewhere) ◆ Vascular malformations ◆ Ischaemia (atherosclerosis, aortic dissection, Takayasu's arteritis, atheromatous emboli, thromboemboli, fibrocartilaginous emboli, decompression sickness, venous infarction, hypotensive-hypoperfusion, fat embolism, idiopathic)
	Inflammatory and autoimmune diseases	◆ Demyelination ◆ Collagen vascular disease (SLE, Sjogren's, rheumatoid, ankylosing spondylitis, vasculitis) ◆ Sarcoidosis ◆ Paraneoplastic ◆ Arachnoiditis
	Radiation related	Radiation myelitis
	Toxic	◆ Organophosphates ◆ Others
	Neoplastic	◆ Benign (Primary vertebral, extradural, intradural and intrameduallary) ◆ Malignant (Neural, primary vertebral, leptomeningeal, secondary, haematological)
	Infection	Viral, bacterial, spirochaetal, fungal, parasitic
	Miscellaneous	◆ Motor neurone disease ◆ Syringomyelia
Congenital	Spinal Dysraphism	e.g. Spina bifida occulta
	Arnold–Chiari malformation	Types 1–4
	Skeletal malformations	e.g. Atlanto-axial dislocation
	Other congenital	Congenital syringomyelia
Genetic Disorders	Hereditary spastic paraparesis	
	Spinocerebellar ataxias	
	Adrenomyeloneuropathies	
	Other leukodystrophies	
	Spinal muscular atrophies	

Adapted by permission from Macmillan Publishers Ltd and International Spinal Cord Society: *Spinal Cord*, New PW and Marshall R, 'International Spinal Cord Injury Data Sets for non-traumatic spinal cord injury', **52**, pp. 123–32, copyright 2013.

For acquired aetiologies, such as acute disc prolapse, epidural abscess and acute infection, the primary injury involves axonal death, gray matter haemorrhage with necrosis, microglial activation, and release of inflammatory cytokines. The pathology of secondary injury evolves with time. In the initial hours to days, the pathological features are predominantly inflammation, vasogenic, and cytotoxic oedema, haemorrhage, demyelination, neuronal death, and axonal swelling. This may be a protracted process when the aetiology is ongoing (e.g. tumour) or recurrent (e.g. MSc). This is followed in the subsequent weeks by resolution and initial repair, and then over months to years there is gliosis, further demyelination, and potentially syrinx formation related to altered CSF flow.

Through preserved axons, adaptive functional plasticity may occur. For genetic and congenital disorders secondary injury phases may not occur.

Management

NTSCI should be considered in any patient presenting with symmetrical weakness or hypoaesthesia at a defined spinal level that continues caudally. Presentation may be highly variable depending on aetiology, the neurological level of injury, and completeness of injury. Specific syndromes also have different presentations (see Table 242.2).

As acquired NTSCI is often an unexpected event, a high index of suspicion may be required for timely diagnosis. An approach of synchronous resuscitation and evaluation should be taken. Resuscitation should be considered in the same manner as TSCI. A careful history and examination considering other differential diagnoses, followed by urgent appropriate investigations is essential.

History

A focused history should be taken, mindful of the potential aetiologies of acquired NTSCI and differential diagnoses. There may be a clear precipitant, such as thoracic abdominal aneurysm surgery, a lumbar puncture in a coagulopathic patient, an air embolism post-diving or previous radiotherapy, making NTSCI a likely diagnosis. Red flag symptoms may point to specific aetiologies, for example, weight loss, night back pain, or a history of cancer may suggest a neoplastic cause. Fever, intravenous drug abuse, recent infections elsewhere, and immunocompromised states make an infective aetiology more likely. Prolonged use of steroids, increasing age, osteoporosis, and mild trauma suggest a degenerative disorder of the vertebral column. A more insidious onset in individuals with pernicious anaemia or nutritional deficiencies may suggest subacute combined degeneration of the cord (SCDC) from Vitamin B12 deficiency. Relapsing and remitting symptoms involving different areas of the CNS is suggestive of MSc.

Examination

This is covered in greater detail in the other chapters involving SCI. A detailed neurological examination is essential, utilizing the globally accepted guidelines of the American Spinal Injury Association [10] documenting the neurological level of injury and the grade of injury, which requires determination of sacral sparing delineating whether the injury is complete or incomplete. Examination may yield clues as to the precipitant, such as a pulsating enlarged aorta with an aneurysmal dissection, features of sepsis for an infectious cause or the other features of a toxidrome such as those seen in organophosphate poisoning

Investigations

Imaging is required to define a lesion's location, extent, relations and features, and the sequence of imaging will depend on the presentation. Magnetic resonance imaging (MRI) is usually required to adequately demonstrate NTSCI. MRI is more sensitive and specific than computed tomography (CT), can differentiate myelopathy from radiculopathy and better visualizes intervertebral discs and ligaments. If MRI is contraindicated (e.g. older cochlear implants or pacemakers), a CT myelogram (with contrast) may provide additional information to a plain CT. Imaging must be performed urgently in NTSCI as aetiologies, such as epidural abscesses or haematoma may require urgent surgical intervention to prevent further or permanent cord injury. A CT angiogram or digital subtraction angiography may be required to diagnose vascular causes of NTSCI and may offer the potential for concurrent intervention with the latter.

Laboratory studies may help with diagnosis. A leucocytosis, elevated CRP, and positive blood cultures suggest an infective aetiology. Coagulation abnormalities, including thrombocytopenia, support a haemorrhagic cause. A low vitamin B12 level supports a diagnosis of subacute combined degeneration. Elevated serum angiotensin-converting enzyme (ACE), hypercalcaemia, and an elevated alkaline phosphatase are consistent with sarcoidosis. Tumour markers or, in the case of lymphoma, flow cytometry may help diagnose a specific malignancy. Cerebrospinal fluid (CSF) analysis may be helpful, but should not delay urgent imaging. For example, oligoclonal bands help in diagnosing MSc, CSF ACE suggests sarcoid, tumour cells may be found, the typical features of bacterial or viral infections demonstrated, and important differential diagnoses such as Guillain–Barré syndrome excluded. For other specific conditions, further investigations may be indicated, such as evoked potential to diagnose MSc or a positron emission tomography in certain malignancies.

Table 242.2 Cord syndromes

Syndrome	Explanation
Central cord	Weakness and sensory loss greater in the arms than the legs. Typically follows a hyperextension injury with pre-existing canal stenosis. Ischaemia or haematoma in the centre of the cord affect the cervical segments more due to the pattern of lamination of the corticospinal and spinothalamic tracts.
Anterior cord	Loss of motor function, and pain and temperature sensation below the neurological level of injury (NLOI), with preservation of fine touch and proprioception. Less common, typically following interruption of the blood supply to the anterior spinal cord.
Brown–Séquard	Ipsilateral loss of motor, proprioception and fine touch, with contralateral loss of pain and temperature sensation below the NLOI. Usually follows a penetrating SCI damaging only one-half of the spinal cord.
Conus medullaris	Sudden onset, symmetrical paraplegia with mixed upper and lower motor neuron findings, caused by injury at T12/L1.
Cauda equina	Often asymmetrical, gradual onset, lower motor neuron lower limb weakness with saddle area hypoaesthesia or paraesthesia, with bladder and bowel areflexia. Caused by injuries below L1 damaging the sacral nerve roots.

Treatment

The supportive care described in other chapters for TSCI also applies to NTSCI, and these patients should also be managed in specialised spinal injury units [11]. However, the specific cause responsible for the NTSCI must be addressed.

Vertebral column degenerative disorders causing demonstrable cord injury usually require surgical decompression and stabilization. Metabolic causes require correction of the underlying pathology, for example, vitamin B12 deficiency requires immediate and ongoing treatment with parenteral or oral cobalamin. Haemorrhage causing NTSCI from a compressing haematoma requires immediate correction of any coagulopathy and commonly surgical decompression to prevent further cord damage. Ischaemic NTSCI is commonly managed conservatively; however, there may be a role for intravenous thrombolysis, or intra-arterial clot lysis or retrieval in specialist centres, although the effectiveness of such treatments is currently unknown. The use of lumbar CSF drains to improve intra-operative spinal cord perfusion pressure during thoracic aortic surgery has been shown to reduce NTSCI [8,12]. Spinal arteriovenous malformations may be managed with endovascular embolization, either alone or in combination with surgery. Inflammatory conditions, such as transverse myelitis, MSc, or sarcoidosis potentially respond to corticosteroid treatment and other immunomodulatory agents. Early-delayed radiation-induced myelopathy is usually reversible and rarely treated, whereas when it is late-delayed, it is likely to be permanent. There is no evidence to support specific treatment for this, although steroids are often used [13]. The management of the wide variety of spinal tumours differs depending on the type and location of the tumour. Treatment options include chemotherapy, radiotherapy, pre-operative embolization, and surgery. Epidural infections usually require surgical or radiological drainage, as well as appropriate antimicrobial therapy. Congenital causes of NTSCI require surgical intervention once they become symptomatic, for example Arnold–Chiari malformation is commonly managed with occipital and cervical vertebral decompression, spinal dysraphism requires early surgery to prevent urinary incontinence, and symptomatic atlanto-axial dislocation requires cervical decompression and fusion. For genetic causes NTSCI, treatment is supportive and should include genetic counselling and provision of screening for relatives.

Online materials

Additional online materials for this chapter are available online at www.oxfordmedicine.com

References

1. van den Berg ME, Castellote JM, Mahillo-Fernandez I, and de Pedro-Cuesta J. (2010). Incidence of spinal cord injury worldwide: a systematic review. *Neuroepidemiology*, **34**(3), 184–92; discussion 192.
2. Parsons KC and Lammertse DP. (1991). Rehabilitation in spinal cord disorders. 1. Epidemiology, prevention, and system of care of spinal cord disorders. *Archives of Physical Medicine and Rehabilitation*, **72**(4-S), S293–4.
3. New PW and Sundararajan V. (2008). Incidence of non-traumatic spinal cord injury in Victoria, Australia: a population-based study and literature review. *Spinal Cord*, **46**(6), 406–11.
4. Gupta A, Taly AB, Srivastava A, and Murali T. (2009). Non-traumatic spinal cord lesions: epidemiology, complications, neurological and functional outcome of rehabilitation. *Spinal Cord*, **47**(4), 307–11.
5. * New PW, Rawicki HB, and Bailey MJ. (2002). Nontraumatic spinal cord injury: demographic characteristics and complications. *Archives of Physical Medicine and Rehabilitation*, **83**(7), 996–1001.
6. Schonherr MC, Groothoff JW, Mulder GA, and Eisma WH. (1996). Rehabilitation of patients with spinal cord lesions in The Netherlands: an epidemiological study. *Spinal Cord*, **34**(11), 679–83.
7. New PW and Marshall R. (2013). International spinal cord injury data sets for non-traumatic spinal cord injury. *Spinal Cord*, **52**, 123–32.
8. Bicknell CD, Riga CV, and Wolfe JH. (2009). Prevention of paraplegia during thoracoabdominal aortic aneurysm repair. *European Journal of Vascular and Endovascular Surgery*, **37**(6), 654–60.
9. Rowland, JW, Hawryluk GW, Kwon B, and Fehlings MG. (2008). Current status of acute spinal cord injury pathophysiology and emerging therapies: promise on the horizon. *Neurosurgery Focus*, **25**(5), E2.
10. * Kirshblum SC, Waring W, Biering-Sorensen F, et al. (2011). Reference for the 2011 revision of the International Standards for Neurological Classification of Spinal Cord Injury. *Journal of Spinal Cord Medicine*, **34**(6), 547–54.
11. New PW. (2006). Non-traumatic spinal cord injury: what is the ideal setting for rehabilitation? *Australian Health Review*, **30**(3), 353–61.
12. Coselli JS, LeMaire SA, Köksoy C, Schmittling ZC, and Curling PE. (2002). Cerebrospinal fluid drainage reduces paraplegia after thoracoabdominal aortic aneurysm repair: results of a randomized clinical trial. *Journal of Vascular Surgery*, **35**(4), 631–9.
13. Giglio P and Gilbert MR. (2010). Neurologic complications of cancer and its treatment. *Current Oncology Reports*, **12**(1), 50–9.

PART 9.12

Neuromuscular syndromes

CHAPTER 243

Epidemiology, diagnosis, and assessment of neuromuscular syndromes

David Orlikowski and Tarek Sharshar

Key points

- Admission to intensive care unit (ICU) with severe limb weakness or respiratory failure or the occurrence of a motor deficit and failure to wean from mechanical ventilation, while in the ICU are the common presentations of a neuromuscular disease.
- An accurate neurological examination and complementary investigations are necessary for both diagnosis and for evaluating the severity of the disease.
- Assessment of respiratory muscle function by measurement and monitoring of vital capacity, and of maximal inspiratory and expiratory pressures guide the need for mechanical ventilation and subsequently its' weaning.
- Hypercapnia often indicates an impending respiratory arrest, but normocapnia can be seen in a patient with a severe reduction in VC. Hypoxaemia can be due to hypercapnia, pulmonary injury (atelectasis or pneumonia), or pulmonary embolism.
- Cardiac evaluation is important as cardiomyopathies are frequent in myopathies.

Circumstances

There are essentially two circumstances in which an Intensive Care Unit (ICU) physician has to manage a patient with a neuromuscular disease. First, a patient is admitted for a severe limb weakness and/or a respiratory failure, which reveals a neuromuscular disease (acute or chronic) or complicates an already diagnosed neuromuscular disorder. The ICU-physician then needs to establish the diagnosis in the former situation and to identify the cause of exacerbation, in the latter one. The second circumstance is when a patient develops a neuromuscular disease after his admission in ICU, usually revealed by limb weakness or through difficulty in weaning from mechanical ventilation. In this latter scenario it is necessary to determine whether the patient has a critical illness neuropathy, myopathy, or neuromyopathy, or another neuromuscular disease that has not been diagnosed at time of admission in ICU. For instance, a patient admitted with pneumonia and in whom an amyotrophic lateral sclerosis (AmLS) complicated by swallowing dysfunction will be a secondary diagnosed.

In all these situations, an accurate neurological examination is necessary for both the diagnostic approach and the choice of complementary investigations, and to evaluate the severity of the disease. Investigations are sometimes urgently required to confirm or exclude time-sensitive lesions, such as spinal cord compression requiring urgent neurosurgical decompression, or an ethical decision not to proceed to invasive mechanical ventilation, or a tracheostomy in a patient with end-stage neuromuscular disease such as AmLS. As almost all neuromuscular diseases occur without alteration of consciousness, patients can be interviewed and give a history, even when invasively mechanically-ventilated. Neurological examination should be completed by a general examination as some neuromuscular disease can affect other organs.

This chapter considers the diagnostic approach of a peripheral nervous system disorder and presents the features of the main neuromuscular diseases requiring admission to ICU. It briefly describes the clinical and neurophysiological features of critical illness neuromyopathy, which are comprehensively presented in Chapter 247, 'Diagnosis, Assessment, and Management of Hyperthermic Crises'.

Clinical assessment

Clinical history

A detailed clinical history should elicit features of the onset of the disease (acute, subacute, or chronic), its course (fluctuating, relapsing, or progressive), the patient's age at onset (childhood or adult), the occurrence of an identifiable triggering event (infection, drugs, other), the presence of pain (myalgia, cramp, paraesthesia, dysaesthesia, etc.) and the symptoms (weakness, dyspnoea). Additionally, a family history may reveal the existence of a neuromuscular disorder in a relative suggesting a genetic aetiology.

Neuromuscular diseases include neuronopathies, neuropathies, myasthenic syndromes, and myopathies, whose main clinical features are described in Table 243.1. Neuropathies encompass mononeuropathy (injury of a nerve trunk, root or plexus), mononeuritis multiplex (multifocal, sequential, and asymmetric injury

Table 243.1 Semiology of main peripheral nervous system syndromes

	Motor neuron disease	Neuropathy	Myasthenic syndrome	Myopathy
Symmetry	Bilateral ± symmetrical	**Variable:** MM: asymmetrical PN: symmetrical PRN: symmetrical	Bilateral and symmetrical	Bilateral and symmetrical
Proximal versus distal	Proximal or distal	MM: distal PN: distal PRN: proximal	Proximal ++	Proximal ++
Topography	Limbs, bulbar, respiratory	MM: ≥1 nerve PN: limbs ± respiratory PRN: limbs, trunk, bulbar, facial, respiratory	**Variable:** Limbs, facial, bulbar, trunk or respiratory Ptosis (often unilateral) and diplopia	**Variable:** Limbs, facial, bulbar, trunk, respiratory
Tone	Flaccidity	Flaccidity	Flaccidity	Flaccidity
Tendon reflexes	Lost or pyramidal signs (AmLS)	Lost or decreased	Preserved	Preserved
Myotatic irritability	Preserved	Preserved	Preserved	Absent
Atrophy	Pronounced	Pronounced	No	Variable
Other motor signs	Fasiculation	—	Fatigability Fluctuation	Myalgia Myotonia
Other neurological signs	Cramps	± sensory loss ± dysautonomia	No sensory loss (except Lamber– Eaton)	No sensory loss

MM, mononeuropathy multiplex; PN, polyneuropathy; PRN, polyradiculoneuropathy.

of nerve trunk), polyneuropathy (distal, bilateral, and symmetric) and polyradiculoneuropathy (proximal, bilateral, and symmetric). Clinically, neuropathy can be pure motor, pure sensory, or sensory motor and associated with dysautonomia. Electrophysiologically neuropathies may be axonal or demyelinating.

Neurological examination must at least assess the motor system (muscle strength and tone, tendon reflexes, Babinski sign, presence of atrophy, fasciculations, and myotonia), the sensory system (pain and temperature, touch and vibration/position sense, presence of sensory level) and the cranial nerves (with a focus on 3rd, 6th, 7th, 9th, and 10th nerves). This chapter focuses on signs that guide the diagnosis or are highly suggestive of a particular disease (Table 243.1). The presence of a sensory level suggests a spinal cord injury. Hypereflexia and hypertonia are not observed in peripheral nervous system disorders, except in AmLS, which combines upper and lower motor neuron degeneration. By definition, neuronopathy, myasthenic syndrome (except Lamber–Eaton disease) and myopathy are not associated with sensory deficit. Alterations in pain and temperature perception are reported in axonal neuropathy and proprioceptive signs in demyelinating ones. Localized muscle atrophy (shoulder, hand, or antero-external part of the leg) is observed in neuronopathic or neuropathic process, while diffuse atrophy is present in most myopathies. Hypertrophy is a feature of particular myopathies. In neuronopathy, fasciculation are frequent and must be sought on limbs and tongue. Delayed relaxation of muscle after contraction indicates a myotonic dystrophy or a paramyotonia when the lack of relaxation increases with effort (often related to channelopathies). Pupillary light reflex and myosis during convergent gaze are preserved in patients with myasthenia gravis, and are abolished in botulism or sometimes in Guillain–Barré syndrome (GuBS). Bilateral lack of facial expression, weakness of orbicularis oculi, and ptosis are frequent in myopathies. In myasthenia gravis, ptosis may be unilateral or bilateral, but asymmetric and fluctuating. In chronic disease, distribution of muscular impairment and weakness is also important to characterize, i.e. symmetric or not, distal or proximal, presence of hyperlaxity, presence and localization of contracture, presence of orthopaedic deformation (limb or paraspinal).

Usually, in neuromuscular disease requiring admission in ICU, the motor deficit is bilateral and symmetric and involves the four limbs and the axis (neck and trunk). Muscle strength can be assessed with the help of Medical Research Council sumscore (Box 243.1). For each motor disease, specific muscle or functional scores have been validated. Evaluation of sensation may be difficult in ICU patients due to inattention, and as a result sensory deficits must be assessed with caution and electrophysiological testing can be used to assess or confirm a sensory neuropathy.

Assessment of respiratory muscle function is a key step for deciding the need for mechanical ventilation and its weaning. Acute respiratory insufficiency may not be clinically obvious in patients with neuromuscular disease and treating clinicians should consider patient's subjective symptoms, such as dyspnea and orthopnoea (i.e. that is a sign of diaphragm weakness), and also assess cough and the presence of rapid shallow breathing, use of accessory

Box 243.1 Medical research council sumscore

Functions assessed

- **Upper extremity**: wrist flexion, forearm flexion, shoulder abduction.
- **Lower extremity**: ankle dorsiflexion, knee extension, hip flexion.

Score for each assessment

- **0**: no visible contraction.
- **1**: visible muscle contraction, but no limb movement.
- **2**: active movement, but not against gravity.
- **3**: active movement against gravity.
- 4: active movement against gravity and resistance.
- 5: active movement against full resistance.

Maximum score: 60 (four limbs, maximum of 15 points per limb—normal).

Minimum score: 0 (quadriplegia).

Reproduced from Medical Research Council. *Aids to the investigation of the peripheral nervous system*. London: Her Majesty's Stationary Office; 1943. Contains public sector information licensed under the Open Government Licence v3.0. http://www.nationalarchives.gov.uk/doc/open-government-licence/version/3/.

Box 243.2 Criteria for invasive mechanical ventilation in Guillain–Barré syndrome and myasthenia gravis

Major criteria

- Signs of respiratory distress.
- VC < 15 mL/kg, PI_{max} or PE_{max} < 25 cmH_2O.
- $PaCO_2$ > 6,4 kPa.
- PaO_2 < 7.5 kPa (FiO_2 = 0.21).

Minor criteria

- Expectoration inefficient.
- Severe bulbar dysfunction.
- Atelectasis.

Adapted from AH Ropper and SM Kehne, 'Guillain-Barré syndrome: Management of respiratory failure', *Neurology*, **35**, 11, pp. 1662–5, Copyright 1985, with permission from the American Academy of Neurology.

muscles and thoraco-abdominal paradox. Bedside measurement of vital capacity (VC), maximal inspiratory and expiratory pressures (MIP and MEP) with a portable spirometer can provide an objective assessment of respiratory muscle strength. Bulbar dysfunction has to be sought as it might contribute to respiratory failure, notably by inducing aspiration. Chest X-ray and arterial blood gas analysis complete the respiratory evaluation. Hypercapnia indicates an impending respiratory arrest but normocapnia should not be reassuring. Indeed, a patient with severe reduction in VC can still be normocapnic. Need for intubation is decided upon objective criteria that include clinical signs, functional tests (VC, MIP, or MEP), blood gases, and chest X-ray (Box 243.2).

Complementary investigations

If any doubt on a spinal cord injury, a magnetic resonance imaging (MRI) should be performed. Electrophysiological testing is very helpful for confirming the diagnosis of neuropathy, neuromuscular junction disorder and myopathy, and for distinguishing axonal from demyelinating neuropathy or a pre- from a post-synaptic myathenic syndrome. Briefly, measurement of motor and sensory conduction velocities is necessary for the diagnosis of neuropathy, search for decrement (or increment) by repetitive stimulation for the diagnosis of neuromuscular junction disorder and needle electromyography (at rest and during voluntary muscle contraction) for the diagnosis of myopathy. Demyelinating neuropathy is characterized by slow conduction velocity, and conduction block and axonal neuropathy by decreased action potential amplitude, increased distal latency, and denervation (muscle spontaneous activity on needle EMG). Decrement is found in post-synaptic disorder and increment in presynaptic ones. As it is a time-demanding test, electroneuromyography has to be guided by neurological symptoms and done by an experienced neurophysiologist, especially because of the electrical artefacts induced by ICU environment. Phrenic nerve and diaphragm electrophysiological testing can be helpful for the diagnosis of neuromuscular respiratory failure. Biological test include at least standard screening exams and measurement of creatinine phosphokinase. Thus, hypo- or hyperkalaemia can be seen in periodic paralyses, hyperlactataemia in mitochondrial diseases, increased plasma CPK level in myopathies. Increased sedimentation rate will suggest an inflammatory process. Secondarily, biochemical, hormonal, immunological, toxicological, and genetic investigations may be indicated depending on clinical, electrophysiological, and biological features. Muscle or muscle-nerve biopsy may be required.

Main diagnoses

Guillain–Barré syndrome

GuBS is an acute inflammatory polyneuropathy with an incidence of 1·2–1·9 per 100,000 per year in Europe [1]. In two-thirds of cases, GuBS it is preceded by an infection within the previous 6 weeks, notably flu-like illness or gastroenteritis. Although the responsible organism is often not identified, a range of bacteria (*Campylobacter jejuni, Mycoplasma pneumonia*) and viruses (cytomegalovirus, influenza) have been incriminated. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most frequent subtype in comparison with pure motor and sensory axonal entities (AMAN and AMSAN) that are associated with gastroenteritis and *C. jejuni* infection [1]. GuBS is discussed in detail in Chapter 246, 'Diagnosis, Assessment, and Management of Guillain–Barré Syndrome'.

Myasthenic syndromes

Myasthenia gravis is an auto-immune disease with auto-antibodies directed against acetylcholine receptors (80% of cases) or against the muscle specific tyrosine kinase (in about 10% of cases) and is often associated with hyperplasia (especially in patients less than 40 years

old) and thymoma (in about 10%). It is the most frequent disorder of the neuromuscular junction, with an incidence of 1 in 20,000 [2]. Myasthenia gravis and myasthenic syndromes are discussed in detail in Chapter 244, 'Diagnosis, Assessment, and Management of Myasthenia Gravis and Paramyasthenic Syndromes'.

Myopathies and spinal muscular atrophy

Patients with chronic neuromuscular disease represent less than 10% of those receiving mechanical ventilation in the intensive care unit (ICU) and have a low probability of death in the ICU [3]. Myopathies are mainly of genetic origins and are rarely acquired (inflammatory, toxic, or endocrine myopathies). Myopathies can be classified by age of onset (congenital, childhood, or late onset), the topography of weakness or muscular wasting (distal myopathy, limb girdle myopathy, facioscapulohumeral myopathy), the characteristics of muscular impairment (myotonia), pathophysiological mechanism (metabolic myopathies) or genetic mechanism (mitochondrial myopathies). Spinal muscular atrophy (SMA) a genetic disease due to *SMN* gene deletion provoking progressive and early degeneration of motor neurons must be also considered for this problematic (Table 243.2) [4].

Improvement of quality of care and development of specialized centres for neuromuscular disease has significantly increased survival and quality of life of patients with neuromuscular disease. This is particularly true for progressive diseases like patients with Duchenne muscular dystrophy (DMD) for whom introduction of respiratory care and home ventilation changed natural course of the disease [5]. Patients with previously diagnosed neuromuscular disease may be admitted to ICU due to an acute episode, rather than evolution of the myopathy. Alternatively, an undiagnosed myopathy may present as acute respiratory insufficiency, is which case the problem is to recognize the neuromuscular origin of respiratory failure. Sometimes acute and transitory episodes of respiratory failure may reveal hypokalaemic periodic paralysis.

Many myopathies are progressive with good correlation between limb and respiratory weakness. The beginning is usually during childhood and disease progression is relatively homogeneous. Respiratory involvement is usually constant for several myopathies like DMD, other muscular dystrophies (Emery–Dreyfuss muscular dystrophy), some limb girdle myopathies (LGMD2C and D, LGMD2I), and some congenital muscular dystrophies (Ullrich CgMD). In congenital myopathies hypotonia, weakness, and respiratory failure occur during neonatal period with usually little progression later in life. Some myopathies may start at adult age like myofibrillar myopathies (desmin-related myopathy).

In other cases LGM2B (Dysferlin), facioscapulohumeral myopathy, respiratory impairment is sometimes observed or is exceptional like in LGM2A (Calpain), or may be dissociated of limb weakness and be present at the first plan. This is the case in subgroups of CgMD (CgMD with rigid spine syndrome mainly due to *SEPN1* gene mutation or collagenopathies like Ullrich's disease). This is also possible for late onset forms of Pompe disease or in rare cases of hereditary myopathy with early respiratory failure related to *Titin* gene mutations [6], where an acute respiratory insufficiency episode may reveal the myopathy.

For SMA, respiratory impairment is common and increases with the severity of disease. Both inspiratory and expiratory muscles may be involved, but with a prominent weakness affecting accessory muscles like intercostal or abdominal muscles explaining that management of cough and respiratory impairment are major targets in this disease even in absence of need of mechanical ventilation [4].

Myotonic dystrophy type 1 (DM1, Steinert's myotonia) merits specific mention. DM1 is the most frequent of adult muscular dystrophies. Respiratory failure is a frequent complication that progresses with the severity of the motor deficit and the duration of the disease; it and is the primary cause of morbidity and mortality [7]. In contrast to other myopathies like DMD or other neuromuscular disease like AmLS, no published data support the use of nocturnal ventilation with regard to survival and quality of life. The causes of respiratory impairment are multiple and complex. If in the severe and advanced forms the muscle deficit can explain the alveolar hypoventilation, in less evolved forms mechanical factors, such as myotonia reduce the compliance of the respiratory system. The consequence is a change of the ventilatory pattern characterized by a decreased of tidal volume and high respiratory rate in spite of a normal or increased respiratory drive [8]. The nervous command of cortical or peripheral origin can be also altered, and irregularities of the respiratory rate are observed during awakening

Table 243.2 Chronic neuromuscular disease expressing respiratory impairment

Constant respiratory weakness	Frequent	Inconstant	Respiratory failure revealing neuromuscular disease
Duchenne muscular dystrophy	Myotonic dystrophy type 1	Limb girdle myopathy 2B (Dysferlin)	Pompe disease
Limb girdle myopathy 2C and D (α and γ sarcoglycanopathy)	Spinal muscular atrophy (accessory ++)	Limb girdle myopathy 2A (calpain)	Myotonic dystrophy type 1
Limb girdle myopathy 2I (α dystroglycanopathy)		Facioscapulohumeral myopathy	Hereditary myopathy with early respiratory failure (Titin)
Ullrich congenital muscular dystrophy		Becker muscular dystrophy	Periodic hypokalaemia (acute episode)
Desmin-related myopathy			
Pompe disease			
Emery–Dreyfuss muscular dystrophy			
SEPN1 congenital muscular dystrophy			

indicating a disorder of the voluntary command of ventilation [9]. Proprioceptive and reflex anomalies modulating the ventilatory response are also possible. These various anomalies increase with effort or during stress (in particular in the post-operative period) and can explain episodes of respiratory failure even in absence of previous hypercapnia. Sleep apnoeas or hypopnoeas, are common and represent an aggravating factor of diurnal anomalies [10].

Patients with chronic myopathies may have orthopaedic deformation, limited mouth opening or macroglossia that makes tracheal intubation difficult, especially in an emergency. Subsequently tracheostomy may be needed for successful weaning from mechanical ventilation and to enable discharge from the ICU. However, a tracheostomy may limit the choice and possibilities of long-term discharge from the hospital [11]. In myopathies with a known course, such as Duchenne muscular dystrophy the option of tracheotomy can be discussed with the patient and their family in advance of it being needed, this may not be possible in myopathies with less stereotypical evolution.

The most frequent cause of acute respiratory failure in patients with myopathies is upper airways infection (UAI), which as accounts for more than 90% of the hospitalizations in this population. Other possible causes are cardiogenic pulmonary oedema, pulmonary embolism, and pneumothorax). The infection, which is usually of viral origin, is responsible for a decrease of respiratory muscles strength and respiratory capacity, but also of maximal inspiratory and expiratory pressures [12]. It is associated with the development or with the worsening of alveolar hypoventilation, when CV or the maximal inspiratory pressure (PI_{max}) became lower than 30% of theoretical values. A major problem is coughing difficulties, which may be exacerbated by associated bulbar weakness [13].

The efficiency of the cough can be objectified by the measure of the cough peak-flow [14]. The 'flow rate cough' is correlated with various respiratory parameters: Vital capacity (VC), total lung capacity (TLC), maximal insufflation capacity (IC_{max}), expiratory reserve volume (ERV), PI_{max} and maximal expiratory pressure (PE_{max}) and peak flow. The main determiners of the cough are essentially the MIC (44%), the ERV (13%) and the PEmax (2%) [14]. A cough flow rate lower than 270 L/min [15] is associated with a more important morbidity and a flow rate lower than 160 L/min is usually considered as the threshold for weaning of invasive ventilation.

Maintaining coughing ability is thus fundamental in these patients, and various techniques are available, [16] including air stacking with glossopharyngeal breathing (frog), volumetric ventilation, hyperinsufflation by using a resuscitation device or intermittent positive pressure breathing (IPPB). These techniques are superior to manual assisted coughing provided by a physiotherapist, although the combination of manual assisted coughing and mechanical insufflation produces a more effective cough than either used alone, [14] as does mechanical insufflation/exsufflation. The major concern during respiratory decompensation of neuromuscular disease and myopathies is to avoid tracheal intubation.

As in acute pathologies, the clinical evidence of acute on chronic respiratory failure will initially be discreet and the classic signs of respiratory distress occur late and indicate imminent decompensation. Orthopnoea and paradoxical abdominal respiration are also warning signs, as is hypoxaemia. When appropriate for the individual patients these signs indicate the need for mechanical ventilation.

Non-invasive ventilation (NIV) is recommended as first line treatment to avoid endotracheal intubation, if possible [17]. Intubation can be hazardous because of the association of little of respiratory reserve, orthopaedic, and/or orofacial deformations, and the potential risk from anaesthetic agents or muscle relaxants [18]. There are no recommendations regarding the choice of mask for NIV; a full face mask can be dangerous in a patient for who it is not correctly fitted or with impaired swallowing. Use of a nasal mask seems preferable but may limit the efficiency of ventilation due to buccal leaks. On the contrary, a nasal mask will limit the risk of inhalation by allowing the oropharyngeal aspiration and easier cough assistance [19,20].

References

1. Hughes RA and Cornblath DR. (2005). Guillain–Barré Syndrome. *Lancet: Neurology*, **366**, 1653–66.
2. Vincent A, Palace J, and Hilton-Jones D. (2001). Myasthenia gravis. *Lancet: Neurology*, **357**, 2122–8.
3. Flandreau G, Bourdin G, Leray V, et al. (2011). Management and long-term outcome of patients with chronic neuromuscular disease admitted to the intensive care unit for acute respiratory failure: a single-center retrospective study. *Respiratory Care*, **56**(7), 953–60.
4. Lissoni A, Aliverti A, Tzeng AC and Bach JR. (1998). Kinematic analysis of patients with spinal muscular atrophy during spontaneous breathing and mechanical ventilation. *American Journal of Physical Medicine & Rehabilitation*, **77**(3), 188–92.
5. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, and Bushby K. (2002). Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscular Disorders*, **12**(10), 926–9.
6. Ohlsson M, Hedberg C, Brådvik B, et al. (2012). Hereditary myopathy with early respiratory failure associated with a mutation in A-band titin. *Brain*, **135**(Pt 6), 1682–94.
7. Begin P, Mathieu J, Almirall J, and Grassino A. (1997). Relationship between chronic hypercapnia and inspiratory-muscle weakness in myotonic dystrophy. *American Journal of Respiratory and Critical Care Medicine*, **156**(1), 133–9.
8. Begin R, Bureau MA, Lupien L, Bernier JP, and Lemieux B. (1982). Pathogenesis of respiratory insufficiency in myotonic dystrophy: the mechanical factors. *American Review of Respiratory Diseases*, **125**(3), 312–18.
9. Zifko UA, Hahn AF, Remtulla H, George CF, Wihlidal W, and Bolton CF. (1996). Central and peripheral respiratory electrophysiological studies in myotonic dystrophy. *Brain*, **119**(Pt 6), 1911–22.
10. Yu H, Laberge L, Jaussent I, et al. (2011). Daytime sleepiness and REM sleep characteristics in myotonic dystrophy: a case-control study. *Sleep*, **34**(2), 165–70.
11. Soudon P. (1995). Tracheal versus noninvasive mechanical ventilation in neuromuscular patients: experience and evaluation. *Monaldi Archives of Chest Diseases*, **50**(3), 228–31.
12. Poponick, J.M., Jacobs I, Supinski G, and DiMarco AF. (1997). Effect of upper respiratory tract infection in patients with neuromuscular disease. *American Journal of Respiratory and Critical Care Medicine*, **156**(2 Pt 1), 659–64.
13. Servera E, Sancho J, Zafra MJ, Catalá A, Vergara P, and Marín J. (2005). Alternatives to endotracheal intubation for patients with neuromuscular diseases. *American Journal of Physical Medicine & Rehabilitation*, **84**(11), 851–7.
14. Trebbia G, Lacombe M, Fermanian C, et al. (2005). Cough determinants in patients with neuromuscular disease. *Respiratory Physiology & Neurobiology*, **146**(2–3), 291–300.
15. Tzeng AC and Bach JR. (2000). Prevention of pulmonary morbidity for patients with neuromuscular disease. *Chest*, **118**(5), 1390–6.

16. Kang SW and Bach JR. (2000). Maximum insufflation capacity. *Chest*, **118**(1), 61–5.
17. Vianello, A., Bevilacqua M, Arcaro G, Gallan F, and Serra E. (2000). Non-invasive ventilatory approach to treatment of acute respiratory failure in neuromuscular disorders. A comparison with endotracheal intubation. *Intensive Care Medicine*, **26**(4), 384–90.
18. Le Corre F and Plaud B. (1998). Neuromuscular disorders. *Current Opinion in Anaesthesiology*, **11**(3), 333–7.
19. Hess DR. (2006). Noninvasive ventilation in neuromuscular disease: equipment and application. *Respiratory Care*, **51**(8), 896–912.
20. Schonhofer B and Sortor-Leger S. (2002). Equipment needs for noninvasive mechanical ventilation. *European Respiratory Journal*, **20**(4), 1029–36.

CHAPTER 244

Diagnosis, assessment, and management of myasthenia gravis and paramyasthenic syndromes

Ugan Reddy and Nicholas Hirsch

Key points

- Acquired myasthenia gravis is an autoimmune disease in which antibodies directed towards the neuromuscular junction cause reduction in the number of post-synaptic acetylcholine receptors.
- The reduced receptor density causes fatigable muscle weakness.
- Treatment aims to enhance neuromuscular transmissions with anticholinesterase drugs, while suppressing autoantibody production with immunosuppressant agents.
- Thymectomy improves most patients with antibody- positive myasthenia gravis.
- Myasthenic crisis is defined as severe muscle weakness occurring in the myasthenic patient who requires tracheal intubation and mechanical ventilation. Treatment includes plasma exchange and intravenous immunoglobulin.

Introduction

The neuromuscular junction (NMJ) provides the link between myelinated motor nerves and skeletal muscle, and is an integral component of a biological amplification system, which converts minute nerve action potentials into muscle contraction. Diseases that affect the NMJ interfere with normal nerve transmission and cause weakness of voluntary muscles [1]. The two most commonly encountered are acquired myasthenia gravis and the Lambert–Eaton myasthenic syndrome (LEMS).

Myasthenia gravis

Acquired myasthenia gravis (MG) is an autoimmune disease in which IgG antibodies are directed towards the post-synaptic acetylcholine receptors (AChR) at the NMJ. It has a prevalence of 200 per million of the population and has a bimodal distribution, tending to affect young women and older men. MG can be divided into several subtypes based on differences in clinical presentation, age at onset, antibody profile and the presence or absence of thymic pathology. The most practical clinical classification divides patients into early-onset MG, late-onset MG, associated thymoma, ocular MG and MuSK MG [2]. Details of the clinical features, antibody distribution and thymic pathology are detailed in Table 244.1.

Clinical features

The clinical hallmark of MG is a fatigable weakness of affected muscle groups that fluctuates daily over months. It is often worse in the evenings and following activity, and improves following periods of rest.

Ocular weakness resulting in ptosis and diplopia is the commonest presenting feature and affects 90% of patients with MG. In 15% of patients the disease is confined to the eyes (ocular MG), but in the remainder it progresses to generalized disease, usually within 2 years.

Bulbar weakness is common and causes dysphagia, dysarthria (especially associated with emotion) and difficulty with chewing. Severe bulbar weakness, often associated with atrophy of bulbar muscles, is a prominent feature of anti-MuSK MG. Respiratory muscle weakness often accompanies bulbar involvement, but is rarely seen in isolation.

The limb weakness seen in MG affects the arms more than the legs and proximal muscles more than distal ones.

The severity of weakness in MG has been classified by the Myasthenia Gravis Foundation of America (MGFA) (Box 244.1).

Pathogenesis

85–90% of patients with acquired MG have detectable levels of anti-AChR antibodies (seropositive MG) that are responsible for the destruction of postsynaptic AChRs. These auto-antibodies cause a reduction in AChR density through three mechanisms, the most important of which is a complement-mediated lysis of the post-synaptic membrane resulting in a distortion of the normally convoluted morphology. In addition, the antibodies cross-link adjacent AChR resulting in an increased rate of degradation of the receptors. Finally, there may be some direct blocking of

Table 244.1 Subtypes of myasthenia gravis

Subtype	Clinical features	Auto-antibodies	Thymic pathology
Early onset MG (<40 years)	Female > male Associated autoimmune diseases, especially thyroid disease	AChR	Thymic hyperplasia
Late onset MG (>40 years)	Male > female Typically more severe disease present with ocular, generalized weakness or oropharyngeal weakness Frequent crises	AChR, to striated muscle proteins (ryanodine, titin)	Normal thymic histology
Thymoma	10% of MG patients. Present in middle age, associated with other autoimmune disorders. Clinical improvement following thymectomy more unusual	none	T-lymphocyte containing epithelial cell tumour
Musk MG	70% of seronegative MG patients. Ocular involvement, frequently evolves to severe bulbar and facial weakness Limbs unaffected	MuSK	Normal
Ocular MG	15% cases disease confined to eyes, but may become generalized later	50% positive for AChR	Maybe associated with thymic hyperplasia

Box 244.1 The MGFA classification of myasthenia gravis

- Class I—ocular myasthenia (may also have weakness of eye closure).
- Class II—mild weakness of non-ocular muscles.
- Class III—moderate weakness of non-ocular muscles.
- Class IV—severe weakness of non-ocular muscles.
- Class V—myasthenic crisis requiring tracheal intubation +/– mechanical ventilation.

Reproduced from Barohn RJ, 'Standards of measurement in myasthenia gravis', *Annals of the New York Academy of Sciences*, **998**, pp. 432–9, copyright 2003, with permission from John Wiley and Sons Ltd and the New York Academy of Sciences.

docking of ACh molecules by the auto-antibody. The net effect of this antibody-mediated reduction in the AChR density is a loss of the safety margin seen with normal neuromuscular transmission (Ruff, Lennon 2008). This leads to a reduction in post-synaptic action potential generation, which in turn leads to weakness of muscle contraction.

10–15% of patients with MG have no detectable AChR antibodies (seronegative MG). About 60% of these patients have been found to have an antibody to another post-synaptic NMJ protein called muscle specific protein kinase (MUSK). This protein is necessary to allow clustering of AChR around the NMJ and its loss causes a reduction in the number of functional AChRs [4].

Patients with MG without AChR or MUSK antibodies have recently been found to have low affinity IgG antibodies that bind specifically to AChRs and it may be that past assay techniques have been too insensitive to detect them.

Although the precise mechanism is unclear, the thymus gland appears to be involved in the generation of AChR antibodies, especially in early-onset MG [5]. Furthermore, removal of the often hyperplastic thymus appears to promote complete or partial remission in a high proportion of these patients. Thymoma is also seen in MG and although its removal is not associated with such a high degree of remission, it is necessary as the tumour may be locally invasive.

Diagnosis

Diagnosis of MG requires a high degree of clinical suspicion coupled with pharmacological and electrophysiological testing and detection of anti-AChR antibodies.

The Tensilon® test consists of administering the short-acting anticholinesterase edrophonium intravenously and assessing clinical improvement in muscle strength. Unfortunately, the test has a limited sensitivity and specificity in diagnosing MG. An alternative relatively non-invasive bedside test consists of placing an icepack over the eyes and looking for an improvement in ptosis.

The mainstay of electrophysiological testing for MG is repetitive nerve stimulation which, at rates of 2–5 Hz, shows a progressive decrement (or fade) in successive compound muscle action potentials. In experienced hands, the test is abnormal in 80% of patients with generalized MG and 50% in those with ocular MG [6]. Single fibre electromyography can raise the sensitivity in the former to 95%.

Finally, detection of anti-AChR or anti-MUSK antibodies confirms the diagnosis. Following confirmation, a chest CT/MRI should be performed to detect any thymic mass.

Treatment of MG

Treatment of MG is directed at enhancing neuromuscular transmission with long-acting anticholinesterases (e.g. pyridostigmine) and long-term immunosuppression with corticosteroids (e.g. prednisone) and steroid-sparing agents (e.g. azathioprine). Patients with exacerbations of their MG may also require short-term immunomodulation with either plasma exchange or intravenous immunoglobulin (Box 244.2).

Thymectomy is usually reserved for patients with anti-AChR antibody positive generalized myasthenia and those with a thymoma. Although no randomized controlled trials exist, meta-analysis suggests thymectomy promotes clinical improvement in the former group of patients [7].

Box 244.2 Treatment options in MG

Long-term treatments

Anticholinesterases: pyridostigmine, neostigmine

Rarely effective as single therapy

Immunosuppressive agents

- Prednisolone:
  - First choice of immunosuppressant therapy.
  - May cause worsening of MG if started on high dose.
  - Aim for lowest possible alternate day dose when stable
- Azathioprine: steroid sparing drug.
- Mycophenolate: steroid sparing drug.
- Ciclosporin: steroid sparing drug.

Thymectomy

- Indicated for anti-AChR antibody positive MG.
- Remission may take up to 2 years to realize.

Acute treatments

- IVIg.
- Plasma exchange:
  - 1–2 g/kg over 5 days.
  - Daily/alternate day exchanges for 5–10 days.

Other forms of myasthenia gravis

Neonatal MG is due to the transplacental flow of maternal anti-AChR antibodies and affects 15% of babies born to mothers with MG. It is usually transient, but may be prolonged if there are associated antibodies which affect fetal AChR.

Congenital MG is a collection of hereditary diseases resulting in defects in the structure and function of the presynaptic, synaptic, or post-synaptic regions of the NMJ. They result in variable degrees of muscular weakness.

Drug-induced MG is indistinguishable from acquired MG and is most commonly caused by D-penicillamine or interferon alfa. Remission usually occurs within 6 months of stopping the drug.

Intensive care management of MG

Patients with MG require intensive care management when they present in myasthenic crisis or for post-operative care following thymectomy.

Myasthenic crisis

Myasthenic crisis is defined as any muscle weakness due to MG severe enough to necessitate tracheal intubation and mechanical ventilation. The definition is also extended to surgical myasthenic patients who require >24 hours of post-operative tracheal intubation due to muscle weakness.

The incidence of myasthenic crisis in early-onset MG is 15–20% and usually occurs within 1 year of diagnosis. Treatment results in a relatively rapid response and recurrence rates are low. In contrast, myasthenic crisis occurs in up to 50% of patients with late-onset myasthenia, is often difficult to treat and has a high relapse rate [8]. Common triggers for both forms include infection and initiation of corticosteroid therapy.

In the past, much emphasis has been placed on differentiating myasthenic weakness and muscle weakness due to overdose of anticholinesterase therapy (cholinergic crisis). In practice, the latter is extremely rare, but is suggested by meiosis, lachyrimation, and bradycardia.

Myasthenic crisis may be the first presenting feature of MG and the diagnosis may not be immediately apparent. Differential diagnoses include Guillain–Barré syndrome, botulism, and polymyositis.

Management

The mainstay of management of myasthenic crisis is early recognition of impending respiratory or bulbar failure, and rapid tracheal intubation and mechanical ventilation. This should be based on clinical signs, rather than waiting for deterioration in arterial blood gases. These include increasing agitation, tachypnoea, use of accessory muscles, paradoxical abdominal movement on inspiration, and an inability to swallow secretions. A bedside measurement of forced vital capacity of <20 mL/kg supports the decision to intubate, but patient technique is often poor when performing the test in these conditions.

Although non-invasive ventilation has been used in myasthenic crisis to avoid tracheal intubation, it is rarely useful because bulbar failure almost invariably co-exists with respiratory failure and intubation is necessary to protect the airway from aspiration.

Following intubation and mechanical ventilation, anticholinesterase therapy is usually stopped as are any other medications, which can worsen neuromuscular function (Box 244.3).

Although randomized controlled trials comparing plasma exchange and IVIg in management of myasthenic crisis have found them to be of equal efficacy most authorities favour plasma exchange because of its more rapid action [9]. Evidence suggests that daily PE is as effective as alternate day exchange. Because its action results in only temporary improvement, PE is supplemented with long-acting immunosuppressive agents (most commonly prenisolone 1 mg/kg/day). PE is contraindicated in patients with severe sepsis, cardiac failure, hypotension and pregnancy, and IVIg is therefore used in these situations.

Extubation should only be considered when any co-existing infection has been thoroughly treated, forced vital capacity is >30 mL/kg and bulbar function has been assessed as adequate. Even

Box 244.3 Drugs to be avoided or used with caution in myasthenic conditions

- Neuromuscular blocking drugs.
- Antibacterial drugs—aminoglycosides, polymixins, ciprofloxacin.
- Chloroquine.
- β-adrenergic receptor antagonists.
- Magnesium.
- Calcium channel antagonists.

when these conditions are met, up to 30% of myasthenic patients need re-intubation, most commonly in older patients, those with atelectasis and patients who have required prolonged periods in the intensive care unit [10]. Bi-level positive pressure ventilation may be helpful in avoiding re-intubation [11].

If managed in a specialized unit, the mortality of myasthenic crisis is 5%. Most deaths are due to cardiac events or sepsis.

Thymectomy

Most myasthenic patients undergoing thymectomy can be safely extubated at the end of the procedure. A small percentage requires more prolonged mechanical ventilation; pre-operative predictive factors for this include severe generalized MG, poor bulbar function, previous myasthenic crisis and a reduced FVC. All patients need careful nursing in an intensive care unit with the close co-operation of anaesthetists, intensivists, and neurologists. Adequate analgesia is essential and thoracic epidural analgesia has been used successfully. Anticholinesterase therapy is restarted in the post-operative period, but reduced requirements are often seen in the first 48 hours.

Lambert–Eaton myasthenic syndrome

The Lambert–Eaton myasthenic syndrome (LEMS) is a rare autoimmune disease in which IgG antibodies are directed towards the presynaptic voltage-gated calcium channels (VGCC) at the NMJ [12]. This results in decreased mobilization and release of acetylcholine vesicles following nerve action potentials that, in turn, causes weakness of muscle contraction. Patients present to the intensive care with respiratory failure or with prolonged paralysis following the administration of neuromuscular blocking agents during anaesthesia, to which they are extremely sensitive.

50–60% of patients with LEMS have associated malignant disease, most commonly a small cell carcinoma of the lung.

The diagnosis of LEMS is based on clinical signs, electromyography, and detection of VGCC antibodies. The characteristic clinical triad consists of proximal muscle weakness (often starting in the legs and rapidly spreading to the arms), reduced tendon reflexes and automonic symptoms. Ocular and bulbar weakness is common and respiratory failure can occur. Autonomic features include dry mouth, erectile dysfunction, and orthostatic hypotension.

Characteristic electromyography findings include an incremental response in the compound muscle action potential on high rates of tetanic stimulation or following exercise [13].

VGCC antibodies can be detected in 90% of patients with LEMS [14]; seronegative patients are thought to have other types of circulating antibodies to proteins at the NMJ.

Treatment

The mainstay of treatment of LEMS is 3,4-diaminopyridine, which by blocking voltage-gated potassium channels presynaptically, prolongs the nerve action potential and lengthens the opening time of the VGCC. In addition, most patients require long-term immunosuppression. Acute exacerbations may require plasma exchange.

References

1. Hirsch NP. (2007). Neuromuscular junction in health and disease. *British Journal of Anaesthesia*, **99**, 132–8.
2. Meriggioli MN and Saunders DB (2009). Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. *Lancet: Neurology*, **8**, 475–90.
3. Ruff RL and Lennon VA (2008). How myasthenia gravis alters the safety factor for neuromuscular transmission. *Journal of Neuroimmunology*, 201–202, 13–20.
4. Shiraishi H, Motomura M, Yoshimura T, et al. (2005). Acetylcholine receptor loss and postsynaptic damage in MuSK antibody positive myasthenia gravis. *Annals of Neurology*, **57**, 289–93.
5. Roxanis I, Micklem K, and Wilcox N (2001). True epithelial hyperplasia in the thymus of early-onset myasthenia gravis: implications for immunopathogenesis. *Journal of Neuroimmunology*, **112**, 163–73.
6. Meriggioli MN and Saunders DB (2005). Advances in the diagnosis of neuromuscular disorders. *American Journal of Physical Medicine & Rehabilitation*, **84**, 627–37.
7. Gronseth GS and Barohn RJ (2000). Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, **55**, 7–15.
8. Chaudhuri A and Behan PO. (2009). Myasthenic crisis. *Quarterly Journal of Medicine*, **102**, 97–107.
9. Qureshi AI, Choudhry MA, Akbar MS, et al (1999). Plasma exchange versus intravenous immunoglobulin treatment in mysthenic crisis. Neurology, **52**, 629–32.
10. Seneviratne J, Mandrekar J, Wijdicks EF, and Rabinstein AA (2008). Predictors of extubation failure in myasthenic crisis. *Archives of Neurology*, **65**, 929–33.
11. Rabinstein AA and Wijdicks EF (2002). BiPAP in acute respiratory failure due to myasthenic crisis may prevent intubation. *Neurology*, **59**, 1647–9.
12. Titulaer MJ, Lang B, and Verschuuren JJGM (2011). Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. *Lancet: Neurology*, **10**, 1098–107.
13. Oh SJ, Kurokawa K, Claussen GC, and Ryan HF Jr (2005). Electrophysiological diagnostic criteria of Lambert-Eaton myasthenic syndrome. *Muscle & Nerve*, **32**, 515–20.
14. Motomura M, Lang B, Johnston I, Palace J, Vincent A, and Newsom-Davis J (1997). Incidence of serum anti-P/Q-type and anti-N-type calcium channel autoantibodies in the Eaton-Lambert myasthenic syndrome. *Journal of Neurological Sciences*, **147**, 35–42.

CHAPTER 245

Diagnosis, assessment, and management of tetanus, rabies, and botulism

Jeffrey Lipman and Robert J. Boots

Key points

- Tetanus and botulism are caused by neurotoxins, whereas rabies is a viral zoonosis.
- *Clostridium tetani* exotoxins cause generalized muscle rigidity, autonomic instability, and sometimes convulsions. Without expensive intensive care treatment the disease is often fatal.
- As tetanus does not produce immunity, active immunization with antitetanus toxin must follow.
- Botulism is a toxin-related illness generally due to food poisoning, which leads to an ascending paralysis with neural destruction. Recovery is prolonged and often incomplete.
- Rabies and associated Lyssavirus encephalitis in the previously unimmunized is a fatal illness.

Tetanus

Clostridium tetani exotoxins cause tetanus, a syndrome characterized by generalized muscle rigidity, autonomic instability, and sometimes convulsions. Without expensive intensive care treatment the disease is often fatal.

Epidemiology and pathogenesis

With widespread immunization programs, tetanus has become a disease of the elderly, debilitated, and neonates of unimmunized mothers.

C. tetani is an obligate anaerobic, spore-bearing, Gram-positive bacillus. Spores are ubiquitous, existing in soil, and in animal and human faeces. Only after gaining access to devitalized tissue, do spores proliferate in the vegetative form, producing the toxins, tetanospasmin, and tetanolysin.

The usual mode of entry is through a puncture wound or laceration, dental infection, abortion, and childbirth. Spores can lie dormant in human bowel and tetanus may follow surgery, burns, gangrene, or chronic ulcers. In 20% of cases there is no history or evidence of a wound [1]. *C. tetani* infection remains localized, but the exotoxin, tetanospasmin, is distributed widely via the blood stream, taken up into motor nerve endings, and transported into the nervous system. The symptoms of tetanus appear only after tetanospasmin has diffused from the cell body through the extracellular space, and gained access to the presynaptic terminals of adjacent neurons [1]. Tetanospasmin is preferentially bound by inhibitory interneurons, i.e. glycinergic terminals in the spinal cord, and *y*-aminobutyric acid (GABA) terminals in the brain [2]. Its principal effect is to block these inhibitory pathways. It affects motor neurone end-plates in skeletal muscle (rigidity, spasms), the spinal cord (dysfunction of polysynaptic reflexes), and the brain (seizures, inhibition of cortical activity, and autonomic dysfunction).

Prevention by active immunoprophylaxis

Natural immunity to tetanus does not occur, nor does the disease result in subsequent immunity [1,3]. Tetanus toxoid (TT) is a cheap and effective vaccine. In adults, a full immunization course consists of three doses. A second should be given 6–12 weeks after the first and the third 6–12 months after that. A single dose will offer no immediate protection in the unimmunized. Neonates of immunized mothers have immunity from maternal antibodies. Children over 3 months should be actively immunized, needing four TT doses in total. Two or more TT doses given to child-bearing women over 14 years will protect any child born within the next 5 years. Pregnant women who are not immunized should be given two spaced-out doses of TT 2 weeks to 2 months before delivery. Booster doses of TT should be given routinely every 10 years.

Clinical presentation

The incubation period (time from injury to symptom onset) varies from 2 to 60 days [1,3]. The period of onset (from first symptom to first spasm) similarly varies. Nearly all cases (90%) present within 15 days of infection [4]. The shorter the incubation period and period of onset, the more severe the disease.

Presenting symptoms are pain and stiffness, which gives way to rigidity and spasms. Most (75%) non-neonatal generalized tetanus present with difficulty in mouth opening, i.e. lock-jaw or trismus [4]. Spasms can be life-threatening when they involve the larynx and/or diaphragm.

Neonatal tetanus presents most often on day 7 of life [3], with a short (usually 1-day) history of the infant failing to feed.

Autonomic dysfunction occurs in severe cases of tetanus[1,3,5], and begins a few days after the muscle spasms. There is increased

basal sympathetic tone, with episodes of marked sympathetic surges, involving both α-and β-receptors, usually of short duration, and occurring with or without provocation.

The role of the parasympathetic nervous system is more debatable. Episodes of bradycardia, low peripheral vascular resistance, low central venous pressure and profound hypotension are occasionally seen [3]. These events have been attributed to total withdrawal of sympathetic tone, since they are unresponsive to atropine [6]. Patients afflicted with the autonomic dysfunction of tetanus are at risk of sudden death.

Local tetanus and **cephalic tetanus** are uncommon forms of tetanus. With the former, the signs and symptoms are confined to a limb or muscle; the latter results from head and neck injuries, eye infections and otitis media.

Diagnosis

Tetanus is a clinical diagnosis, often straightforward, with no specific laboratory tests. In only one-third of cases can *C. tetani* be cultured from the wound. Differential diagnoses include dystonic reaction to tricyclic antidepressants, strychnine poisoning, local temporomandibular disease, local oral disease, convulsions, tetany (for example, secondary to hypocalcaemia), intracranial infections or haemorrhage, or psychiatric disorders.

Management

Here, there are four objectives [3]:

- To neutralize circulating toxin (passive immunization).
- Prevent it from entering peripheral nerves and eradicating the source of the toxin (wound care, extensive surgery, and antibiotics).
- Minimize the effect of toxin already bound in the nervous system.
- Provide general supportive care.

Passive immunization

Human antitetanus immunoglobulin (HIG) has now largely replaced horse antitetanus serum (ATSe) as it is less antigenic. HIG will, at best, neutralize only circulating toxin, not affecting toxin already fixed in the CNS. It does not ameliorate symptoms already present. The minimum dose for prophylaxis is 250 IU or 500 IU if the wound is grossly contaminated or more than 24 hours old [5]. Some suggest that unimmunized patients or those with unknown immunization status should be given HIG on presentation with contaminated wounds.

Intrathecal administration of HIG or ATSe is still controversial. Two meta-analyses reported differing results [7,8]. If HIG is not available, equine ATSe can be used after testing and desensitization [1].

Eradication of the organism

Wound care

Often the wound can look 'normal' as the spores are non-immunogenic. Nevertheless, once HIG has been given, the infected site should be thoroughly cleaned and all necrotic tissue extensively debrided.

Antibiotics

Metronidazole 500 mg given intravenously (iv) 8-hourly for 10 days is the drug of choice. Alternatively benzylpencillin G 1–3 MU iv 6-hourly for 10 days, noting the drug is a GABA antagonist in the CNS [9].

Suppression of effects of tetanospasmin

Controlling muscle spasms

Initially, the patient is most at risk from laryngeal and respiratory muscle spasms, and the airway should be secured urgently if such spasms occur. If respiratory muscles are affected full mechanical ventilation with neuromuscular blockade may be required. Deep sedation alone may prevent such spasms and improve autonomic dysfunction.

Management of autonomic dysfunction

Autonomic dysfunction manifests in increased basal sympathetic activity and episodic catecholamine surges [3]. Hypertension, tachycardia, and sweating do not always occur concurrently. Traditionally, a combination of various α and β-adrenergic blockers has been used to treat sympathetic overactivity. Unopposed β-adrenergic blockade cannot be advised as it may worsen hypertension.

Rather than blocking effects of catecholamines, it may be more logical to decrease catecholamine output with sedatives. Benzodiazepines and morphine have been used successfully. Morphine and diazepam act centrally to minimize the effects of tetanospasmin. Morphine probably acts by replacing deficient endogenous opioids [1]. Benzodiazepines increase the affinity and efficacy of GABA [1]. Very large doses of these agents are well-tolerated.

Magnesium has been used as an adjunct to sedation [3,10]. Calcium supplementation may be needed. Anecdotally, clonidine, a central α2 stimulant, has been used successfully to produce sedation with control of autonomic dysfunction. Intrathecal baclofen has produced similar beneficial results in a series of cases, but may cause significant respiratory depression [11].

Supportive treatment

Basic intensive care support is important, with special attention paid to prevention of contractures.

Complications

Muscle spasms usually disappear by 3 weeks, but residual stiffness may persist [1,3,5]. Although most survivors recover completely by 6 weeks, cardiovascular complications, including cardiac failure, arrhythmias, pulmonary oedema, and hypertensive crises can be fatal.

Outcome

Recovery from tetanus can be complete. However, in 25 non-neonatal patients followed for up to 11 years [12], 15 were reported to have one or more abnormal neurological features, such as intellectual or emotional changes, fits and myoclonic jerks, sleep disturbance, and decreased libido.

Mortality figures depend on the availability of intensive care. In neonates, the mortality from African countries with no ICU facilities can be up to 80%, but decreases to under 10% with intensive care. However, as tetanus is easily and completely preventable, any loss of life may be considered unacceptable.

Rabies

Epidemiology and pathogenesis

Rabies is an RNA viral zoonosis (Lyssavirus) that occurs on all continents except Antarctica. It causes a neurological illness with

a high mortality rate. Common modes of transmission are the bite of a rapid animal, or saliva contamination of wounds or mucosa. Rare modes are from viral laboratory aerosols, and corneal or solid organ transplants [13]. Worldwide, dogs represent 90% of the animal reservoir [14], although bats are the commonest reservoir in North America.

The virus remains latent at the inoculation site. It enters nerves via the neuromuscular end plate with retrograde axonal transport to the CNS and subsequent anterograde transport along the peripheral nerves. It may be found in hair follicles in diagnostic skin biopsies.

Clinical presentation and differential diagnosis

Incubation is usually 1–3 months, but can vary from years to under a week [15]. A 7-day viral prodrome is associated with paraesthesia, pruritus, pain, hyperaesthesia, and anaesthesia at the site of virus entry.

There are two common clinical presentations, the furious form occurs in 80% and the paralytic form in 20%.

The furious form (80%) develops in patients with intact cell-mediated immunity to rabies virus. It is characterized by agitation with hyperactivity and typically autonomic dysfunction manifest as priapism, pilo-erection, cardiac arrhythmias, hyperpyrexia, mydriasis, increased salivation, sweating, and lacrimation. Hydrophobia and aerophobia represent painful muscle spasms of the oropharynx and larynx following drinking or air blowing onto the face. The clinical illness lasts a few days, and ends in death from coma or cardiac arrhythmia.

The paralytic form is characterized by the insidious onset of symmetrical or asymmetrical ascending paralysis from the infected limb, leading to quadriplegia, bulbar paralysis, and respiratory failure, with bladder and bowel dysfunction developing over longer periods.

The differential diagnosis includes other viral encephalitides, Guillain–Barrè syndrome, poliomyelitis, cerebral malaria, diphtheria, botulism, drug intoxication (e.g. the serotonin syndrome), and drug withdrawal syndromes.

Diagnostic work-up

Examination of CSF during the first week typically shows a predominant mononuclear pleocytosis of only 100 cells/μL with mild protein elevation and a normal glucose. Human infection may show viral RNA using PCR in saliva, tears, or in nuchal skin biopsies. Serum antibodies maybe found in vaccinated individuals, but CSF antibodies represent clinical infection.

Prevention

Vaccination programs of potential domestic wildlife animal vectors, stray animal controls, leashing of pets, and pet owner education, generally control animal rabies.

Pre-exposure prophylaxis

Modern tissue culture vaccines reduce neurological side effects with weekly intramuscular doses for three weeks providing 98% seroconversion [15]. Cell culture vaccines are safe in pregnancy.

Post-exposure prophylaxis

The most important component of therapy is wound cleaning and care, leaving the wound unsutured [16].

For previously non-immune patients, up to 20 IU/kg of human rabies immune globulin is injected into the wound as tolerated, the remainder given intramuscularly distant to the wound. Equine rabies immune globulin (40 IU/kg) is has a higher incidence of hypersensitivity reactions. Active immunization should be commenced with four intramuscular injections on days 0, 3, 7, and 14. Previously vaccinated individuals only require two injections on day 0 and day 1. There have been no recorded failures of the combined pre- and post-exposure vaccination with subsequent post-exposure treatment.

Therapy

There is no effective therapy once symptoms develop, with rare reports of survival in the previously immunized.

Botulism

Epidemiology and pathogenesis

Botulism, caused by the exotoxin of *Clostridium* botulin and related species, is most typically associated with food poisoning, but can result from contaminated wounds or directly inhalation.

C. botulinum, an anaerobic Gram-positive, spore-forming bacillus. It is found in soils and aquatic beds worldwide. Human neurological disease is caused by serotypes A, B, E, and more rarely F. Serotype G has been associated with sudden death, but not neurological disease. Related *Clostridium* species associated with disease are *C. argentinese, C. baratii*, and *C. butyricum*. The highly toxic exotoxin is destroyed by heat (greater than 121°C or 250°F for 30 minutes) and most water purification systems [17]. Spore germination does not occur in intact adult gastrointestinal tracts, but may cause disease in infants and adults with a diseased or surgically-altered gut. Food-borne botulism typically results from ingestion of preformed toxin in contaminated food. Germination in food occurs generally in preservation processes under anaerobic and moist conditions with low acidity and salinity.

Botulinum toxin is actively absorbed across the gastrointestinal tract and being too large to cross the blood–brain barrier manifests illness in the peripheral nervous system. Toxicity results from inhibiting acetylcholine mediated neurotransmission at the neuromuscular junction, sympathetic, and parasympathetic ganglia and parasympathetic post-ganglionic sites. Recovery is prolonged requiring regrowth of the axon and severely affected patients may require many weeks of intensive care treatment [18].

Clinical presentation and differential diagnosis

Infant botulism results from early intestinal colonization [19]. Botulism from food ingestion results from anaerobic growth from food spoilage and contamination. Type E toxin is associated with fish products from the arctic regions. Preserved vegetables are the most common source in Europe, China (bean curd), and the USA. Meats are a common source in Central Europe. Wound botulism results from bacterial contamination.

The incubation period depends on the amount of preformed toxin. Mild nausea, vomiting, and diarrhoea can occur. In severe disease, the initially manifestation is a descending pure motor flaccid paralysis with bulbar palsies. Pupillary dilation, diplopia, and ptosis are followed by facial, and bulbar paralysis, and then paralysis of the larger muscle of the arms. Intercostal, diaphragm, and leg involvement occur late. Weakness may not be symmetrical and

deep tendon reflexes may remain intact. There is typically no fever or leukocytosis.

Wound botulism may take a week or longer for the onset of symptom and maybe associated with fever due to concomitant wound infection by other organisms.

Diagnostic possibilities should include myasthenia gravis, Guillian–Barré syndrome (Miller Fisher variant), tick paralysis, and polio.

Diagnostic work-up

Diagnosis is usually clinical. Anaerobic transport of serum, gastric contents or stool may isolate *Clostridium* organisms and can be screened for toxin [19].

Therapy

Although not reversing symptoms, administration of equine antitoxin arrests disease progression [20]. Progression to respiratory failure occurs in only 10% of patients receiving antitoxin within 24 hours of symptom onset, but in 46% when antitoxin is not given.

Heptavalent

Botulinum antitoxin (H-BAT) covers all serotypes and is administered in 20 mL over 60 minutes. Baby botulinum immune globulin (BabyBIG-IV) is human antitoxin derived from plasmapheresis and used in the management of infant botulism.

Prevention

Clostridium botulinum is killed by heating food above 121°C and storage at less than 4°C [19]. The addition of acidifying agents, such as citric acid is recommended for canning of vegetables to prevent spore formation.

References

1. Bleck TP. (1991). Tetanus: pathophysiology, management and prophylaxis. *Disease-a-month*, **37**(9), 556–603.
2. Ackerman AD. (1987). Immunology and infections in the pediatric intensive care unit. Part B: Infectious diseases of particular importance to the pediatric intensivist. In: Rogers MC (ed.) *Textbook of Pediatric Intensive Care*, Vol. 26, pp. 866–75. Baltimore: Williams and Wilkins.
3. Lipman J. (2008). Tetanus. In: Berston AD, Soni N (eds) *Oh's Intensive Care Manual*, 6th edn, Vol. 48, pp. 593–97. Oxford: Butterworth Heinemann Elsevier.
4. Alfery DD and Rauscher LA. (1979). Tetanus: a review. *Critical Care Medicine*, **7**, 176–81.
5. Kerr J. (1979). Current topics in tetanus. *Intensive Care Medicine*, **5**, 105–10.
6. Afshar M, Raju M, Ansell D, and Bleck TP. (2011). Narrative review: tetanus—a health threat after natural disasters in developing countries. *Annals of Internal Medicine*, **154**, 329–35.
7. Abrutyn E and Berlin JA. (1991). Intrathecal therapy in tetanus: a meta-analysis. *Journal of the American Medical Association*, **266**, 2262–7.
8. Kabura L, Ilibagiza D, Menten J, and Van den Ende J. (2006). Intrathecal vs. intramuscular administration of human antitetanus immunoglobulin or equine tetanus antitoxin in the treatment of tetanus: a meta-analysis. *Tropical Medicine & International Health*, **11**, 1075–81.
9. Clarke G and Hill RG. (1972). Effects of a focal penicillin lesion on responses of rabbit cortical neurones to putative neurotransmitters. *British Journal of Pharmacology*, **44**, 435–41.
10. Thwaites CL, Yen LM, Loan HT, et al. (2006). Magnesium sulphate for treatment of severe tetanus: a randomised controlled trial. *Lancet*, **368**, 1436–43.
11. Saissy JM, Demaziere J, Vitris M, et al. (1992). Treatment of severe tetanus by intrathecal injections of baclofen without artificial ventilation. *Intensive Care Medicine*, **18**, 241–4.
12. Illis LS and Taylor FM. (1971). Neurological and electroencephalographic sequelae of tetanus. *Lancet*, **1**, 826–30.
13. Jackson AC. (2011). Rabies in the critical care unit: diagnostic and therapeutic approaches. *Canadian Journal of Neurological Sciences*, **38**, 689–95.
14. WHO expert consultation on rabies (2005). http://www.who.int/rabies/trs931_%2006_05.pdf (Accessed October 31, 2015).
15. Warrell M. (2010). Rabies and African bat lyssavirus encephalitis and its prevention. *International Journal of Antimicrobial Agents*, **36**(Suppl. 1), S47–52.
16. Jackson AC. (2011). Therapy of human rabies. *Advances in Virus Research*, **79**, 365–75.
17. Dembek ZF, Smith LA, and Rusnak JM. (2007). Botulism: cause, effects, diagnosis, clinical and laboratory identification, and treatment modalities. *Disaster Medicine*, **1**, 122–34.
18. Zhang J-C, Sun L, and Nie Q-H. (2010). Botulism, where are we now? *Clinical Toxicology*, **48**, 867–79.
19. Horowitz BZ. (2010). Type E botulism. *Clinical Toxicology*, **48**, 880–95.
20. Chalk C, Benstead TJ, and Keezer M. (2011). Medical treatment for botulism. Cochrane Database in Systematic Reviews, **3**, CD008123.

CHAPTER 246

Diagnosis, assessment, and management of Guillain–Barré syndrome

David Brealey and Nicholas Hirsch

Key points

- Guillain–Barré syndrome is an acute polyneuropathy consisting of several variants of differing pathology, presentation and outcome.
- 10–30% of patients with Guillain–Barré syndrome require mechanical ventilation for respiratory and/or bulbar failure.
- IVIg or plasma exchange significantly accelerates recovery and reduces disability. Corticosteroids are not indicated.
- Autonomic disturbance is common and potentially life threatening.
- Overall mortality is approximately 5%, with 20% remaining severely disabled.

Introduction

Guillain–Barré Syndrome (GuBS) is an acute inflammatory polyneuropathy first described by George Guillain, Jean-Alexandre Barré, and Andre Strohl in 1916. They described an acute transient motor weakness with loss of tendon reflexes in two soldiers. This was associated with an increased albumin in the cerebrospinal fluid (CSF) without a cellular reaction. Since the eradication of poliomyelitis, GuBS is the commonest cause of acute flaccid paralysis in the Western world. Up to one-third of patients with GuBS require mechanical ventilation and, therefore, the condition is of importance to all those involved in intensive care.

Variants of GuBS

GuBS represents a spectrum of acute neuropathies with a number of variants. The most common form in Europe and the United States (95% of cases) is **acute inflammatory demyelinating polyradiculoneuropathy** (AIDP). In the remainder, the nerve axon, rather than the myelin sheath is affected the axons targeted may be purely motor (**acute motor axonal neuropathy** (AMAN), more common in China), purely sensory (**acute sensory neuropathy**) or both (**acute motor and sensory axonal neuropathy** [AMSAN]). Neurophysiological testing allows distinction between these variants. In its pure form the **Fisher syndrome** variant consists of the triad of acute ophthalmoplegia, ataxia, and areflexia; if the triad is accompanied by degrees of limb and respiratory muscle weakness it is known as the **Fisher overlap syndrome**.

Epidemiology

The incidence of GuBS increases with age and in Europe and the USA is reported as 1.2–1.9 per 100,000. Men are affected 1.5 times more frequently than women.

In about two-thirds of cases, the onset of weakness is associated with an infective episode such as an influenza-type illness or gastroenteritis within the preceding 6 weeks. Possible infective triggers for the condition include *Camplylobacter jejuni*, cytomegalovirus, Epstein–Barr virus, *Mycoplasma pneumoniae*, and the human immunodeficiency virus (HIV). Seasonal fluctuations of GuBS are seen in China with an increased incidence following *Camplyobacter* outbreaks.

An increased incidence of GuBS in the Southern US in 1976 following a swine influenza vaccination programme, raised concerns that immunization may trigger the condition. However surveillance programmes have estimated that vaccination against influenza may result in only one additional case per million vaccinated. GuBS can often be linked temporally to the administration of other vaccines, but the actual incidence appears to be no higher than that of the general population. Case reports and small series have also linked GuBS with a diverse range of aetiologies, such as systemic lupus erythematosus, trauma, surgery, transplantation, and lightning strikes.

Pathophysiology

GuBS is considered an immune-mediated condition and half the patients with the condition have detectable antibodies in their sera. Most commonly, these antibodies are directed towards gangliosides, present in high concentrations in neurons and involved in neural development, calcium homeostasis, and synaptic transmission. Although no consistent antibodies are found in AIDP, specific antiganglioside antibodies have been commonly detected in patients with axonal forms of GuBS (Table 246.1).

The most attractive hypothesis to explain the presence of ganglioside antibodies in GuBS is that infecting agents (e.g. *Campylobacter jejuni*) raise antibodies, which then cross-react with peripheral nerve gangliosides. This molecular mimicry theory is supported

Table 246.1 Anti-ganglioside antibodies associated with GuBS and its variants

Variant	Associated antibodies
AIDP	Unknown
AMSAN and AMAN	GM1, GM1b, GD1a
Acute sensory neuropathy	GD1b
Fisher syndrome	GQ1b, GD3, GT1a

by the finding that lipo-oligosaccharides present on *Campylobacter jejuni* contain ganglioside-like structures.

Clinical features of GuBS

The diagnosis of GuBS is usually straightforward although the variable rapidity of onset of weakness provides a wide differential diagnosis (Box 246.1).

Patients classically present with a symmetrical ascending motor paralysis that develops acutely and progressively evolves over hours to weeks. Weakness usually involves both distal and proximal muscle groups. 90% of patients have reached the nadir of their weakness within 3 weeks and recovery tends to occur 2–4 weeks after progression has ceased. If the weakness continues to progress after four weeks, the alternative diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) should be considered. Differentiation between GuBS and CIDP is essential as the treatment of these conditions fundamentally differs. Occasionally, GuBS has an explosive onset causing total motor and autonomic paralysis, which can mimic brainstem death.

Although approximately 25% of patients with GuBS remain mobile, the remainder are more severely affected, with 10–30% of patients requiring mechanical ventilation for severe respiratory muscle weakness.

Deep tendon reflexes almost invariably disappear during the first week of the condition. Although sensory changes may be profound in the rare acute sensory variant, in AIDP mild distal parasthesia and numbness are usual. Approximately 50% of patients with GuBS have pain at presentation usually affecting the back and legs and 90% will experience pain during the course of their illness. The cranial nerves are involved in up to 75% of patients causing facial and bulbar weakness and ophthalmoplegia.

Autonomic nerve involvement occurs and is more commonly seen in those with severe weakness and those requiring mechanical ventilation; common manifestations include tachy- and bradyarrhythmias, labile blood pressure, abnormal sweating, ileus and urinary retention.

Box 246.1 Differential diagnosis of GuBS

Brainstem pathology: stroke
- Encephalitis.
- Brainstem death.

Spinal cord pathology
- Acute poliomyelitis.
- Transverse myelitis.
- Space-occupying lesion.
- Paralytic rabies.

Peripheral neuropathy: critical illness neuropathy
- Vasculitic neuropathy.
- Acute intermittent porphyria.
- Heavy metal poisoning.
- Tick bite paralysis.
- Marine toxins.

Neuromuscular junction disorders
- Myasthenia gravis.
- Lambert–Eaton myasthenic syndrome.
- Botulism.
- Organophosphate poisoning.

Muscle disorders: critical illness myopathy
- Hypokalaemia.
- Periodic paralyses.
- Inflammatory myopathies.

Diagnosis of GuBS

The diagnosis of GuBS relies on history, clinical features, examination of the cerebrospinal fluid (CSF) and neurophysiological studies. Essential and supporting criteria for the diagnosis were defined in 2003 [1].

Examination of CSF

The immune-mediated destruction of neuronal myelin and/or axons results in an inflammatory infiltration of nerve roots and disruption of the blood–CSF barrier with leakage of albumin into the CSF. Although CSF protein concentration may be normal in 15% of patients in the first week [2], most patients with GuBS will have a raised CSF protein 1 week after the onset of the weakness. In contrast, 90% of patients will have a cell count of < 3 per mm^3. A cell count of > 50 per mm^3 should raise doubts about the diagnosis or the co-existence of HIV infection.

Neurophysiological examination

Nerve conduction studies (NCS) and electromyography (EMG) are central to confirming the diagnosis, identifying the sub-type and helping with prognosis.

NCS may be normal early in the condition, but as the disease progresses certain electrophysiological changes occur. In AIDP absent or pronged F waves (conduction block) recorded from motor nerves occur in up to 80% of patients [3]. Abnormal sensory nerve action potentials (low amplitude or absent) are often found, particularly in the upper limbs, but with relative sparing of the lower limbs. Axonal disease is associated with small motor action potentials and, in AMAN, normal sensory potentials.

Management of GuBS

The admission of a GuBS patient is often protracted and complex. The key to successful management is a cohesive multi-disciplinary team approach with close cooperation between neurologists, intensivists, specialized nursing staff, physiotherapists, speech and language therapists, and specialists in neurorehabilitation.

The management of GuBS can be divided into immunotherapy (plasma exchange and IVIg) [4] aimed at shortening the acute phase of the disease and supportive treatment including intensive care management.

Plasma exchange

Plasma exchange (PE) significantly accelerates recovery and reduces disability at 4 weeks compared to supportive care alone.

Although arbitrarily set, most authorities perform five single plasma volume exchanges (200–250 mL/kg) over 7–14 days. PE requires central venous access, specialist equipment, and staff expertise, and is therefore often confined to specialist centres. Adverse events (haemodynamic compromise, sepsis, and technical difficulties) occur in approximately 75% of patients and in 14% of patients these result in the procedure being abandoned [5,6]. Co-existing infection is a relative contraindication to PE as removal of circulating antibodies may result in worsening of sepsis.

Intravenous immunoglobulin (IVIg)

The action of IVIg is poorly understood, but is thought to interfere with the immune system in a number of ways including neutralization of activated complement factors, interference with Fc receptor signalling and inactivation of pro-inflammatory cytokines.

Five trials, have demonstrated IVIg to be as efficacious as PE in the treatment of GuBS [4]. The usual dosing regimen of IVIg is 0.4 g/kg/day for 5 days. There is no benefit in combining PE and IVIg. Many authorities now consider IVIg the treatment of choice for GuBS as it has equal efficacy to PE, is easy to administer and has fewer side effects.

Corticosteroids

Despite widespread use of corticosteroids in other autoimmune diseases no overall benefit has been demonstrated in GuBS. A systematic review [7] concludes that oral corticosteroids are probably harmful, while intravenous steroids in conjunction with IVIg have, at best, a small short term benefit. Corticosteroids are currently not indicated in the management of GuBS (unlike CIDP).

Little evidence exists to guide treatment of the patients who do not respond or relapse after initial treatment. Small case series suggest patients who have not responded to treatment with IVIg may improve with repeated courses or subsequent PE [8,9].

Intensive care management of GuBS

Intensive care management of the patient with GuBS consists of providing appropriate ventilatory support, treatment of autonomic instability and pain, while maintaining meticulous supportive care.

Respiratory support

Up to 30% of patients with GuBS need tracheal intubation and ventilation. Respiratory and bulbar failure are the most common cause of intensive care admission. Respiratory muscle weakness and immobility lead to atelectasis, and the inability to clear secretions, while bulbar failure results in aspiration.

Changes in clinical signs or gas exchange are highly variable and may only markedly alter just prior to respiratory collapse. A gradual decline in vital capacity (VC) is often seen in the days leading up to intubation. A VC of 60% predicted [10] or a 30–50% fall from admission [11,12] are predictive of subsequent ventilation. A VC of <1L is associated with imminent requirement for ventilation [11].

Autonomic dysfunction and paralytic ileus can make the induction of anaesthesia and intubation hazardous. Administration of suxamethonium may induce a fatal hyperkalaemia from the denervated muscle; rocuronium is a suitable alternative.

As median duration of ventilation ranges from 15 to 43 days, early tracheostomy is often indicated.

Weaning from ventilation cannot begin until muscle strength has started to return and is unlikely to be successful if VC is <15–20 mL/kg.

Autonomic manifestations

Autonomic dysfunction affects up to 27% of patients. It tends to occur early and is maximal at the peak point of paralysis. It manifests as cardiovascular disturbance, gastrointestinal disturbances, urinary retention, and abnormal sweating abnormalities [13].

Approximately 20% of patients admitted to ICU suffer from cardiac arrhythmias, which may be life threatening [14]. These may be supraventricular tachycardias or bradycardias, which may require temporary pacing or progress to asystole. Bradycardia may be precipitated by other complications or interventions, such as endotracheal suctioning.

Although large swings in blood pressure with episodic hypertension and hypotension can occur, blood pressure can remain persistently elevated or depressed. ECG changes including, ST depression, T wave inversion and prolonged QT intervals may occur.

Urinary symptoms tend to improve as the disease regresses, but occasionally persist requiring surgical intervention.

Autonomic dysfunction can result in constipation, diarrhoea, paralytic ileus, and gastric paresis. Management is supportive and may include rectal tubes, gastric drainage via nasogastric tubes and parenteral nutrition.

Venous thromboembolism

The incidence of clinical DVT in patients with GuBS ranges from 4%-9%, 2-7% have evidence of pulmonary emboli. All immobile patients should receive venous thromboembolism prophylaxis.

Management of pain

Pain in GuBS is almost invariable, often precedes the onset of weakness and usually affects the back and legs. It is both nociceptive and neuropathic and may be severe [14]. Allodynia and dysaesthesia may persist many years after the resolution of the acute disease. Patients often require a combination of simple and opioid analgesics, and adjuvant analgesics, such as gabapentin or carbamazepine.

Other complications and management

Major morbidity affects up to two thirds of GuBS patients treated in intensive care [14]. Lower respiratory tract infections complicate between 27 and 54%, urinary tract infections 20–46%, and line sepsis 3%.

Prolonged immobilization results in wasting, contractures, hypercalcaemia, and pressure sores, particularly in those with more sensory involvement. An individual neurorehabilitation programme needs to start from the outset [15]. Alterations in mental state are common in patients with severe GuBS and are not due to critical illness alone. Anxiety or depression affects up to 82% of patients.

Outcome of GuBS

The overall mortality of GuBS ranges from 2.4 to 8%, increasing to 7 to 20% in patients treated with mechanical ventilation. Lower mortality rates are seen in neuro-medical ICUs experienced in managing the condition [16]. Causes of death include respiratory failure, aspiration, and ventilator associated pneumonia, sepsis, thromboembolic events, and unexpected cardiac arrest.

Recovery is often prolonged with 20% of patients being unable to walk at 6 months and a similar percentage remaining severely disabled. Recovery of muscle strength can continue for up to 2 years and a neurorehabilitation programme is recommended. Many patients are left with long term sensory deficits, pain and fatigability. Poor prognostic factors include advancing age, severity of disease, and axonal involvement.

References

1. Van der Meche FG, van Doorn PA, Meulstee J, and Jennekens FG. (2001). Diagnostic and classification criteria for the Guillain–Barré syndrome. *European Neurology*, **45**(3), 133–9.
2. Gonzalez-Quevedo A, Carriera RF, O'Farrill ZL, Luis IS, Becquer RM, and Luis Gonzalez RS. (2009). An appraisal of blood-cerebrospinal fluid barrier dysfunction during the course of Guillain–Barré syndrome. *Neurology India*, **57**(3), 288–94.
3. Al Shekhlee A, Hachwi RN, Preston DC, and Katirji B. (2005). New criteria for early electrodiagnosis of acute inflammatory demyelinating polyneuropathy. *Muscle Nerve*, **32**(1), 66–72.
4. Hughes RA, Swan AV, Raphael JC, Annane D, van Koningsveld R, and van Doorn PA. (2007). Immunotherapy for Guillain–Barré syndrome: a systematic review. *Brain*, **130**(Pt 9), 2245–57.
5. Bouget J, Chevret S, Chastang C, and Raphael JC. (1993). Plasma exchange morbidity in Guillain-Barre syndrome: results from the French prospective, randomized, multicenter study. The French Cooperative Group. *Critical Care Medicine*, **21**(5), 651–8.
6. French Cooperative Group on Plasma Exchange in Guillain–Barré syndrome (1987). Efficiency of plasma exchange in Guillain-Barre syndrome: role of replacement fluids. French Cooperative Group on Plasma Exchange in Guillain–Barré syndrome. *Annals of Neurology*, **22**(6), 753–61.
7. Hughes RA, Swan AV, van Koningsveld R, and van Doorn PA. (2006). Corticosteroids for Guillain–Barré syndrome. *Cochrane Database of Systematic Reviews*, **2**,CD001446.
8. Dada MA and Kaplan AA. (2004). Plasmapheresis treatment in Guillain–Barré syndrome: potential benefit over IVIg in patients with axonal involvement. *Therapeutic Apheresis and Dialysis*, **8**(5), 409–12.
9. Farcas P, Avnun L, Frisher S, Herishanu YO, and Wirguin I. (1997). Efficacy of repeated intravenous immunoglobulin in severe unresponsive Guillain–Barré syndrome. *Lancet*, **350**(9093), 1747.
10. Sharshar T, Chevret S, Bourdain F, and Raphael JC. (2003). Early predictors of mechanical ventilation in Guillain-Barre syndrome. *Critical Care Medicine*, **31**(1), 278–83.
11. Chevrolet JC and Deleamont P. (1991). Repeated vital capacity measurements as predictive parameters for mechanical ventilation need and weaning success in the Guillain-Barre syndrome. *American Review of Respiratory Diseases*, **144**(4), 814–18.
12. Lawn ND, Fletcher DD, Henderson RD, Wolter TD, and Wijdicks EF. (2001). Anticipating mechanical ventilation in Guillain-Barre syndrome. *Archives of Neurology*, **58**(6), 893–8.
13. Lyu RK, Tang LM, Hsu WC, Chen ST, Chang HS, and Wu YR. (2002). A longitudinal cardiovascular autonomic function study in mild Guillain–Barré syndrome. *European Neurology*, **47**(2), 79–84.
14. Dhar R, Stitt L, and Hahn AF. (2008). The morbidity and outcome of patients with Guillain-Barre syndrome admitted to the intensive care unit. *Journal of Neurological Sciences*, **264**(1–2), 121–8.
15. Hughes RA, Wijdicks EF, Benson E, et al. (2005). Supportive care for patients with Guillain–Barré syndrome. *Archives of Neurology*, **62**(8), 1194–8.
16. Ng KK, Howard RS, Fish DR, et al. (1995). Management and outcome of severe Guillain–Barré syndrome. *Quarterly Journal of Medicine*, **88**(4), 243–50.

CHAPTER 247

Diagnosis, assessment, and management of hyperthermic crises

Kevin Thornton and Michael Gropper

Key points

- MH is a life-threatening hypermetabolic disorder associated with exposure to halogenated volatile anaesthetics and succinylcholine that should be treated by discontinuing the anaesthetic agent, active cooling, and the administration of dantrolene.
- NMS is a syndrome classically associated with exposure to antipsychotic medications, but may also be caused by withdrawal of medications such as L-dopa.
- Serotonin syndrome probably represents one end of a spectrum of symptoms associated with increased central nervous system (CNS) serotonergic activity. It is associated with the use of selective serotonin reuptake inhibitors, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants; clonus is the most significant clinical finding.
- In patients who may have been exposed to an MAOI, extreme care should be exercised to avoid prescribing any medications that may increase CNS serotonin levels including pethidine (meperidine) and indirect sympathomimetic agents.
- As all three of these disorders may progress to life-threatening hyperthermia, supportive therapy should include active cooling, intravenous hydration, and monitoring for laboratory abnormalities, including those associated with rhabdomyolysis, hepatic dysfunction, coagulation abnormalities, and electrolyte disturbances.

Introduction

Hyperthermic crises in the intensive care unit (ICU) are often challenging for the clinician due to their relative rarity, their complex underlying mechanisms and predisposing factors, and their high morbidity and mortality if not recognized and treated appropriately. Malignant hyperthermia, neuroleptic malignant syndrome, and serotonin syndrome are the prototypical disorders associated with hyperthermia in the ICU. While they share many similarities, they are distinct clinical entities with different aetiologies, pathophysiological mechanisms, clinical characteristics, and treatments.

Malignant hyperthermia

Malignant hyperthermia (MH) is a rare, life-threatening disorder characterized by a combination of muscle rigidity, severe hyperthermia, and mixed respiratory and metabolic acidosis associated with exposure to halogenated volatile anaesthetics (e.g. sevoflurane, desflurane, isoflurane) or depolarizing muscle relaxants (succinylcholine). It may occur intra-operatively or up to 24 hours following exposure to triggering agents. Without the correct treatment, mortality can be as high as 70%, although prompt recognition and management can reduce mortality to less than 5% [1,2].

Epidemiology and pathophysiology

Estimates of the prevalence of MH vary widely from 1 in 10,000 anaesthetics to 1 in 250,000. A recent cohort study in New York State demonstrated the risk to be approximately 1 in 100,000 in surgical patients with a substantially greater risk among male patients [3]. The clinical syndrome results in uncontrolled release of calcium from the sarcoplasmic reticulum in skeletal muscle and is thought to be mediated by an abnormal ryanodine receptor calcium channel. Numerous genetic mutations to this receptor (inherited in an autosomal dominant fashion) have been shown to produce MH and it has been postulated that the common mechanism may be disruption of the inhibitory function that magnesium ions normally exert on calcium flux. All volatile anaesthetics currently in clinical use are able to trigger MH. Succinylcholine administered alone may trigger MH, albeit this may be quite rare. However, when succinylcholine is administered in combination with volatile anaesthetics a more fulminant form of MH often develops [2].

Clinical features and diagnosis

MH presents as a syndrome characterized by a variety of manifestations that result from hypermetabolism. The features can be divided into muscular manifestations (masseter spasm, generalized muscle rigidity, evidence of rhabdomyolysis, hyperkalaemia), respiratory manifestations (increased CO_2 production, respiratory acidosis, tachypnoea) and metabolic acidosis. In a review of 196 cases of MH in North America, the most common presentation pattern seen was a combination of muscular symptoms and

respiratory acidosis. Metabolic acidosis was present or the sole presentation in a minority of cases which may indicate that this is a later feature of the disease process. Complications include cardiovascular collapse, ventricular arrhythmias, disseminated intravascular coagulation, bleeding, renal failure, hepatic dysfunction, and death. Importantly, more than half of the patients in this analysis had previously undergone uncomplicated general anaesthesia and prior uneventful anaesthesia does not preclude the diagnosis of MH [4].

The diagnosis of MH must be made clinically as confirmatory testing requires either a muscle biopsy for the 'caffeine-halothane contracture test', which serves as the gold standard, or genetic testing to confirm the presence of a mutation in the ryanodine receptor [5]. In a patient who has recently been exposed to either volatile anaesthetics or succinylcholine, signs of rapidly increasing temperature, increased carbon dioxide production (respiratory acidosis, increasing minute ventilation or tachypnoea) and muscular rigidity (which is not always present) should prompt the concern for MH. Rapid recognition is critical as the syndrome evolves rapidly and patients deteriorate quickly without proper treatment [5].

Management

Discontinuation of all volatile anaesthetics and the administration of dantrolene, a ryanodine receptor antagonist, are the foundations of therapy. Dantrolene is notoriously difficult to dissolve in solution and treatment may require the aid of multiple providers. The initial recommended dose is 2.0–2.5 mg/kg, which may be repeated every 5 minutes up to a total dose of 10 mg/kg until a decrease in CO_2 production is seen. Continuous end-tidal CO_2 monitoring is recommended as a means of monitoring the response to treatment in real time. As dantrolene itself is a mild muscle relaxant and may cause respiratory weakness, non-intubated patients may require endotracheal intubation [1]. In the United States, the Malignant Hyperthermia Association of the United States (MHAUS) operates a 24-hour telephone hotline for providers seeking expert clinical assistance and has material online that can be of assistance when treating a patient having an acute crisis (www.mhaus.org).

In addition to discontinuation of the offending agent(s) and administration of dantrolene, treatment focuses on supportive care and monitoring for organ dysfunction. Active cooling is recommended as is the administration of bicarbonate to treat the metabolic acidosis and to alkalinize the urine. Administration of 100% oxygen and an increase in the minute ventilation being delivered are essential to meet the demands of the increased metabolic rate and to compensate for the resultant respiratory acidosis. As rhabdomyolysis may occur in severe cases, monitoring of urine output and laboratory evaluation for elevated creatine kinase, urine myoglobin, and other electrolyte abnormalities as well as for hepatic dysfunction and DIC is also recommended [6].

Recrudescence up to 24 hours following the initial episode occurs in up to 50% of cases so continued vigilance for signs of hyperthermia and increased CO_2 production is warranted and additional doses of dantrolene are often required [7]. Following recovery, patients should be counselled as to the risks and implications of MH for both themselves and their family members. Additionally, they should be referred for confirmatory testing by either muscle biopsy or genetic testing especially if the diagnosis is in question [8].

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a clinical syndrome seen most commonly in patients who are taking traditional antipsychotic medications, but may also be seen less commonly in those being treated with atypical antipsychotics, promethazine, or metoclopramide. NMS is characterized by altered mental status, muscular rigidity, fever, and autonomic dysfunction, which can lead to rhabdomyolyis, acute renal failure, metabolic acidosis, and other life-threatening systemic manifestations [6].

Epidemiology and pathophysiology

NMS is seen most commonly in patients taking potent antipsychotic medications such as haloperidol. However, it remains quite rare with estimates of the incidence of occurrence in this patient population of 0.2–12% and it may be decreasing in frequency with the increasing use of atypical antipsychotic agents [9]. NMS is associated with use of medications that decrease dopaminergic activity along nigrostriatal and hypothalamic pathways in the central nervous system (and the withdrawal of medications that increase it). This reduction of dopaminergic activity has been postulated to be causative in the disorder. In addition to patients taking antipsychotic medications, it has been described in patients receiving other dopamine-receptor blocking agents, including promethazine, metoclopramide, and following withdrawal of drugs such as L-dopa. It can occur at any point during treatment with these agents, not just during the initiation of therapy. How the peripheral effects (muscle rigidity and rhabdomyolysis) of this syndrome develop is not well understood [10].

Clinical features and diagnosis

The hallmarks of NMS are altered mental status followed by the development of rigidity, hyperthermia, and autonomic dysfunction including diaphoresis, incontinence, and haemodynamic instability. However, in critically-ill patients, NMS often remains a diagnosis of exclusion. Tachycardia and labile blood pressure are common, and overt shock may develop. Mortality estimates range from 11.9 to 18.8%. Laboratory manifestations include the development of leukocytosis, elevated creatine phosphokinase (CK), rhabdomyolysis, elevated lactate dehydrogenase (LDH), and alanine and aspartate transaminases (AST and ALT). Renal failure may develop due to rhabdomyolysis. While the DSM-IV diagnostic criteria require the presence of treatment with an antipsychotic medication, it is clear that this is not always the case. New criteria have been proposed whereby the patient must have hyperthermia, rigidity, and elevated CK in addition to four out of five of the following: tachycardia, abnormal blood pressure, altered consciousness, leukocytosis, and diaphoresis [6].

Management

Discontinuation of the offending agent is the most important intervention that should be made. Otherwise, care is largely supportive and should be aimed at reducing fever via active cooling, hemodynamic support, hydration, and the relief of muscular rigidity. Treatment may need to continue for up to 10 days or as long as 2–3 weeks in patients who have received depot forms of antipsychotic medications. Patients with NMS are at increased

risk for venous thromboembolism and pharmacologic prophylaxis is recommended [10]. Benzodiazepines have been described as potential agents to aid in the treatment of rigidity, but may worsen mental status. Dantrolene and bromocriptine have both been described as potential agents that may be used to treat NMS, but it is unclear if they offer benefit compared with supportive therapy alone. Bromocriptine, a dopamine agonist, may worsen hypotension, if present, and its use should be considered carefully. Electroconvulsive therapy (ECT) has also been evaluated in refractory or severe cases of NMS and found to have some benefit. Finally, there is significant risk for recurrence of NMS if the offending agents are reintroduced and affected patients should be counselled regarding this [6].

Serotonin syndrome

The serotonin syndrome (SS) represents a spectrum of clinical findings seen in patients who are taking medications, or combinations thereof, which increase serotonergic activity in the CNS. The clinical syndrome varies from mild to life-threatening. Classically, it is described as a triad of tremor or neuromuscular abnormalities (clonus and hyperreflexia being most common), altered mental status, and autonomic dysfunction. Hyperthermia is often a late finding in more severe cases. It is most commonly associated with the use of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs), but a variety of medications have been implicated including opiate analgesics, dextromethorphan, antibiotics including linezolid, and illicit drugs, such as 3,4-methylenedioxy-N-methylamphetamine (MDMA or 'ecstasy') [11].

Epidemiology and pathophysiology

It is estimated that approximately 14% of patients suffering from SSRI overdose will have SS and the incidence increases with ingestion of multiple serotonergic medications [12]. Additionally, the accidental combination of certain medications, such as MAOIs and pethidine (meperidine), may cause a very severe form of SS. With the increasing use of serotonergic agents, it is suspected that the incidence may be increasing but good epidemiologic data are lacking [12].

Serotonin (5-HT) functions as a neurotransmitter in the CNS and there are several subtypes of 5-HT receptors. It appears that the 5-HT_{2A} receptor may contribute substantially to the development of serotonin syndrome. Since serotonin receptors in the CNS play a key role in the regulation of wakefulness, thermoregulation, motor tone, gastrointestinal motility, and vascular tone it is likely via these receptors that the clinical manifestations of the syndrome are mediated [11].

Clinical features and diagnosis

While classically described as a triad of altered mental status, neuromuscular abnormalities including tremor, and autonomic dysfunction, serotonin syndrome exists as a spectrum of clinical manifestations that range from mild to life-threatening. Mental status changes range from mild agitation to delirium and coma. Tremor, hyperreflexia, and myclonus are the hallmarks of the neuromuscular findings and clonus and hyperreflexia may be worse in the lower extremities [11]. In fact, the presence of clonus may be the most sensitive physical exam finding [13]. Hyperreflexia and clonus may progress to muscular rigidity with increased tone sufficient to produce rhabdomyolysis, metabolic acidosis, renal failure, and DIC. Autonomic manifestations range from mild tachycardia and diaphoresis, gastrointestinal hypermotility, and mydriasis, to severe hypertension, and shock [11].

The Hunter Serotonin Toxicity Criteria (Box 247.1) have been shown to have superior sensitivity and specificity to older diagnostic models when evaluating a patient for serotonin syndrome. The authors stress the importance of clonus (spontaneous, inducible, or ocular) as a physical finding that is strongly associated with SS [13].

Management

Treatment of SS primarily involves the discontinuation of the inciting agent, supportive therapies aimed at relieving agitation and autonomic instability, and treatment of hyperthermia. In mild cases, sedation with benzodiazepines is usually sufficient. In moderate to severe cases, $5HT_{2A}$ antagonists such as cyproheptadine may have a role. In cases where hyperthermia is severe, deep sedation, tracheal intubation, and neuromuscular paralysis with a non-depolarizing muscle relaxant are recommended in addition to active cooling [14].

Benzodiazepines are the mainstay of therapy in mild to moderate cases as they will improve both the agitation and muscular rigidity. Additionally, they have been shown in animal models to improve survival. When treating hypotension that results from autonomic instability, it is important to recognize that indirect-acting sympathomimetics such as dopamine may have exaggerated and dangerous effects in patients who have been exposed to MAOIs and direct-acting agents are preferred [11].

The use of $5HT_2$ antagonists such as cyproheptadine have been described, but their clinical efficacy has not been clearly established in human studies. Typically recommended for only moderate and severe cases, cyproheptidine is only available as an oral agent and the recommended initial dose is 12 mg followed by 2 mg every 2 hours if symptoms persist. Some data suggests that for optimal

Box 247.1 The Hunter Serotonin Toxicity Criteria

The hunter serotonin toxicity criteria predict serotonin syndrome if . . .

- The presence of serotonergic agent

And one of the following . . .

- Spontaneous clonus
- Inducible clonus **and** agitation or diaphoresis
- Ocular clonus **and** agitation or diaphoresis
- Tremor **and** hyperreflexia
- Hypertonia **and** temp >38°C **and** ocular or inducible clonus

Adapted from Dunkley EJC et al., 'The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity', *Quarterly Journal of Medicine*, **96**(9), pp. 635–42, copyright 2003, by permission of Oxford University Press on behalf of The Association of Physicians.

Table 247.1 Comparison of MH, NMS, and SS

	Malignant Hyperthermia (MH)	Neuroleptic Malignant Syndrome (NMS)	Serotonin Syndrome (SS)
Associated medications	◆ Volatile halogenated anaesthetics ◆ Succinylcholine	◆ Antipsychotics ◆ Metoclopramide ◆ Promethazine	◆ SSRIs, MAOIs, TCAs ◆ Opiates ◆ Dextromethorphan ◆ Linezolid
Common clinical findings	◆ Hypercarbia and respiratory acidosis ◆ Tachycardia ◆ Rigidity	◆ Muscular rigidity ◆ Fever ◆ Altered mental status ◆ Autonomic dysfunction	◆ Clonus (spontaneous or induced) ◆ Hyperreflexia ◆ Altered mental status ◆ Autonomic dysfunction
Onset and duration	◆ Onset within minutes up to 24 hours following exposure ◆ Recrudescence may occur up to 24 hours later	◆ Can occur at any time during treatment with offending medications ◆ Often associated with dosage increase or medication change ◆ Prolonged course if depot antipsychotic used (2–3 weeks).	◆ Unpredictable onset ◆ Exists as a clinical spectrum ◆ Resolution dependent on half-life of causative agent—usually in 24 hours

receptor blockade, a dose as high as 30 mg may be needed [14]. Chlorpromazine use has also been described in the past, but is no longer recommended for routine use. Both olanzapine and risperidone also have $5HT_2$ blocking effects but their use in the treatment of SS has not been well studied [14].

In severe cases, rhabdomyolysis, renal failure and DIC may develop and patients should be closely monitored for the development of these complications. In most instances, the syndrome resolves within 24 hours, although patients who were exposed to medications with extended half-lives may require prolonged therapy.

Conclusion

Malignant hyperthermia, neuroleptic malignant syndrome, and serotonin syndrome are all life-threatening clinical disease processes associated with hyperthermia. While they have many similar features, they are distinct entities, which clinicians must be able to distinguish as the outcome will be largely dependent on timely recognition and initiation of appropriate therapy (Table 247.1). Vigilance is necessary to evaluate for the signs of systemic involvement that can lead to serious complications including rhabdomyolysis, renal failure, and death.

References

1. Miller R, (ed.) (2005). *Miller's Anesthesia*, 6th edn. London: Elsevier, Churchill, Livingstone.
2. Hopkins PM. (2011). Malignant hyperthermia: pharmacology of triggering. *British Journal of Anaesthesia*, **107**(1), 48–56.
3. Brady JE. (2009). Prevalence of malignant hyperthermia due to anesthesia in New York State, 2001–2005. *Anesthesia and Analgesia*, **109**(4), 1162–6.
4. Larach M. (2010). Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. *Anesthesia and Analgesia*, **110**(2), 498–507.
5. Denborough M. (1998). Malignant hyperthermia. *Lancet*, **352**(9134), 1131–6.
6. McAllen KJ and Schwartz DR. (2010). Adverse drug reactions resulting in hyperthermia in the intensive care unit. *Critical Care Medicine*, **38**(Suppl. 6), S244–52.
7. Burkman JM, Posner K, and Domino KB. (2007). Analysis of the clinical variables associated with recrudescence after malignant hyperthermia reactions. *Anesthesiology*, **106**, 901–6.
8. MHAUS (2012). Malignant Hyperthermia Testing. Available at: http://www.mhaus.org/
9. Adityanjee AY and Matthews T (1999). Epidemiology of neuroleptic malignant syndrome. *Clinical Neuropharmacology*, **22**(3), 151–8.
10. Pelonero AL, Levenson J, and Pandurangi AK. (1998). Neuroleptic malignant syndrome: a review. *Psychiatric Services*, **49**(9), 1163–72.
11. Boyer EW and Shannon M. (2005). The serotonin syndrome. *New England Journal of Medicine*, **352**, 1112–20.
12. Isbister GK, Bowe SJ, Dawson A, and Whyte IM. (2004). Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *Clinical Toxicology*, **42**(3), 277–85.
13. Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM (2003). The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity.' *Quarterly Journal of Medicine*, **96**(9), 635–42.
14. Gillman PK. (1999). The serotonin syndrome and its treatment. *Journal of Psychopharmacology*, **13**(1), 100–9.

CHAPTER 248

Diagnosis, assessment, and management of ICU-acquired weakness

Nicholas Hart and Tarek Sharshar

Key points

- ICU-acquired weakness (ICU-AW) is common in critically-ill patients.
- ICU-AW can be categorized as critical illness polyneuropathy (CIP), critical illness myopathy (CIM) and critical illness neuromyopathy (CINM) by detailed electrophysiological investigation, but this is only required when there is diagnostic uncertainty.
- ICU-AW can be diagnosed using the Medical Research Council sumscore with a value less than 48 out of 60.
- Risk factors for ICU-AW include illness severity on ICU admission, duration of mechanical ventilation, prolonged immobility, and duration of sedation.
- Intervention exercise therapy and rehabilitation strategies are required to minimize the effects of developing of skeletal muscle wasting and weakness.

Introduction

In the eighteenth century, William Osler first reported the physical manifestation of prolonged sepsis, describing the progressive 'loss of flesh' with pronounced 'weakness'. Over a century later, there is a widespread acknowledgement of the major psychological and physiological consequences of critical illness. Enhanced survival rates, as a result of advances in modern intensive care medicine, have resulted in greater attention being focused on diagnosing, characterizing and treating these adverse consequences. In particular, neuromuscular deficits in survivors of critical illness contribute to long term impairment in physical function, which persists for many years following the index admission [1]. Intensive care unit-acquired weakness (ICU-AW) is the clinical term applied to weakness developed secondary to critical illness, but this seemingly simplistic label significantly underestimates the complex pathophysiological changes occurring in nerves and muscle during critical illness. In addition to the term ICU-AW, which simply reports muscle strength, other terms have been described such as critical illness polyneuropathy (CIP), critical illness myopathy (CIM) and critical illness neuromyopathy (CINM), all of which require detailed electrophysiological investigation to confirm the diagnosis. Although this level of detail has limited clinical utility in terms of long term clinical outcome [2], CIP has been shown to be associated with more severe long-term disability. Despite these inconsistencies in terminology, an important consequence of this growing interest in critical illness induced weakness is the emphasis on early identification of those at greatest risk of developing weakness. The current therapeutic goal is to develop targeted interventions and strategies that ameliorate, or even prevent, muscle wasting and weakness.

Definitions of muscle weakness associated with critical illness

Muscle wasting and weakness are characteristic in survivors of critical illness [3,4] and ICU-AW is a collective term for the neuromuscular deficit observed. It is defined as clinical weakness in the absence of any neurological or metabolic cause, other than the systemic inflammatory response stemming from the original critical illness [2]. Weakness is bilateral, affecting proximal muscle groups to a greater extent than distal groups, with sparing of the facial muscles. Less commonly sensation can be altered, in particular, temperature and pain perception, indicating the presence of an axonopathy. In general, however, patients typically present with profound generalized weakness resulting in impaired mobilization and difficulty weaning from mechanical ventilation [2,5]. Two comprehensive reviews of the diagnosis and classification of ICU-AW propose clear schematic approaches to differentiating between clinical presentations [2,5]. Fig. 248.1 outlines the classification of ICU-AW.

Where ICU-AW is present, use of electrophysiological and other techniques, such as electromyography, nerve conduction studies and muscle histology, will add more diagnostic accuracy, e.g. to diagnose CIP, CIM, or CINM [2,5,6], but this is often only required when there is diagnostic uncertainty. Tables 248.1 and 248.2 highlight the definitions and diagnostic criteria of the differing terms that describe critical illness induced neuromuscular deficit [2].

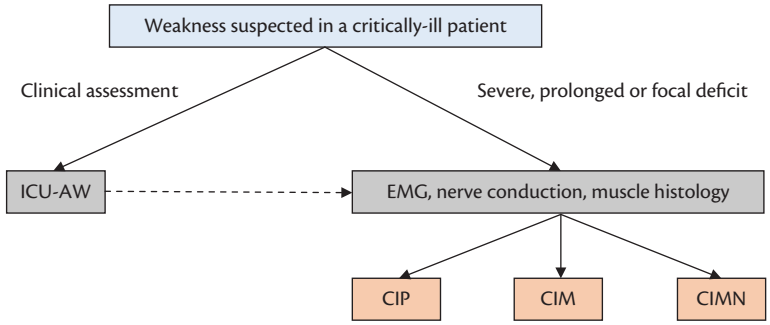


Figure 248.1 ICU-AW classification.
ICU-AW, intensive care unit-acquired weakness; EMG, electromyography; CIP, critical illness polyneuropathy; CIM, critical illness myopathy; CINM, critical illness neuromyopathy.
Adapted from Stevens RD et al., 'A framework for diagnosing and classifying intensive care unit-acquired weakness', *Critical Care Medicine*, **37**, pp. S299–308, copyright 2009, with permission from Wolters Kluwer Health and Society of Critical Care Medicine.

Table 248.1 Different terminology used to describe neuromuscular deficit in critically-ill patients

Term	Definition
Intensive care unit-acquired weakness (ICU-AW)	Weakness solely attributable to critical illness
Critical illness polyneuropathy (CIP)	Sensorimotor axonal polyneuropathy with reduced compound muscle and sensory nerve action potential amplitudes, but normal nerve conduction velocity
Critical illness myopathy (CIM)	Acute primary myopathy with reduced amplitude of sensory nerve action potentials, low-amplitude motor unit potentials +/−fibrillation and reduced excitability on direct muscle stimulation
Critical illness neuromyopathy (CINM)	Syndrome involving overlap between both CIP and CIM

Table 248.2 Diagnostic criteria for presentations of neuromuscular deficit in critically-ill patients

ICU-AW	CIP	CIM	CINM
◆ Generalized weakness post-critical illness ◆ Diffuse and symmetric in nature, of proximal and distal muscles with sparing of cranial nerves ◆ MRC sumscore <48/60 (Box 243.1) ◆ Protracted weaning from mechanical ventilation ◆ All other causes of weakness excluded	◆ Criteria for ICU-AW met ◆ CMAP amplitudes decreased to <80% of lower normal limit in ≥2 nerves ◆ SNAP amplitudes decreased to <80% of lower normal limit in ≥2 nerves ◆ Normal nerve conduction velocities without conduction block ◆ Absence of a decremental response on repetitive nerve stimulation	◆ Criteria for ICU-AW met ◆ SNAP amplitudes >80% of lower normal limit in ≥2 nerves ◆ Needle EMG in ≥2 muscle groups showing short-duration, low-amplitude motor unit potentials with early or normal full recruitment ◆ Direct muscle stimulation demonstrates reduced excitability in ≥2 muscle groups ◆ Muscle histology consistent with myopathy (such as fibre atrophy, necrosis)	◆ Criteria for ICU-AW met ◆ Criteria met for CIP ◆ Criteria met for CIM

ICU-AW, intensive care unit-acquired weakness; CIP, critical illness polyneuropathy; CIM, critical illness myopathy; CINM, critical illness neuromyopathy; MRC, Medical Research Council; CMAP, compound motor action potential; SNAP, sensory nerve action potential; EMG, electromyogram.

Risk factors for development of weakness during critical illness

The absence of a robust experimental animal model to investigate risk factors in isolation has led to the current established risk factors being reported from regression analysis following observation cohort studies and clinical trials [5]. The risk factors described include illness severity on ICU admission, duration of mechanical ventilation, prolonged immobility, duration of sedation, and hyperglycaemia [5,7,8]. Contrary to earlier belief, a recent review of the evidence, including randomized controlled data, has demonstrated limited harmful effect from the use of neuromuscular blocking agents in modern critical care practice [9]. In addition, a deleterious effect of treatment with corticosteroids is also now controversial.

Clinical assessment of ICU-AW

Electrophysiological testing

Although confirming CIP, CIM and CINM has diagnostic utility, these neuromyopathic conditions often have limited correlation with the severity, distribution or the clinical consequences of ICU-AW [10]. Furthermore, such testing requires a high level of operator skill, as well as expert clinical interpretation rendering the general availability of these tests limited. This is also true for the objective tests that measure the strength of isolated muscle groups, such as adductor pollicis muscle, which can be performed using either electrical, and more recently, magnetic stimulation of the nerve [11]. Furthermore, these complex tests are not always practical in the ICU environment where factors such as oedema, signal artefact from other electrical devices, and the presence of monitoring lines make technical application difficult [5]. Finally, and more important to the clinician, is the lack of any current effective treatment for CIP, CIM, or CINM. Outcome studies have therefore focused on changing aspects of critical care management, such as early exercise therapy and subsequent rehabilitation, which can modify the severity of ICU-AW rather than focussing on the electrophysiological diagnosis [5].

Manual muscle testing

As ICU-AW is primarily a 'bedside diagnosis' [5], it requires a clinically appropriate tool for screening. The most commonly used tool is the Medical Research Council MRC sumscore (MRC-SS) [12], a form of manual muscle testing (MMT). The MRC-SS assesses the strength of six upper and lower limb muscle groups using the ordinal MRC scale from 0 (no strength) to 5 (normal strength). The test is relatively quick, simple and easy to perform requiring no additional equipment and therefore can be used to sequential chart the MRC-SS during the ICU admission and following discharge from the ICU. It has been used in retrospective and prospective studies with a MRC-SS less than 48/60 indicative of ICU-AW e.g. a score of less than 4 in each muscle assessed [3,4]. Handgrip dynamometry, another form of MMT, has also been used to measure muscle strength in critically-ill patients. A direct relationship has been demonstrated between handgrip dynamometry and MRC-SS, with ICU-AW diagnosed at a cut-off level of 11 kg-force for males and 7 kg-force for females [3].

Challenges using manual muscle testing in critically-ill patients

Volitional tests in critically-ill patients

The use of MMT to diagnose ICU-AW in critically-ill patients has clinical limitations. Patients must be sufficiently awake, alert, and cognitively intact to follow the instructions necessary for testing each muscle. Screening tools can facilitate assessment of this, gauging patient response to simple commands such as 'Open your eyes', 'Follow my finger' or 'Nod your head' [3,4]. Clinicians must be confident that patients perform their maximum volitional effort, given that the ICU environment is not always conducive to such testing. Extraneous factors, such as pain and analgesia, level of sedation, arterial monitoring and venous access lines, patient motivation, and compliance with the assessment can influence the outcome of this test and adversely impact the validity and reliability of the results. In addition, the MRC scale for grading muscle strength has a flawed construct with differential sensitivity evident across the range of scores. For example, scores at level 3 or below incorporate gravity as an objective reference quantity, whereas for levels 4 and 5, quantity of additional resistance required is not specified. The validity and reliability of scores greater than level 3 are dependent on the context of the interaction between clinician and patient, and the experience of the clinician in delivering and interpreting the assessment. These inconsistencies have resulted in conflicting data reporting the reliability of the MRC-SS for diagnosing ICU-AW. In stable patients recovering from critical illness, high levels of inter-rater reliability have been demonstrated [13]. However, agreement between clinicians remains poor when testing critically-ill patients whilst in the ICU, assessed at the time of awakening [14]. Assessment at this time point is also difficult as up to a third of patients are unable to perform manual muscle testing [14]. Finally, the clinical predictive value of the MRC-SS at awakening is poor, in particular, there was no relationship between an MRC-SS <48/60 at awakening, considered the diagnostic cut-off for ICU-AW, and ICU or hospital mortality. Although there was a significant association evident for ICU and hospital length of stay, further test characteristic analysis revealed a poor positive predictive value, but a high negative predictive value for an ICU length of stay of more than 2 weeks. Clinically, this suggests that a diagnosis of ICU-AW based on an MRC-SS <48/60 had poor predictive value, whereas an MRC-SS greater than 48 predicted a more favourable outcome [14].

ICU-AW and physical functional ability

Only moderate correlations have been shown between MRC-SS and two common measures of physical function (Barthel score and the elderly mobility scale), which is not unexpected given these represent different domains, i.e. muscle weakness versus physical function [14]. Indeed, the MRC-SS is a composite score of peripheral muscle strength, based on single muscle group manoeuvres. It fails to capture the spectrum of complex motor tasks and interaction between skeletal muscle strength and endurance, balance, co-ordination, and higher-level cognition required for complex physical function activities.

Clinical outcome associated with ICU-AW

Using an MRC-SS cuff off of less than 48/60, the reported prevalence of ICU-AW at the time of awakening ranges from around 24% to 65% [5,6,12] with a significant proportion of such patients demonstrating ICU-AW 7 days after awakening. In terms of short-term outcome, ICU-AW is an independent predictor of prolonged mechanical ventilation [15], with an associated increase in ICU and hospital length of stay [3]. In addition, a direct relationship has been shown between MRC-SS and vital capacity, maximal inspiratory and expiratory pressures, with an MRC-SS less than 41 demonstrated as an independent risk factor for weaning failure [16]. We must emphasize that post-extubation respiratory failure in patients can occur after 48 hours, indicating that patients with ICU-AW should not be discharged from ICU prematurely. Furthermore, ICU-AW is associated with increased ICU and hospital mortality [4]. In the long-term, ICU-AW impacts significantly

on health-related quality of life [17] with impairments in physical function persisting for up to 5 years following index critical illness [1]. Despite these observations, a recent study has shown that an MRC-SS <48/60, indicative of ICU-AW, has no clinical predictive value in terms of ICU and hospital mortality and, indeed, it has a low positive predictive value for determining clinical outcome such as ICU and hospital length of stay [14].

Prevention and treatment

Physical and occupational therapy delivered to patients within the ICU has been shown to improve functional outcome in critical illness survivors when compared with standard treatment [18]. However, a subsequent study rehabilitation trial, which was novel in that it advocated the continuum of rehabilitation from admission to the ICU to the home setting, showed no clinical benefit [19]. Although these results were disappointing, this was not unexpected as it highlighted the difference in therapy provision to critically-ill patients between different healthcare systems, and, in particular, the frequency, duration and intensity of physical rehabilitation therapy treatment delivered. Future management of such patients will require a thorough understanding of the trajectory of acute skeletal muscle wasting. Data from the MUSCLE-UK study [20] showed that muscle wasting occurs early and rapidly during the first week of critical illness and it was greater in those patients with multi-organ failure compared with single organ failure. Importantly, muscle protein synthesis was at the same level as starved controls on admission to the ICU, but with recovery to the synthetic level of fed controls by the end of the first week. Muscle protein breakdown was shown to be elevated on admission and remained elevated after one week. These pathophysiological observations occurred despite enteral feeding and higher protein delivery was associated with greater muscle wasting. These data highlight that future work to prevent muscle wasting and weakness should consider a combination of nutrition, exercise therapy and pharmacological anabolic and anti-catabolic agents.

Conclusion

ICU-AW and weakness is a major clinical consequence of critical illness. It has an impact on clinical outcome with significant short-term and long-term effects on the patients, carers and healthcare organizations. More robust clinical tools are required to diagnose both wasting and weakness to risk stratify those patients most likely to benefit from interventions, such as exercise therapy.

Acknowledgements

The authors wish to acknowledge Bronwen Connolly for her detailed input and comments on this chapter.

References

1. Herridge MS, Tansey CM, Matté A, et al. (2011). Functional disability 5 years after acute respiratory distress syndrome. *New England Journal of Medicine*, **364**, 1293–304.
2. Stevens RD, Marshall SA, Cornblath DR, et al. (2009). A framework for diagnosing and classifying intensive care unit-acquired weakness. *Critical Care Medicine*, **37**, S299–308.
3. Ali NA, O'Brien JM, Jr, Hoffmann SP, et al. (2008). Acquired weakness, handgrip strength, and mortality in critically ill patients. American Journal of Respiratory and Critical Care Medicine, **178**, 261–8.
4. Sharshar T, Bastuji-Garin S, Stevens RD, et al. (2009). Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality. *Critical Care Medicine*, **37**(12), 3047–53.
5. Schweickert WD and Hall J. (2007). ICU-acquired weakness. *Chest*, **131**, 1541–49.
6. Lacomis D, Zochodne DW, and Bird SJ. (2000). Critical illness myopathy. *Muscle and Nerve*, **23**, 1785–8.
7. de Jonghe B, Lacherade J-C, Sharshar T, and Outin H. (2009). Intensive care unit-acquired weakness: Risk factors and prevention. *Critical Care Medicine*, **37**, S309–15.
8. Nanas S, Kritikos K, Angelopoulos E, et al. (2008). Predisposing factors for critical illness polyneuromyopathy in a multidisciplinary intensive care unit. *Acta Neurologica Scandinavica*, **118**, 175–81.
9. Puthucheary Z, Rawal J, Ratnayake G, Harridge S, Montgomery H, and Hart N. (2012). Neuromuscular blockade and skeletal muscle weakness in critically ill patients: Time to re-think the evidence? *American Journal of Respiratory and Critical Care Medicine*, **185**, 911–17.
10. Bittner EA, Martyn JA, George E, Frontera WR, and Eikermann M. (2009) Measurement of muscle strength in the intensive care unit. *Critical Care Medicine*, **37**, S321–30.
11. Harris M, Lou Y, Watson A, et al. (2000). Adductor pollicis twitch tension assessed by magnetic stimulation of the ulnar nerve. *American Journal of Respiratory and Critical Care Medicine*, **162**, 240–5.
12. Kleyweg RP, van der Meche FG, and Schmitz PI. (1991). Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle and Nerve*, **14**, 1103–9.
13. Fan E, Ciesla N, Truong A, Bhoopathi V, Zeger S, and Needham D. (2010). Inter-rater reliability of manual muscle strength testing in ICU survivors and simulated patients. *Intensive Care Medicine*, **36**, 1038–43.
14. Connolly BA, Jones GD, Curtis AA, et al. (2013). Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study. *Critical Care*, **17**(5), R229.
15. De Jonghe B, Bastuji-Garin S, Sharshar T, Outin H, and Brochard L. (2004). Does ICU-acquired paresis lengthen weaning from mechanical ventilation? *Intensive Care Medicine*, **30**, 1117–21.
16. Sharshar T, Basruji-Garin S, Stevens RD, et al. (2009). Presence and severity of intensive care acquired paresis at the time of awakening are associated with increased intensive care unit and hospital mortality. *Critical Care Medicine*, **37**, 3047–53.
17. Dowdy D, Eid M, Sedrakyan A, et al. (2005). Quality of life in adult survivors of critical illness: a systematic review of the literature. *Intensive Care Medicine*, **31**, 611–20.
18. Schweickert WD, Pohlman MC, Pohlman AS, et al. (2009). Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*, **373**(9678), 1874–82.
19. Denehy L, Skinner EH, Edbrooke L, et al. (2013). Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. *Critical Care*, **17**(4), R156
20. Puthucheary ZA, Rawal J, McPhail M, et al. (2013). Acute skeletal muscle wasting in critical illness. *Journal of the American Medical Association*, **310**(15), 1591–600.

SECTION 10

The metabolic and endocrine systems

PART 10.1

Physiology

CHAPTER 249

Normal physiology of the endocrine system

Simon Baudouin and Steve Ball

Key points

- The endocrine system describes an array of chemical signals (hormones).
- Working in concert with the nervous system, the endocrine system forms a complex neurohumoral network communicating changes in the environment to facilitate adaptive responses.
- The endocrine system has inherent rhythmicity. This has important implications for the integration and coordination of metabolism, and how we measure endocrine signals in clinical settings.
- At a cellular level, hormone action is mediated through a series of discrete, but interacting signal transduction pathways.
- Specificity, sensitivity, amplification, and integration of endocrine signalling reflect the combined properties of hormones, hormone receptors, and down-stream intracellular signal transduction cascades.

Introduction

Hormones as biological messengers

Human physiology encompasses complex processes through which we adapt to changes in the external and internal environment. These adaptations are characterized by coordinated responses across a range of systems. While each component of a given response may appear distinct, taken together they form an integrated package. This requires a complex coordination function, able to both sense and produce an effect, respond over an appropriate time span, and articulate with other mechanisms that may be working in parallel. The endocrine system is a key communication component of this function, one based on circulating chemical signals. In concert with the central and peripheral nervous systems, the endocrine system forms a sophisticated neurohumoral network linking cell-, organ-, and system-based processes to produce coherent adaptive responses (Table 249.1)

Hormone chemistry and hormone production

The endocrine system is composed of a series of discrete glands, each producing one or more chemical messengers (hormones) that act on target sites following release into the general circulation. Some hormones have additional effects close to the site of production (paracrine), or at the very site of production (autocrine), independent of distribution through the circulation.

Hormones range from small and relatively simple molecules to large, multi-subunit complexes (see Table 249.2 for classification). Hormone chemistry is important, as physical characteristics contribute to mechanism and range of action. Larger, water-soluble hormones (such as peptides) do not readily access the interior of target cells. In contrast, lipid-soluble hormones, such as steroid and thyroid hormones are more likely to circulate bound to plasma proteins and can readily cross the cell membrane.

Endocrine physiology

The endocrine system adapts physiology to environmental context. All endocrine glands have a method to sense the internal and external environment. This may be neural, humeral (through another hormone), or a combination of both.

The hypothlamo-pituitary endocrine axes

The hypothalamus is a discrete collection of nuclei lying in close relationship to the floor of the third ventricle, integrated through afferent and efferent projections with key higher and lower centres, including those regulating autonomic function. Functionally, the hypothalamus is a neurohumoral junction where the two communication systems meet information is integrated and a coordinated output generated through both neural and humoral (endocrine) pathways.

The pituitary gland lies inferior to the hypothalamus, linked though the pituitary stalk. While anterior and posterior components of the gland are anatomically related, they are developmentally and functionally discrete [1].

Hypothalamic neurosecretory efferents project to terminals lining the venous hypophyseal-portal system that drains to the anterior pituitary via the pituitary stalk. Small peptides and amines released into the portal venous system constitute the principle mechanism of positive and negative regulation of anterior pituitary hormone secretion. The posterior pituitary hormones (oxytocin and vasopressin) are synthesized in the cell bodies of magnocellular neurones in the paraventricular (PVN) and supra-optic nuclei (SON) of the hypothalamus. These magnocellular neurones project directly to the posterior pituitary, through the hypophyseal-portal tract and pituitary stalk, where they terminate in the vascular bed draining the posterior pituitary gland.

Within the anterior pituitary, specific hormones are produced by discrete populations of cells and released into the systemic circulation through the venous system draining the gland. Arginine-vasopressin (AVP) and oxytocin are produced by discrete

Table 249.1 Hormones have a wide range of physiological actions. Some have a single point of action, some act at multiple points in the same physiological process, while others act at multiple points in a range of different, un-related pathways

Hormone	Physiological action
ACTH	Regulation of adrenocortical steroid hormone production
TSH	Regulation of thyroid hormone production
LH	Regulation of gonadal hormone function
FSH	Regulation of gonadal function
Prolactin	Stimulation and maintenance of lactation
Growth hormone	Promotion of linear growth, regulation of intermediary metabolism
Vasopressin	Increases renal water reabsorption, stimulation of glycogenolysis and gluconeogenesis
Oxytocin	Milk let down, reproductive tract contraction
Thyroxine (T4), triiodothyronine (T3)	Cell growth and differentiation, intermediary metabolism
Cortisol	Vascular integrity, intermediary metabolism
Aldosterone	Increased renal sodium reabsorption and potassium excretion
Epinephrine and norepinephrine	Vascular smooth muscle tone, intermediary metabolism
Oestrogen and testosterone	Reproductive function, bone metabolism, intermediary metabolism
Insulin	Blood glucose control, intermediary metabolism
Glucagon	Blood glucose control, intermediary metabolism
Somatostatin	Paracrine regulation of islet cell function, gut motility, growth hormone production

magnocellular neurones and released independently in response to chemical and neural inputs to the PVN and PVN.

Anterior pituitary hormones fall into one of two categories:

- Hormones that act directly on target tissues to enable physiological change.
- Hormones that act on other endocrine glands and produce indirect effects through the action of hormones produced by these secondary target glands.

Production and release of specific anterior pituitary hormones reflects the balance of positive and negative stimuli acting on the respective populations of cells producing the hormone. Systemic hormone feedback is also exerted at the level of the hypothalamus. (Fig. 249.1, Table 249.3)

In keeping with a predominant role in the regulation of renal water excretion, AVP is released in response to increasing osmotic pressure or reduced vascular volume, with relevant afferent sensory input affecting both AVP production and release by PVN/SON neurones. Oxytocin production/release is triggered through reproductive tract and breast sensory afferents.

Biological clocks and rhythms

In common with many biological processes, many endocrine systems have intrinsic pulsatility or rhythm. The frequency and amplitude of

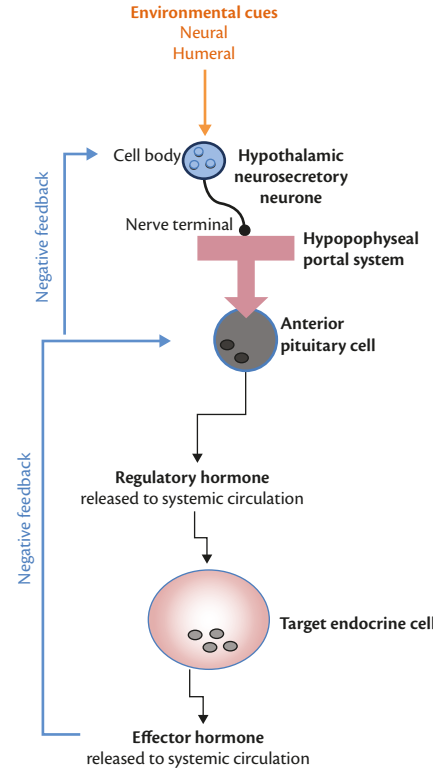


Fig. 249.1 The hypothalamo-pituitary-endocrine axis and feedback control systems.

these rhythms are key characteristics of specific endocrine systems and have critical functional roles. Cellular responses to endocrine signals are rarely simple, binary responses reflecting the presence or absence of a hormone. The magnitude of response can be influenced by the magnitude or amplitude of the signal (quantitative modulation). Moreover, responses may be modified by the frequency of the hormone rhythm (frequency modulation). In some systems, frequency modulation can be profound. Anterior pituitary gonadotrophs produce luteinising hormone (LH) and follicle stimulating hormone (FSH) in response to pulsatile gonadotropin-releasing hormone (GnRH) signals *in vivo* and *in vitro*. In contrast, gonadotroph LH and FSH production is reduced when the GnRH signal is constant, reflecting functional desensitization [2].

Classification of endocrine rhythms

- *Ultradian rhythms*: these cycle over several days. In mammals, this periodicity can parallel seasonal environmental changes, such as light period or temperature.
- *Circadian rhythms*: periodicity that runs within or close to a 24-hour cycle is described as circadian. Circulating levels of several hormones cycle over this range in phase with the day–night photoperiod.
- *Infra-radian rhythms*: cyclical oscillations that demonstrate pulsatility over minutes are described as infra-radian. Many hypothalamic hormones regulating anterior pituitary hormone production demonstrate infra-radian rhythmicity.

The origins and integration of endocrine rhythms

The dominant central 'pacemaker' controlling neurohumeral rhythms is the suprachiasmatic nucleus (SCN) of the hypothalamus. SCN neurons are sensitive to day–night photoperiodicity,

Table 249.2 Hormone classification. Hormones can be classified by chemistry, site of origin, or mechanism of action

Hormone	Source	Chemistry	Receptor	Subtype	Second messenger cascade
Adrenocorticotrophic hormone	Pituitary	Peptide	Plasma membrane	G-protein coupled	Cyclic nucleotide-mediated intracellular phosphorylation cascade
Thyroid-stimulating hormone	Pituitary	Glycopeptide			
Luteinizing hormone and follicle stimulating hormone	Pituitary	Glycopeptide			
Glucagon	Pancreas	Peptide			
Epinephrine and norepinephrine	Adrenal medulla	Amine			
Growth hormone	Pituitary	Peptide		Tyrosine kinase	Receptor- mediated intracellular phosphorylation cascade
Prolactin	Pituitary	Peptide			
Insulin	Pancreas	Peptide			
Cortisol	Adrenal cortex	Steroid	Cell nucleus	Glucocorticoid receptor (GR)	Regulation gene expression with transcriptional co-activators and repressors
Aldosterone	Adrenal cortex	Steroid		Mineralocorticoid receptor (McR)	
Oestrogen	Ovary	Steroid		Oestrogen receptor (ER) α and β	
Progesterone	Ovary	Steroid		Progesterone receptor (PR)	
Testosterone	Testes	Steroid		Androgen receptor (AR)	
Thyroxine (T4) & triiodothyronine (T3)	Thyroid	Iiodothyronine		Thyroid hormone receptor (TR) α and β	

receiving direct input from retinal-SCN afferents. In turn, the SCN has efferent connections with autonomic centres in addition to other hypothalamic nuclei regulating anterior pituitary hormone production. The hard-wiring of the SCN enables integration of photo-period and metabolic signals, facilitating a coordinated neurohumeral output response adapted to these two key 'zeitgebers' (time-givers) determining the central clock-set [3].

Important recent data have demonstrated the presence of key clock-machinery in many peripheral tissues. The concept of a central, neural pacemaker driving physiological rhythms through neurohumoral mechanisms must be modified to take into account the potential for peripheral clocks to generate their own, intrinsic rhythms: influenced by the local metabolic environment in addition to SCN-generated control [4].

Endocrine rhythms and hormone measurement

There are additional, important impacts of endocrine rhythms. While we have sophisticated methods for laboratory-based hormone measurement, measuring a dynamic system can be problematic. In some situations, we need to consider standardized timing. In others, a simple 'snapshot' may not be a reliable assessment of the function or functional capacity of the system—a dynamic evaluation may have greater reliability and validity. There are clear implications for valid reference ranges and data interpretation.

Signal transduction: the principles of hormone action

Generic signal transduction

Good communication-effector systems run on generic principles—fidelity, specificity, reliability. The right message gets to the right place and the right thing happens every time. These are the key principles of hormone action. Signalling molecules released into the circulation (hormones) need a mechanism through which they communicate with individual target cells to bring about change. This requires signalling, receiving, and signal transduction [5]. Signal

Table 249.3 Anterior pituitary hormones and their regulation. Anterior pituitary hormone production is controlled through a combination of specific hypothalamic factors and the feedback of hormones produced in response by target glands, controlled by the anterior pituitary

Anterior pituitary hormone	Hypothalamic regulation		Target tissue	Negative feedback
	Positive	Negative		
Adrenocorticotrophic hormone	Corticotrophin-releasing factor, arginine-vasopressin		Adrenal cortex	Cortisol
Thyroid-stimulating hormone	Thyrotropin-releasing hormone		Thyroid gland	Thyroxine, triiodothyronine
Luteinizing hormone	Gonadotropin-releasing hormone		Gonad	Testosterone, oestrogen
Follicle-stimulating hormone	Gonadotropin-releasing hormone		Gonad	Testosterone, oestrogen
Prolactin	Thyrotropin-releasing hormone	Dopamine	Breast Liver	
Growth hormone	Growth hormone-releasing factor	Somatostatin	Liver, skeletal muscle, adipocytes, bone	Insulin-like growth factor-1

reception and transduction are brought about by hormone binding to a receptor on or within a target cell. This hormone–receptor interaction underpins the fidelity, sensitivity, and specificity of the communication system. Hormone–receptor interaction is coupled to a further, multistep signal transduction cascade with amplification and integration leading to the target cell response (Fig. 249.2).

Hormone receptors

Peptide and other hydrophilic hormones bind to receptors on the cell surface, triggering an intracellular signal-transduction cascade. This cascade can impact rapidly on a range of intracellular metabolic processes; longer-term effects can be produced via effects on the expression of target genes. In contrast, the receptors for steroid and thyroid hormones are hormone-sensitive nuclear transcription factors. In response to hormone–receptor binding, they interact with DNA directly and influence gene expression through recruiting co-activators and co-repressors of the transcriptional machinery.

Affinity, specificity, sensitivity

Affinity and specificity are dictated by the degree of 'fit' of the given hormone for the ligand-binding domain of the cognate receptor in both absolute fit (affinity) and relative (specificity) terms. Sensitivity reflects the bio-physical impact of hormone–receptor interaction on downstream processes. The number of receptors activated and the impact of hormone binding on receptor conformation initiates and drives subsequent steps in the signal transduction cascade. Key to fidelity in hormone action is the specificity of hormone–receptor interaction. While ligands of similar chemical composition may cross-interact with a number of related receptors in vitro, cross-interaction is rarely a problem in vivo, except in circumstances of aberrant receptor expression or supraphysiological hormone levels.

Pre- and post-receptor modification of hormone action

Control of hormone production, fidelity, and sensitivity of hormone-receptor interaction provide a substantial degree of control over hormone action. Many hormones (e.g. steroid and thyroid hormones, growth hormone, and insulin-like growth factor-1) circulate bound to plasma proteins. The hormone is only able to interact with its cognate receptor or enter the target cell in the 'free' state. Concentration of 'free' hormone depends on a number of factors. including total hormone concentration, concentration of the binding protein, and affinity of the binding protein for the given hormone. Concentration of binding protein is open to physiological regulation and can change significantly in a range of pathophysiological situations [6]. In addition, hormone-binding protein kinetics can be affected by a range of substances that may compete for non-specific ligand binding sites on plasma binding proteins (e.g. free fatty acids).

Additional prereceptor modification of hormone action occurs in some systems through local generation or inactivation of active hormone. While the major hormone produced by the thyroid gland is thyroxine (T4), the active thyroid hormone is triiodoyhyronine (T3), generated from T4 by deiodination of the outer thyronine ring. Local deiodinase activity can modulate thyroid hormone action through increasing or reducing local T3 concentrations [7]. The mineralocorticoid receptor (McR) mediating the actions of aldosterone also binds cortisol with high affinity. Circulating cortisol levels are much higher than corresponding levels of aldosterone. Mineralocorticoid target tissues express high levels of the enzyme 11-β-hydroxysteroid dehydrogenase type 2 (11 βHSD2), which metabolizes cortisol to the inactive cortisone, thus protecting the McR from inappropriate activation by glucocorticoids. The reciprocal process, generation of cortisol from cortisone through the action of 11 βHSD1, can also modify local glucocorticoid action. The activities of both 11 βHSD enzymes are under physiological regulation. Breakdown in the regulation of 11 βHSD activity has significant pathophysiological consequences [8].

There are additional receptor and post-receptor mechanisms for modifying hormone action—alteration of receptor number or modification of downstream transduction cascades can produce either sensitization or desensitization to hormone signalling.

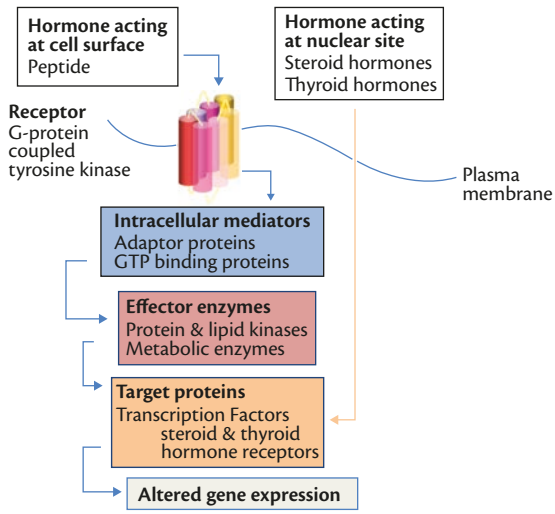


Fig. 249.2 Mechanisms of hormone action and signal transduction. While mechanisms of hormone action are diverse, they encompass generic principles of signal sensing, signal transduction, and activation of effector pathways.

Amplification, cross talk, and integration of signal transduction

Cell physiology is complex and involves multiple, integrated processes. Systems regulating these processes require similar characteristics to be fit for purpose. A number of hormones may impact on common or related cell processes. Integration of these multiple inputs is managed through convergence on key points in cell physiology pathways. The phenomenon of a hormone having differential effects on a number of cell processes (divergence and selective amplification of signal transduction) also involves signal flux through key regulatory points, each of which may be influenced by a number of parallel systems [9].

Taken together, the mechanisms of hormone action cover a bewildering range and complexity that match those of the very cellular processes they regulate.

Biochemical characteristics of endocrine pathology

Failure of a component in any complex system may be primary (reflecting a problem with the individual component) or secondary (reflecting a problem with an upstream component that is responsible for regulating/controlling the component in question). Similarly, underproduction of a given hormone may

reflect a problem with the gland making the hormone in question (primary failure). Alternatively, it may reflect a problem with the hypothalamo-pituitary axis that drives the gland in question (secondary failure). In secondary failure, the relevant hypothalamo-pituitary hormone will be low or normal, while in primary failure it will be high.

Hormone resistance states can produce unusual patterns of clinical features and biochemical test results that appear incongruous. Clinical features generally suggest normal or underactivity of the hormone in question, in contrast with biochemical test data that are dominated by high levels of the hormone. Acquired insulin resistance secondary to obesity is common, characterized by normal or high fasting glucose levels, and elevated insulin levels. Other hormone resistance states are more unusual. They can be congenital or acquired. Congenital hormone resistance can be isolated or involve multiple endocrine systems. Congenital isolated hormone resistance suggests loss of receptor function through gene deletion or loss of function mutation. A more wide-ranging problem suggests loss of function in downstream signal transduction, given transduction cascades of several hormones may share common components.

Constitutive activity within an endocrine pathway in the absence of hormone can also produce incongruous data. The molecular pathology may also reflect a problem at receptor or post-receptor level [10].

References

1. Melmed S (ed.). (2010). *The Pituitary*, 3rd edn. London: Academic Press.
2. Gan E-H and Quinton R. (2010). Physiological significance of the rhythmic secretion of hypothalamic and pituitary hormones. *Progress in Brain Research*, **181**, 111–26.
3. Bonnefont X. (2010). Circadian timekeeping and multiple timescale neuroendocrine rhythms. *Journal of Neuroendocrinology*, **22**, 209–16.
4. Katada S, Imhof A, and Sassone-Corsi P. (2012). Connecting threads: epigenetics and metabolism. *Cell*, **148**, 24–8.
5. Downward J. (2001). The ins and outs of signaling. *Nature*, **411**, 759–62.
6. Brooks AJ and Waters MJ. (2010). The growth hormone receptor: mechanism of activation and clinical implications. *Nature Reviews Endocrinology*, **6**, 515–25.
7. Williams GR and Bassett D. (2011). Local control of thyroid hormone action—role of type 2 deiodinase. *Journal of Endocrinology*, **209**, 261–72.
8. Draper N and Stewart PM. (2005). 11β-Hydroxysteroid dehydrogenase and the pre-receptor regulation of corticosteroid hormone action. *Journal of Endocrinology*, **186**, 251–71.
9. McNeill H and Woodgett JR. (2010). When pathways collide: collaboration and connivance among signaling proteins in development. *Nature Reviews Molecular Cell Biology*, **11**, 404–13.
10. Spiegel AM and Weinstein LS. (2004). Inherited diseases involving G proteins and G protein-coupled receptors. *Annual Review of Medicine*, **55**, 27–39.

PART 10.2

Electrolyte disturbance

CHAPTER 250

Disorders of sodium in the critically ill

Howard L. Corwin and John K. McIlwaine

Key points

- Hypernatraemia and hyponatraemia are common clinical conditions.
- Maintenance of normal sodium concentration is a balance between water intake and water excretion. Water excess results in hyponatraemia and water deficit results in hypernatremia.
- Central nervous system symptoms predominate in patients with serum sodium abnormalities.
- The severity of symptoms reflects the degree of sodium abnormality and the time over which the abnormality has developed.
- The rapidity with which serum sodium abnormalities should be corrected depends upon the presence of symptoms and the length of time over which the abnormality has developed. Too rapid correction of patients with more chronic sodium abnormalities can lead to neurological deterioration.

Introduction

Sodium disorders, i.e. hyponatraemia and hypernatraemia, are among the most common clinical problems observed in the critically ill. Up to one-third of patients have some degree of dysnatraemia on admission to ICU [1,2]. Hyponatraemia is more common than hypernatraemia—18% of patients present with some degree of hyponatraemia, while 7% of patients present with hypernatraemia [1]. These disorders also develop commonly during an intensive care unit (ICU) admission, with approximately 30% of surgical patients in one study developing an ICU-acquired dysnatraemia [3]. While these disorders are often asymptomatic, there may be symptoms ranging from minor to life threatening. Independent of the severity of symptoms, dysnatraemias, including very mild abnormalities, are associated with worse clinical outcomes [1–3]. Even fluctuations of sodium within the normal range have been associated with an increase in mortality [3]. Mortality in hypernatraemia can be as high as 70% [4–6]. Although this high mortality rate no doubt reflects the severity of underlying disease in these patients, there is still important morbidity related to hypernatraemia [4]. Neurological sequelae from hypernatraemia are common, particularly in the paediatric population [6]. Mortality in acute hyponatraemia is reportedly as high as 50%, and 10–20% in chronic hyponatraemia [7–10]. Whether prevention or treatment of these disorders will improve clinical outcomes remains to be proved, although the treatment of dysnatraemia is an important challenge in the ICU.

The approach to treating sodium disorders in the ICU patient involves balancing the risk of treatment versus the risk of the disorder, as too vigorous treatment can result in complications. In treating dysnatraemia it is important to keep in mind that sodium disorders generally reflect abnormalities of water balance that may at times also involve changes in sodium balance. Plasma sodium concentration is the main factor in plasma osmolality. Hyponatraemia generally reflects hypo-osmolality, while hypernatraemia reflects hyperosmolarity.

Hypernatraemia

The maintenance of a normal serum sodium concentration (135–145 mmol/L) is dependent on the balance between water intake and water excretion. Hypernatraemia usually results from a net free water deficit that leads to an increase in serum tonicity or osmolality. Hypernatraemia may be associated with either volume depletion, euvolaemia, or hypervolaemia, depending on the balance of salt and water loss and intake. At the same time, sodium content may be low, normal, or high, in each of these circumstances. Hypernatraemia can occur when water loss exceeds sodium loss resulting in hypovolaemia and hypernatraemia. Hypernatraemia can also occur with positive sodium balance such as with hypertonic saline infusion or with replacing water loss with normal saline. Relative sodium and volume status has important implications for the treatment of hypernatraemia patients.

The brain is particularly susceptible to the effects of hypernatraemia. In the presence of hypernatraemia, achieving osmotic equilibrium results in intracellular dehydration as fluid moves out of cells in response to the acute increase in extracellular tonicity resulting from the hypernatraemia. The net result is a loss of brain volume, which in turn can place mechanical stress on cerebral vessels, possibly resulting in bleeding [6]. This is particularly the case with acute hypernatraemia. In contrast, with chronic hypernatraemia, cellular adaptation occurs due to the accumulation of so-called idiogenic osmoles in brain cells, minimizing cellular dehydration. The presence of these idiogenic osmoles presents a risk for the development of cerebral oedema during the treatment of hypernatraemia.

Central nervous system (CNS) symptoms are most common with hypernatraemia. However, hypernatraemia symptoms are often non-specific and thus difficult to distinguish from those of underlying illnesses, particularly in critically ill patients. Symptoms

in early stages can include encephalopathy, delirium, weakness, and lethargy that may progress to seizures, coma, and death in the later stages. CNS symptoms result from the water movement out of the brain cells and resulting cellular dehydration, rather than the hypernatraemia per se. Neurological deterioration can be seen during rapid correction of hypernatraemia as a result of decreasing extracellular tonicity and the resultant movement of water back into cells causing the development of cerebral oedema. This is particularly seen in more chronic states in which idiogenic osmoles are present in brain cells. Depending on the aetiology of the hypernatraemia, signs of either volume depletion or volume overload may be present with the hypernatraemia on presentation.

Treatment

The treatment for hypernatraemia is water repletion. Assuming total body water is 60%, the water deficit may be estimated as follows:

$$\text{Water deficit} = [0.6 \times \text{Total body Weight}] \times [(\text{Plasma sodium concentration}/140) - 1] \quad \text{[eqn1]}$$

While the percentage of water relative to total body weight is 60% for males, it is closer to 50% in women, so 0.5 should be used; however, it is independent of gender in the elderly. The optimal correction rate for hypernatraemia has not been definitively determined. Treatment (water deficit replacement) should be at a rate that balances the risk of hypernatraemia, particularly if symptomatic, with the risk of too rapid correction, particularly in cases of chronic hypernatraemia. It has been suggested that rate of correction of sodium should be no more than 0.5 mEq/L per hour or 12 mEq/L per day [11]. However, the speed of correction should be determined by the acuteness of onset and severity of symptoms. Neurological status needs to be closely monitored during replacement for evidence of the development of cerebral oedema. Ongoing fluid and electrolyte losses also need to be replaced during treatment.

In patients with volume depletion who have haemodynamic instability associated with the hypernatraemia, volume replacement with isotonic saline is indicated. Once the patient is haemodynamically stable, water replacement can be initiated. Hypotonic saline (e.g. 0.45% saline) may be preferable to water as the replacement fluid for these patients. If hypernatraemia is associated with hypervolaemia treatment should be directed towards removing the excess sodium. Reducing sodium intake while inducing sodium loss with diuretics and replacing urine loss with free water can be use in this situation. Dialysis may be necessary if renal failure is present.

Hyponatraemia

Hyponatraemia is a water, rather than a sodium problem. Although total sodium balance may be abnormal, when hyponatraemia is present there is almost always water excess relative to sodium. Hyponatraemia is generally associated with hypo-osmolality. Hyponatraemia with elevated plasma osmolality can be seen in clinical situations in which solutes are added to the extracellular space, e.g. elevated glucose, drawing water out of cells, resulting in hyponatraemia. Hyponatraemia with normal osmolality used to be seen with severe hyperlipidaemia or hyperproteinaemia, which interfered with the correct measurement of sodium concentration. In many of the clinical conditions associated with hyponatraemia there is impaired water excretion by the kidney impairing the ability of the kidney to correct the sodium concentration. Patients who are hyponatraemic may be volume depleted (water deficit and sodium deficit), euvolaemic (water excess with normal sodium balance), or hypervolaemic (water excess and sodium excess). Similar to hypernatraemia, volume status has implications for the treatment of hyponatraemia.

In the presence of hyponatraemia, the extracellular compartment is hypotonic relative to the intracellular compartment. This hypotonicity results in water movement from the extracellular into the intracellular space resulting in cell swelling. In the CNS, cell swelling manifests as cerebral oedema and results in the symptoms associated with hyponatraemia. The degree of cerebral cell swelling correlates with the symptom severity. The CNS can adapt to hyponatraemia in two ways. First, cerebral oedema causes an increase in interstitial hydrostatic pressure and results in the movement of fluid from the interstitial space into the cerebrospinal fluid (CSF), leading to some amelioration of cerebral oedema, assuming normal CSF production and reabsorption. Secondly, solutes are lost from cells, resulting in a decrease in intracellular osmolarity and cellular water efflux back into the extracellular space. The initial solutes lost are sodium and potassium, followed over several days by organic solutes. Because of this cerebral adaptation, the severity of neurological symptoms is related to the acuity and magnitude of the hyponatraemia. If hyponatraemia develops gradually, brain cells can compensate by decreasing intracellular osmolality, limiting the degree of cerebral oedema and resultant neurological dysfunction. On the other hand, during the correction of chronic hyponatraemia, the regeneration of these intracellular osmolytes can lag behind the correction of the sodium; as a consequence, cerebral dehydration can occur with too rapid correction.

In acute hyponatraemia, nausea, vomiting, lethargy, and confusion can occur and in turn may progress to coma, seizures, eventual cerebral herniation and death [10,12]. The elderly and the young are more likely to be symptomatic from hyponatraemia [8]. Menstruating women also tend to be more symptomatic and are at greater risk for neurological complications from acute hyponatraemia [10]. Early in the development of hyponatraemia, the symptoms are difficult to distinguish from those related to the underlying disease process.

Treatment

Treatment of hyponatraemia is primarily dependent on symptoms, although the acuteness of the hyponatraemia is also a consideration. More severe symptoms tend to occur with acute hyponatraemia. Since brain adaption to hyponatraemia occurs rapidly, after 24–48 hours hyponatraemia is considered chronic. Acute (<48 hours) or chronic (>48 hours) hyponatraemia with severe symptoms (e.g. seizures) requires immediate therapy. Treatment must balance the risk of the hyponatraemia versus the risk of rapid correction—with severe symptoms the risk favours treatment. However, the optimal approach for the treatment has been controversial [13–15]. The controversy results from reports of the occurrence of a central demyelination syndrome, osmotic demyelination, associated with the correction of hyponatraemia in some patients [12,16–18]. This syndrome appears to be more common with chronic hyponatraemia (>48 hours), overcorrection of hyponatraemia, or large rapid corrections; more than 10–12 mmol/L per 24 hours or 18 mmol/L in 48 hours [12,17–19].

The approach to the treatment of acute symptomatic hyponatraemia is infusion of hypertonic (3%) saline. Therapy is targeted toward resolution of symptoms, which usually can be achieved with a 4 to 6 mmol/L increase in serum sodium concentration [19]. Bolus infusions of 3% saline, e.g. 100 mL are recommended [19]. If symptoms persist, an additional one or two boluses can be given. Current recommendations suggests that the goal of treatment should be an increase in sodium of no more than 6–8 mmol/L in 24 hours, 12–14 mmol/L in 48 hours, and 14–16 mmol/L in 72 hours in order to avoid iatrogenic injury due to overcorrection while treating the acute symptoms. In treating patients with chronic (>48 hours, or of unknown duration) symptomatic hyponatraemia, the higher risk of neurological complications related to therapy mandates a cautious approach. As with acute hyponatraemia, neurological symptoms predominate in the clinical presentation of these patients. Initial treatment with 3% sodium chloride should be directed toward the resolution of symptoms as noted previously.

The hypertonic saline necessary to correct the serum sodium concentration to a safe level (e.g. 120 mEq/L) can be estimated by calculating the sodium deficit:

$$\begin{aligned}\text{Sodium deficit} = {} & 0.5 \times \text{lean body weight} \\ & \times (\text{desired serum sodium concentration} \\ & - \text{observed serum sodium concentration})\end{aligned} \quad \text{[eqn 2]}$$

The amount of hypertonic saline required to replace the deficit is then infused at a rate that permits correction within the parameters noted in eqn 2. Frequent checking of electrolytes is necessary to ensure that correction is not too rapid. Diuresis is often the cause for overcorrection and can be reversed by administration of desmopressin [19].

Most patients with hyponatraemia are asymptomatic, or have subtle neurological symptoms. Aggressive correction of serum sodium in these patients is not indicated. Treatment in asymptomatic patients is based on the underlying cause of the hyponatraemia and the patient's volume status: euvolaemic, hypovolaemic, or hypervolaemic (oedema).

Patients with chronic hyponatremic are often euvolaemic. In this group, the syndrome of inappropriate antidiuretic hormone (SIADH) is the most common diagnosis. The inappropriate (non-osmotic) presence of antidiuretic hormone impairs free water excretion by the kidney; impaired water excretion coupled with water intake results in hyponatraemia. Water restriction is the mainstay of therapy for these patients. The amount of water restriction must be sufficient to achieve negative water balance (i.e. the difference between the total intake and excretion of water), or hyponatraemia correction will not occur. Therefore, all water losses (insensible losses, urinary losses, and gastrointestinal losses) must be considered when deciding on the degree of water restriction. If urine osmolarity is high, it may be necessary to decrease it to achieve a negative water balance. This can be achieved by adding a loop diuretic; however, salt intake must be increased to correct for losses resulting from the increased natriuresis with diuresis. Less commonly, demeclocycline (300–600 mg bd), which interferes with the action of antidiuretic hormone, is used to decrease urine osmolarity. In patients with more pronounced hyponatraemia, the combination of normal saline (or high salt intake) and a loop diuretic can be used to correct hyponatraemia. In asymptomatic patients the use of hypertonic saline is rarely, if ever, indicated.

Hyponatraemia associated with volume depletion is a result of the loss of both sodium and water, combined with the simultaneous intake of water or hypotonic fluids. The release of antidiuretic hormone stimulated by hypovolaemia inhibits the kidney's ability to excrete water. The net result is positive water balance relative to sodium and hyponatraemia. The treatment of hyponatraemia in this setting is infusion of normal saline to correct the volume depletion. As volume status is corrected, antidiuretic hormone excretion is turned off, and the kidney excretes the excess water, correcting the serum sodium concentration. The cause of the initial sodium and water loss should also be identified and treated.

Hyponatraemia associated with hypervolaemia is very common and is generally associated low 'effective' volume states, such as, but not limited to, heart failure, cirrhosis, and nephrotic syndrome. The hallmark of these conditions is the presence of oedema. The mechanism for the development of hyponatraemia in these settings is diminished effective circulating volume leading to sodium and water retention. The water retention is a result of non-osmotic antidiuretic hormone release impairing the kidney's ability to excrete water. In this respect, the mechanism is similar to that responsible for hyponatraemia associated with volume depletion. Therapy is directed toward correcting the primary disease process responsible for the decrease in effective circulating volume. Specific treatment of the hyponatraemia consists of sodium and water restriction. The use of loop diuretics may facilitate free water excretion and correction of the hyponatraemia; notably, thiazide diuretics may exacerbate hyponatraemia and should be avoided.

Conclusion

There are now vasopressin receptor antagonists available—either selective V_2 or non-selective V_{1A} and V_2, tolvaptan and conivaptan, respectively [20]. Both have indications for euvolaemic hyponatraemia and tolvaptan has an additional indication for hypervolaemic hyponatraemia. At this point vasopressin receptor antagonists are not recommended for the routine treatment of hyponatraemia [20].

References

1. Funk GC, Lindner G, Duml W, et al. (2010). Incidence and prognosis of dysnatremias present on ICU admission. *Intensive Care Medicine*, **36**, 304–11.
2. Darmon M, Diconne E, Souweine B, et al. (2013). Prognostic consequences of borderline dysnatremia: pay attention to minimal sodium change. *Critical Care*, **17**, R12.
3. Sakr Y, Rothe S, Pires AM, et al. (2013). Fluctuations in serum sodium level are associated with an increased risk of death in surgical ICU patients. *Critical Care Medicine*, **41**, 133–42.
4. Snyder NA, Feigal DW, and Arieff AI. (1987). Hypernatremia in elderly patients: A heterogeneous, morbid, and iatrogenic entity. *Annals of Internal Medicine*, **107**, 309–19.
5. Polderman KH, Schreuder WO, Strack van Schijndel RJ, and Thijs LG. (1999). Hypernatremia in the intensive care unit: An indicator of quality of care? *Critical Care Medicine*, **27**, 1105–8.
6. Simmons MA, Adcock EW 3rd, Bard H, and Battaglia FC. (1974). Hypernatremia and intracranial hemorrhage in neonates. *New England Journal of Medicine*, **291**, 6–10.
7. Madiba TE, Haffejee AA, and Mokoena TR. (1998). Hyponatraemia—a prospective analysis of surgical patients. *South African Journal of Surgery*, **36**, 78–81.

8. Kennedy PG, Mitchell DM, and Hoffbrand BI. (1978). Severe hyponatraemia in hospital inpatients. British Medical Journal, **2**, 1251–3.
9. DeVita MV, Gardenswartz MH, Konechy A, et al. (1990). Incidence and etiology of hyponatremia in an intensive care unit. *Clinical Nephrology*, **34**, 163–6.
10. Ayus JC, Wheeler JM, and Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Annals of Internal Medicine*, **117**, 891–7.
11. Kahn A, Brachet E, and Blum D. (1979). Controlled fall in natremia and risk of seizures in hypertonic dehydration. *Intensive Care Medicine*, **5**, 27–31.
12. Sterns RH, Cappuccio JD, Silver SM, et al. (1994). Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. *Journal of the American Society for Nephrology*, **4**, 1522–30.
13. Fraser CL and Arieff AI. (1997). Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. *American Journal of Medicine*, **102**, 67–77.
14. Ayus JC and Arieff AI. (1999). Chronic hyponatremic encephalopathy in post-menopausal women: Association of therapies with morbidity and mortality. *Journal of the American Medical Association*, **281**, 2299–304.
15. Sterns RH. (1992). Severe hyponatremia: the case for conservative management. *Critical Care Medicine*, **20**, 534–9.
16. Cohen BJ, Jordan MH, Chapin SD, et al. (1991). Pontine myelinolysis after correction of hyponatremia during burn resuscitation. *Journal of Burn Care and Rehabilitation*, **12**, 153–6.
17. Karp BI and Laureno R. (1993). Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia. *Medicine*, **72**, 359–73.
18. Sterns RH, Riggs JE, and Schochet SS Jr. (1986). Osmotic demyelination syndrome following correction of hyponatremia. *New England Journal of Medicine*, **314**, 1535–42.
19. Sterns RH, Nigwekar SU, and Hix JK. (2009). The treatment of hyponatremia. *Seminars in Nephrology*, **29**, 282–7.
20. Gross PA, Wagner A, and Decaux G. (2011). Vaptans are not the mainstay of treatment in hyponatremia: perhaps not yet. *Kidney International*, **80**, 594–600.

CHAPTER 251

Disorders of potassium in the critically ill

Matthew C. Frise and Jonathan B. Salmon

Key points

- Most true hyperkalaemia results from renal insufficiency since the kidney is responsible for the vast majority of potassium excretion.
- Acidosis favours potassium shift from within cells to the extracellular fluid in exchange for hydrogen ions.
- Glucose-insulin infusions and sodium bicarbonate promote entry of potassium into cells and loop or thiazide diuretics increase potassium excretion.
- Calcium salts are appropriate for patients with severe hyperkalaemia or dysrhythmias.
- Hypokalaemia may be present in patients with low, normal, or high total body potassium.

Physiology of potassium balance

Potassium is the major intracellular cation with only 2% found extracellularly. Plasma levels are maintained in health between 3.5 and 5.0 mmol/L, and are determined by the balance between absorption and excretion, and by internal shifts between extracellular and intracellular compartments. There is no regulation of gastrointestinal absorption; of the normal daily intake of 50–150 mmol, 85–90% is absorbed with the remainder excreted in faeces. Excess potassium is renally excreted—if renal function is compromised plasma potassium rises sharply.

Renal excretion is normally 3–300 mmol/day, but adaptation allows excretory capacity to reach 500 mmol/day in chronically high potassium intake. Renal responses to excessive intake are relatively rapid [1] with approximately half an acute load appearing in the urine within 12 hours. Conversely, renal responses to dietary depletion are slow, with excretion falling gradually over 7–14 days such that total body deficits of 200 mmol or more may develop.

Plasma potassium reflects total body potassium only in stable states at normal pH. In acutely-ill patients, particularly those with acid–base disturbances, plasma and total body potassium may vary in opposite directions, with plasma potassium rising in acidosis and falling in alkalosis. These changes are more marked with metabolic than with respiratory disturbances.

Hyperkalaemia

Aetiology and pathophysiology of hyperkalaemia

Causes of hyperkalaemia are given in Box 251.1. Since the kidney is responsible for 90% of potassium excretion, most true hyperkalaemia results from renal insufficiency. Hypertrophy of renal tubules usually maintains the ability to balance potassium until the glomerular filtration rate falls below 10 mL/min, provided that dietary intake is normal. An increased potassium intake or tissue release may lead to hyperkalaemia at much higher glomerular filtration rates, as may drugs that modify renal handling of potassium. Hyperosmolar infusions may also provoke hyperkalaemia [2].

The major physiological effects of changes in potassium levels are seen in excitable tissues. Electrocardiogram (ECG) changes of hyperkalaemia include peaked T waves, widening of the QRS complex, loss of the P wave, a sine wave configuration [3] and ventricular fibrillation. Unfortunately, this well ordered sequence is not always observed and cardiac arrest may occur due to hyperkalaemia with an unremarkable ECG.

Hyperkalaemia is convincingly associated with early and late mortality in critical illness [4]. Signs and symptoms are usually absent and appropriate treatment depends upon clinical suspicion and monitoring of potassium levels. This is particularly important in conditions where potassium may be released in large quantities in association with incipient renal dysfunction, for example rhabdomyolysis [5], tumour lysis syndrome and reperfusion of ischaemic tissue. Rapid metabolic changes in such circumstances may produce lethal hyperkalaemia in a short period of time. Suxamethonium, when used for rapid sequence intubation, predictably produces a rapid rise in serum potassium of around 0.5–1.0 mmol/L, but levels may rise much more steeply in susceptible patients, provoking life-threatening dysrhythmias [6]. This effect is particularly important in those with a prolonged ICU stay, certain neurological conditions and burns.

True hyperkalaemia must be distinguished from pseudohyperkalaemia, which may follow *in vitro* haemolysis or lysis of white blood cells (usually only at levels above 200×10^9/L) or platelets (usually only when the platelet count is above 750×10^9/L). Aggressive, inappropriate treatment of pseudohyperkalaemia risks iatrogenic hypokalaemia.

Treatment of hyperkalaemia

Irrespective of the cause, the primary goals of therapy are myocardial protection and return of plasma potassium to a safe level. Secondary goals are the correction of co-existing metabolic disturbances and treatment of the underlying cause. Measures to correct plasma potassium are commonly initiated above 5.5 mmol/L. Treatment includes discontinuation of drugs that promote potassium retention, while limiting potassium intake in feeds and

Box 251.1 Causes of hyperkalaemia

Pseudohyperkalaemia

- Faulty venesection technique.
- *In vitro* haemolysis.
- Extreme leucocytosis.
- Thrombocytosis.
- Leaky cell syndrome.

Transcellular shift

- Acidosis.
- Diabetic ketoacidosis.
- Hyperosmolality.
- Hyperglycaemia.
- Drugs
  - Beta-blockers.
  - Suxamethonium.
  - Digoxin.
- Rhabdomyolysis.
- Tumour lysis syndrome.
- Haemolysis.
- Malignant hyperthermia.
- Exercise.
- Hyperkalaemic periodic paralysis.

Renal

- Severe renal failure.
- Excess potassium load with renal dysfunction.
- Adrenocortical insufficiency.
- Aldosterone deficiency.
- Hyporeninaemic hypoaldosteronism.
- Drugs
  - Non-steroidal anti-inflammatory drugs.
  - Angiotensin-converting enzyme inhibitors.
  - Cyclosporin.
  - Potassium-sparing diuretics.
  - Heparin.
- Enzymatic defects.
- Tubular disorders.
- Ureterojejunostomy.

infusions. At levels above 6.5 mmol/L, aggressive measures should be adopted and calcium salts given if there are cardiac dysrhythmias or broadening of the QRS complex. Temporary control is achieved most effectively by promoting potassium shifts into cells; these methods require at least **15 minutes to begin to take effect** [7].

Calcium

Calcium salts, which antagonize the membrane depolarizing effects of hyperkalaemia, should be reserved for patients with severe hyperkalaemia or life-threatening dysrhythmias. The usual dose is 10 mL of 10% calcium gluconate given rapidly intravenously, repeated where necessary up to 30 mL. The duration of effect is less than an hour. Calcium chloride is more irritant if peripheral access is used. Care must be taken to avoid the simultaneous infusion of sodium bicarbonate because of the risk of precipitation. If concomitant digoxin toxicity is suspected calcium is not contraindicated, but should be given cautiously and the theoretical risk of provoking malignant dysrhythmias remembered [8].

Glucose–insulin infusions

Insulin promotes potassium entry into cells by mechanisms separate from glucose entry; glucose is given to prevent hypoglycaemia. Commonly used prescriptions include 15 units of soluble insulin in 50 mL 50% glucose given over 20–30 min, and 15–20 units of insulin in 500 ml of 10 or 20% glucose over 30 to 60 min. All methods reduce plasma potassium by approximately 1 mmol/L over a period of 30–60 min and will usually maintain potassium at the lower level for several hours. This is usually inadequate in hypercatabolic patients and those with established renal failure. In such cases it may, however, act as a temporizing measure.

Supraphysiological levels of insulin are required for a therapeutic effect [9], and although oral glucose stimulates insulin secretion in normal individuals to a sufficient degree to cause a fall in plasma potassium, a paradoxical hyperkalaemic response to a glucose load is recognized [10,11]. Administration of an insulin bolus alone where hyperkalaemia is accompanied by significant hyperglycaemia is perhaps more reasonable, but iatrogenic hypoglycaemia is a risk with this strategy [12].

Beta-2-agonists

Nebulized beta-2-agonists are as effective as glucose-insulin and valuable where immediate intravenous access is a problem, but appear most effective when combined with glucose-insulin [13]. Clinicians may worry about arrhythmogenic effects in severely-ill patients, particularly those with co-existent cardiac disease that frequently accompanies CKD, but there is no good evidence for harm [14]. The usual adult dose of salbutamol is 10–20 mg by nebulizer over 10 minutes or 0.5 mg intravenously over 10–15 minutes.

Sodium bicarbonate

Sodium bicarbonate theoretically promotes entry of potassium into cells by reducing hydrogen–potassium exchange, but there is uncertainty about its clinical utility [13]. It may be valuable in extreme cases. Concerns exist about volume overload and exacerbating hyperkalaemia by an effect on plasma osmolality. Preparations range in strength from 1.26–8.4%, the latter must be given centrally except in arrest situations.

Diuretics

Promotion of a diuresis with loop diuretics or thiazides increases potassium excretion. Since this effect is augmented by increasing sodium delivery to the distal tubule, combining volume loading with diuretics in patients with prerenal failure may augment kaliuresis.

Haemofiltration and haemodialysis

Acute renal replacement therapy (RRT) is usually unnecessary in patients with intact renal function. Those with predictably transient

hyperkalaemia can usually be managed with a combination of the therapies discussed previously. In established acute or acute-on-chronic renal failure, or if these methods fail, hyperkalaemia usually reflects a generalized metabolic disturbance and is an indication to start RRT. In extremis, peritoneal dialysis has been used successfully in the management of hyperkalaemic cardiac arrest pending institution of more conventional treatments [15].

Cation-exchange resins

These can be administered orally or by retention enema. Although these resins may have a place in the management of isolated renal failure, duration of onset is slow and initial effect small. Moreover, gut function in critically-ill patients is often compromised and there is a significant risk of causing intestinal necrosis with some preparations that may be fatal [16]. For these reasons, acute RRT is usually a better choice if an acute reduction in total body potassium is required. Sodium zirconium cyclosilicate is a new non-absorbed oral cation exchanger that is effective in treating hyperkalaemia associated with chronic renal failure. It has been suggested as a potential therapy for acute severe hyperkalaemia [17], though data on its safety and efficacy in the setting of critical illness are awaited.

Special cases

Rhabdomyolysis and cell lysis syndromes

Plasma potassium levels may rise very rapidly in these situations. Provided swift action is taken it is usually possible to prevent lethal hyperkalaemia. The key is to correct hypovolaemia and stimulate a diuresis. Alkalinization with intravenous sodium bicarbonate is controversial and, aside from data from uncontrolled case series, there is no good evidence for a benefit over volume repletion with crystalloid [5]; similarly, mannitol probably offers no benefit and may be harmful. Urine outputs of up to 12 L/day have been advocated, but 4–6 L/day is usually adequate. Following resolution of the acute phase of these syndromes, total body potassium will be low and will require replenishment.

Diabetic ketoacidosis

In diabetic ketoacidosis hyperkalaemia may develop as a consequence of metabolic acidosis, insulin deficiency, and reduced renal excretion, but a significant whole-body potassium deficit is the rule. It is unusual for extreme methods of potassium control to be needed, and potassium levels will usually return to normal with correction of the volume and insulin deficits. Indeed, significant hypokalaemia may be an issue if potassium containing fluids are not used relatively early in the course of volume resuscitation. Very occasionally, it is necessary to give calcium salts for myocardial protection. A period of RRT may be required in patients with coexistent oliguric renal failure.

Potassium channel syndrome

A life-threatening syndrome associated with excessive drug-induced K_{ATP} channel activation has been reported, characterized by refractory hypotension and hyperkalaemia in the setting of drugs such as nicorandil, cyclosporin, and isoflurane. Therapy with glibenclamide appeared to be effective [18]. Further work in this area is required before firm conclusions can be drawn.

Hypokalaemia

Causes of hypokalaemia

Hypokalaemia and potassium depletion are common in critically-ill patients. Box 251.2 gives an overview of causes.

Box 251.2 Causes of hypokalaemia

Potassium depletion

- Non-renal (urine K^+ <20 mmol/day).
  - Inadequate intake.
  - Excessive sweating.
  - Gastrointestinal losses.
    - Diarrhoea.
    - Vomiting.
    - Laxative abuse.
- Renal losses (urine K^+ >20 mmol/day).
  - Renal tubular acidosis.
  - Diabetic ketoacidosis.
  - Chloride depletion.
  - Mineralo- and glucocorticoid excess.
  - Magnesium depletion.
  - Antibiotic therapy.
  - Amphotericin.
  - Leukaemia.
  - Bartter's or Gitelman's syndrome.
  - Osmotic diuresis.
  - Polyuria.

Transcellular shift

- Alkalosis.
- Insulin excess.
- Beta-2 adrenergic stimulation.
- Poisoning.
- Theophyllines.
- Chloroquine.
- Barium.
- Toluene.
- Hypothermia.
- Hypokalaemic periodic paralysis.

Diuretics

Diuretics (except for triamterene, amiloride, and spironolactone) promote kaliuresis by increasing delivery of sodium to the distal tubule. Carbonic anhydrase inhibitors increase potassium loss by increasing the tubular concentration of bicarbonate, which acts as a non-reabsorbable anion.

Vomiting

The low concentration of potassium in upper gastrointestinal secretions prevents even severe vomiting from causing profound potassium depletion in its own right. It is instead the accompanying hypochloraemic alkalosis, which leads to a shift of potassium into

cells and increased potassium loss from the kidney that causes the hypokalaemia seen in this setting.

Diarrhoea

Stool contains 50–100 mmol/L of potassium. Diarrhoea is usually associated with significant losses of bicarbonate and, hence, a metabolic acidosis. This may be further exacerbated by the effects of hypovolaemia. The consequent shift of potassium from cells may mask the true extent of potassium depletion. In certain conditions, such as villous adenoma of the rectum and non-insulin-secreting islet cell tumours, diarrhoea may contain high chloride concentrations. In such cases, potassium loss occurs without an accompanying acid-base disturbance, and hence, hypokalaemia tends to be more profound for a given whole-body potassium deficit. Laxative abuse similarly produces a profound hypokalaemia without alterations in acid-base status. Patients with ureterosigmoidostomies, where urine is allowed to stagnate in the colon, may develop a profound hypokalaemic hyperchloraemic acidosis. Potassium losses are increased in conditions of rapid intestinal transit, small bowel fistulas, intestinal drains, malabsorption, and small bowel bypass.

Mineralocorticoids and hyperaldosteronism

Secondary hyperaldosteronism due to Bartter's syndrome, renin-secreting tumours and malignant hypertension may produce severe potassium depletion. Bartter's syndrome may be mimicked by bulimia nervosa, laxative or diuretic abuse, and primary renal tubular disorders, such as cystinosis. In Bartter's syndrome, there is failure to retain chloride on a high-chloride diet, whereas in bulimia and following diuretic abuse chloride is retained avidly.

Effects of hypokalaemia

Cardiac muscle

The ECG changes of hypokalaemia consist of ST depression, flattening of the T wave and prominent U waves. Subsequently, there may be widening of the QRS complex and atrioventricular block. More significant are arrhythmias, ranging from single or multiple ectopics to atrial or ventricular tachycardia and fibrillation. Membrane hyperpolarization and an increased refractory period lead to prolongation of the action potential, and an increased tendency to re-entrant tachycardias. ECG changes are rare at serum potassium levels above 3 mmol/L and arrhythmias uncommon in healthy subjects at these levels. In critical illness even small reductions in plasma potassium may be associated with dysrhythmias, and it is common practice to maintain plasma potassium levels towards the upper end of the normal range. The range of serum potassium observed to be associated with the lowest risk of mortality in patients with acute myocardial infarction has received attention [19] as has the excess mortality seen in those who are hyperkalaemic on admission to critical care environments [7], but evidence to guide a minimum safe level as a target is lacking.

Effects on other muscles

Profound potassium depletion may lead to impaired skeletal muscle function with weakness and hyporeflexia, compromising weaning from mechanical ventilation. Accompanying hypophosphataemia, common because potassium depletion leads to renal tubular phosphate wasting, may exacerbate the situation. Impaired gut motility may lead to paralytic ileus, whilst vascular smooth muscle contractility may be reduced, leading to reduced pressor responses to catecholamines and angiotensin.

Renal effects

Hypokalaemia may produce a state resembling diabetes insipidus as a result of reduced medullary solute concentrations. There is an association between potassium depletion and metabolic alkalosis, particularly in the hypovolaemic patient, at least partly due to shifts of hydrogen ions into cells, but probably also reflecting increased renal sodium and bicarbonate retention.

Metabolic effects

These include reduced protein synthesis, a negative nitrogen balance, glucose intolerance, metabolic alkalosis, and reduced carbohydrate synthesis.

Treatment of hypokalaemia

Underlying causes should be corrected where possible. Potassium should be replaced in conjunction with correction of other metabolic and electrolyte abnormalities. If there are symptoms or ECG changes, or plasma potassium is below 2 mmol/L, this should be replaced rapidly (up to 40 mmol/hour). At higher potassium levels and in asymptomatic patients, intravenous correction rates of 10–20 mmol/hour are usually adequate. Replacement is typically with potassium chloride, although potassium phosphate can be used if there is concomitant phosphate deficiency. Potassium citrate has a role in the setting of renal tubular acidosis where a chloride load is undesirable. In extremis (malignant arrhythmias in the presence of severe hypokalaemia), potassium can be given by rapid infusion of 50–100 mL of 40 mmol/L KCl over 2–5 minutes. In patients with co-existent metabolic acidosis and hypokalaemia, potassium should be replaced before correction of the acidosis in order to prevent further severe falls in serum potassium.

After the extracellular deficit has been corrected, there will usually be a whole-body intracellular deficit to correct. There is no single satisfactory way of judging adequacy of potassium repletion, but an increase in urinary potassium, tendency for plasma potassium to stay elevated after potassium infusion and correction of a metabolic alkalosis may all give useful clues. Continuing replacement of magnesium should accompany potassium replacement. Hypomagnesaemia is found in up to 40% of patients with hypokalaemia [20] and magnesium is needed for potassium to enter cells and prevent continuing renal potassium wasting. Hypokalaemia in hyperaldosteronism may be minimized by reducing sodium intake. Spironolactone may also be useful for reducing renal potassium wasting.

References

1. Rabelink TJ, Koomans HA, Hene RJ, and Dorhout Mees EJ. (1990). Early and late adjustment to potassium loading in humans. *Kidney International*, **38**(5), 942–7.
2. Conte G, Dal Canton A, Imperatore P, et al. (1990). Acute increase in plasma osmolality as a cause of hyperkalemia in patients with renal failure. *Kidney International*, **38**(2), 301–7.
3. Petrov DB. (2012). Images in clinical medicine. An electrocardiographic sine wave in hyperkalemia. *New England Journal of Medicine*, **366**(19), 1824.
4. McMahon GM, Mendu ML, Gibbons FK, and Christopher KB. (2012). Association between hyperkalemia at critical care initiation and mortality. *Intensive Care Medicine*, **38**(11), 1834–42.
5. Huerta-Alardin AL, Varon J, and Marik PE. (2005). Bench-to-bedside review: Rhabdomyolysis—an overview for clinicians. *Critical Care*, **9**(2), 158–69.

6. Martyn JA and Richtsfeld M. (2006). Succinylcholine-induced hyperkalemia in acquired pathologic states: etiologic factors and molecular mechanisms. *Anesthesiology*, **104**(1), 158–69.
7. Lens XM, Montoliu J, Cases A, Campistol JM, and Revert L. (1989). Treatment of hyperkalaemia in renal failure: salbutamol v. insulin. *Nephrology, Dialysis, Transplantation*, **4**(3), 228–32.
8. Levine M, Nikkanen H, and Pallin DJ. (2011). The effects of intravenous calcium in patients with digoxin toxicity. *Journal of Emergency Medicine*, **40**(1), 41–6.
9. DeFronzo RA, Felig P, Ferrannini E, and Wahren J. (1980). Effect of graded doses of insulin on splanchnic and peripheral potassium metabolism in man. *American Journal of Physiology*, **238**(5), E421–7.
10. Nicolis GL, Kahn T, Sanchez A, and Gabrilove JL. (1981). Glucose-induced hyperkalemia in diabetic subjects. *Archives of Internal Medicine*, **141**(1), 49–53.
11. Goldfarb S, Cox M, Singer I, and Goldberg M. (1976). Acute hyperkalemia induced by hyperglycemia: hormonal mechanisms. *Annals of Internal Medicine*, **84**(4), 426–32.
12. Schafers S, Naunheim R, Vijayan A, and Tobin G. (2012). Incidence of hypoglycemia following insulin-based acute stabilization of hyperkalemia treatment. *Journal of Hospital Medicine*, **7**(3), 239–42.
13. Batterink J, Cessford TA, and Taylor RAI. (2015) Pharmacological interventions for the acute management of hyperkalaemia in adults. *Cochrane Database of Systematic Reviews*, **10**, CD010344.
14. Maak CA, Tabas JA, and McClintock DE. (2011). Should acute treatment with inhaled beta agonists be withheld from patients with dyspnea who may have heart failure? *Journal of Emergency Medicine*, **40**(2), 135–45.
15. Jackson MA, Lodwick R, and Hutchinson SG. (1996). Hyperkalaemic cardiac arrest successfully treated with peritoneal dialysis. British Medical Journal, **312**(7041), 1289–90.
16. Sterns RH, Rojas M, Bernstein P, and Chennupati S. (2010). Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? *Journal of the American Society of Nephrology*, **21**(5), 733–5.
17. Kosiborod M, Peacock WF, and Packham DK. (2015). Sodium zirconium cyclosilicate for urgent therapy of severe hyperkalemia. *New England Journal of Medicine*, **372**(16), 1577–8.
18. Singer M, Coluzzi F, O'Brien A, and Clapp LH. (2005). Reversal of life-threatening, drug-related potassium-channel syndrome by glibenclamide. *Lancet*, **365**(9474), 1873–5.
19. Goyal A, Spertus JA, Gosch K, et al. (2012). Serum potassium levels and mortality in acute myocardial infarction. *Journal of the American Medical Association*, **307**(2), 157–64.
20. Whang R, Whang DD, and Ryan MP. (1992). Refractory potassium repletion. A consequence of magnesium deficiency. *Archives of Internal Medicine*, **152**(1), 40–5.

CHAPTER 252

Disorders of magnesium in the critically ill

Figen Esen

Key points

- Magnesium is the main intracellular earth metal cation and plays an essential role in fundamental cellular reactions.
- Hypomagnesaemia is frequent post-operatively and in the intensive care unit (ICU), and this often unrecognized condition is responsible for increased morbidity and mortality.
- The assessment of actual magnesium status in critical illness is problematic. There is no agreed laboratory method beyond serum total magnesium level.
- Hypomagnesaemia should be detected and corrected systematically.
- Magnesium is an effective medical therapy in many different medical conditions in the ICU.

Introduction

Magnesium is a critical ion that is essential for life. It is the fourth most common cation in the body, and the second most common intracellular cation after potassium. It is involved in many enzymatic reactions for energy metabolism and is essential for protein synthesis, fat, and carbohydrate metabolism, and for cellular functions including membrane stability, ion permeability, and action potential generation. Although magnesium has been the 'forgotten ion' for many years, its importance in critical care practice has been highlighted by the high incidence of hypomagnesaemia in patients admitted to an intensive care unit (ICU). Magnesium deficiency has been reported in 20–65% of patients in an intensive care unit [1]. Reduction in serum total magnesium on admission to ICU has been shown to be associated with increased morbidity and mortality [2]. Hypomagnesaemia has also been implicated in the development of organ dysfunction and systemic inflammatory response syndrome in ICU patients [3]. However, there is little guidance for clinicians treating critically-ill patients on the best way of magnesium supplementation in critically-ill patients [4].

Magnesium physiology and metabolism

Magnesium serves as an important cofactor for numerous enzymes and in many biochemical reactions. It is essential for the function of important enzymes that use nucleotides as cofactors. It is also required for cellular energy metabolism and has an important role in membrane stabilization, nerve conduction, ion transport, and calcium channel activity. With these physiological functions, magnesium is involved in muscle contraction, neuronal activity, control of vasomotor tone, cardiac excitability, and neurotransmitter release.

Magnesium modulates ion transport by pumps, carriers, and channels. It intervenes in the action of calcium and sodium-potassium ATPase activation. Serving as a cofactor in this enzyme system, it influences sodium and potassium flux across cell membranes. Magnesium blocks outward movement of potassium through potassium channels in cardiac cells [5]. Decreases in magnesium cause outward movement of potassium, inducing depolarization and causing cardiac arrhythmias. Moreover, disorders of magnesium, by altering sodium/potassium gradients and transmembrane potentials, may result in neuromuscular excitability or irritability.

Magnesium acts as a calcium antagonist either on intracellular sites or in membrane channels. Its interaction with calcium channels exerts a competitive antagonist action against calcium inflow. By inhibiting calcium activation on sarcoplasmic channels, it also limits the outflow of calcium from the sarcoplasmic reticulum, which is the main site of intracellular calcium storage [6]. With this mechanism magnesium regulates the intracellular calcium levels and thereby influences smooth muscle tone. By failure of regulation of smooth muscle tone, magnesium deficiency may cause hypertension, neuromuscular hyperexcitability, bronchial airway constriction, coronary spasms, and seizures [4].

Magnesium is primarily an intracellular cation. The body normally contains 21–28 g magnesium, of which more than half is stored in bone, and the rest in muscle and soft tissue. Extracellular magnesium accounts for only 1% and serum magnesium comprises only approximately 0.3% of total body magnesium. Two-thirds of serum magnesium is found in the ionized form and the rest is protein bound and complexed [7]. In contrast to calcium, the maintenance of magnesium homeostasis is highly dependent on dietary intake. Compensatory mechanisms to maintain magnesium homeostasis are not fully understood. Early studies have proposed a specific hormonal control of magnesium homeostasis; however, knowledge of endocrine factors that control circulating or urinary magnesium is incomplete. Neither vitamin D nor parathyroid hormone (PTH) have been shown to affect magnesium status directly [8]. A number of factors cause shifts in the usual intracellular: extracellular ratio of magnesium. Both acidosis and ischaemia promote release of magnesium from intracellular binding sites and lead to an efflux of magnesium from the cell. A number of commonly encountered

situations in critical care, such as re-feeding syndromes, insulin use, intravenous (iv) solutions containing glucose and amino acid infusions may lead to an acute shift of magnesium into the cells [9].

Magnesium units are expressed in mg, mmol, or mEq; 1 g of magnesium sulphate is equivalent to 4 mmol, 8 mEq, or 98 mg of elemental magnesium. The daily average requirement is 200 mg for females and 250 mg for males [10]. A healthy person will ingest 200–350 mg of magnesium daily, and half of the ingested magnesium is absorbed in the jejunum and ileum by both active and passive mechanisms. Unlike other cations, magnesium is absorbed equally well in the ileum and the jejunum by passive absorption. This absorption is inversely proportional to the amount ingested. The kidney serves as the principal organ involved in magnesium regulation. The kidney filters about 2.5 g of magnesium per day and excretes about 5% of this total. The remainder is reabsorbed by the renal tubules with 60–70% of the reabsorption of magnesium taking place within the ascending loop of Henlé. Many factors, both hormonal and non-hormonal, e.g. parathyroid hormone, calcitonin, glucagon, vasopressin, magnesium restriction, acid-base changes, and potassium depletion influence reabsorption of magnesium. The major regulator is the plasma magnesium itself [11].

Magnesium deficiency and hypomagnesaemia in the critically ill

Magnesium deficiency is common in the general population and it is multifactorial. Epidemiological studies demonstrated a relationship between cardiovascular disease, cardiac deaths, and magnesium depletion induced by a diet and drinking water low in magnesium. Intake of magnesium seems to be declining in the western population due to the increased use of processed foods [9].

Magnesium deficiency has been demonstrated in 7–11% of hospitalized patients and in up to 40% of patients with other electrolyte abnormalities.

Hypomagnesaemia (serum magnesium concentration <1.5 mg/dL) is frequently observed in critically-ill patients and has been associated with increased mortality. The prevalence of hypomagnesaemia among ICU patients ranges from 11 to 65%. When present, hypomagnesaemia is usually undetected [4].

Critically-ill patients who are hypomagnesaemic fall into three categories—those with decreased intake, those with altered intracellular-extracellular distribution, and those with increased losses.

Increased losses may occur from either the kidney or gastrointestinal tract. Surgery, trauma, infection or sepsis, burns, blood transfusion, and malnutrition are major causes of hypomagnesaemia in the ICU. Certain medications (e.g. digoxin, diuretics, aminoglycosides, amphotericin B, cisplatin, cyclosporin) have also been associated with hypomagnesaemia. Total parenteral nutrition (TPN) is often associated with hypomagnesaemia. High glucose and amino acid infusions drive magnesium into the cell and lipid solutions chelate free magnesium in serum. Diarrhoea, nasogastric suctioning, removes significant amount of magnesium from the body. Various malabsorption syndromes, short bowel syndromes, and pancreatitis can lead to hypomagnesaemia in the ICU setting [9].

Renal magnesium wasting (urinary magnesium >12 mg or 0.5 mmol/day) is associated with diabetes, alcoholism, hyperthyroidism, hypercalcaemia, and hypophosphataemia. Acute renal injury may promote wasting of magnesium. Drugs like diuretics, especially loop diuretics, many chemotherapy agents, amphotericin B, and aminoglycosides induce severe hypomagnesaemia together with hypokalaemia. Metabolic acidosis, elevated levels of circulating cathecolamines cause intracellular shift of magnesium. Large volume of hypotonic fluids also promote hypomagnesaemia.

Clinical sequel of hypomagnesaemia

Hypomagnesaemia is usually asymptomatic. The clinical consequences of isolated hypomagnesaemia are difficult since patients with hypomagnesaemia may also have hypokalaemia, hypocalcaemia, and hyponatraemia. Symptoms due to hypomagnesaemia have been reported at modest degrees of depletion, but in general serious effects are rare until total serum levels drop below 1.0–1.2 mg/dL [6].

Neuromuscular irritability is a common sign of magnesium depletion. Patients can develop Trouseau's and Chvostek's signs despite a normal ionized serum calcium concentration. Severe depletion can cause nystagmus, tetany, and seizures, and sometimes muscle weakness and fatigue. Hypokalaemia is commonly associated with hypomagnesaemia. Other than common causes like diuretics, alcoholism, and diarrhoea that result in both hypokalaemia and hypomagnesaemia, hypomagnesaemia itself causes renal potassium wasting that is refractory to potassium supplementation until magnesium is replete. Low intracellular magnesium slows ATP production, which causes a negative effect on sodium-potassium ATPase and results in the loss of intracellular potassium. Hypocalcaemia is common in hypomagnesaemia. Hypomagnesaemia supresses the release of PTH. Additionally, hypomagnesaemic patients have end-organ resistance to PTH and low vitamin D levels. Like hypomagnesaemic hypokalaemia, this hypocalcaemia is refractory to calcium supplementation until the magnesium deficit is corrected [11].

Hypomagnesaemia has been associated with a variety of arrhythmias, both atrial and ventricular. The arhythmogenic effect of magnesium depletion was shown to be independent of changes in serum potassium. Ventricular arrhythmias caused by hypomagnesaemia do not respond to conventional therapy and require replacement therapy. So this has led to the recommendation for empiric magnesium infusions for torsades de pointes. ECG findings with hypomagnesaemia include flattened T waves, U-waves, prolonged QT interval and widened QRS complexes. ECG findings are similar to hypokalaemia and they may be secondary to changes in potassium [12].

Measuring magnesium

Magnesium exists in four forms in the body. In addition to intracellular magnesium, extracellular magnesium exists in three forms—30% protein bound, 15% chelated to anions, and 55% ionized or active form. Like calcium, low albumin levels are associated with decreased total magnesium levels due to a decrease in the protein bound fraction. Assessment of magnesium status is a complex area. The most common test is serum magnesium concentration. Standard measurement of serum total magnesium includes ionized, protein bound and complexed forms, which account for 0.3% of total body magnesium content. It is obvious that measuring total serum magnesium does not give much information about the body stores of magnesium or the biologically active ionized form. An alternative to total serum magnesium is

the assessment of the ionized serum magnesium concentration as an active form. Recent technological advances in ion selective electrodes for magnesium have provided a rapid determination of ionized magnesium on an analyser [13]. Discordance between total serum and ionized magnesium has been reported in some, but not in all studies. Reports have conflicting results in terms of deciding whether measurement of serum ionized magnesium has a greater impact than total serum magnesium in patients for whom magnesium status is required. In situations of suspected hypomagnesaemia, ionized magnesium is preferred over the routinely measured serum total magnesium. However, problems with the ion selectivity and interference from calcium ions have been suggested to reduce the relevance of the ionized magnesium assay [14]. As ionized magnesium determinations have not yet proved to be superior to the routinely used available measurement of total serum magnesium, further assessments are needed in critically-ill population.

Erythrocyte, mononuclear cell and muscle magnesium levels have been used to assess magnesium status more accurately; however, no advantage over measurement of serum levels could be demonstrated. In normal subjects there is no correlation among magnesium levels in mononuclear cells compared with serum and erythrocytes [15]. There are also recently introduced techniques for measuring intracellular free magnesium using magnetic resonance imaging and magnesium sensitive dyes, or isotopic analysis of magnesium [6]. However, these are largely used as research tools and have little clinical application. A parenteral loading test with subsequent evaluation of percentage retained has been used for many years as a reliable assessment of total body magnesium status in those patients at risk of hypomagnesaemia. Retention of more than 50% of the administered dose indicates magnesium deficiency. However, the 'loading' test may not be practical and reliable in critically-ill patients as necessary steady state conditions are infrequent.

Replacement strategies

Measuring serum magnesium is still the standard, although we know that it might not reflect the total body stores. Low levels indicate deficiency, but normal levels does not rule out hypomagnesaemia. Symptoms and signs are absent most of the time in the ICU so the clinical assessment of patients at risk for magnesium deficiency remains vital for making a timely diagnosis. The goals of therapy should be to avoid symptoms, if present, and return the serum magnesium concentration to 1.5–2.4 mg/dL. The iv route of administration is preferred in critically-ill patients.

Treatment recommendations for hypomagnesaemia in the intensive care are not very clear because of a lack of data regarding the complex magnesium homeostasis and assessment issues. It is not clear if correction is associated with definable clinical changes, although several generalizations are appropriate for treatment in which the kidney function should be assessed prior to therapy. Renal elimination of magnesium is rapid, with up to 50% of an iv dose of magnesium excreted in the urine, so additional supplementation may be required in patients with normal creatinine levels [7].

For patients with mild to moderate hypomagnesaemia, 4–16 mmol (1–4 g magnesium sulphate or up to 0.5 mmol/kg) of magnesium should be given. Severe hypomagnesaemia should be treated with 16–32 mmol of magnesium (up to 0.75 mmol/kg) up to 6 g of magnesium sulphate can be infused over 8–12 hours, with higher doses infused over 24 hours. Maximum administration rate for magnesium is 1 g/hour (4 mmol/hour) with a total dose not exceeding 12 g over 12 hours. Serum magnesium levels should be monitored at least once daily during magnesium repletion, in addition to routine monitoring.

Supplemental magnesium in critical illness

Magnesium has been used as a therapeutic agent for several hundred years. There are large number of theoretical benefits of magnesium therapy, although obstetrics and cardiology provide the most compelling evidence. Parenteral magnesium therapy has been used in the treatment of pre-eclampsia since the beginning of last century. Magnesium is used in peri-operative analgesia, post-operative shivering, and tetanus. It has been and is still being studied in myocardial infarction, cardiac dysrhythmias, and asthma in the emergency department. Many of the studies in these clinical conditions have shown beneficial effects of magnesium administration and the guidelines for iv use have been presented with specific focus on the low risk of adverse effects [12]. Other current interest in magnesium therapy are cerebral protection, adjunctive analgesia and its effect on the inflammatory response. Possible roles of magnesium on the immune system have been widely studied in experimental models. Experimental magnesium deficiency produces a clinical inflammatory syndrome characterized by leukocyte and macrophage activation, release of inflammatory cytokines, acute phase proteins, and production of free radicals. Although the underlying mechanism for inflammatory response in magnesium deficiency are not clearly elucidated, it has been suggested that magnesium deficiency may induce a pro-inflammatory response by modulation of intracellular calcium concentrations, release of neurotransmitters or the activation of nuclear factor kappa B (NF- κB) implicated in the regulation of immune and inflammatory response. Experimental trials demonstrated magnesium deficient animals are more sensitive to septic shock [15]. In humans an inverse association between markers of systemic inflammation and endothelial dysfunction has been reported [16]. Magnesium supplementation in patients with heart failure significantly reduced CRP levels (a marker of systemic inflammation, and a well-known predictor of both diabetes and cardiovascular disease). There is a lack of human data on the association between magnesium levels and sepsis. In the prevalence study, the incidence of hypomagnesaemia was particularly common in patients with sepsis and septic shock. Sepsis was reported as one of the independent risk factors for developing hypomagnesaemia, which is also associated with poor outcome in sepsis. More experimental and clinical data are needed to determine whether magnesium supplementation in sepsis and septic shock can alter outcomes.

References

1. Ryzen E, Wagers PW, Singer FR, and Rude RK. (1985). Magnesium deficiency in a medical ICU population. *Critical Care Medicine*, **13**, 19–21.
2. Rubeiz GJ, Thill-Baharozian M, Hardie D, and Carlson RW. (1993). Association of hypomagnesemia and mortality in acutely ill medical patients. *Critical Care Medicine*, **21**, 203–9.
3. Soliman HM, Mercan D, Lobo SS, Mélot C, and Vincent JL. (2003). Development of ionized hypomagnesemia is associated with higher mortality rates. *Critical Care Medicine*, **31**, 1082–7.

4. Tong GM and Rude DK. (2005). Magnesium deficiency in critical illness. *Journal of Intensive Care Medicine*, **20**, 3–17.
5. Agus ZS and Morad M. (1991). Modulation of cardiac ion channels by magnesium. *Annual Review of Physiology*, **53**, 299–307.
6. Saris NEL, Mervaala E, Karppanen H, Kwawaja JA, and Lewenstam A. (2000). Magnesium: an update on physiological, clinical and analytical aspects. *Clinica Chimica Acta*, **294**, 1–26
7. Noronha JL and Matuschak GM. (2002). Magnesium in critical illness: metabolism, assessment and treatment. *Intensive Care Medicine*, **28**, 667–79.
8. Jachen-Dechent W and Ketteler M. (2012). Magnesium basics. *Clinical Kidney Journal*, **5**, 3–14.
9. Dacey MJ. (2001). Hypomagnesemic disorders. *Critical Care Clinics*, **17**, 155–73.
10. Fawcett WJ, Haxby EJ, and Male DA. (1999). Magnesium: physiology and pharmacology. *British Journal of Anaesthesia*, **83**(2), 302–20.
11. Topf JM and Murray PT. (2003). Hypomagnesemia and hypermagnesemia. *Reviews in Endocrine and Metabolic Disorders*, **4**, 195–206.
12. Mclean RM. (1994). Magnesium and its therapeutic uses: a review. *American Journal of Medicine*, **96**, 63–76.
13. Dubé L and Granry JC. (2003). The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review. *Canadian Journal of Anesthesia*, **50**, 732–46.
14. Huijgen HJ, Sanders R, Cecco SA, Rehak NN, Sanders GT, and Elin RJ. (1999). Serum ionized magnesium: comparison of results obtained with three ion-selective analyzers. *Clinical Chemistry and Laboratory Medicine*, **37**, 465–70.
15. Altura BM and Altura BT (1996). Role of magnesium in patho-physiological processes and the clinical utility of magnesium ion selective electrodes. *Scandinavian Journal of Clininical and Laboratory İnvestigations*, Suppl. **224**, 211–34.
16. Salem M, Kasinski N, Munoz R, and Chernow B (1995). Progressive magnesium deficiency increases mortality from endotoxin challenge: protective effects of acute magnesium replacement. *Critical Care Medicine*, **23**, 108–18.

CHAPTER 253

Disorders of calcium in the critically ill

Matthew R. Rosengart

Key points

- Critical illness related hypocalcaemia occurs in up to 88% of intensive care unit (ICU) patients.
- Despite hypocalcaemia, intracellular calcium concentration is elevated in severely injured and severely septic ICU patients.
- Calcium is toxic and the primary objective of cellular regulatory mechanisms is to compartmentalize calcium and maintain a low (100 nM) cytosolic calcium concentration.
- A systematic review concluded there are no data to support the routine parenteral administration of calcium in the management of asymptomatic critical illness related hypocalcaemia.
- Acute, symptomatic hypocalcaemia necessitates parenteral supplementation as 10% calcium gluconate or 10% calcium chloride to prevent tetany, seizures, and cardiac arrhythmias.

Introduction

Evolutionary pressures have yielded several regulatory mechanisms to maintain total body quantity and distribution of each electrolyte within the intracellular and extracellular compartments at concentrations compatible with life. The preservation of such electrochemical gradients is fundamental for homeostatic cell function and ultimately organ physiology. Thus, life and patient survival are dependent upon these balances despite the continual changes imposed by both internal physiological processes and external stressors.

During periods of critical illness these process are commonly overwhelmed, and disorders of electrolyte homeostasis are highly prevalent among ICU patients. Merely normalizing measured concentrations to within 'normal' laboratory ranges without addressing the underlying pathophysiology does little to improve outcome. Understanding the biochemistry, physiology, and pathophysiology of calcium regulation, in combination with a systematic approach to diagnosis and therapy are complementary components that, at the bedside, are essential for patient recovery.

Normal homeostasis

Calcium is vitally important for normal cellular signalling and function. However, its toxicity necessitates that intracellular calcium concentration [Ca^{2+}] be tightly regulated and compartmentalized. Recognize that high intracellular [Ca^{2+}] is incompatible with life, and all cells require an effective homeostatic system to maintain intracellular calcium at 100 nM, about 20,000 times lower than the extracellular milieu. Similarly, organ physiology, most notably cardiac conduction and neuromuscular function is dependent upon rapid Ca^{2+} transients; yet, physiologically active [Ca^{2+}] is kept within a narrow range: 1.0–1.25 mmol/L. Although originally addressing an evolutionary pressure for cell survival, these electrochemical Ca^{2+} gradients, the components maintaining them (endoplasmic reticulum, mitochondria, and sarco-/endoplasmic reticulum calcium ATPase), have been integrated into one of the most versatile and ubiquitous signalling machineries of the cell.

Normal homeostasis of total body and plasma Ca^{2+}, and phosphate (PO_4^{3-}) is maintained by parathyroid hormone (PTH) and vitamin D, which regulate gastrointestinal absorption, bone formation and resorption, and urinary excretion. Most PO_4^{3-} and 98% of total body Ca^{2+} are compartmentalized in the skeletal system. The physiologically active form of plasma Ca^{2+} is distributed into three phases—ionized (50%), protein bound (40%), and complexed (10%) with organic anions, such as HCO_3^- or PO_4^{3-} [1]. A true disorder of Ca^{2+} concentration and regulation necessitates confirming an alteration in the ionized form: $[Ca^{2+}]_i$ [2].

In responding to low $[Ca^{2+}]_i$, PTH is released and effects the metabolism of large Ca^{2+} stores within bone and the renal metabolism of vitamin D and handling of Ca^{2+} and PO_4^{3-} [2]. Osteoclastic bone resorption releases Ca^{2+} and PO_4^{3-}. The renal conversion of calcitriol (i.e. vitamin D_3) increases bone resorption of Ca^{2+} and PO_4^{3-}, intestinal absorption of Ca^{2+} and PO_4^{3-}, and the renal reabsorption of Ca^{2+} and excretion of PO_4^{3-}. This last step minimizes the formation of Ca_2PO_4, and enables PTH and vitamin D to alter Ca^{2+} and PO_4^{3-} concentrations independently [3]. Calcitriol may also be induced directly by hypophosphataemia. Calcitonin is produced by the thyroid C-cells and acts to decrease bone resorption and to decrease urinary calcium excretion [4].

Pathophysiology

During critical illness, derangements in calcium homeostasis occur with considerable frequency. Indeed, hypocalcaemia occurs in up to 88% of critically ill intensive care unit (ICU) patients suffering from trauma, sepsis, and burns [5]. Prior studies suggest that the development of hypocalcaemia is an independent risk factor for increased mortality. The aforementioned observations, in combination with the known importance of calcium for homeostatic organ function, led to the current practice guidelines of treating

low serum $[Ca^{2+}]_i$ with the parenteral administration of calcium [5,6]. However, a causal relationship between hypocalcaemia and multiple organ dysfunction syndrome (MODS) or mortality has not been elucidated. Furthermore, evidence has emerged to challenge this common practice. A recent systematic review concluded that no study has been conducted to identify a benefit in treating critical illness related hypocalcaemia [7].

Although **systemic** hypocalcaemia is prevalent during critical illness, **intracellular** calcium concentration $[Ca^{2+}]_i$ is elevated in the liver [8], the myocardium, and vasculature [9,10], and immune cells [11] in experimental models of sepsis or septic patients, in models of ischaemia/reperfusion and in severely-injured trauma patients. Impaired intracellular calcium handling is often cited as the mediator of aberrant inflammation underlying toxic cell death and subsequent organ injury and dysfunction [12]. It has been hypothesized that persistent elevation of $[Ca^{2+}]_i$ sustains the septic inflammatory response after the infection has been eliminated and leads to organ dysfunction (MOD). In accordance with this hypothesis, several animal models of sepsis and trauma document increased mortality and organ dysfunction with calcium replacement [13–15], and others report improvement with calcium antagonism [16,17].

Myocardial dysfunction consequent to sepsis, trauma, or ischaemia has been correlated with elevated $[Ca^{2+}]_i$ [18]. Clinical trials of calcium supplementation during cardiopulmonary bypass or sepsis note worsened myocardial function with supplementation [19], whereas reducing calcium overload improved contractility [10,17] Similar dysfunction or cellular injury consequent to elevated cytosolic $[Ca^{2+}]_i$ is observed in skeletal muscle, red blood cells, and the liver, and reductions in cellular dysfunction and injury in models of sepsis have been achieved by maintaining low extracellular $[Ca^{2+}]_i$ or administering calcium antagonists [4,8]. Despite such evidence and, in part, because of the integral role of calcium in nearly every vital and cellular function, supplementation to normalize serum $[Ca^{2+}]_i$ in critically-ill patients is recommended [6,20].

Calcium and inflammation

A prominent feature of sepsis and major trauma is a systemic inflammatory response with an elevation of pro-inflammatory cytokines such as platelet-activating factor (PAF), tumour necrosis factor-α (TNFα), IL-1, IL-8, IL-6, and HMGB1. Clinical and experimental evidence suggest perturbations in intracellular calcium homeostasis potentiate the inflammatory response. Initial leukocyte recruitment is mediated by integrin and intercellular adhesion molecules whose cell surface concentrations and affinity are increased with elevated $[Ca^{2+}]_i$. Increased cytosolic $[Ca^{2+}]_i$ activates pro-inflammatory signalling cascades, such as the mitogen-activated protein kinases (MAPK), which mediate signal transduction for both septic and traumatic insults. During endotoxaemia, the irrepressible influx of calcium into Kupffer cells results in cell activation and subsequent synthesis of several inflammatory mediators, such as PAF, nitric oxide (NO), and eicosanoids. Elevating basal neutrophil and monocyte $[Ca^{2+}]_i$ induces cytokine production and markedly enhances lipopolysaccharide (LPS)-induced TNFα, IL- 8, reactive oxygen species (ROS), and procoagulant activity; inhibiting this elevation abrogates the response [15,16]. Furthermore, a sustained increase in macrophage or platelet intracellular $[Ca^{2+}]_i$ is sufficient for inducing arachidonic acid release, which may fuel the production of pro-inflammatory mediators. We have observed that calcium supplementation in an in vivo murine model of sepsis markedly increased TNFα, IL-6, IL-10 and HMGB1 production, observations that were reproduced in vitro in macrophages. This was associated with a marked increase in vascular leak, renal and hepatic dysfunction, and increased mortality. The 'receptor' interpreting these alterations in calcium transients has not been identified, although work in our laboratory implicates the family of calcium/calmodulin-dependent protein kinases (CaMK) as potential mediators.

Diagnosis and treatment

Hypocalcaemia: $i[Ca^{2+}]_p$ < 1.1 mmol/l

Hypocalcaemia is most commonly the result of chronic renal failure due to diminished calcitriol formation and hyperphosphataemia (Table 253.1). More contemporary and better risk-adjusted studies suggest that although hypocalcaemia may be associated with ICU mortality, it is not in the causal pathway. Other causes of hypocalcaemia include sepsis, alkalosis, rhabdomyolysis, acute pancreatitis, and vitamin D deficiency (Table 253.1) [1].

Symptoms stem from neuromuscular excitability, and include muscle spasms, carpopedal spasm (Trousseau's sing), facial grimacing (Chvostek's sing) laryngeal spasm, and convulsions. Hypotension and heart failure have been reported in hypocalcaemia. Prolongation of the QT interval may progress to malignant arrhythmias.

A careful history and physical examination will usually determine the cause. If the diagnosis remains elusive, simple laboratory measurements of serum albumin, blood urea nitrogen (BUN),

Table 253.1 Aetiology of calcium disorders

Hypocalcaemia	Hypercalcaemia
PTH absent	Parathyroid
Hypoparathyroidism	Primary hyperparathyroidism
Hypomagnesaemia	Familial hypocalciuric hypercalcaemia
PTH ineffective	Ectopic PTH/malignancy
Deficient active vitamin D	*Metastasis*: breast
	Humoral: lung, renal
Inactive vitamin D	Hypervitaminosis D
Anticonvulsant therapy	Granulomatous disease (TB)
Pseudohypoparathyroidism	Vitamin D intoxication
PTH overwhelmed	High bone turnover
Hyperphosphataemia	Hyperthyroidism
Acute pancreatitis	Immobilization
	Paget's disease
Drugs	Drugs
Protamine	Thiazide diuretic
Heparin	Milk–alkali syndrome
Plicamycin	
Glucagon	
Chronic renal failure	Chronic renal failure
Vitamin D deficiency	Secondary hyperparathyroidism
Hyperphosphataemia	Milk–alkali syndrome

Table 253.2 Treatment of calcium disorders

Hypocalcemia	Hypercalcemia
Parenteral therapy Calcium chloride Calcium gluconate	Hydration normal saline *Onset*: hours *Duration*: during infusion
Oral therapy Calcium: 1–2 g/day	Bisphosphonates *Onset*: 1–2 days *Duration*: 5–7 days
Calcitriol: 0.25–2.0 μg/day	Calcitonin *Onset*: hours *Duration*: 10–14 days
Thiazide diuretic	Plicamycin *Onset*: after 5 days *Duration*: 7–10 days
	Dialysis *Onset*: hours *Duration*: 1–2 days

$[Ca^{2+}]_i$, PO_4^{3-}, pH, and $PaCO_2$ should be obtained. Measurement of intact PTH is necessary if hypoparathyroidism or pseudohypoparathyroidism is suspected.

Acute, symptomatic hypocalcaemia necessitates parenteral supplementation as 10% calcium gluconate or 10% calcium chloride to prevent tetany, seizures, and cardiac arrhythmias (Table 253.2) [1]. Intravenous calcium in a concentration of 5–7.5 mmol may be given immediately and followed by 0.375 mmol/kg elemental Ca^{2+} over 4–6 hours. Long-term therapy depends upon the cause and includes oral Ca^{2+} supplementation, vitamin D administration (ergocalciferol: 50,000 to 100,000 unit/day; calcitriol: 0.5–2 μg/day), and thiazide diuretics.

Hypercalcaemia: $i[Ca^{2+}]_p$ >1.35 mmol/l

Hypercalcaemia may result from an alteration in the equilibrium between the bone mineral and extracellular fluid, from increased gastrointestinal absorption of Ca^{2+} or from a combination of these factors (Table 253.1) [1]. In the general population it is uncommon, and primarily due to hyperparathyroidism or malignancy (Table 253.1). Malignancy is a more prevalent cause among hospitalized patients, producing hypercalcaemia through either destruction of bone or the secretion of ectopic PTH, called humoral hypercalcaemia of malignancy. Granulomatous diseases (e.g. sarcoidosis, tuberculosis) elevate vitamin D activity.

The signs and symptoms of hypercalcaemia are protean. As Ca^{2+} serves a fundamental role in neuromuscular function, neuromuscular signs and symptoms predominate—fatigue, depression, mental confusion, and proximal muscle weakness. Moderate hypercalcaemia has a positive inotropic effect on the heart, causing hypertension; severe hypercalcaemia is associated with short QT intervals and arrhythmias. Several renal manifestations have been described including nephrolithiasis, nephrocalcinosis, nephrogenic diabetes insipidus (DI), and acid-base disorders. Constipation occurs with mild hypercalcaemia due to an inhibitory action on smooth muscle; this progresses to nausea, anorexia, and vomiting due to delayed gastric emptying. Metastatic calcification into soft tissues, blood vessels, and joints can occur, particularly in primary hyperparathyroidism and a high $Ca^{2+} \times PO_4^{3-}$ product (>70).

The diagnosis of hypercalcaemia is confirmed by measuring an elevated $[Ca^{2+}]_i$. Determining the aetiology is relatively straightforward, recognizing that the most common causes are hyperparathyroidism and malignancy. Additional laboratory measurements of serum PO_4^{3-}, arterial pH and PCO_2, intact PTH, and calcidiol/calcitriol are guided by the history and physical examination, and will narrow the differential [1].

Treatment depends upon the acuity and magnitude of hypercalcaemia (Table 253.2). Mild hypercalcaemia may require no therapy other than diagnosing and correcting the primary disorder. In the outpatient setting, this is most commonly due to primary hyperparathyroidism, for which surgery is typically curative. Hypercalcaemic crisis or symptomatic hypercalcaemia, because of the attendant risks of alterations in cardiac conduction and neuromuscular function, necessitates urgent institution of therapy. The standard interventions include saline, loop diuretics, inorganic phosphate, calcitonin and bisphosphonates (Table 253.2) [1]. Rarely haemodialysis is needed. Serial monitoring of $[Ca^{2+}]_i$ is necessary to ensure an appropriate response to therapy.

References

1. Rosengart MR and Maier RV. (2004). Electrolyte disorders. In: Cameron JL (ed.) *Current Surgical Therapy*, 8th edn, pp. 1152–9. Philadelphia: Elsevier Mosby.
2. Kurokawa K. (1087). Calcium-regulating hormones and the kidney. *Kidney International* [Case Reports], **32**(5), 760–71.
3. Kumar R. (1991). Vitamin D and calcium transport. *Kidney International* [Case Reports Clinical Conference Review], **40**(6), 1177–89.
4. Rose BD. (1994). Effects of hormones on renal function. In: Rose BD (ed.) *Clinical Physiology of Acid-Base and Electrolyte Disorders*, pp. 150–215. New York, NY: McGraw-Hill.
5. Zivin JR, Gooley T, Zager RA, and Ryan MJ. (2001). Hypocalcemia: a pervasive metabolic abnormality in the critically ill. *American Journal of Kidney Diseases*, **37**(4), 689–98.
6. Burchard KW, Gann DS, Colliton J, and Forster J. (1990). Ionized calcium, parathormone, and mortality in critically ill surgical patients. *Annals of Surgery*, **212**(4), 543–9; discussion 9–50.
7. Forsythe RM, Billiar TR, Wessel CB, Angus DC, and Rosengart MR. (2008). Parenteral calcium supplementation in critical illness. *Cochrane Database of Systemic Reviews*, **4**, CD006163.
8. Sayeed MM. (1986). Alterations in cellular Ca^{2+} regulation in the liver in endotoxic shock. *American Journal of Physiology*, **250**(5 Pt 2), R884–91.
9. Song SK, Karl IE, Ackerman JJ, and Hotchkiss RS. (1993). Increased intracellular Ca^{2+}: a critical link in the pathophysiology of sepsis? *Proceedings of the National Academy of Sciences, USA*, **90**(9),3933–7.
10. White DJ, Maass DL, Sanders B, and Horton JW. (2002). Cardiomyocyte intracellular calcium and cardiac dysfunction after burn trauma. *Critical Care Medicine*, **30**(1), 14–22.
11. Zaloga GP, Washburn D, Black KW, and Prielipp R. (1993). Human sepsis increases lymphocyte intracellular calcium. *Critical Care Medicine*, **21**(2), 196–202.
12. Forman DT and Lorenzo L. (1991). Ionized calcium: its significance and clinical usefulness. *Annals of Clinical and Laboratory Sciences*, **21**(5), 297–304. [Review.]
13. Carlstedt F, Eriksson M, Kiiski R, Larsson A, and Lind L. (2000). Hypocalcemia during porcine endotoxemic shock: effects of calcium administration. *Critical Care Medicine*, **28**(8), 2909–14.

14. Zaloga GP, Sager A, Black KW, and Prielipp R. (1992). Low dose calcium administration increases mortality during septic peritonitis in rats. *Circulation Shock*, **37**(3), 226–9.
15. Hugtenburg JG, Van Voorst MJ, Van Marle J, et al. (1990). The influence of nifedipine and mioflazine on mitochondrial calcium overload in normoxic and ischaemic guinea-pig hearts. *European Journal of Pharmacology [In Vitro]*, **178**(1), 71–8.
16. Hotchkiss RS, Bowling WM, Karl IE, Osborne DF, and Flye MW. (1997). Calcium antagonists inhibit oxidative burst and nitrite formation in lipopolysaccharide-stimulated rat peritoneal macrophages. *Shock* [Research Support, Non-US Gov't Research Support, US Gov't, PHS], **8**(3), 170–8.
17. Bosson S, Kuenzig M, and Schwartz SI. (1986). Increased survival with calcium antagonists in antibiotic-treated bacteremia. *Circulatory Shock*, **19**(1), 69–74.
18. Zhu X, Bernecker OY, Manohar NS, et al. (2005). Increased leakage of sarcoplasmic reticulum Ca^{2+} contributes to abnormal myocyte Ca^{2+} handling and shortening in sepsis. *Critical Care Medicine*, **33**(3), 598–604.
19. Vincent JL, Bredas P, Jankowski S, and Kahn RJ. (1995). Correction of hypocalcaemia in the critically ill: what is the haemodynamic benefit? *Intensive Care Medicine*, **21**(10), 838–41.
20. Zaloga GP. (1992). Hypocalcemia in critically ill patients. *Critical Care Medicine*, **20**(2), 251–62.

CHAPTER 254

Disorders of phosphate in the critically ill

Daniël A. Geerse and Marcus J. Schultz

Key points

- Critically-ill patients have a high prevalence of hypophosphataemia due to the presence of multiple causal factors—the prevalence of hyperphosphataemia in critically-ill patients is uncertain.
- Hypophosphataemia may lead to a multitude of symptoms, including cardiac and respiratory failure, and is associated with higher mortality.
- The relevance of hyperphosphataemia in critically-ill patients is less clear and symptoms are mainly associated with subsequent hypocalcaemia.
- Correction of hypophosphataemia has not been shown to improve outcome.
- Although multiple studies confirm the efficacy and safety of intravenous phosphate administration, it is unknown which treatment strategy is superior.

Introduction

Hypophosphataemia is a frequently encountered electrolyte disorder in critically-ill patients. Reliable data about the prevalence of hyperphosphataemia in critically-ill patients are lacking. It is uncertain when and how to correct hypophosphataemia, and whether correction affects outcome in critically-ill patients. While evidence-based guidelines for monitoring serum phosphate levels, and treatment of hypophosphataemia and hyperphosphataemia are lacking, this chapter provides a practical approach to diagnosis and treatment of hypophosphataemia and hyperphosphataemia in critically-ill patients.

Phosphate metabolism

Phosphorus is an essential element for all living cells, with many different functions including energy storage and modulation of oxygen release by haemoglobin, activation of enzymes and intracellular signalling, acid–base buffering of the blood, and genetic translation [1]. Phosphorus is also an essential element of the cell membrane and bone structures.

Of the total phosphorus content of the human body (approximately 700 g) 85% is stored in bones, 14–15% in other tissues, and <1% circulates in the extracellular fluid. The phosphate balance is a complex interplay between uptake and excretion (Fig. 254.1). Dietary intake of phosphorus is approximately 20 mg/kg/day, of which more than half is absorbed. Under normal conditions, most of filtered phosphorus is reabsorbed in the kidneys. Reabsorption of phosphate increases significantly with low phosphate states.

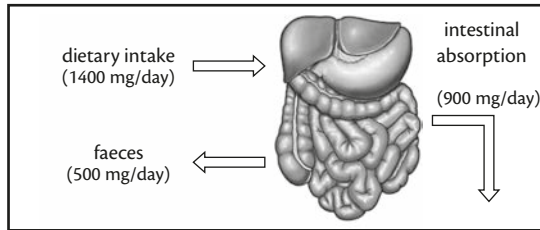
Laboratory assessment

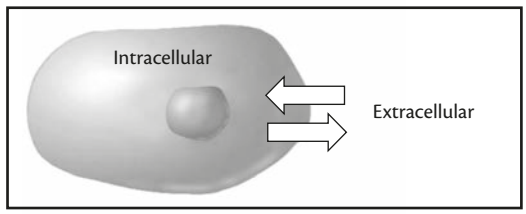
Laboratory assessments of serum phosphate measure mainly $H_2PO_4^-$ and HPO_4^{2-}, and report this as total serum phosphorus levels, with normal values of approximately 0.80–1.45 mmol/L (2.5–4.5 mg/dL). Hypophosphataemia is typically defined as mild, moderate or severe, when serum phosphate levels are 0.65–0.80 mmol/L (2.0–2.5 mg/dL), 0.32–0.65 mmol/L (1.0–2.0 mg/dL) or < 0.32 mmol/L (< 1.0 mg/dL). Hyperphosphataemia is considered significant when phosphate levels are higher than 1.6 mmol/L (5.0 mg/dL).

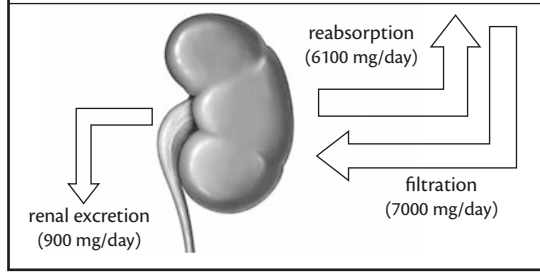
Pathophysiology

Hypophosphataemia

Hypophosphataemia can result from decreased intestinal absorption, increased renal excretion or internal redistribution of inorganic phosphate (Fig. 254.1). In most patients with severe hypophosphataemia, there is both depletion of total body phosphorus stores and redistribution of phosphate to the intracellular space [1,2]. Decreased intestinal absorption of phosphate is rarely a cause for hypophosphataemia, since a low phosphate diet enhances intestinal uptake of phosphate and increases renal reabsorption. Renal excretion of phosphate is increased by metabolic acidosis. Diuretics, glucocorticoids, aminoglycosides, antiretroviral drugs, and anti-cancer drugs increase renal phosphate excretion. Redistribution across the cell membrane is the most common cause of hypophosphataemia in critically-ill patients [3]. Redistribution can be caused by multiple clinical conditions, including respiratory alkalosis (the increase of intracellular pH causes phosphate to enter the cell by stimulating glycolysis), administration of glucose, and insulin (stimulates phosphate transport into the cells along with glucose), and high serum levels of catecholamines, whether endogenous or exogenous (stimulation of cellular metabolism increases phosphate uptake). Cellular uptake of phosphate is also increased under certain specific conditions, such as the hungry bone syndrome, and diseases with rapid cell proliferation, such as acute leukaemia. Hypophosphataemia is frequently seen in alcohol addicts, in whom there is often a combination of poor dietary







	HYPOPHOSPHATAEMIA	HYPERPHOSPHATAEMIA
	Decreased intestinal absorption	Increased intake
	Malnutrition Phosphate binding agents Vitamin D deficiency/resistance Secretory diarrhoea Steatorrhoea Vomiting Nasogastric suctioning	Vitamin D intoxication Phosphate suppletion Phosphate containing enemas
	Internal redistribution	Release from cells
	Respiratory alkalosis Recovery from malnutrition Recovery from diabetic ketoacidosis Glucose/insulin therapy Catecholamines Rapid cell uptake/proliferation (e.g. hungry bone syndrome, acute leukaemia)	Rhabdomyolysis Tumour lysis Haemolysis
	Increased renal excretion	Decreased renal excretion
	Metabolic acidosis Diuretics Volume expansion Corticosteroids Tubular disorders Hereditary syndromes Malignancy-induced hypophosphataemia Hyperparathyroidism Parathyroid hormone-related protein	Chronic renal failure Acute renal failure Parathyroid hormone deficiency Parathyroid hormone resistance

Fig. 254.1 Phosphate metabolism, and causes of hypophosphataemia and hyperphosphataemia.

intake, vitamin D deficiency and increased urinary loss due to secondary hyperparathyroidism and a direct toxic effect of alcohol on the renal tubules [1].

Serum phosphate levels are inversely correlated to levels of the inflammatory cytokines interleukin–6 and tumour necrosis factor–alpha [4]. The exact mechanism is unclear. Renal phosphate excretion is very low in patients receiving interleukin therapy for cancer, suggesting that high interleukin levels must cause internal redistribution of phosphate. Hypophosphataemia may be caused by increased phosphate utilization by immune cells.

Hypophosphataemia can also be found in patients with severe infections, such as sepsis. Patients with Gram-negative bacteraemia may be particularly prone to developing hypophosphataemia. Hypophosphataemia correlates with severity of illness and has even been suggested as a prognostic parameter in septic patients. Infection with *Legionella* species is particularly associated with hypophosphataemia.

Hypophosphataemia often develops after surgery. Multiple causal factors may be present, such as respiratory alkalosis, administration of insulin, and the use of diuretics. This is particularly true for major surgery, such as cardiac and abdominal aortic [5]. The role of cardiopulmonary bypass is unclear. After major hepatic surgery hypophosphataemia is extremely frequent. Reported mechanisms involve both shifts of phosphate into hepatocytes, as well as renal phosphate wasting [6]. Hypophosphataemia is frequently encountered in trauma patients in whom an altered renal phosphate handling results in inadequately increased urinary phosphate excretion. Hypophosphataemia is even more frequent in burn wound victims, in whom phosphate is lost through the skin. In patients with head trauma, induction of polyuresis may be an aggravating factor.

Patients with malnutrition may develop hypophosphataemia as part of the so–called refeeding syndrome when receiving enteral or parenteral feeding. With refeeding depletion of total body phosphorus stores and redistribution of phosphate to the intracellular compartment can result in severe hypophosphataemia.

Hypothermia induces polyuria and as such may cause hypophosphataemia. The use of (continuous) renal replacement therapy may also lead to hypophosphataemia, unless phosphate enriched replacement solutions or dialysates are used. Patients who require high flux dialysis for intoxications are especially at risk.

Finally, patients with diabetic ketoacidosis commonly present with hypophosphataemia due to increased urinary phosphate excretion. Phosphate levels generally decrease further during treatment due to intracellular shifting along with glucose and potassium.

Hyperphosphataemia

Hyperphosphataemia in critically-ill patients can be caused by increased intake of phosphate, decreased phosphate excretion, and redistribution of phosphate from the intracellular space (Fig. 254.1). Increased intake of phosphate can be caused by vitamin D intoxication, intravenous or oral supplementation, and sporadically by the use of phosphate-containing enemas. Decreased excretion of phosphate most commonly occurs in acute or chronic renal failure. Patients with renal failure usually have a low phosphate diet and are treated with phosphate-binding agents. Redistribution of

phosphate occurs when phosphate is released from damaged cells, as in rhabdomyolysis, tumour lysis, or haemolysis.

Epidemiology

The reported incidence of moderate and severe hypophosphataemia in the general hospital population ranges between 2.2–3.1% and 0.2–0.4%, respectively. Hypophosphataemia occurs much more frequent in critically-ill patients, with reported incidences of hypophosphataemia in medical and surgical intensive care unit patients from 30 to 80%. The incidence of severe hypophosphataemia in this population ranges from 3 to 6% [2,4].

Hypophosphataemia has a higher incidence in certain patient groups such as patients with diabetic ketoacidosis, sepsis, and after major surgery, such as cardiac and hepatic surgery. Trauma patients have a higher incidence of hypophosphataemia, especially patients with burn wounds and head trauma.

There are no studies reporting the incidence of hyperphosphataemia in critically-ill patients.

Symptoms

Hypophosphataemia

Since serum phosphate levels do not accurately reflect total body phosphorus stores, the degree of hypophosphataemia may not always correlate to the presence of symptoms. Although the majority of patients with hypophosphataemia do not develop symptoms, severe complications of hypophosphataemia may occur [7]. A common mechanism in hypophosphataemia-caused symptoms is impaired energy metabolism, leading to cellular dysfunction in multiple organ systems.

Hypophosphataemia may cause respiratory muscle dysfunction, potentially resulting in (acute) respiratory failure and weaning problems [8]. The mechanism is considered to be decreased availability of phosphate-containing energy sources. In addition, depletion of 2,3-diphosphoglycerate shifts the oxygen dissociation curve to the left, decreasing oxygen delivery to peripheral tissue [9]. This might be especially relevant in patients with chronic pulmonary disease, as these patients tend to have higher 2,3- diphosphoglycerate levels to compensate for hypoxaemia.

Hypophosphataemia may also lead to myocardial dysfunction. Phosphate depletion causes impaired energy metabolism in the myocardium, leading to decreased contractility, e.g. in patients after cardiac surgery [10]. Hypophosphataemia also correlated with development of supraventricular and ventricular arrhythmias and premature beats [11].

Finally, hypophosphataemia may cause haematological dysfunction, including haemolysis and leukocyte dysfunction, insulin resistance, and a number of neuromuscular complications, including polyneuropathy, skeletal muscle weakness, seizures, central pontine myelinolysis, and rhabdomyolysis.

There is a clear association between hypophosphataemia and increased mortality [2]. Severe hypophosphataemia has been reported to predict up to 8-fold increased mortality rate in septic patients [12]. It remains unclear whether hypophosphataemia actually contributes to mortality, or is merely a marker for severity of illness. In a recent study hypophosphatemia was not an independent predictor of ICU or in-hospital mortality in critically ill patients[13]. Whether correction of hypophosphataemia reduces mortality is uncertain. Notably, hypophosphataemia has not been associated with increased mortality after cardiac surgery [5,10] and in diabetic ketoacidosis [14].

Hyperphosphataemia

Hyperphosphataemia-associated symptoms are mainly associated with hypocalcaemia caused by the precipitation of phosphate with calcium. Hypocalcaemia, in turn, can cause neuromuscular symptoms, such as paraesthesia, tetany, and convulsions, as well as cardiovascular symptoms, such as hypotension, decreased myocardial function, and arrhythmia. There is few data demonstrating the effects of acute hyperphosphataemia in the absence of hypocalcaemia, although hyperphosphataemia is associated with increased tissue and vascular calcification in patients with chronic renal failure. Also, the combination of acute hyperphosphataemia and volume depletion may lead to acute phosphate nephropathy, in which tubular deposition of calcium and phosphate leads to acute renal failure. While hyperphosphataemia is clearly associated with increased mortality in patients with chronic kidney disease [15], there is no data on the association between hyperphosphataemia and mortality in the critically ill.

Practical approach

Hypophosphataemia

With the high prevalence of hypophosphataemia in critically-ill patients, as well as their susceptibility to life-threatening symptoms, frequent laboratory monitoring seems warranted, especially in the previously mentioned high-risk groups. It is generally recommended that hypophosphataemia should be corrected in patients with severe hypophosphataemia and in any hypophosphataemic patient with associated symptoms [3,8]. However, it should be noted that there is no randomized controlled evidence for whether correction of hypophosphataemia in apparently asymptomatic patients leads to improved outcome [2]. Taking this into account, the indication for and recommended frequency of laboratory monitoring, as well as treatment of hypophosphataemia, remains debatable.

Correction of hypophosphataemia is possible via oral or intravenous route. Intravenous administration of phosphate is not without complications, however. Phosphate may precipitate with calcium. Large intravenous doses of phosphate may cause hypotension and can result in hyperphosphataemia, hypomagnesaemia, and hypocalcaemia. Intravenous therapy is generally recommended in symptomatic hypophosphataemia and where phosphate levels are <0.32 mmol/L. Multiple studies have evaluated the efficacy and safety of intravenous phosphate repletion regimens [16–20]. These studies generally agree that aggressive phosphate supplementation is safe with phosphate doses up to 45 mmol with infusion rates up to 20 mmol/hour. Hyperkalaemia can be prevented by using sodium phosphate instead of potassium phosphate in patients with potassium levels > 4 mmol/L. Moderate hypophosphataemia can be treated by oral supplementation of phosphate. One should keep in mind that active vitamin D is required for intestinal absorption of phosphate. Typical oral supplementation amounts are three times the normal daily intake, with advised doses of 2.5–3.5 g (80–110 mmol) per day, divided over 2–3 doses. Patients who receive feeding after a period of starvation are often phosphate depleted, so additional

phosphate should be added to nutritional preparations. An additional preventive strategy is to slowly build up the caloric intake. The required amount of phosphate cannot be predicted by serum phosphate levels, as phosphate shifts between multiple body compartments.

Hyperphosphataemia

Correction of hyperphosphataemia can be achieved by minimizing the intake of phosphate, increasing renal phosphate excretion, and renal replacement therapy. In the absence of renal failure, phosphate excretion can be increased by means of fluid loading and diuretics. In most patients with hyperphosphataemia associated with renal failure, renal replacement therapy is warranted for reasons other than hyperphosphataemia. Both haemodialysis and haemofiltration effectively remove phosphate from the body.

References

1. Gaasbeek A and Meinders AE. (2005). Hypophosphatemia: an update on its etiology and treatment. *American Journal of Medicine*, **118**(10), 1094–101.
2. Geerse DA, Bindels AJ, Kuiper MA, Roos AN, Spronk PE, and Schultz MJ. (2010). Treatment of hypophosphatemia in the intensive care unit: a review. *Critical Care*, **14**(4), R147.
3. Bugg NC and Jones JA. (1998). Hypophosphataemia. Pathophysiology, effects and management on the intensive care unit. *Anaesthesia*, **53**(9), 895–902.
4. Barak V, Schwartz A, Kalickman I, Nisman B, Gurman G, and Shoenfeld Y. (1998). Prevalence of hypophosphatemia in sepsis and infection: the role of cytokines. *American Journal of Medicine*, **104**(1), 40–7.
5. Zazzo JF, Troche G, Ruel P, and Maintenant J. (1995). High incidence of hypophosphatemia in surgical intensive care patients: efficacy of phosphorus therapy on myocardial function. *Intensive Care Medicine*, **21**(10), 826–31.
6. Salem RR and Tray K. (2005). Hepatic resection-related hypophosphatemia is of renal origin as manifested by isolated hyperphosphaturia. *Annals of Surgery*, **241**(2), 343–8.
7. Roldan CJ. (2004). A case of near-fatal hypophosphatemia. *Journal of Emergency Medicine*, **26**(2), 241–2.
8. Amanzadeh J and Reilly RF, Jr. (2006). Hypophosphatemia: an evidence-based approach to its clinical consequences and management. *Nature Clinical Practice Nephrology*, **2**(3), 136–48.
9. Lichtman MA, Miller DR, Cohen J, and Waterhouse C. (1971). Reduced red cell glycolysis, 2, 3-diphosphoglycerate and adenosine triphosphate concentration, and increased hemoglobin-oxygen affinity caused by hypophosphatemia. *Annals of Internal Medicine*, **74**(4), 562–8.
10. Cohen J, Kogan A, Sahar G, Lev S, Vidne B, and Singer P. (2004). Hypophosphatemia following open heart surgery: incidence and consequences. *European Journal of Cardio-thoracic Surgery*, **26**(2), 306–10.
11. Schwartz A, Gurman G, Cohen G, et al. (2002). Association between hypophosphatemia and cardiac arrhythmias in the early stages of sepsis. *European Journal of Internal Medicine*, **13**(7), 434.
12. Shor R, Halabe A, Rishver S, et al. (2006). Severe hypophosphatemia in sepsis as a mortality predictor. *Annals of Clinical and Laboratory Science*, **36**(1), 67–72.
13. Suzuki S1, Egi M, Schneider AG, Bellomo R, Hart GK, and Hegarty C. (2013). Hypophosphatemia in critically ill patients. *Critical Care*, **28**(4), 536.e9–19.
14. Wilson HK, Keuer SP, Lea AS, Boyd AE, 3rd, and Eknoyan G. (1982). Phosphate therapy in diabetic ketoacidosis. *Archives of Internal Medicine*, **142**(3), 517–20.
15. Young EW, Akiba T, Albert JM, et al. (2004). Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *American Journal of Kidney Diseases*, **44**(5 Suppl. 2), 34–8.
16. Brown KA, Dickerson RN, Morgan LM, Alexander KH, Minard G, and Brown RO. (2006). A new graduated dosing regimen for phosphorus replacement in patients receiving nutrition support. *Journal of Parenteral and Enteral Nutrition*, **30**(3), 209–14.
17. Charron T, Bernard F, Skrobik Y, Simoneau N, Gagnon N, and Leblanc M. (2003). Intravenous phosphate in the intensive care unit: more aggressive repletion regimens for moderate and severe hypophosphatemia. *Intensive Care Medicine*, **29**(8), 1273–8.
18. Perreault MM, Ostrop NJ, and Tierney MG. (1997). Efficacy and safety of intravenous phosphate replacement in critically ill patients. *Annals of Pharmacotherapy*, **31**(6), 683–8.
19. Rosen GH, Boullata JI, O'Rangers EA, Enow NB, and Shin B. (1995). Intravenous phosphate repletion regimen for critically ill patients with moderate hypophosphatemia. *Critical Care Medicine*, **23**(7), 1204–10.
20. Taylor BE, Huey WY, Buchman TG, Boyle WA, and Coopersmith CM. (2004). Treatment of hypophosphatemia using a protocol based on patient weight and serum phosphorus level in a surgical intensive care unit. *Journal of the American College of Surgeons*, **198**(2), 198–204.

PART 10.3

Metabolic acidosis and alkalosis

CHAPTER 255

Pathophysiology and causes of metabolic acidosis in the critically ill

Patrick J. Neligan and Clifford S. Deutschman

Key points

- Metabolic acidosis results from any process that decreases the strong ion difference (SID) or increases serum levels of albumin or phosphate.
- Hyperchloraemic acidosis is most often associated with isotonic saline administration. It may reduce splanchnic blood flow and impair renal function.
- Lactic acidosis is associated with global or regional hypoxaemia (type A), stress, catechloamines and/or sepsis (type B). Failure to clear high level of serum lactate, in the presence of acidosis, is associated with poor critical care outcomes.
- Ketoacidosis is associated with hypercatabolism and low intracellular glucose levels.
- Renal acidosis is multifactorial and combines hyperchloraemia, hyperphosphataemia, and dilutional acidosis with the accumulation of a number of protein metabolites.

Introduction

The human body tightly controls the acidity of the intracellular and extracellular spaces as part of a variety of homeostatic systems that maintain transcellular ion pumps. Critical illness is typically characterized by changes in this electrochemical balance, frequently resulting in alterations in extracellular pH. Acidosis (pH <7.35) is the acid-base abnormality most frequently observed in acute critical illness. As the patient's condition becomes more chronic, mixed acid base disorders become evident, and alkalosis secondary to hypoalbuminaemia is frequently present (pH > 7.45) [1].

Metabolic acidosis results from alterations in the water and electrolyte composition of the extracellular fluid. Respiratory and metabolic acidosis often co-exist in critical illness. Metabolic acidosis usually indicates the presence of serious underlying disorder and predict mortality [2]. One multicentre study observed that 6% of critically-ill patients had severe metabolic or mixed acidosis, a finding associated with a 57% ICU mortality rate [3].

Acids and bases

The body is an aqueous environment. All acid–base reactions are directly dependent on the auto-ionization of water molecules into moieties that express H^+ or OH^-, and on the ionization of dissolved salts. In chemistry, an acid is a proton donor and a base is a proton acceptor. Water is an amphiprotic substance—it can act as either a proton donor or proton acceptor, as an acid or a base. The concentration of hydrogen ions in extracellular fluid (the pH) is determined by the water dissociation constant (Kw'), the $PaCO_2$ (effectively H_2CO_3) and the degree of dissociation of all of the fully and partially dissociated ions in that fluid compartment [4]. Strong ions, such as sodium, chloride, potassium, and lactate are fully dissociated at physiological pH. Weak acids such as bicarbonate, albumin, and phosphate are partially dissociated, and the degree of dissociation is itself pH dependent.

When one molecule of hydrochloric acid is added to water, it fully dissociates to release a hydrogen ion (H^+) to water and a chloride anion. Chloride is the proton donor (an acid) and water the proton acceptor. For each Cl^- atom there is an associated hydrogen ion. Due to the need to maintain electrochemical balance, virtually all H^+ are bound to OH^- delivered to water by strong or weak cations, forming water. For example, sodium hydroxide (NaOH) immediately dissociates in water to Na^+ and OH^-. In this scenario, water donates a hydrogen ion to sodium: sodium is a proton acceptor –a base, and water a proton donor—an acid.

$$NaOH + H_2O <-> Na^+ + OH^- + H^+ \quad + OH^- <-> Na^+ + H_3O^+ \qquad \text{[eqn 1]}$$

So,

$$HCl + NaOH + H_2O <-> Na^+ + Cl^- + 2H_2O \qquad \text{[eqn 2]}$$

Strong ion difference

In chemistry, electrical neutrality must always be maintained. All of the hydrogen ions in extracellular fluid derive from strong (fully dissociated) ions, weak (partially dissociated) acids, or carbon dioxide (which reacts, to some degree, with water, yielding H^+ and HCO_3^- -bicarbonate ion—and, with dissociation of bicarbonate, another H^+ and CO_3^{-2}). Electrochemical balance between the non-volatile components of this system is known as the Strong Ion Difference (SID). The SID is difference in total charge carried by all measured strong cations and the charge carried by all measured

Box 255.1 Strong Ion Gap

- The SIDa (apparent SID) = ($[Na^+]$ + $[K^+]$ + $[Mg^{2+}]$ + $[Ca^{2+}]$) – $[Cl^-]$.
- The SIDe (effective) is $[HCO_3^-]$ + [charge on albumin] + [charge on Pi] (in mmol/L).
- Weak acids' degree of ionization is pH dependent, so one must calculate for this:

$$[alb-] = [alb\ g/L] \times (0.123 \times pH - 0.631) \quad \text{[Box eqn 1]}$$

$$[Pi]\ (in\ mg/dL) = [Pi]/10 \times pH - 0.47. \quad \text{[Box eqn 2]}$$

- Strong Ion Gap (SIG) = SIDa–SIDe.

strong anions. The SID is always positive, usually 40-44mEq/L (SIDa—apparent SID, see Box 255.1) as the number of strong cations exceeds the number of strong anions and, because these are charged species, is reflected in a net positive charge. Because the solution must be electrically neutral, this net positive charge must be balanced by an equivalent amount of charge carried by weak acids—albumin, phosphate and bicarbonate (SIDe—effective SID) [5]. In order for there to be a gain in net $[H^+]$, there must be a net gain of anions relative to cations: this can result from excess chloride (hyperchloraemia), a loss of Na^+ (hyponatraemia, dilutional acidosis) accompanied by an increase in H^+, or the generation of metabolic acids at a rate more rapid than their clearance (lactate, ketones, and 'renal acids'). Functionally, in each of these scenarios, there is a reduction in the SID. In a scenario where 10 mEq/L of lactate is present in the extracellular fluid, the SID falls to 34 mEq/L. The strong ion gap (SIG) is SIDa–SIDe, and it reflects unmeasured anions, such as lactate (Box 255.1) [6]. This gap increases by the magnitude of the additional extracellular anions, in this case lactate. The introduction of 10 mEq/L of lactate is associated with an equal quantity of H^+ delivered to water. In the absence of extracellular buffering capacity this would result in a catastrophic fall in extracellular pH; the 'free' hydrogen ions are buffered by bicarbonate molecules, the product is carbon dioxide (CO_2): this induces increased alveolar ventilation and respiratory alkalosis. Effectively, the acid introduced with lactate is converted to CO_2 and excreted. The consequence is a fall in serum HCO_3^- levels, and a reduction in SIDe. In critically-ill patients SIG is usually above zero. This is due to a combination of hypercatabolism with release of large quantities of uric acid, amino acids, organic acids (all anions), and the impact of gelatin (an anion) used for resuscitation.

Metabolic acidosis

Metabolic acidosis results from the accumulation of strong or weak acids in the extracellular fluid (Box 255.2). These acids reflect the presence of certain anions—chloride, lactate, ketone bodies, a variety of difficult-to-measure renal acids, phosphate, and occasionally albumin. Although bicarbonate is a weak acid, its production is associated with whole body CO_2 balance, and its extracellular concentration is determined by the $PaCO_2$: there appears to be no paradigm in which changes in $[HCO_3^-]$can independently influence acid base balance [7]. In effect, the measured bicarbonate

Box 255.2 Causes of metabolic acidosis

Reduced strong ion difference (sid)

***Dilutional acidosis* (↓Na^+:Cl^-)**

- Hypotonic fluid administration.
- Increased osmolar gap:
  - Ethanol.
  - Ethylene glycol poisoning.
- Increased sodium loss: diarrhoea.
- Water overload (acute):
  - Congestive heart failure.
  - Cirrhosis.
  - Acute kidney injury.

***Hyperchloraemia* (↑Cl^-:Na^+)**

- Increased administration: 0.9% NaCl.
- Reduced excretion:
  - Renal tubular acidosis.
  - Ureteric implantation.

Unmeasured anions

- Lactic acidosis:
  - *Type A*—anaerobic glycolysis.
  - *Type B*—aerobic glycolysis.
- Ketoacidosis:
  - Diabetic ketoacidosis.
  - Starvation/alcoholic ketoacidosis.
- 'Renal acidosis':
  - Hyperchloraemia.
  - Hyperphosphataemia.
  - 'Renal acids'.
  - Hyponatraemia.

Increased weak acids

Hyperalbuminaemia

- Albumin administration.
- Cholera.

Hyperphosphataemia

- Reduced clearance—acute kidney injury.
- Increased production:
  - Refeeding syndrome.
  - Tumour lysis syndrome.
  - Rhabdomyolysis.
  - Bowel ischaemia.
  - Neuroleptic malignant syndrome.
- Increased intake:
  - Intravenous.
  - Phosphate enemas.

concentration 'adjusts', **responding** to changes in the other determinants of acid-base balance but almost never **causing** these changes.

Lactic acidosis

Lactic acid is a physiological product of glycolytic metabolism. It is continuously generated by lactate dehydrogenase from pyruvate; the normal lactate to pyruvate ratio is 10–20:1 or less. In anaerobic conditions, such as strenuous exercise, lactate levels may increase dramatically. Lactate is also produced in aerobic conditions. Beta-adrenergic receptor activation, from either stress (increased circulating catecholamines) or catecholamine infusions, increases lacate. Lactate can be metabolized in the liver to carbon dioxide and water or can be used to regenerate glucose (Cori cycle). This first pathway explains why the lactate in Hartmann's solution (Ringer's lactate solution) is functionally equivalent to bicarbonate. Lactic acidosis occurs when the production of lactate is greater than the liver's capacity to clear lactic acidosis. Thus, it may reflect excessive production or inadequate/impaired clearance, most often as a result of liver dysfunction/hypoperfusion.

Measurement of serum lactate concentration is valuable, but elevations do not always indicate the presence of acidosis. A lactate concentration of 2 mmol/L is clinically significant and a level of 5 mmol/L or more is considered severe—if metabolic acidosis is indeed present. Otherwise, in the absence of acidosis, interpreting the clinical implications of elevated serum lactate concentrations are unclear.

Many clinicians identify two types of lactic acidosis. Type A results from a global defect in oxygen delivery, such as occurs in haemorrhagic shock while Type B occurs when acidosis is present despite normal oxygen delivery and tissue perfusion. Type B lactic acidosis is most commonly seen during the aerobic glycolysis that accompanies acute stress or when sepsis, carbon monoxide or cyanide poisoning induce mitochondrial dysfunction. Type B lactic acidosis can result from excess cyanide (associated with Sodium nitroprusside infusion) or biguanides (from metformin use) and hypercatabolic diseases—such as lymphoma, leukaemia, AIDS or diabetic ketoacidosis.

The presence of lactic acidosis is a sensitive marker of the severity of injury. A lactic acidosis that persists for more than 24 hours predicts adverse outcomes [8,9]. This abnormality does not necessarily signify poor tissue perfusion or global hypoxia, and therefore may result in inappropriate therapy. Type A (hypoxia-associated) acidosis is usually, but not always, accompanied by a low mixed venous oxygen saturation (SvO_2), a high lactate, and a very high lactate/pyruvate ratio (>20:1). The presence of an SvO_2 in the normal range does not exclude significant regional hypoperfusion or mitochondrial failure. In this scenario, where acidosis persists despite normal or increased tissue oxygen delivery, regional hypoperfusion such as bowel ischaemia should be considered.

Hyperchloraemic acidosis

The relative ratio of sodium to chloride in the extracellular fluid is approximately 1.4:1. Any reduction in this ratio results in dilutional (hyponatraemic) or hyperchloraemic acidosis. Chloride is the second most abundant extracellular ion, and is active in a variety of systems in the body that depend on chloride channels to generate electrical impulses (i.e. GABA receptors in the central nervous system) or utilize chloride for metabolism (e.g. the parietal cells of the stomach). Hyperchloraemia is caused by excessive administration or inadequate excretion. As sodium and chloride are absorbed in the diet in roughly equimolar concentrations, the kidneys must excrete a relatively greater quantity of chloride than sodium daily.

Diseases that result in reduced chloride excretion, such as renal tubular acidosis, or in chloride reabsorption following excretion (ureteric implantation into the bowel after cystectomy) result in hyperchloraemic acidosis. More commonly, hyperchloraemic acidosis is associated with excessive administration of 0.9% NaCl solution (normal saline). This widely used product contains 154 mmol/L of Na^+ (functionally NaOH) and 154 mmol/L of Cl^- (functionally HCl); therefore, relative to plasma, each administered litre of isotonic saline solution delivers 50 mmol of HCl to extracellular fluid. The immediate impact of this is blunted by dilution of serum albumin (itself a weak acid). Scheingraber and colleagues [10] demonstrated that even relatively small quantities of Saline (30 mL/kg) resulted in a clinically apparent metabolic acidosis.

Is hyperchloraemic acidosis clinically significant? Certainly lactic acidosis, associated with a variety of underlying pathologies, is associated with worse outcomes [11]. Nevertheless, hyperchloraemia may result in clinically significant organ dysfunction. An observational study of 31,000 surgical patients [12] comparing intravenous saline with intravenous balanced salt solutions (BSS) demonstrated significant outcome differences, favouring BSS, including post-operative infections, blood transfusions, and renal failure requiring dialysis. In addition, hyperchloraemia may lead to inappropriate continuation of therapy for treatment of keto- or lactic acidosis.

There is reason to believe that hyperchloraemia may be nephrotoxic—saline infusion has been associated with reduced renal blood flow [13], renal vasoconstriction, reduced glomerular filtration [14], splanchnic hypoperfusion [15], and perhaps an increased risk of contrast nephropathy [16]. Critically-ill patients with sepsis frequently develop hyperchloraemic acidosis that appears to be associated with worse outcomes [17]. In a study of critically-ill patients with various acid base disorders, mortality was highest for lactic acidosis (56%); for strong ion gap (SIG) acidosis it was 39% and for hyperchloraemic acidosis 29% ($p < 0.001$) [11].

Until more data are available, 0.9% NaCl is not recommended as a first line resuscitation fluid for critically-ill patients, in particular those at risk for development of acute kidney injury.

Ketoacidosis

Ketones are an end-product of fat metabolism. Ketones are produced in the mitochondria of liver cells. Fatty acids are beta oxidized to acetyl-coA. Acetyl-CoA normally enters the citric acid (Kreb's) cycle and is metabolized to carbon dioxide and water. However, this process requires insulin, whose release is, in turn, stimulated by an abundance of glucose. In the absence of this hormone, ketones—initially acetoacetate, subsequently beta-hydroxybutyrate and acetone—are produced. Ketosis is seen in starvation, either due to limited food availability, alcoholism, or in carbohydrate limited diets. When the amount of ketones produced exceeds the hepatic clearance rate, ketoacidosis ensues. The most common cause of ketoacidosis is absolute insulin deficiency (as in type 1 diabetes mellitus) or relative insulin deficiency (as occurs in hypercatabolic diabetics who become ill for any reason). Although extracellular glucose levels may be very high, there is intracellular depletion of

glucose due to hypoinsulinaemia. This is less likely to occur in type 2 diabetics, who tend to be hyperinsulinaemic. Ketoacidosis can cause a dramatic fall in pH that may actually produce air hunger. Patients typically develop an osmotic dieresis from hyperglycaemia, and thus develop significant intravascular volume depletion.

Patients with acute ketoacidosis present initially with increased SIG acidosis due to ketones. Subsequently, they develop hyperchloraemic acidosis secondary to treatment with normal saline, the traditional rehydration therapy for diabetic ketoacidosis.

Renal acidosis

Acute kidney injury is characterized by the inability of the nephron to excrete metabolic by-products, primarily protein metabolites, and excess electrolytes. Typically, the patient develops uraemia, hyperkalaemia, hyperphosphaetaemia, hyperchloraemia, and water overload, resulting in hyponatraemia. Hence, the metabolic acidosis associated with kidney injury is multifactorial associated with both measured and unmeasured anions, and haemodilution [18]. Acidosis generally becomes manifest once the GFR falls below 25 mL/min/1.73 m^2.

In early AKI, hyperchloraemia is the major cause of acidosis [19]. Chloride is actively excreted from the nephron in exchange for ammonium (NH_4^+), thus preserving the sodium and potassium levels. Hyperphosphataemia accounts for up to 30% of acidosis. In critically-ill patients, lactate may also contribute. As AKI proceeds, a large variety of metabolites—such as formate, sulphate, urate, oxaloacetate, citrate, fumate, hydroxypropionate, etc., accumulate and are responsible for much of the acidosis. This results in an increased SIG.

Other causes of metabolic acidosis

In the majority of patients that present with metabolic acidosis, the problem is explained by a change in the strong ion difference. However, it is possible to develop acidosis due to an increase in the weak acid concentration. Hyperphosphataemia results from excess administration (occasionally from phosphate containing enemas), reduced excretion (in acute kidney injury) or increased production. This may occur in any situation where there is widespread release of intracellular material: refeeding syndrome, tumour lysis syndrome, rhabdomyolysis, bowel ischaemia or neuroleptic malignant syndrome. Hyperalbuminaemia is rare; it has been reported in cholera but is more likely to be seen as a consequence of excessive intravenous administration of human albumin solution [20].

References

1. Figge J, Rossing TH, and Fencl V (1991). The role of serum proteins in acid-base equilibria. *Journal of Laboratory and Clinical Medicine*, **117**, 453–67.
2. Kaplan LJ and Kellum JA (2008). Comparison of acid-base models for prediction of hospital mortality after trauma. *Shock*, **29**, 662–6.
3. Jung B, Rimmele T, Le Goff C, et al. (2011). Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy. a prospective, multiple-center study. *Critical Care*, **15**, R238.
4. Stewart PA (1983). Modern quantitative acid-base chemistry. *Canadian Journal of Physiology and Pharmacology*, **61**, 1444–61.
5. Fencl V, Jabor A, Kazda A, and Figge J. (2000). Diagnosis of metabolic acid-base disturbances in critically ill patients. *American Journal of Respiratory and Critical Care Medicine*, **162**, 2246–51.
6. Kellum JA, Kramer DJ, and Pinsky MR. (1995). Strong ion gap: a methodology for exploring unexplained anions. *Journal of Critical Care*, **10**, 51–5.
7. Stewart PA. (1978). Independent and dependent variables of acid-base control. *Respiratory Physiology*, **33**, 9–26.
8. Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, and Greenspan J. (1993). Lactate clearance and survival following injury. *Journal of Trauma*, **35**, 584–8.
9. Arnold RC, Shapiro NI, Jones AE, et al. (2009). Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock*, **32**(1), 35–9.
10. Scheingraber S, Rehm M, Sehmisch C, and Finsterer U (1999). Rapid saline infusion produces hyperchloraemic acidosis in patients undergoing gynecologic surgery. *Anesthesiology*, **90**, 1265–70.
11. Gunnerson K, Saul M, He S, and Kellum J. (2006). Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. *Critical Care*, **10**, R22.
12. Shaw AD, Bagshaw SM, Goldstein SL, et al. (2012). Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to plasma-lyte. *Annals of Surgery*, 255(5), 821–9.
13. Chowdhury AH, Cox EF, Francis ST, and Lobo DN. (2012). A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Annals of Surgery*, 256, 18-24.
14. Wilcox CS. (1983). Regulation of renal blood flow by plasma chloride. *Journal of Clinical Investigation*, **71**, 726–35.
15. Wilkes NJ, Woolf R, Mutch M, et al. (2001). The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesthesia and Analgesia*, **93**, 811–16.
16. Merten GJ, Burgess WP, Gray LV, et al. (2004). Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *Journal of the American Medical Association*, **291**, 2328–34.
17. Noritomi DT, Soriano FG, Kellum JA, et al. (2009). Metabolic acidosis in patients with severe sepsis and septic shock: a longitudinal quantitative study. *Critical Care Medicine*, 37(10), 2733–9.
18. Havlin J, Matousovic K, Schuck O, et al. (2009). [Pathophysiology of metabolic acidosis in patients with reduced glomerular filtration rate according to Stewart–Fencl theory]. *Vnitrní Lékarství*, **55**, 97–104.
19. Liborio AB, da Silva AC, Noritomi DT, Andrade L, and Seguro AC. (2006). Impact of chloride balance in acidosis control: the Stewart approach in hemodialysis critically ill patients. *Journal of Critical Care*, **21**, 333–8.
20. Bruegger D, Jacob M, Scheingraber S, et al. (2005). Changes in acid-base balance following bolus infusion of 20% albumin solution in humans. *Intensive Care Medicine*, **31**, 1123–7.

CHAPTER 256

Management of metabolic acidosis in the critically ill

Patrick J. Neligan and Clifford S. Deutschman

Key points

- Metabolic acidosis (MA) commonly complicates critical illness and is recognized as a fall in arterial pH (<7.4) and a fall in [HCO_3^-].
- The anion gap (AG) is used to distinguish hyperchloraemic versus unmeasured anion (UMA) acidosis. It should be corrected for lactate and albumin.
- Lactic acidosis is commonly due to global or regional tissue hypoperfusion, liver dysfunction, catecholamines, or poisoning. The primary treatment is fluid resuscitation.
- Ketoacidosis is due to hypoinsulinaemia or starvation. The former is treated with isotonic crystalloid and insulin.
- Renal acidosis is treated with renal replacement therapy.

Introduction

Metabolic acidosis is an early indicator of critical illness. Arterial blood is sequentially sampled to identify acidosis, to follow its progress by treating the underlying cause and to prognosticate.

Diagnosis of metabolic acidosis

Metabolic acidosis is associated with a fall in the arterial pH below 7.4. However, due to powerful buffering systems and respiratory compensation, significant acidosis may be present despite a normal range pH. Moreover, in critical illness, several simultaneous acid–base abnormalities may be present, leading to missed or incorrect diagnosis, and potentially inappropriate therapy [1]. Several systems have been introduced for interpreting blood gas results with the objective of teasing out acid–base abnormalities. These can be divided, roughly, into two schools of thought—the traditional observational approach uses the serum bicarbonate level or a mathematical derivative of it (the base deficit) to identify acidosis. An alternative, electrochemical or quantitative approach uses the law of electrical neutrality to identify problems. These approaches are complementary and, in many ways, interchangeable.

Observational approaches: bicarbonate

Bicarbonate is a metabolic derivative of carbon dioxide. Carbon dioxide is hydrated within the erythrocyte to carbonic acid, the hydrogen ion is buffered by haemoglobin and the bicarbonate molecule is ejected from the cell into the extracellular fluid (ECF). This prevents a damaging reduction in pH of venous blood. The body stores a relatively large quantity of bicarbonate in extracellular fluid and the bicarbonate concentration varies in proportion to PCO_2 (Box 256.1). In acute respiratory acidosis, the [HCO_3^-] increases by 1 mEq/L (1 mmol/L) for every 10 mmHg (1.3 kPa) increase in the $PaCO_2$ above 40 mmHg (5.25 kPa). In chronic respiratory acidosis the [HCO_3^-] increases by 4 mEq/L for every 10 mmHg (1.3 kPa) increase in $PaCO_2$ above 40 mmHg (5.25 kPa). Chronic respiratory acidosis is handled by the body by increased intracellular buffering and increased chloride excretion from the kidney, increasing the ECF strong ion difference (SID).

Bicarbonate is a weak acid (pKa = 6.1) that functions as the major extracellular buffer of strong anions. If, for example, 10 mmol/L of lactate is produced and persists in the ECF, in the absence of buffering the pH would drop to life-threatening levels. The majority of the hydrogen ions delivered alongside lactate become bound to HCO_3^-, generating CO_2, activating the respiratory centre, and resulting in increased alveolar ventilation. Conveniently, the [HCO_3^-] falls by an equivalent quantity to the reduction in SID, and for each 1 mEq/L (or mmol/L) fall in [HCO_3^-] there is a 1 mmHg (0.13 kPa) reduction in $PaCO_2$. So, in a patient presenting to the emergency room with a pH < 7.4, a [HCO_3^-] of 14 mEq/L and a $PaCO_2$ of 30 mmHg, will alert the clinician to the presence of excess anions in the extracellular space. The [HCO_3^-] falls because of the anions, not the hydrogen ions, due to the law of mass conservation.

The observational system works well in patients who have normal $PaCO_2$ levels at baseline, but it becomes more complicated in patients who have chronic respiratory failure. In this scenario, a patient may have a significant metabolic acidosis despite a $PaCO_2$ of 40 mmHg [5.3kPa] and [HCO_3^-] of 24 mEq/L.

Anion gap

The anion gap (AG) was introduced in the 1970s to assist clinicians in determining whether the acidosis is associated with hyperchloraemia ('non-gap acidosis') or unmeasured anions ('widened gap acidosis'). UMA may include lactate, ketones, or a variety of metabolic by-products often referred to as 'renal acids.' The AG is calculated by the formula:

$$\text{Anion gap} = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-]) = 4\text{–}18 \text{ mEq/L} \quad \text{[eqn 1]}$$

The 'gap' refers to the charge carried by albumin and phosphate, and is usually approximately 8–18 mEq/L. As the [HCO_3^-] falls

Box 256.1 Observational approach to acid base. Changes in the $[HCO_3^-]$ and $PaCO_2$ associated with various acid-base disturbances: the six rules

Acute respiratory acidosis

$$\text{Expected } [HCO_3^-] = 24 + (PaCO_2 - 40)/10 \quad \text{[Box eqn 1.1]}$$

Chronic respiratory acidosis

$$\text{Expected } [HCO_3^-] = 24 + 4 \times (PaCO_2 - 40)/10 \quad \text{[Box eqn 1.2]}$$

Acute respiratory alkalosis

$$\text{Expected } [HCO_3^-] = 24 - 2 \times (40 - PaCO_2)/10 \quad \text{[Box eqn 1.3]}$$

Chronic respiratory alkalosis

$$\text{Expected } [HCO_3^-] = 24 - 5 \times (40 \times PaCO_2)/10 \quad \text{[Box eqn 1.4]}$$

Metabolic acidosis

$$\text{Expected } PaCO_2 = 1.5\,[HCO_3^-] + 8 \quad \text{[Box eqn 1.5]}$$

Metabolic alkalosis

$$\text{Expected } PaCO_2 = 0.9\,[HCO_3^-] + 9 \quad \text{[Box eqn 1.6]}$$

$[HCO_3^-]$ is represented in mEq/L or mmol/L; $PaCO2$ is represented in mmHg (for kPa divide by 7.5).

irrespective of the cause of acidosis, an increase in the $[Cl^-]$ is associated with a similar fall in $[HCO_3^-]$. The gap remains the same. If unmeasured anions (UMA) are present in the system, then the anion gap appears to widen (as $[HCO_3^-]$ falls, but $[Cl^-]$ remains normal). As the majority of hospitals now directly measure lactate, it is appropriate to add the lactate measurement to the AG:

$$\text{Anion gap (modern)} = \left(\begin{matrix} [Na^+] + [K^+] - ([Cl^-]) \\ + [HCO_3^-] + [\text{lactate}^-] \end{matrix} \right) = 14\text{–}18 \text{ mEq/L} \quad \text{[eqn 2]}$$

Although remarkably popular, the AG is a flawed and frequently misleading calculation when applied to critically-ill patients. Universally, these patients have low serum albumin, and this masks the presence of UMA. Hence, the AG should be corrected for both albumin and lactate [2]:

$$\text{Anion gap corrected } (AG_c) = [(Na^+ + K^+) - (Cl^- + HCO_3^- + \text{lactate}^-)] + [0.25(40 - \text{albumin in g/L})] \quad \text{[eqn 3]}$$

The anion gap is most frequently combined with the traditional, observational approach, as described in Fig. 256.1.

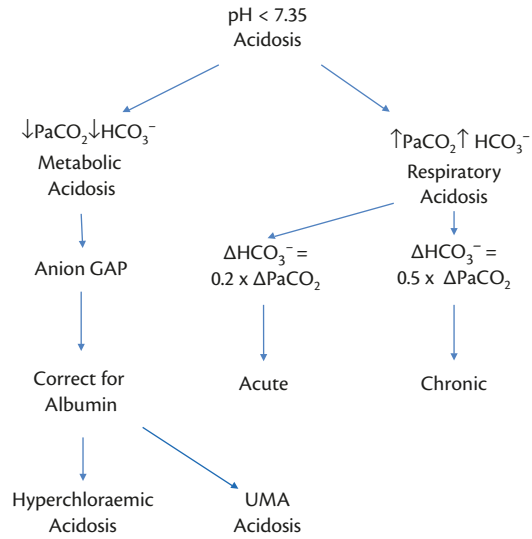


Fig. 256.1 Traditional approach to acid base, combining bicarbonate and the anion gap.

Semi-quantitative approach: base deficit/excess

The base deficit/excess (BDE) was introduced by Siggard–Anderson and colleagues in the 1960s and is often referred to as the 'Copenhagen' approach. The base deficit was an attempt to separate out metabolic acidosis from disorders of CO_2 metabolism/clearance (respiratory acidosis/alkalosis). The base deficit is the amount of strong cation (strong base) required to bring an acidic pH up to 7.4, correcting for a PCO_2 of 40 mmHg and a temperature of 37°C. Originally, the BDE was derived in vitro, but this was limited by changes in CO_2 binding to haemoglobin and referred to the BDE of blood, rather than extracellular fluid (ECF).The Van Slyke Equation facilitated calculation of BDE for whole blood rather than plasma [3].

van Slyke equation

$$BDE = \left\{ \begin{matrix} \left[HCO_3^- \right] - 24.4 + \left(2.3 \times [Hb] + 7.7 \right) \\ \times \left(pH - 7.4 \right) \times 14.83 \times \left(pH - 7.4 \right) \end{matrix} \right\} \times \left(1 - 0.023 \times [Hb] \right) \quad \text{[eqn 4]}$$

The most commonly used formula today is the standard base excess (SBE)—modified to reflect 1/3rd of the normal haemoglobin concentration (blood is only 1/3rd of ECF volume)—the haemoglobin is set at 5 g/dL; SBE is very easy to calculate [4]:

$$SBDE = 0.93 \times \left\{ [HCO_3^-] - 24.4 + 14.83 \times (pH - 7.4) \right\} \quad \text{[eqn 5]}$$

Quantitatively, the standard base deficit (BD) equals the change in the strong ion difference (apparent SID—SID_a) associated with alterations in serum bicarbonate. It is very useful as a rapid screening tool to indicate the presence or absence of a single acid base problem. Moreover, a set of rules (Box 256.2) may be applied to determine the nature of, and respiratory compensation for, the acid base problem. However, in the presence of multiple simultaneous

Box 256.2 The four $PaCO_2$/SBDE rules (SBDE in mmol/L, $PaCO_2$ in mmHg)

- Acute respiratory acidosis and alkalosis: $\Delta SBDE = 0 \times \Delta PaCO_2$.
- Chronic respiratory acidosis: $\Delta SBDE = 0.4 \times \Delta\uparrow PaCO_2$.
- Metabolic acidosis: $\Delta\downarrow PaCO_2 = \Delta SBD$.
- Metabolic alkalosis: $\Delta\uparrow PaCO_2 = 0.6 \times \Delta SE$.

acid base problems, a seemingly normal BDE (–3 to +3) may be misleading.

Electrochemical approaches

Base deficit gap

The base deficit, as calculated, reflects the change in bicarbonate concentration away from normal, corrected for CO_2 and temperature. As such, it measures the response to acidifying or alkalinizing processes. However, as such processes may be multiple and simultaneous, the absolute number of the base deficit or base excess may not accurately reflect strong anion or strong cation gain [5]. It is possible to calculate the impact of sodium, chloride, free water, and albumin on the base deficit-excess (calculated BDE), and subtract that from the measured BDE [6]. The base deficit gap (BDG) [7] should reflect the quantity of unmeasured anions, such as ketones or renal acids, in arterial blood. The BDG should mirror the strong ion gap, and the AGc. There are a number of variations of the calculations for BDG [5–7]. The simplified calculation of Story et al. is most useful (Box 256.3) [6]. They use two equations to calculate the base deficit excess for sodium/chloride/free water (BDE_{NaCl}) and for albumin. A system for using the BDE and the BDG is demonstrated in Fig. 256.2. The 'gap' reflects unmeasured anions, which should be evaluated using a process similar to that demonstrated in Fig. 256.3.

Strong ion gap

The strong ion gap (SIG), in many ways, is a more advanced and accurate version of the AG. It represents a fully quantitative approach to acid base. Like AG, SIG is based on the concept of electrical neutrality [8]. The apparent strong ion difference (SID_a) reflects the difference in charge between all the strong cations minus the strong anions:

$$SID_a = [(Na^+ + Mg^{2+} + Ca^{2+} = K^+) - (Cl^- + A^-)]. \quad \text{[eqn 6]}$$

SID changes quantitatively due to the contraction and dilutional effects associated with loss or gain of extracellular free water. This may be addressed by correcting the chloride concentration for free water (Cl^-_{corr}) and feeding the corrected chloride into the SID_a equation:

$$[Cl^-]_{corr} = [Cl^-]_{observed} \times ([Na^+]_{normal} / [Na^+]_{observed}). \quad \text{[eqn 7]}$$

SID_a is always positive with a magnitude of 40–44 mEq/L. This charge reflects an equivalent quantity of OH^- molecules and is balanced by an equal negative charge carried by weak acids: known as the effective SID (SID_e).

$$SID_e = [HCO_3^-] + [\text{charge on albumin}] + [\text{charge on Pi}]\ (\text{in mmol/L}) \quad \text{[eqn 8]}$$

Weak acids' degree of ionization is pH dependent, so one must adjust for this:

$$[\text{alb}-] = [\text{alb g/L}] \times (0.123 \times pH - 0.631) \quad \text{[eqn 9]}$$

$$[Pi]\ (\text{in mg/dL}) = [Pi]/10 \times pH - 0.47. \quad \text{[eqn 10]}$$

There is a small difference between SID_a and SID_e, the SIG, that quantifies the amount of unmeasured anion present [8].

$$\text{Strong ion gap (SIG)} = SID_a - SID_e \quad \text{[eqn 11]}$$

The 'normal' range for SIG remains unclear: it may be 6–10 mEq/L [1]. In the majority of cases, calculation of SIG is unnecessary as the AG or BDE will reveal the acidosis. In emergency medicine, SIG accurately predicts adverse outcome [9]. However, in ICU, the predictive value of this measure is weaker [10]. It is likely that hypercatabolism associated with critical illness, results in large increases in UMA derived from protein breakdown. Also, succinylated gelatin-based resuscitation fluids (popular in Northern Europe) increase SIG due to the anionic gelatin compound.

Box 256.3 Calculation of base deficit gap

$$BDE_{NaCl} = ([Na+] - [Cl^-]) - 38 \quad \text{[Box eqn 3.1]}$$

$$BDE_{Alb} = 0.25\,(42 - \text{albumin g/L}) \quad \text{[Box eqn 3.2]}$$

$$BDE_{NaCl}{}^{-}BDE_{Alb} = BDE_{calc} \quad \text{[Box eqn 3.3]}$$

$$BDE - BDE_{calc} = BDE\ gap = \text{the effect of unmeasured anions or cations} \quad \text{[Box eqn 3.4]}$$

BDE_{NaCl} component of BDE consequent of sodium concentration, chloride concentration and free water. BDE_{Alb} component of BDE consequent of serum albumin concentration. The serum phosphate concentration does contribute to BDE, but is numerically insignificant. BDE is the base deficit or excess that is derived from the SBE calculation by the blood gas machine.

Treatment of metabolic acidosis

Although acid base disturbances are associated with adverse outcomes, pharmacologically correcting the pH has never been demonstrated to improve outcomes. The use of sodium bicarbonate remains particularly controversial. Sodium bicarbonate expands volume as the 7.5%/8.4% solutions are hypertonic, increases SID due to the administration of sodium without accompanying strong anion, and increases CO_2 generation. Much discussion has focused on bicarbonate inducing intracellular acidosis [11], but this is probably clinically insignificant. In general, treatment of the underlying cause of the acidosis will resolve the problem. Nevertheless, administering sodium-bicarbonate/citrate/acetate solutions in situations

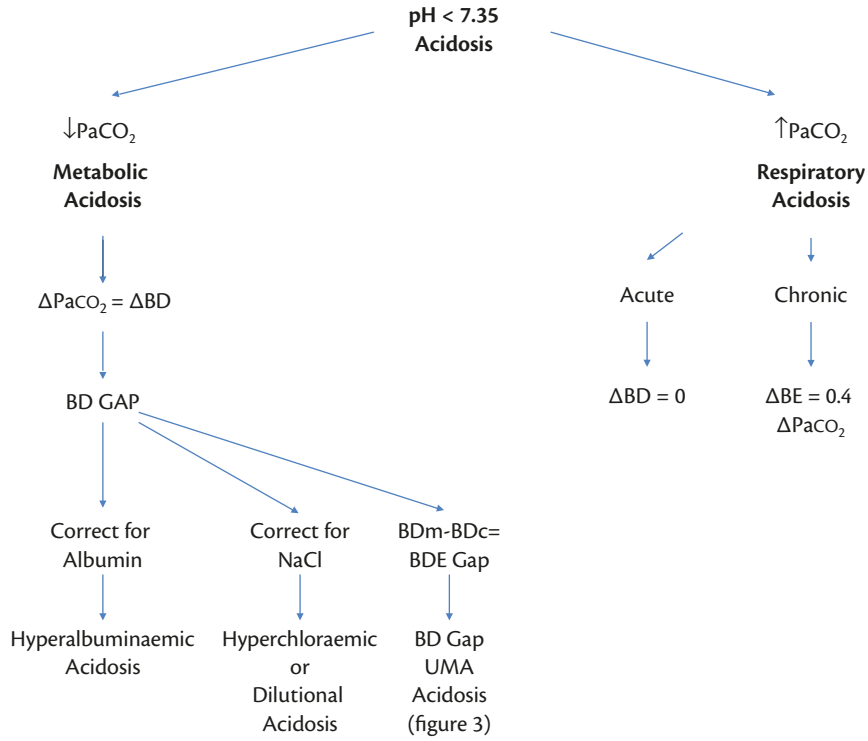


Fig. 256.2 The base deficit-excess approach & the base deficit gap.
BD, base deficit; BE, base excess; BDm, base deficit measured; BDc, base deficit calculated.

such as hyperchloraemic acidosis or renal acidosis (as a bridge to dialysis) reduces symptoms (tachypnoea, headache, etc.).

Hyperchloraemic acidosis

Hyperchloraemic acidosis may result from isotonic 0.9% saline administration, renal tubular acidosis, or ureteric transplantation to the bowel. In patients with normal kidneys, the additional chloride will clear over 2–3 days. However, during the stress response, or in the presence of acute kidney injury or renal tubular problems, resolution may be slow or incomplete. Hyperchloraemic or dilutional acidosis, is treated by increasing the SID of infused fluids, for example by infusing sodium without chloride (e.g. isotonic sodium bicarbonate or sodium acetate solutions).

Lactic acidosis

Serum lactate and arterial pH should be measured early in any critically ill patient. A [lactate] >2 mEq/L is clinically significant and a level of 5 mEq/L is severe in the presence of metabolic acidosis. Isolated hyperlactataemia in the absence of acidosis is of unclear clinical significance.

The presence of a low mixed venous oxygen saturation (SvO_2 <70% or $ScVO_2$ (central vein) <65% with a high lactate, and

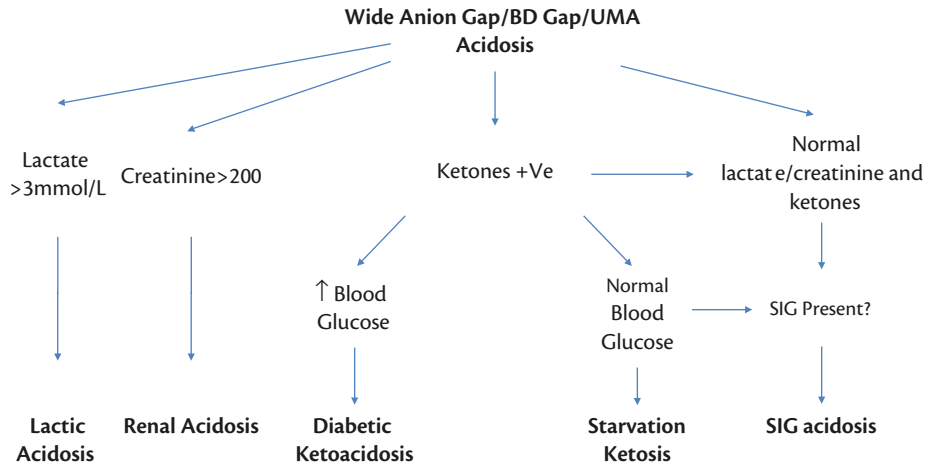


Fig. 256.3 Acidosis associated with unmeasured anions as characterized by a widened corrected anion gap, a base deficit gap (BDG), or a strong ion gap (SIG).

a very high lactate to pyruvate ratio (>20:1) is indicative of type A (hypoxia-associated) acidosis. Patients should be treated with quantitative 'goal'-directed fluid resuscitation, targeting $ScvO_2$, stroke volume, pulse pressure variability etc. The surviving sepsis guidelines (SSG) recommend 30 mL/kg fluid bolus and quantitative haemodynamic measurement [12](survivingsepsis.org).

Following implementation of resuscitation, type A lactic acidosis should begin to resolve and lactate levels should fall. SSG recommends the use of lactate clearance as an endpoint of resuscitation in sepsis [12]. The recommendation is based on data that rapid clearance of lactate has been associated with improved outcomes [13,14]. Better overall perfusion presumably reduces production and increases metabolism of lactate. If lactate does not fall following fluid resuscitation associated with normalization of $ScVO_2$, stroke volume, or other haemodynamic endpoints, clinicians should look for an alternative source of lactate production. This may simply involve turning off epinephrine infusions or may require extensive investigation for sites of regional hypoperfusion, particularly the bowel. In late stage sepsis, high levels of lactate are associated with mitochondrial failure. Patients who fail to clear lactate have worse outcomes [15]. Continued fluid resuscitation despite normalization of stroke volume or $ScVO_2$ for a high lactate, does not benefit the patient, and is likely to lead to pathologies associated with fluid overload, such as ARDS and abdominal compartment syndrome.

Ketoacidosis

Ketoacidosis occurs due to accumulation of fat breakdown products either due to an absolute or relative deficiency of insulin or due to starvation, resulting in low carbohydrate intake. Diabetic ketoacidosis is treated with fluid resuscitation and intravenous insulin. The type of fluid used to resuscitate the patient with DKA is controversial. Hyperchloraemic acidosis has been recognized as a complication of early resuscitation for decades. It is known that in anephric patients NaCl 0.9% increases serum potassium more than lactated Ringers' solution [16]. Modern isotonic balanced salt solutions (BSS) are fully isotonic with plasma, and will not worsen cerebral oedema.

Accumulating data have suggested that BSS may be a superior alternative to saline. In a small randomized study in patients with DKA BSS achieved faster initial resolution of metabolic acidosis and less hyperchloraemia after 24 hours [17]. Potassium levels were lower at 6 and 12 hours in the BSS group. Blood pressure and urinary output was greater in the BSS versus the NS group at 4 and 6 hours, respectively. They also had transiently improved blood pressure profile and urine output. Mahler and colleagues reported higher bicarbonate and lower chloride levels (i.e. less hyperchloraemic acidosis) in 45 patients randomized to NS versus BSS (plasmalyte 148) [18]. Emerging data suggest that NaCl 0.9% may increase the risk of kidney injury [19]. It is likely that BSS will replace NS for early resuscitation of DKA in the future.

Renal acidosis

Continuous renal replacement therapy (CRRT) is used in critical illness where patients are haemodynamically unstable. CRRT resolves the acidosis of acute renal failure by removing strong ions and phosphate [20]. However, metabolic alkalosis may ensue due to the unmasking of metabolic alkalosis due to hypoalbuminaemia. CRRT is not an effective treatment for either type A or type B lactic acidosis.

References

1. Fencl V, Jabor A, Kazda A, and Figge J. (2000). Diagnosis of metabolic acid-base disturbances in critically ill patients. *American Journal of Respiratory & Critical Care Medicine*, **162**, 2246–51.
2. Figge J, Jabor A, Kazda A, and Fencl V. (1998). Anion gap and hypoalbuminemia. *Critical Care Medicine*, **26**, 1807–10.
3. Siggaard-Andersen O (1977). The van Slyke equation. *Scandinavian Journal of Clinical and Laboratory Investigation*, **37**(Suppl.), 15–20.
4. Wooten EW. (2003). Calculation of physiological acid-base parameters in multicompartment systems with application to human blood. *Journal of Applied Physiology*, **95**, 2333–44.
5. Gilfix BM, Bique M, and Magder S. (1993). A physical chemical approach to the analysis of acid-base balance in the clinical setting. *Journal of Critical Care*, **8**, 187–97.
6. Story DA, Morimatsu H, and Bellomo R. (2004). Strong ions, weak acids and base excess: a simplified Fencl-Stewart approach to clinical acid-base disorders. *British Journal of Anaesthesia*, **92**, 54–60.
7. Balasubramanyan N, Havens PL, and Hoffman GM. (1999). Unmeasured anions identified by the Fencl-Stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. *Critical Care Medicine*, **27**, 1577–81.
8. Kellum JA, Kramer DJ, and Pinsky MR. (1995). Strong ion gap: a methodology for exploring unexplained anions. *Journal of Critical Care*, **10**, 51–5.
9. Kaplan LJ and Kellum JA. (2008). Comparison of acid-base models for prediction of hospital mortality after trauma. *Shock*, **29**(6), 662–6.
10. Cusack RJ, Rhodes A, Lochhead P, et al. (2002). The strong ion gap does not have prognostic value in critically ill patients in a mixed medical/surgical adult ICU. *Intensive Care Medicine*, **28**, 864–9.
11. Goldsmith DJ, Forni LG, and Hilton PJ. (1997). Bicarbonate therapy and intracellular acidosis. *Clinical Sciences (London)*, **93**, 593–8.
12. Dellinger RP, Levy MM, Rhodes A, et al. (2013). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. *Critical Care Medicine*, **41**(2), 580–637
13. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, and Kline JA. (2010). Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *Journal of the American Medical Association*, **303**, 739–46.
14. Jansen TC, van Bommel J, Schoonderbeek FJ, et al. (2010). Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *American Journal of Respiratory & Critical Care Medicine*, **182**, 752–61.
15. Arnold RC, Shapiro NI, Jones AE, et al. (2009). Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock*, **32**, 35–9.
16. O'Malley CMN, Frumento RJ, Hardy MA, et al. (2005). A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. *Anesthesia & Analgesia*, **100**, 1518–24.
17. Chua HR, Venkatesh B, Stachowski E, et al. (2012). Plasma-lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. *Journal of Critical Care*, **27**, 138–45.
18. Mahler SA, Conrad SA, Wang H, and Arnold TC (2011). Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis. *American Journal of Emergency Medicine*, **29**, 670–4.
19. Yunos N. (2012). Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *Journal of the American Medical Association*, **308**, 1566–72.
20. Rocktaschel J, Morimatsu H, Uchino S, Ronco C, and Bellomo R. (2003). Impact of continuous veno-venous hemofiltration on acid-base balance. *International Journal of Artificial Organs*, **26**, 19–25.

CHAPTER 257

Pathophysiology, causes, and management of metabolic alkalosis in the critically ill

Serge Brimioulle

Key points

- Metabolic alkalosis is frequent in hospitalized patients, and causes respiratory, cardiovascular, and neurological complications.
- Metabolic alkalosis is generally initiated by alkali administration, digestive losses, and diuretic therapy.
- Metabolic alkalosis is maintained by blood volume depletion, potassium depletion, and chloride depletion.
- Treat metabolic alkalosis by suppressing causative factors, and by giving sodium chloride and potassium chloride.
- If metabolic alkalosis is severe or causes clinical complications, give intravenous HCl.

Introduction

Metabolic alkalosis is the most frequently observed acid-base abnormality in hospitalized patients. In a study of 13,430 acid–base analyses, metabolic alkalosis was identified in 51% of samples with abnormal acid-base status [1]. Metabolic alkalosis causes significant clinical and metabolic complications, and requires early recognition and appropriate management.

Definitions

The term alkalosis refers to abnormal processes decreasing the amount of acid or increasing the amount of alkali in the organism, and thus increasing blood pH. Respiratory alkalosis results from a primary decrease in $PaCO_2$, and metabolic alkalosis from a primary increase in bicarbonate concentration. Alkalaemia refers to a blood pH value above 7.45, without regard to its mode of generation.

Acidosis and alkalosis elicit, in the normal subject, an adaptive response that tends to bring the pH back to its normal value (Table 257.1). Metabolic alkalosis causes a decrease in ventilation and an increase in $PaCO_2$ [2]. Referring to this secondary change as respiratory acidosis should be avoided, because it is a normal compensatory response, and not an abnormal process due to respiratory dysfunction.

Compensatory responses are essentially proportional to the primary acid-base disturbance, and are effective in limiting the change in pH. Respiratory responses are rapid and reach their maximum within hours, whereas renal responses are complete after only 3–5 days. If, for example, $PaCO_2$ rises to 70 mmHg, arterial blood pH first decreases to 7.20 (acute condition), and then progressively increases to reach 7.32 (chronic condition). The correct assessment of compensation therefore requires that the recent history be taken into account. While compensatory responses limit the change in pH, they do not bring the pH back to normal. A pH of 7.40 in a patient with chronic hypercapnia of 70 mmHg should not be interpreted as an appropriate response because of the so-called normal pH, but as a superimposed metabolic alkalosis. In the same way, 'overcompensation' does not occur and must be interpreted as indicating the presence of an additional primary acid–base disturbance.

Table 257.1 Normal compensatory responses to primary acid–base disturbances

Acid–base disturbance	Expected secondary response
Metabolic acidosis	$\Delta PaCO_2 = 1.20\ (0.16) \times \Delta HCO_3^-$
Metabolic alkalosis	$\Delta PaCO_2 = 0.70\ (0.09) \times \Delta HCO_3^-$
Respiratory acidosis, acute	$\Delta HCO_3^- = 0.10\ (0.75) \times \Delta PaCO_2$
Respiratory acidosis, chronic	$\Delta HCO_3^- = 0.35\ (2.60) \times \Delta PaCO_2$
Respiratory alkalosis, acute	$\Delta HCO_3^- = 0.20\ (1.50) \times \Delta PaCO_2$
Respiratory alkalosis, chronic	$\Delta HCO_3^- = 0.40\ (3.00) \times \Delta PaCO_2$

Data from in vivo studies in man or intact animals with an isolated primary acid–base disturbance. The term 'chronic' refers to the delay of 7–11 days required to reach a new steady state. Bicarbonate concentration (HCO_3^-) is expressed in mmol/L and $PaCO_2$ in mmHg or (value in brackets) in kPa.

Data from Adrogue HJ and Madias NE, 'Secondary responses to altered acid-base status: the rules of engagement', *Journal of the American Society of Nephrology*, 2010, **21**, pp. 920–3.

Generation and maintenance

Metabolic alkalosis results from a gain of alkali or a loss of non-respiratory acid [3]. The most common causes are listed in Table 257.2. In health, kidneys are able to excrete large amounts of bicarbonate and reverse alkalosis rapidly. Alkalosis therefore only persists if the kidneys, for any reason, contribute to maintain the bicarbonate excess. The principal factors maintaining alkalosis are

Table 257.2 Causes of metabolic alkalosis

Mechanism	Example
Alkali intake or administration	
Bicarbonate	Treatment of metabolic acidosis
Citrate	Blood transfusions, plasmapheresis
Carbonate	Antacids, milk-alkali syndrome
Acetate	Dialysis, parenteral nutrition
Acid losses, digestive	
Gastric	vomiting, gastric suction
Faecal	Chloride-losing diarrhoea
Acid losses, urinary	
Increased tubular sodium content	Diuretics
Hypercapnia	Post-hypercapnic alkalosis
Hyperaldosteronism	Hypovolaemia, Cushing's syndrome
Non-re-absorbable anions	Penicillin, carbenicillin

chloride depletion, decreased effective blood volume, potassium depletion, and mineralocorticoid stimulation.

Chloride depletion is the most common and most important factor [4]. Decreased glomerular filtration rate is usually observed, but is not universal, at least in some models. The exact mechanisms by which these factors contribute to maintain the alkalosis and their relative importance in different conditions remains to be clarified. In many cases, and particularly in critically-ill patients, several maintenance factors are present and contribute to the typical picture of hypochloraemic hypokalaemic metabolic alkalosis. Identification of maintenance factors is necessary, because they can maintain the alkalosis even when the generating factors have disappeared.

Alkali administration

Isolated alkali ingestion or administration only causes persistent metabolic alkalosis when the absorption is massive and prolonged. Much more commonly, metabolic alkalosis occurs after alkali administration in patients who present or develop oliguric renal failure. Typical situations in critically-ill patients are abundant transfusions of citrated blood for haemorrhagic shock or sodium bicarbonate therapy for metabolic acidosis due to circulatory arrest. Considerable alkalosis may develop when excess lactate is metabolized and administered bicarbonate cannot be eliminated. In patients with renal failure, metabolic alkalosis can also result from the administration of lactate in the haemofiltration replacement fluid.

Digestive loss of acid

Gastric alkalosis occurs when substantial amounts of acid gastric juice are eliminated from the organism by vomiting or gastric suction [3]. Chloride is lost together with hydrogen ions. Bicarbonate generated during acid secretion is not neutralized by more distal buffering in the gut and blood bicarbonate concentration increases above the renal reabsorption ability.

Bicarbonaturia is associated with natriuria, kaliuria, and fluid excretion worsening the gastric electrolyte and fluid losses. Whether, how and how much the chloride, sodium, potassium, and fluid deficits each contribute to the maintenance of the alkalosis has been the subject of much debate. The question is of considerable pathophysiological interest, but of less clinical importance because all the deficits can be corrected concomitantly to reverse the alkalosis.

Diarrhoea due to metabolic defects and villous adenomas can cause metabolic alkalosis due to failure of the colonic mucosa to reabsorb chloride adequately. Diarrhoea with normal chloride concentration can also cause metabolic alkalosis when large fluid, sodium and potassium losses result in sodium and water retention at the expense of hydrogen ion and potassium excretion by the kidney.

Urinary loss of acid

Most diuretics generate metabolic alkalosis by chloride, sodium, potassium, and fluid loss to the urine [4]. Volume contraction, aldosterone secretion, chloride depletion, and potassium depletion all contribute in some way to enhance proximal bicarbonate reabsorption and/or distal proton excretion [3].

Post-hypercapnic alkalosis is a two-step process commonly observed in critically ill patients. First, sustained respiratory acidosis determines a compensatory retention of bicarbonate and a concomitant excretion of chloride by the kidney. If chloride is not available when the hypercapnia is reversed, the bicarbonate excess cannot be eliminated [3]. Such a post-hypercapnic alkalosis commonly occurs when patients with congestive heart failure due to respiratory disease are treated with salt restriction or diuretic therapy.

Mineralocorticoid excess causes mild metabolic alkalosis when isolated, but much more serious alkalosis when potassium depletion is also present [3]. The mechanisms by which both factors combine to generate the alkalosis remain to be fully clarified. Mineralocorticoid excess, potassium depletion, and chloride depletion all contribute to the alkalosis in Bartter's syndrome [3].

Severe isolated potassium depletion has been reported to generate metabolic alkalosis by causing renal chloride wasting [4]. Penicillin and related dugs can generate mild metabolic alkalosis, possibly as non-re-absorbable anions. Hypercalcaemia may be associated with metabolic alkalosis or acidosis.

Clinical manifestations

The compensatory response to metabolic alkalosis is a decrease in ventilation and an increase in $PaCO_2$. Multiple cases of severe hypercapnia, clearly due to metabolic alkalosis, have been reported. Whether the response is or is not always present, and whether its magnitude depends on the cause of the alkalosis or on associated factors has been questioned in numerous studies [2]. It is now accepted that the increase in $PaCO_2$ is proportional to the increase in bicarbonate concentration, and that it is independent of the mode of generation of the alkalosis. $PaCO_2$ normally increases by about 0.7 mmHg for each 1 mmol/L increase in bicarbonate concentration, and can exceed 80 mmHg in severe cases. Hypoxaemia is almost always present, and has generally been attributed to the decreased ventilation and resulting atelectasis. Metabolic alkalosis also inhibits hypoxic pulmonary vasoconstriction [5], which contributes to deteriorate pulmonary gas exchange and to worsening hypoxaemia in patients with respiratory failure [6,7].

Cardiovascular complications mainly consist of various cardiac arrhythmias—supraventricular and ventricular premature beats, supraventricular tachycardia, atrioventricular block, ventricular tachycardia, and fibrillation. The arrhythmias seem to result from the associated potassium depletion, rather than from the increase in pH, and are enhanced by myocardial ischaemia and by digitalis therapy. Alkalosis has a small positive inotropic effect.

Neurological complications generally consist of altered orientation and behaviour, decreased consciousness, and neuromuscular hyperexcitability. Coma and grand mal seizures may occur, but are generally precipitated by concomitant hypovolaemia, hypercapnia, hypoxaemia, or other metabolic disturbances (e.g. hyperammonaemia in hepatic failure). Muscle weakness may occur in presence of severe potassium depletion.

Alkalosis shifts the oxyhaemoglobin dissociation curve to the left, thereby increasing oxygen uptake in the lung and decreasing oxygen release to peripheral tissues [3]. Alkalosis also increases red cell 2,3-DPG concentration, which has an opposite effect and returns the dissociation curve to its original position after 6–8 hours. Alkalosis increases the oxygen consumption, and increases the blood lactate concentration by a pH-induced enzymatic activation. Potassium depletion is almost invariably present in metabolic alkalosis and contributes to its clinical manifestations. Calcium concentration is typically normal, and the hyperexcitability results from decreased calcium ionization or from associated magnesium depletion. Alkalosis enhances the conversion of ammonium ion to ammonia.

Mixed acid–base disorders are common in critically-ill patients and should be actively sought. Particular attention should be paid to the combination of respiratory acidosis and metabolic alkalosis, which is very common, but frequently misdiagnosed when the resulting pH remains close to 7.40. Spontaneous correction is unlikely, since each disturbance enhances the other. Metabolic alkalosis may cause serious alkalaemia when the patient is mechanically ventilated, and serious hypercapnia and hypoxaemia when weaning is attempted.

Diagnosis

Determination of urine electrolyte concentrations helps to identify causal and maintenance factors, and monitors the treatment efficiency. Chloride concentration allows separation of patients into two major groups and prediction of their response to therapy. Urine chloride is generally lower than 10 mmol/L in patients with digestive losses, post-hypercapnic states, and after diuretic therapy [4]. It is typically higher than 50 mmol/L (if chloride intake is preserved) in cases of alkali intake, urinary acid losses, and during diuretic therapy. Metabolic alkalosis is chloride-responsive in the former group, and chloride-resistant in the latter. Urine pH is of little diagnostic value in metabolic alkalosis, particularly in critically-ill patients.

Management

Prevention

Metabolic alkalosis commonly occurs in settings where it could have been anticipated. Prevention of the generating factors is often possible, e.g. by limiting bicarbonate administration in acute metabolic acidosis, by preventing acid losses due to gastric drainage (e.g. proton pump inhibitors), by restricting diuretic administration, or by providing chloride at reversal of sustained hypercapnia. Prevention of the development of maintenance factors may be possible, by providing sufficient amounts of fluids, sodium, potassium, and chloride.

Generating factors

When metabolic alkalosis has developed, initial treatment is, whenever possible, the correction of the underlying disease and elimination of the generating factors. Suppression of further bicarbonate generation or reabsorption may include H2-receptor antagonists [8] or proton pump inhibitors in gastric alkalosis, prostaglandin synthetase inhibitors, or angiotensin-converting enzyme inhibitors in Bartter's syndrome, anti-emetic, and antidiarrhoeal drugs in digestive losses, reduction, or discontinuation of diuretic therapy, etc. Treatment of the underlying disease and elimination of generating factors should always be associated with the identification and reversal of maintenance factors that can maintain the alkalosis, even when generating factors have disappeared.

Maintenance factors

Metabolic alkalosis is always characterized by a chloride deficit. Chloride depletion is typically associated with blood volume and potassium depletion, so that chloride is best administered as sodium chloride and potassium chloride solutions. The blood volume deficit is variable, and sodium chloride should be given until blood volume and natraemia are corrected (as shown by an increase in urine sodium excretion if renal function is normal). The potassium deficit can reach 1000 mmol, and the potassium urinary wasting will persist until the alkalosis is corrected. Potassium chloride should be infused at the rate of 150–300 mmol/day, to restore and maintain a serum potassium concentration above 4 mmol/L.

When given in sufficient amount, sodium chloride and/or potassium chloride solutions generally reverse the alkalosis within a few days. Although mineralocorticoid excess should be identified as a maintenance factor when present, its correction is less important in critically-ill patients because it only causes mild metabolic alkalosis. If reversal of maintenance factors is ineffective or is not possible (e.g. in renal or cardiac failure), or if severe clinical complications require rapid correction, more specific approaches can be considered.

Haemodialysis and haemofiltration

Haemodialysis and peritoneal dialysis, when required because of renal failure, effectively reverse metabolic alkalosis if bicarbonate concentration is decreased and chloride concentration is increased in the dialysate. Similarly, continuous haemofiltration allows treatment of metabolic alkalosis by adapting the composition of solutions used to compensate fluid losses through the membrane. These techniques are not required to correct metabolic alkalosis in the absence of renal failure.

Acetazolamide

Acetazolamide, a carbonic anhydrase inhibitor, is a diuretic drug that enhances renal excretion of water, sodium, potassium, and bicarbonate. Although increased excretion of water, sodium, and potassium are generally unwelcome in metabolic alkalosis, acetazolamide has been proposed as a treatment of alkalosis in patients

Table 257.3 Clinical experience of hydrochloric acid (HCl) infusion in the treatment of metabolic alkalosis: administration modalities and complications

		n	Concentration (mmol/L)	Rate (mmol/hour)	Amount (mmol)	Complication*
1974	Abouna et al. [11]	8	150–200	8–25	150–200	*
1979	Wagner et al. [12]	20	100–200	unknown	8–1200	*
1980	Wagner et al. [13]	17	100	17–25	100–400	*
1980	Williams et al. [14]	12	150	1–8	60–400	**
1981	Finkle et al. [15]	21	unknown–200	4–15	60–2100	
1983	Kwun et al. [16]	24	100	60	Mean 90	
1985	Brimioulle et al. [17]	15	250	25	150–300	
1986	Worthley et al. [18]	15	200	8	200–450	
1989	Brimioulle et al. [10]	15	250	25	75–300	
1990	Brimioulle et al. [6]	8	1000	65	250–500	

*Venous and/or cutaneous necrosis.

**HCl diluted in a solution of amino-acids acting as buffer.

Data from various sources (see references).

with cardiac and respiratory failure. Its diuretic effect may be useful in oedematous cardiac failure, provided potassium losses can be effectively corrected by appropriate intake. It is more hazardous in respiratory failure and particularly in hypercapnic patients. Effects of acetazolamide persist for 24–48 hours, which may be a problem when the drug is found to decrease the pH and not the $PaCO_2$. Acetazolamide inhibits carbonic anhydrase and thus interferes with tissue CO_2 elimination. In COPD patients, it has been shown to cause a sustained and significant increase in the difference between tissue CO_2 tension and $PaCO_2$ [9]. The decrease in $PaCO_2$ reported during acetazolamide therapy thus reflects, at least in part, altered tissue removal rather than improved pulmonary elimination of CO_2. Acetazolamide has been reported to cause haematuria and renal failure. It should be avoided in renal and hepatic failure, and is ineffective in anuric patients.

Acidifying agents

Treatment of metabolic alkalosis with chloride-containing acids has been suggested, but most of these substances have been associated with deleterious side effects. Lysine chloride and arginine chloride can cause hyperglycaemia and hyperkalaemia, and worsen pre-existing renal failure. Ammonium chloride can result in cardiac, respiratory, and neurological complications, especially in cases of rapid administration or patients with renal or hepatic failure. These substances are best avoided in the treatment of metabolic alkalosis.

Hydrochloric acid

Hydrochloric acid (HCl) is proposed as the most efficient way to rapidly and selectively correct the deficits in hydrogen and chloride ions that characterize metabolic alkalosis. Suggested indications for HCl therapy are:

- Serious clinical complications due to the alkalosis (coma, arrhythmias).
- Contraindications to or ineffectiveness of other treatments.
- Severe alkalaemia (arterial pH > 7.55).
- Respiratory failure with hypercapnia and/or hypoxaemia [10].

The efficiency of HCl in reversing alkalosis has been reported in several clinical studies (Table 257.3) [6,10–18].

Pulmonary oedema due to HCl therapy has been reported and attributed to the amount of fluid required to correct the alkalosis. Haemolysis has been reported in animal experiments, but not in clinical series. Vascular and perivascular necrosis have been observed in earlier series, after HCl infusion into a peripheral vein [19]. Extensive tissue necrosis has only been reported after leakage or infusion to extravascular sites [20].

HCl can be infused without complication into the superior vena cava, provided adequate precautions are taken [17]. HCl is prepared in a glass bottle as a 250- or 500-mmol/L solution (25 or 50 mL of 36% HCl in 1 L of sterile water). After very careful verification of the adequate position of the catheter tip on a chest X-ray, the solution is infused at the rate of 1 mL/kg/hour without being mixed to other than electrolytic solutions. Arterial blood gases are measured every 2 hours (500 mmol/L) or 4 hours (250 mmol/L), and the infusion is discontinued when the alkalosis is reversed (i.e. base excess below zero). When rapid correction is required, a 1000 mmol/L solution may be infused at the same rate, while blood gases are measured hourly. After achievement of the HCl infusion, metabolic alkalosis may relapse if generating or maintenance factors have not been corrected.

References

1. Hodgkin JE, Soeprono FF, and Chan DM. (1980). Incidence of metabolic alkalemia in hospitalized patients. *Critical Care Medicine*, **12**, 725–8.
2. Adrogue HJ and Madias NE. (2010). Secondary responses to altered acid-base status: the rules of engagement. *Journal of the American Society for Nephrology*, **21**, 920–3.
3. Palmer BF and Alpern RJ. (1997). Metabolic alkalosis. *Journal of the American Society for Nephrology*, **8**, 1462–9.
4. Galla JH. (2000). Metabolic alkalosis. *Journal of the American Society for Nephrology*, **11**, 369–75.

5. Brimioulle S, Lejeune P, Vachiéry JL, Leeman M, Mélot C, and Naeije R. (1990). Effects of acidosis and alkalosis on hypoxic pulmonary vasoconstriction. *American Journal of Physiology*, **258**, H347–53.
6. Brimioulle S and Kahn RJ. (1990). Effects of metabolic alkalosis on pulmonary gas exchange. *American Review of Respiratory Disease*, **141**, 1185–9.
7. Brimioulle S, Vachiéry JL, Lejeune P, Leeman M, Mélot C, and Naeije R. (1991). Acid-base status affects gas exchange in canine oleic acid pulmonary edema. *American Journal of Physiology*, **260**, H1080–6.
8. Rowlands BJ, Tindall SF, and Elliott DJ. (1978). The use of dilute hydrochloric acid and cimetidine to reverse severe metabolic alkalosis. *Postgraduate Medical Journal*, **54**, 118–23.
9. Krintel JJ, Baxholft OS, Berthelsen P, and Brockner J. (1983). Carbon dioxide elimination after acetazolamide in patients with chronic obstructive pulmonary disease and metabolic alkalosis. *Acta Anaesthesia Scandinavica*, **27**, 252–4.
10. Brimioulle S, Berré J, Dufaye P, Vincent JL, Degaute JP, and Kahn RJ. (1989). Hydrochloric acid infusion for treatment of metabolic alkalosis associated with respiratory acidosis. *Critical Care Medicine*, **17**, 232–6.
11. Abouna GM, Veazey PR, and Terry DB Jr. (1974). Intravenous infusion of hydrochloric acid for treatment of sever metabolic acidosis. *Surgery*, **75**, 194–202.
12. Wagner CW, Nesbit RR Jr, and Mansberger AR Jr. (1979). Treatment of metabolic alkalosis with intravenous hydrochloric acid. *Southern Medical Journal*, **72**, 1241–5.
13. Wagner CW, Nesbit RR Jr, and Mansberger AR Jr. (1980). The use of intravenous hydrochloric acid in the treatment of thirty-four patients with metabolic alkalosis. *American Surgery*, **46**, 140–6.
14. Williams DB and Lyons JH Jr. (1980). Treatment of severe metabolic alkalosis with intravenous infusion of hydrochloric acid. *Surgery, Gynecology & Obstetrics*, **150**, 315–21.
15. Finkle D and Dean RE. (1981). Buffered hydrochloric acid: a modern method of treating metabolic alkalosis. *The American Surgeon*, **47**, 103–6.
16. Kwun KB, Boucherit T, Wong J, Richards Y, and Bryan-Brown CW. (1983). Treatment of metabolic alkalosis with intravenous infusion of concentrated hydrochloric acid. *American Journal of Surgery*, **146**, 328–30.
17. Brimioulle S, Vincent JL, Dufaye P, Berré J, Degaute JP, and Kahn RJ. (1985). Hydrochloric acid infusion in metabolic alkalosis: effects on acid-base balance and oxygenation. *Critical Care Medicine*, **13**, 738–42.
18. Worthley LI. (1986). Intravenous hydrochloric acid in patients with metabolic alkalosis and hypercapnia. *Archives of Surgery*, **121**, 1195–8.
19. Rothe KF and Schimek F. (1986). Necrotic skin lesion following therapy of severe metabolic acidosis. A case report. *Acta Anaesthesiologica Belgica*, **37**, 137–9.
20. Jankauskas SJ, Gursel E, and Antonenko DR. (1989). Chest wall necrosis secondary to hydrochloric acid use in the treatment of metabolic alkalosis. *Critical Care Medicine*, **17**, 963–4.

PART 10.4

Blood glucose control

CHAPTER 258

Pathophysiology of glucose control

Ulrike Madl

Key points

- Hyperglycaemia is a common phenomenon in critically-ill patients, associated with higher morbidity and mortality in different clinical settings.
- Hyperglycaemia exerts negative effects through increased pro-inflammatory mediators, osmotic diuresis, impaired immune function, impaired wound healing, pro-coagulatory effects, endothelial cell dysfunction, increased oxidative stress, causing cell and tissue injury, and adverse cardiovascular effects.
- Both severe and moderate hypoglycaemia are associated with intensive insulin therapy and have been identified as independent risk factors of mortality in critically-ill patients.
- Glucose variability seems to be another independent risk factor influencing mortality in critically-ill patients.
- In critically-ill patients with diabetes negative effects of hyperglycaemia and glucose variability seem to be reduced, depending on glucose control before critical illness.

Stress metabolism and incidence of hyperglycaemia

Hyperglycaemia is a common phenomenon during critical illness. Up to 80–100% of patients develop stress hyperglycaemia during the course of their critical illness independent of diabetes status. This hyperglycaemia was accepted as an adaptive response to injury until many studies linked hyperglycaemia with increased morbidity and mortality in different clinical settings. The stress caused by critical illness or injury disturbs glucose homeostasis and is characterized by hyperglycaemia, glucose intolerance, and peripheral and hepatic insulin resistance with high blood-glucose levels despite high levels of insulin release. Hepatic glucose production is upregulated in the acute phase of critical illness. Increased release of counter regulatory hormones such as glucagon, cortisol, and growth hormone and also cytokines contribute to the enhanced gluconeogenesis [1]. They lead to enhanced lipolysis and increased concentrations of free fatty acids (FFAs) and increased proteolysis. Increased FFA levels also produce dose-dependent insulin resistance in peripheral tissues and serve as a substrate to increase hepatic gluconeogenesis. The hyperglycaemic state caused by these mechanisms is frequently worsened by iatrogenic administration of glucose in the form of parenteral or enteral nutrition or intravenous glucose in critically-ill patients [2].

Furthermore, catecholamines, which are also elevated in acute critical illness, contribute to the disturbed glucose homeostasis by induction of hepatic glycogenolysis and inhibition of glycogenesis [3].

Another factor contributing to hyperglycaemia in critical illness is disturbed glucose uptake mechanisms. Insulin dependent glucose uptake in myocardium, skeletal muscle and adipose tissue by glucose transporter 4 (GLUT 4) is impaired [4]. Moreover, exercise-stimulated skeletal muscle glucose uptake is absent in immobile critically-ill patients. Nevertheless, whole body glucose uptake is increased. Insulin-independent glucose uptake in tissues such as brain and blood cells accounts for this [4,5].

Stress hyperglycaemia

Studies performed in various clinical settings have found an association between stress hyperglycaemia and poor outcome. Several studies identified hyperglycaemia as a major risk factor of mortality and morbidity in critically-ill patients. A large retrospective cohort study including more than 250,000 patients found hyperglycaemia is an independent risk factor for mortality in patients with cardiac disease, sepsis, and respiratory insufficiency. In patients undergoing cardiac surgery, hyperglycaemia is associated with a higher mortality and delayed extubation [6]. In patients with myocardial infarction, congestive heart failure and cardiogenic shock hyperglycaemia was associated with an increased risk of death. In patients with stroke and subarachnoid haemorrhage severe hyperglycaemia is associated with poor clinical outcome and a higher risk of mortality [7].

Several potential mechanisms have been identified that may explain the negative impact of hyperglycaemia:

> Hyperglycaemia negatively influences the immune system. Multiple mechanisms of the hyperglycaemic effect on immune function include: derangement of neutrophil activity, enhanced expression of intercellular adhesion molecules and E-selectins, elevated levels of pro-inflammatory cytokines, and promotion of adherence and sequestration of neutrophils and monocytes in peripheral tissues. Hyperglycaemia also interferes with wound healing by reducing proliferation and migration of fibroblasts and by limiting vasodilatory properties of vascular smooth muscle cells. Moreover, severe hyperglycaemia induces osmotic diuresis, which may result in dehydration and electrolytes loss. [7]

Acute hyperglycaemia also has a negative effect on the myocardium. It can attenuate ischaemic preconditioning of the heart, a protective mechanism for ischaemic injury, possibly by inhibiting activation of ATP-sensitive potassium channels. These activate glycolysis and

may induce cardiac myocyte death through apoptosis or by aggravation of ischaemia-reperfusion cellular injury [7].

In addition, hyperglycaemia has procoagulatory effects and is associated with platelet hyperactivation and hyperaggregation. Increased thromboxane synthesis is related to platelet hyper-reactivity and is tightly regulated by glucose control [7].

Oxidative stress in diabetes

Hyperglycaemia is also associated with the development of increased oxidative stress in diabetes, partly caused by increased mitochondrial superoxide production. Superoxide interacts with nitric oxide (NO) to form peroxynitrite, a reactive oxygen species (ROS) that can modify proteins and alter their function [5]. Oxidative stress represents another modulator of platelet activation, which induces vasoconstriction and platelet hyper-reactivity [7].

Insulin

Insulin exerts several positive effects when administered in acute critical illness, including anti-inflammatory and anabolic effects in addition to glucose control. For example, insulin increases amino acid uptake, lipid synthesis, esterification of fatty acids and decreases proteolysis, lipolysis, and gluconeogenesis [1]. Insulin attenuates counter regulatory hormones, pro-inflammatory transcription factors, and may even inhibit the development of reactive oxidation species. Insulin influences electrolyte homeostasis by decreasing renal sodium excretion and enhancing potassium uptake from the bloodstream into body cells [7]. Strict separation of direct insulin effects and effects mediated by glucose lowering on different tissues and cell systems is difficult.

The main effect of insulin is the stimulation of peripheral glucose uptake via the insulin dependent GLUT-4 in skeletal muscle and adipose tissue. In contrast to this, hepatic insulin resistance cannot be improved by insulin administration, resulting in high gluconeogenesis and low insulin-stimulated glucose uptake and glycogen synthesis [1].

Glucose uptake

The glucose lowering effect can effectively decrease acute glucose toxicity mainly in the insulin independent tissues such as liver, kidney, pancreas, gastrointestinal tract, endothelial cells, neurons, and immune cells. In these tissues, glucose uptake is performed via the insulin independent transporters GLUT-1, -2, and -3, which allow glucose to enter the cells according to the glucose concentration difference [1]. Healthy subjects downregulate the expression of these transporters in the presence of hyperglycaemia in order to protect the cells from glucose overload. However, in critical illness, cytokines upregulate these insulin-independent glucose transporters [8]. This effect may overcome the protective effect of the normal downregulatory response, and consequently result in cellular glucose overload and toxic adverse effects of glycolysis and oxidative phosphorylation, especially in tissues with insulin-independent glucose uptake. Therefore, insulin-dependent glucose uptake via GLUT-4 seems to protect tissues like skeletal muscle or myocardium against uncontrolled glucose overload [2].

In the critically-ill patient, the association between hyperglycaemia and poor outcome is well established. However, trials of glucose control [2] were associated with an increased occurrence of hypoglycaemic events.

Hypoglycaemia

Hypoglycaemia is defined as blood glucose <3.9 mmol/L (70 mg/dL), while severe hypoglycaemia is defined as blood glucose <2.2 mmol/L (40 mg/dL). In healthy individuals, a reduction in blood glucose below 4.44 mmol/L (80 mg/dL) results in inhibition of endogenous insulin production and unblocking of hepatic gluconeogenesis [9]. Further decline of blood glucose below 3.6 mmol/L (65 mg/dL) causes release of glucagon and a further increase in hepatic gluconeogenesis and glycogenolysis. However, in critically-ill patients endogenous glucose production is often impaired. Especially in patients with hepatic failure, adrenal insufficiency during septic shock, renal failure, and patients suffering from severe malnutrition endogenous glucose production may fail. Untreated low blood glucose levels are particularly dangerous for neural cells as they are dependent on glucose supply and glucose from other sources is limited. During severe hypoglycaemia glial glycogen, as well as glial lactate and ketone bodies can serve as an energy source for neurons for a limited time [9].

Brain metabolism

Nevertheless, brain metabolism depends on continuous diffusion of glucose from the blood. Glucose levels in the brain are normally between 0.7 and 2.28 mmol/L (14 and 41 mg/dL) and are directly related to blood glucose levels. Therefore, blood glucose levels below 2 mmol/L (36 mg/dL) result in brain glucose concentration near zero because metabolic requirements exceed supply.

Accordingly, neuroglycopenia first results in functional brain failure with subsequent brain tissue damage due to neuronal cell death in the case of severe and prolonged hypoglycaemia.

Neuronal damage

The pathophysiology of neuronal damage during severe hypoglycaemia is not fully explored yet. However, neuronal death seems to be due to activation of neuronal glutamate receptors, production of reactive oxygen species, DNA damage, neuronal zinc release, activation of poly(ADP-ribose)polymerase-1 and mitochondrial permeability transition, rather than the direct effect of energy failure [1].

Moreover, glucose reperfusion may play a role in hypoglycaemia-induced neuronal cell death [10]. In vitro experiments demonstrated the amount of superoxide production (oxidative stress) and neuronal death were positively correlated with increasing glucose concentrations during the reperfusion period [10]. Hence, in this model, glucose reperfusion after hypoglycaemia was as deleterious as hypoglycaemia itself, implicating the need to avoid over-correction of hypoglycaemia.

Cardiovascular effects

Severe hypoglycaemic events may have cardiovascular effects as well. They may induce cardiac rate and rhythm disturbances, including ventricular tachycardia, atrial fibrillation, and sinus tachy- and bradycardia [9].

Glycaemic control

In all randomized controlled trials investigating the effect of tight glycaemic control in critically-ill patients, intensive insulin therapy was associated with a substantially increased occurrence of hypoglycaemic events (5.1–28.6% in the intervention group) [2,11].

Post-hoc analysis of several trials identified severe hypoglycaemic events as an independent risk factor of mortality, even though there seems to be a difference between iatrogenic and spontaneous hypoglycaemic events with the latter being even more deleterious.

Several observational cohort studies have elucidated the impact of mild hypoglycaemic events (blood glucose < 4.5 mmol/L (81mg/dL)) on outcome [12]. Again, multivariate analysis demonstrated even mild hypoglycaemia was independently associated with increased mortality. Association between mild or moderate hypoglycaemia and mortality persisted even after adjustment for insulin therapy or timing of hypoglycaemic episode. In another analysis hypoglycaemia, was independently associated with increased mortality even after compensating for severity of illness, diagnostic category, diabetic status, mean blood glucose during intensive care unit (ICU) admission, and glycaemic variability [13].

Predisposing factors for the development of hypoglycaemia

Predisposing factors for development of hypoglycaemia include intensive insulin therapy, use of bicarbonate-based substitution fluid during renal replacement therapy, a decrease of nutrition without adjustment of insulin infusion, a prior diagnosis of diabetes mellitus, sepsis, and the need for inotropic support. Other studies identified septic shock, elevated serum creatinine levels >3 mg/dL, mechanical ventilation, severity of disease, medical or non-elective admissions, being female, and being immune-compromised as independent risk factors for the development of severe hypoglycaemic events. Additionally, different glycaemic targets, and differences in monitoring frequency and monitoring technology may also contribute to the development of hypoglycaemic events [9].

Glucose variability

Glycaemic variability, a marker of exogenous glucose regulation, defined as standard deviation, glucose lability index or mean daily blood glucose, was independently associated with mortality in critically-ill patients, independent of the hyper- or hypoglycaemia [14,15]. However, prospective interventional studies have not directly focused on glucose variability in critically-ill patients, since methods of influencing it have not been defined yet. Interestingly, one study proposes the relationship between glycaemic variability and mortality may be even stronger in non-diabetics than in diabetics [16].

The underlying pathophysiology of the harmful effect of elevated glycaemic variability might be the induction of endothelial cell damage and apoptosis by short-time fluctuations of glucose levels. In diabetes mellitus type 2 patients, glycaemic variability was also associated with markers of oxidative stress and mediators of organ dysfunction. Increased oxidative stress and increased monocyte adhesion to endothelial cells may cause endothelial dysfunction and contribute to vascular damage [17].

Finally, in critically-ill patients, glucose complexity has been proposed as a marker of endogenous glucose regulation. Glucose complexity is a dynamic measure of glucose time series and seems to provide more powerful information on endogenous glucose regulation than does conventional glycaemic analysis. In a small number of patients glycaemic profile was shown to be more complex in ICU survivors than in ICU non-survivors. Loss of complexity in glucose time series is significantly associated with higher mortality. This can be explained by the ability of a healthy organism to detect even minor changes in glucose concentration. These changes are promptly followed by endogenous counter regulatory measures leading to a complex glucose profile. In contrast, an impaired regulatory system responds slowly and imprecisely to varying glucose concentrations and therefore displays low glucose complexity. This finding is analagous to the loss of heart rate variability in critically-ill patients, which is associated with a higher mortality [18].

Influence of pre-existing diabetes mellitus

The impact of hyperglycaemia on outcome in critically-ill patients with and without diabetes is different. A diabetic patient with significant hyperglycaemia may be less severely ill than a non-diabetic patient with the same or even a lesser degree of hyperglycaemia. This may be explained by biological adjustment to pre-existing hyperglycaemia. Diabetic patients are used to high glucose levels based on the development of relative insulin resistance, the release of counter regulatory hormones and pro-inflammatory cytokines. Thus, in diabetic critically-ill patients adapted to high glucose levels hyperglycaemia is better tolerated than in non-diabetics [16].

The pathophysiological and molecular background explaining the difference between diabetic and non-diabetic critically-ill patients during hyperglycaemia is not clear yet. The expression of the receptor for advanced glycation end-products (sRAGE) might be involved in different responses of diabetics and non-diabetics to sepsis [16].

In clinical trials, association between hyperglycaemia and outcome is much weaker in diabetic critically-ill patients than in non-diabetic patients. Moreover, response of diabetic critically-ill patients to the normalization of glycaemia compared with non-diabetics is different. In almost all clinical trials, non-diabetics benefitted more from the intervention than did diabetics. Also pre-admission glucose control (HbA1c concentration) in diabetic critically-ill patients seems to play a role in the response to glucose control and mortality. In a retrospective analysis high blood glucose values (>10mmol/L (>180mg/dL)) during the ICU stay were associated with lower mortality in patients with HbA1c >7% compared with patients with good glycaemic control before the ICU stay (HbA1c <7%) [19]. The ACCORD study, showed that aggressive glycaemic control of diabetic patients, resulting in reduction of HbA1c levels from 8.3 to 6.4%, resulted in increased mortality compared with the patients in the control group, who were treated more conservatively [20].

Additionally, the relationship between glucose variability and mortality may be considerably weaker in diabetics than in non-diabetics [16].

Furthermore, glucose complexity was lower in diabetic critically-ill patients compared with non-diabetics. This suggests that the endogenous glucose regulation in diabetic ICU patients is not able to correct alterations of the glucose level as frequently as in non-diabetics [16].

References

1. Derde S, Vanhorebeek I, and Van den Berghe G. (2009). Insulin treatment in intensive care patients. *Hormone Research*, **71**(1), 2–11.
2. Van den Berghe G, Wouters P, Weekers F, et al. (2001). Intensive insulin therapy in critically ill patients. *New England Journal of Medicine*, **345**(19), 1359–67.
3. Watt MJ, Howlett KF, Febbraio MA, Spriet LL, Hargreaves M. (2001). Adrenaline increases skeletal muscle glycogenolysis, pyruvate

dehydrogenase activation and carbohydrate oxidation during moderate exercise in humans. *Journal of Physiology*, **534**, 269–78.
4. Stephens JM, Bagby GJ, Pekala PH, Shepherd RE, Spitzer JJ, Lang CH. (1992). Differential regulation of glucose transporter gene expression in adipose tissue or septic rats. *Biochemistry and Biophysics Research Communications*, **183**, 417–22.
5. Langouche L, Vanhorebeek I, and Van den Berghe G. (2007). Therapy insight: the effect of tight glycemic control in acute illness. *Nature Clinical Practice Endocrinology & Metabolism*, **3**(3), 270–8. [Review.]
6. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. (2009). Hyperglycemia related mortality in critically ill patients varies with admission diagnosis. *Critical Care Medicine*, **37**(12), 3001–9.
7. Umpierrez GE and Smiley D. (2012). Pathophysiology of in hospital hyperglycemia. In: Holzinger U (ed.) *Glucose Management and Insulin Treatment in Intensive Care*. Bremen: UNI-MED.
8. Klip A, Tsakiridis T, Marette A, and Ortiz PA. (1994). Regulation of expression of glucose trans- porters by glucose: a review of studies in vivo and in cell cultures. *Federations of American Societies for Experimental Biology Journal*, **8**, 43–53.
9. Krinsley J and Brunner R. (2012) Side effects and cost of insulin treatment in the ICU. In: Holzinger U (ed.) *Glucose Management and Insulin Treatment in Intensive Care*. Bremen: UNI-MED.
10. Suh SW, Gum ET, Hamby AM, Chan PH, and Swanson RA. (2007). Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. *Journal of Clinical Investigation*, **117**, 910–18.
11. Van den Berghe G, Wilmer A, Hermans G, et al. (2006). Intensive insulin therapy in the medical ICU. *New England Journal of Medicine*, **354**(5), 449–61.
12. Bagshaw SM, Bellomo R, Jacka MJ, et al. (2009). The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. *Critical Care*, **13**(3), R91.
13. Egi M, Bellomo R, Stachowski E, et al. (2010). Hypoglycemia and outcome in critically ill patients. *Mayo Clinic Proceedings*, **85**(20176928), 217–24.
14. Egi M, Bellomo R, Stachowski E, et al. (2006). Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology*, **105**(16871057), 244–52.
15. Hermanides J, Vriesendorp TM, Bosman RJ, et al. (2010). Glucose variability is associated with intensive care unit mortality. *Critical Care Medicine*, **38**(3), 838–42.
16. Krinsley J and Brunner R. (2012). The critically ill patient with known diabetes mellitus. In Holzinger U (ed.) *Glucose Management and Insulin Treatment in Intensive Care*. Bremen: UNI-MED, 2012.
17. Monnier L, Mas E, Ginet C, et al. (2006). Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *Journal of the American Medical Association*, **295**(16609090), 1681–7.
18. Lundelin K, Vigil L, Bua S, et al. (2010). Differences in complexity of glycemic profile in survivors and nonsurvivors in an intensive care unit: a pilot study. *Critical Care Medicine*, **38**(20068460), 849–54.
19. Egi MMD, Bellomo RMD, Stachowski EMD, et al. (2011). The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. *Critical Care Medicine*, **39**(1), 105–11.
20. Dluhy RG and McMahon GT. (2008). Intensive glycemic control in the ACCORD and ADVANCE trials. *New England Journal of Medicine*, **358**(24), 2630–3.

CHAPTER 259

Glycaemic control in critical illness

Simon Finfer

Key points

- Hyperglycaemia, hypoglycaemia, and the degree by which blood glucose fluctuates (blood glucose variability) are all independently associated with increased mortality.
- The optimum target range for blood glucose concentration is not clearly established, current recommendations suggest commencing treatment if blood glucose exceeds 10 mmol/L (180 mg/dL) and continuing treatment when necessary to keep blood glucose in the range of 8–10 mmol/L (144–180 mg/dL).
- Expert opinion on the measurement of blood glucose in critically-ill patients is evolving. Point-of-care glucose analysers (glucometers) are inaccurate. Continuous glucose monitors may be preferable to intermittent measurement, but are not yet in routine clinical use.
- Intensive care units should have a protocol for the management of blood glucose that defines a target range and aims to avoid hyperglycaemia, hypoglycaemia, and excessive blood glucose variability.
- Protocols should address blood sampling (site and frequency), method of measurement of blood glucose concentration, the administration of insulin, avoidance and treatment of hypoglycaemia, and integration of glucose control with feeding and other treatments.

Introduction

In 2001, Van den Berghe and colleagues published research suggesting that targeting normoglycaemia, (blood glucose concentration of 4.4–6.1 mmol/L (80–110 mg/dL)), reduced both morbidity and mortality in patients treated in a surgical ICU [1]. This research radically changed the perception of blood glucose management in critically-ill patients and stimulated a large body of research that has produced a much clearer, but still incomplete, understanding of the complexities of measuring, monitoring, and controlling blood glucose in critically-ill patients. It is now clear that both hypoglycaemia and hyperglycaemia, and the degree by which blood glucose concentration fluctuates (blood glucose variability) are strongly associated with increased risk of death. Strategies for glycaemic control in the intensive care unit (ICU) should seek to avoid all three of these features of dysglycaemia and need to be integrated with other aspects of patient care.

What is the optimum target for blood glucose concentration?

The optimum target for blood glucose concentration is not clearly established. Van den Berghe and colleagues conducted two trials in adults comparing a target of 4.4–6.1 mmol/L; (80–110 mg/dL, normoglycaemia) with a target of 10.0–11.1 mmol/L. In their surgical ICU they found this reduced both mortality and morbidity [1], while, in their medical ICU, only measures of morbidity were reduced [2]. Other investigators have not been able to reproduce these results and a large international multicentre trial found that mortality was significantly lower in patients assigned a target of less than 10 mmol/L than in those where normoglycaemia was targeted [3]. Recent meta-analyses have concluded that targeting normoglycaemia provides no overall mortality benefit in critically-ill patients and consistently increases the risk of severe hypoglycaemia [4,5]. Currently, the American Diabetes Association recommends treating hyperglycaemia when the blood glucose concentration exceeds 10.0 mmol/L and, once insulin treatment is started, targeting a blood glucose concentration of 7.8–10.0 mmol/L [6]. The American College of Physicians recommends similar targets [7].

How and how often should blood glucose be measured?

In most ICUs, and in most trials of intensive glucose control, blood glucose concentration has been measured using point-of-care glucose meters with capillary blood samples being obtained by needlesticks, or with samples from arterial or central venous catheters. Both the use of glucose meters and sampling capillary blood by needle sticks have the potential to introduce unacceptable errors into the measurement of blood glucose concentration [8]; capillary samples also have increased inaccuracy in patients who are shocked or being treated with vasopressors. It is now clear that glucose meters that were not designed for use in ICUs or for regulating insulin infusions are not accurate enough for these purposes, particularly when targeting a narrow range for blood glucose concentration (Fig. 259.1) [9]. Awaiting results of hospital laboratory measurements is generally impractical and, for most ICUs, a readily available accurate blood glucose measurement can best be obtained from a blood gas analyser. Blood samples should be drawn from an arterial catheter whenever possible and arterial catheters should never be flushed with glucose-containing solutions. An alternative for patients without a functioning arterial catheter is to draw blood

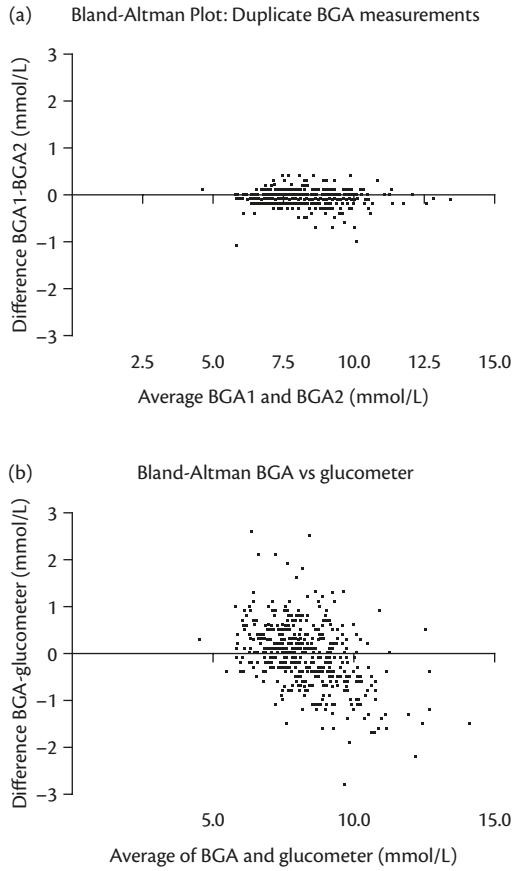


Fig. 259.1 Bland–Altman plots. (a) Blood glucose was analysed twice from the same sample in the same blood gas analyser (BGA). (b) The same sample was analysed in a blood gas analyser and a bedside glucometer.

from a central venous catheter; again, great care must be taken to avoid contamination with glucose-containing fluids, including parenteral nutrition, and to avoid increasing the risk of catheter-related sepsis.

Apart from concerns over inaccuracy, sampling glucose by needlesticks is undesirable as blood glucose concentration should be measured frequently. In critically-ill patients treated with insulin infusions, blood glucose concentration should be checked at least every 2 hours. In unstable patients and during recovery from hypoglycaemia blood glucose concentration should be checked more frequently. In different clinical circumstances, it may be appropriate to measure blood glucose at intervals varying from every 15 minutes to every 2 hours.

Just as continuous monitoring of arterial blood pressure and oxygen saturation are now considered standards of care in ICUs, the optimum solution for monitoring blood glucose may be the use of continuous glucose monitors (cGM). A variety of cGM systems are either in early clinical use or under development. Sensors monitor interstitial or intravascular glucose concentration with the faster response time being advantageous for intravascular monitoring. Initial data from cGM systems suggest blood glucose may fluctuate more widely and more rapidly in critically-ill patients than intermittent monitoring suggests (Fig. 259.2). In future accurate cGM systems should improve blood glucose control and patient safety.

Administration of insulin

As hyperglycaemia is common in critical illness many patients treated in ICUs will be treated with insulin. Patients who are eating or who have intermittent calorie intake should be treated with either oral hypoglycaemic agents or intermittent doses of subcutaneous insulin. Critically-ill patients who are receiving a constant calorie source through enteral or parenteral feeding, and patients who are hyperglycaemic, but not being fed can be treated with a continuous intravenous infusion of short-acting insulin. Insulin infusions should be given via a dedicated port or catheter using an accurate infusion pump or volumetric syringe. Infusion rates to achieve the same blood glucose concentration may vary widely between patients and in the same patient over time as insulin sensitivity and resistance can change with changes in the patient's clinical condition; they are also affected by other treatments. Insulin dosing and control of blood glucose concentration can be unprotocolized where frequency of blood glucose monitoring and changes to insulin dosing are left to the discretion of the individual nurse caring for the patient, or protocolized by use of paper-based or computerized protocols. Paper-based protocols are passive as they rely on the nurse or other individual to measure blood glucose concentration and alter the treatment in response to that measurement. Computerized protocols or computerized decision support systems (CDSS) may also be passive and only give advice when it is requested. The advent of clinical information systems and active decision support means that systems now exist that can require the blood glucose concentration to be measured at set time points, can provide electronic reminders to nurses and other clinicians to measure a patient's blood glucose concentration, and can provide advice on insulin dosing and other treatments to optimize the control of blood glucose. These systems have the potential to improve blood glucose control and patient safety, but are not yet in widespread clinical use and have not yet been proved to improve patient-centred outcomes [10].

The major adverse effect of insulin administration is hypoglycaemia. This is particularly dangerous in sedated patients or those with a reduced level of consciousness as even severe hypoglycaemia may go undetected. Recent data confirm that the occurrence of even moderate hypoglycaemia (blood glucose concentration <3.9 mmol/L or <70 mg/dL) is associated with a significant increase in the risk of death [11]. Risk factors for hypoglycaemia are listed in Box 259.1; common preventable causes of hypoglycaemia include insulin dosing errors, not measuring blood glucose concentration sufficiently frequently, and reducing or stopping feeding without reducing or stopping insulin administration at the same time.

Integration with feeding and other treatments

Critical care treatments other than the administration of insulin affect blood glucose concentration (see Table 259.1). Notable amongst these are the administration of enteral and parenteral nutrition, catecholamines, and corticosteroids.

Feeding

The glycaemic response of critically-ill patients to feeding is not clearly documented or understood. In patients who are unable to

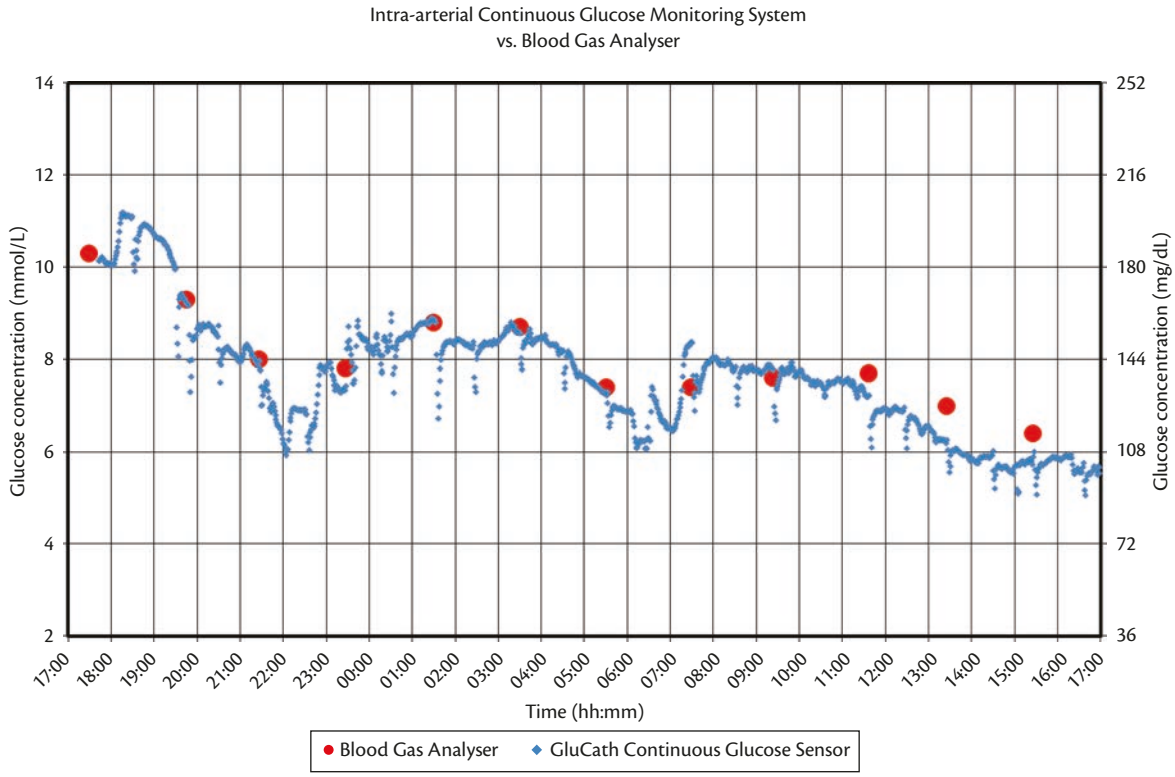


Fig. 259.2 Continuous plot of blood glucose concentration from GluCath® continuous glucose monitoring sensor placed via a radial arterial line. Red dots are simultaneous second hourly measurements using blood drawn from same arterial catheter with blood glucose concentration measured in a Radiometer 800 Flex blood gas analyser.

eat, enteral feeding is preferred over parenteral feeding, and this is most commonly achieved by continuous delivery of feeds through a gastric tube. While the delivery of feed into the stomach can be controlled, the delivery and absorption of feeds in the small intestine is highly variable, and often limited by gastric stasis. Parenteral nutrition can be delivered with greater certainty, but is only recommended for patients with an absolute contraindication to enteral feeding or who have failed a 5–7-day trial of enteral feeding. Stopping or reducing the delivery of feeds (enteral or parenteral) is a common cause of severe hypoglycaemia particularly when

Table 259.1 Common factors affecting blood glucose concentration in critically-ill patients

Factor	Effect
Insulin	Lowers blood glucose in dose-dependent fashion
Enteral nutrition	Blood glucose increases with increased absorption of enteral feeds, may decrease precipitously if feeds stopped and insulin therapy continued
Parenteral nutrition	Blood glucose increases with increased administration of parenteral nutrition , may decrease precipitously if feeds stopped and insulin therapy continued
Catecholamines	Increase insulin resistance, especially with adrenaline
Corticosteroids	Increase insulin resistance in dose-dependent fashion
Therapeutic hypothermia	Decreased metabolic rate may increase blood glucose; glucose may decrease precipitously during rewarming

Box 259.1 Patient- and treatment-related risk factors for hypoglycaemia

Patient risk factors for hypoglycaemia

- Increased age.
- Increase severity of illness score (e.g. APACHE II).
- Lower body mass index (BMI).
- Female sex.
- Medical admission diagnosis.
- Severe sepsis.
- Diabetes mellitus.
- Prior treatment with insulin.
- Prior corticosteroid treatment.
- Vasopressor treatment.
- Targeted intensive glucose control.
- Terminal event in patient dying with or of hepatic failure.

Treatment-related risk factors for severe hypoglycaemia

- Failure to measure blood glucose frequently.
- Stopping or decreasing enteral or parenteral feeding without reducing insulin administration.

- Stopping glucose containing fluid (e.g. peritoneal dialysis) without reducing insulin administration.
- Insulin dosing errors—staff error in dosing.
- Insulin dosing errors in response to inaccurate BG measurement.
- Rewarming from therapeutic hypothermia.

APACHE, acute physiology and chronic health evaluation.

intensive glycaemic control is employed. To reduce glucose variability and the risk of severe hypoglycaemia enteral feeds should be stopped as infrequently as possible. When feeds are stopped or reduced in patients being treated with an insulin infusion the administration of insulin should be reduced or stopped, and blood glucose concentration measured more frequently until it has stabilized.

Other concomitant treatments

Similar consideration should be given to the administration of drugs that influence insulin resistance. This includes treatments commonly used in ICUs, such as catecholamine infusions (particularly adrenaline) and corticosteroids. The blood glucose concentration should be measured with increased frequency when such drugs are given in intermittent dosage or the rate of a continuous infusion is changed substantially.

Other interventions, such as the use of therapeutic hypothermia, also significantly alter metabolic rate and glucose homeostasis. Blood glucose concentration should be measure with increased frequency and insulin treatment supervised closely during rewarming from therapeutic hypothermia as increasing metabolic rate may precipitate severe hypoglycaemia.

Conclusion

Control of blood glucose with the goals of avoiding hyperglycaemia, hypoglycaemia, and excessive blood glucose variability is now established as an important component of the care of critically-ill patients. Future developments will hopefully see the introduction of accurate and continuous monitoring systems leading to better understanding and control of dysglycaemia.

References

1. Van den Berghe G, Wouters P, Weekers F, et al. (2001). Intensive insulin therapy in critically ill patients. *New England Journal of Medicine*, **345**, 1359–67.
2. Van den Berghe G, Wilmer A, Hermans G, et al. (2006). Intensive insulin therapy in the medical ICU. *New England Journal of Medicine*, **354**(5), 449–61.
3. NICE-SUGAR Study Investigators (2009). Intensive versus conventional glucose control in critically ill patients. *New England Journal of Medicine*, **360**, 1346–9.
4. Griesdale DEG, de Souza RJ, van Dam RM, et al. (2009). Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *Canadian Medical Association Journal*, **180**, 821–7.
5. Kansagara D, Fu R, Freeman M, Wolf F, and Helfand M. (2011). Intensive insulin therapy in hospitalized patients: a systematic review. *Annals of Internal Medicine*, **154**(4), 268–82.
6. American Diabetes Association (2012). Standards of medical care in diabetes—2012. *Diabetes Care*, **35**(Suppl. 1), S11–63.
7. Qaseem A, Humphrey LL, Chou R, Snow V, and Shekelle P. (2011). Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine*, **154**(4), 260–7.
8. Kanji S, Buffie J, Hutton B, et al. Reliability of point-of-care testing for glucose measurement in critically ill adults. *Critical Care Medicine*, **33**(12), 2778–85.
9. Scott MG, Bruns DE, Boyd JC, and Sacks DB. (2009). Tight glucose control in the intensive care unit: are glucose meters up to the task? *Clinical Chemistry*, **55**(1), 18–20.
10. Hoekstra M, Vogelzang M, Verbitskiy E, and Nijsten MW. (2009). Health technology assessment review: computerized glucose regulation in the intensive care unit—how to create artificial control. *Critical Care*, **13**(5), 223.
11. NICE-SUGAR Study Investigators (2012). Hypoglycemia and risk of death in critically ill patients. *New England Journal of Medicine*, **367**(12), 1108–18.

CHAPTER 260

Management of diabetic emergencies in the critically ill

Dieter Mesotten and Sophie Van Cromphaut

Key points

- The initial management of diabetic emergencies is aimed at airway, breathing, and circulation.
- Hospital grade blood glucose meters or blood gas analysers are essential for the safe and effective management of diabetic emergencies.
- Correction of hypovolaemia and electrolyte disturbances should prevail in hyperglycaemic crises. Insulin treatment is a secondary priority.
- Slowly correct hyperglycaemia by continuous, low (physiological) dose insulin therapy.
- Hypoglycaemia is suspected in any case of altered mental status, necessitating immediate treatment with intravenous glucose 50% or intramuscular glucagon 1 mg.

Introduction

The hyperglycaemic emergencies diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS) are potentially fatal complications of unidentified or uncontrolled diabetes mellitus [1]. The annual incidence of DKA, mainly observed in type 1 diabetes patients, is approximately 4.5 per 10.000 population. The incidence of HHS is estimated to be about 1% of all diabetic admissions, predominantly in type 2 diabetics. The incidence of these hyperglycaemic emergencies continues to rise, but its associated mortality has diminished remarkably due to better understanding of the pathogenesis and the use of evidence-based treatment guidelines [1,2]. DKA remains a leading cause of mortality in children and young adults with type 1 diabetes, and mortality from DKA and HHS remains high in the elderly and patients with severe co-morbid conditions. Prolonged hypoglycaemia is an important side effect of treatment in type 1 and 2 diabetics and is the third life-threatening diabetic emergency [3–5]. Although these conditions infrequently lead to ICU-admission for treatment, the consequences may be grave.

Diabetic emergencies

There is some similarity in the presentation of the three diabetic emergencies (Table 260.1). Hypoglycaemia and DKA can develop acutely, while HHS may develop insidiously over days or weeks. When requiring emergency care, neurological symptoms, such as lethargy, obtundation, and coma in the later stages, are usually in the foreground. As the respiratory and cardiovascular system may also be compromised, a meticulous assessment of the airway, breathing, and circulation (ABC) status, neurological status, and predisposing factors and lead causes has to be done. A comatose patient with a Glasgow Coma Scale of less than 8 always needs airway protection by endotracheal intubation. This should be followed by monitoring of breathing (continuous oxygen saturation and arterial blood gas) and circulation (electrocardiogram (ECG), blood pressure measurement). The use of sedative agents is to be kept to a minimum to allow regular clinical neurological monitoring and to minimize interference with respiratory compensatory mechanisms in the ketoacidotic patient [6]. It is important to look for predisposing factors, such as the type of diabetes mellitus, diabetic medication, as well as factors that may have acutely precipitated the diabetic emergency, such as infection, acute myocardial infarction, or psychiatric problems [1,6]. The blind emergency treatment of a comatose patient with intravenous glucose (25 g: 50 mL of a glucose 50% solution) and 100 mg of thiamine, with/without naloxone and flumazenil, will improve hypoglycaemia, but may complicate the diagnosis of DKA and HHS.

Hyperglycaemic emergencies

Hyperglycaemic diabetic emergencies are associated with a relatively high mortality [1]. In developing countries up to 20% of patients with DKA may die, compared with approximately 5% in the developed world. Mortality in HHS is fairly consistent between 10 and 20%. Patients presenting with a hyperglycaemic emergency rarely die of the hyperglycaemia and the concomitant biochemical disturbances. The underlying diabetes with micro- and macrovascular complications and the precipitating stress factors, such as infection and acute illness are much more important contributors to mortality.

The effective lack of circulating insulin, combined with increased concentrations of counter-regulatory hormones (catecholamines, cortisol, glucagon, and growth hormone) triggers hyperglycaemia and lipolysis in DKA [6]. The same imbalance between insulin and counter-regulatory hormones leads to unrestrained hepatic free fatty acid oxidation in the liver to ketone bodies. The pathogenesis of HHS is more enigmatic. A greater degree of dehydration and some residual endogenous insulin secretion distinguish it from DKA. The latter prevents lipolysis and ketogenesis, but not the development of severe hyperglycaemia.

Table 260.1 Rapid initial assessment of diabetic emergencies

Diabetic keto-acidosis	Hyperglycemic hyperosmolar state	Hypoglycaemia (coma)
History		
DM type 1	DM type 2	DM type 1 or 2
Prodromal illness: 24–72 hours	Prodromal illness: days-weeks	Prodromal illness: hours
Non-compliance	Possible complication of:	Inappropriate caloric intake
Possible infection	Parenteral feeding	Excessive exercise
Weight loss	Drug therapy	Excessive alcohol intake
	Peritoneal or haemodialysis	Drug overdosing: insulin/sulponylureas/meglitinides
		Autonomic neuropathy: hypoglycaemia unawareness
Signs and symptoms		
Polyuria, polydipsia, dehydration	Polyuria and dehydration	Glycaemia < 3,7 mM: autonomic responses
Fruity breath, Kussmaul breathing		Glycaemia < 2,5 mM: neuroglycopenia
Nausea, vomiting, abdominal pain	Serum osmolality > 340 mM: confusion	
Diagnostic criteria		
Ketoacidosis	*Hyperglycaemia and hyperosmolality*	*Hypoglycaemia*
Glycaemia > 13,8 mM*	Glycaemia > 35 mM*	Glycaemia < 2,5 mM
rarely > 40 mM		
Effective serum osmolality variable	Effective serum osmolality > 320 mM*	
pH < 7,3*	pH > 7,2	
Serum HCO_3 < 18 mM*	Serum HCO_3 > 15 mM	
mostly < 15 mM		
Anion gap > 10–12	Anion gap variable	
Urinary and serum ketones: +++	Urinary and serum ketones: minimal	
Deteriorating conscious level	Deteriorating conscious level, seizures	Conscious level: confusion, coma, seizures

Presentation and diagnostic criteria for hyperglycaemic and hypoglycaemic crises.

Effective serum osmolality = 2[measured Na^+(mmol/L) + glycaemia (mg/dL)/18 (mOsm/kg)].

Anion gap = Na^+(mmol/L) – [Cl^- + HCO_3^- (mmol/L)].

*According to the criteria of the American Diabetes Association [12].

Data from: Nyenwe EA and Kitabchi AE, 'Evidence-based management of hyperglycemic emergencies in diabetes mellitus', *Diabetes Research and Clinical Practice*, 2011, **94**(3), pp. 340–51; De Beer K et al., 'Diabetic ketoacidosis and hyperglycaemic hyperosmolar syndrome – clinical guidelines', *Nursing in Critical Care*, 2008, **13**(1), pp. 5–11; Choudhary P and Amiel SA, 'Hypoglycaemia: current management and controversies', *Postgraduate Medical Journal*, 2011, **87**(1026), pp. 298–306; and American Diabetes Association, Standards of medical care in diabetes, 2012, *Diabetes Care*, 2012, **35**(Suppl. 1), pp. S11–63.

Diagnosis, treatment, and management

After Airway–Breathing–Circulation, and diagnosis and treatment of the precipitating factors and complications of hyperglycaemia the management of DKA or HHS should focus on fluid resuscitation, correction of metabolic acidosis, substitution of electrolyte deficits, and finally insulin administration (Fig. 260.1) [1,2,7]. Table 260.2 shows the average fluid and electrolyte loss in DKA and HHS. The fluid loss is caused by osmotic diuresis due to glycosuria. The loss of water exceeds that of sodium. The first priority is to correct the generalized dehydration and hypovolaemia, or shock in severe cases of hyperglycaemic crises. Adequate fluid resuscitation is a prerequisite for the effectiveness of the subsequent insulin therapy. In a shocked patient, the insulin will insufficiently reach the insulin sensitive organs, skeletal muscle, and adipose tissue, which are responsible for glucose uptake. NaCl 0.9%, an isotonic solution, is recommended for severe hypovolaemia and cardiogenic shock (Fig. 260.1). As recent large trials showed no benefit for colloids in fluid resuscitation, their use cannot be supported [8,9]. Aggressive, unmonitored resuscitation with inflexible fluid regimens is dangerous in patients with limited cardiorespiratory capacity. When dehydration is mild, one can start with a 0.45% saline infusion (Fig. 260.1). To further replenish the fluid losses from the interstitial and intracellular space, glucose 5% is given when blood glucose concentrations are decreasing. In this phase, more fixed fluid recipes (150–250 mL/h) can safely be used.

Diabetic ketoacidosis

A hallmark of DKA is an anion gap metabolic acidosis, due to the accumulation of the ketones β-hydroxybutyrate and acetoacetate (Table 260.1). The arterial pH in DKA is less than 7.30 and the anion gap often exceeds 20 mmol/L. Nevertheless, alkali therapy is only necessary when the pH is below 6.90, since metabolic acidosis will be corrected by insulin therapy (Fig. 260.1, Table 260.3). Inappropriate use of bicarbonate will lead to a prolongation of the ketosis, hypernatraemia, hypokalaemia, paradoxical intracellular acidosis, and rebound alkalosis. Obviously, the administration of bicarbonate is not indicated in HHS.

Patients with DKA or HHS always present with profound potassium deficits by urinary loss (Table 260.2). However, serum potassium concentrations are variable (Table 260.3). Rarely, the patient

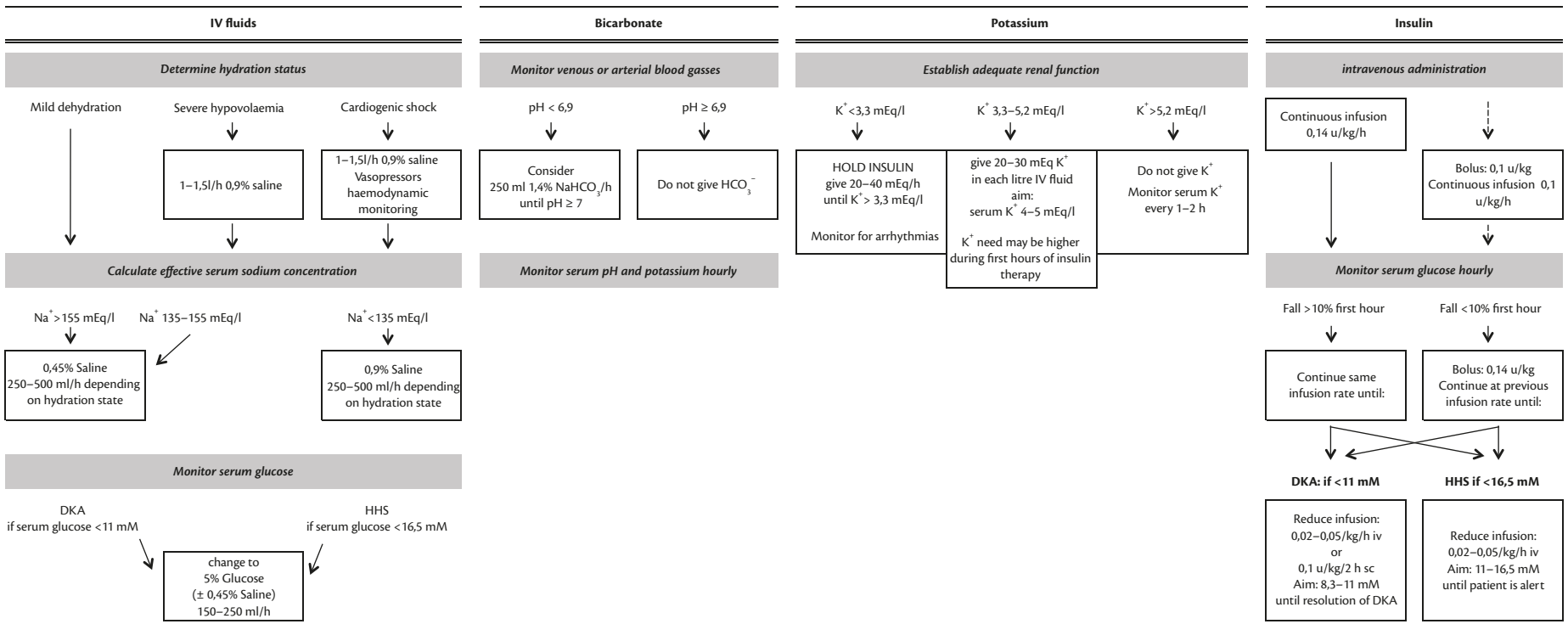


Fig. 260.1 Management of hyperglycaemic crises.

kg, per kg of body weight.

Data from: Nyenwe EA and Kitabchi AE, 'Evidence-based management of hyperglycaemic emergencies in diabetes mellitus', *Diabetes Research and Clinical Practice*, 2011, **94**(3), pp. 340–51; De Beer K et al., 'Diabetic ketoacidosis and hyperglycaemic hyperosmolar syndrome–clinical guidelines', *Nursing in Critical Care*, 2008, **13**(1), pp. 5–11; and Kitabchi AE et al., 'Hyperglycemic crises in adult patients with diabetes', *Diabetes Care*, 2009, **32**(7), pp. 1335–43.

Table 260.2 Typical deficits upon admission for hyperglycaemic crisis

	DKA	HHS
Total water	6 liter	9 liter
Water (ml/kg)	100	100–200
Na^+ (mEq/kg)	7–10	5–13
K^+ (mEq/kg)	3–5	4–6
PO4 (mmol/kg)	5–7	3–7
$Mg2^+$ (mEq/kg)	1–2	1–2

kg = per kg of body weight.

Adapted from *Diabetes Research and Clinical Practice*, **94**(3), Nyenwe EA and Kitabchi AE, 'Evidence-based management of hyperglycemic emergencies in diabetes mellitus', pp. 340–51, Copyright 2011, with permission from Elsevier.

has overt hypokalaemia (<3.3 mmol/L). In this case insulin infusion should not be started until potassium has been properly supplemented and corrected. Usually, normokalaemia and sometimes hyperkalaemia is measured at presentation. Hyperosmolarity, acidosis, and insulin deficiency are driving this relative rise in serum potassium levels, despite the overall potassium depletion (Table 260.3). Impaired kidney function due to the shock may also play a role. As insulin therapy lowers potassium levels, careful monitoring, and timely supplementation is essential. Monitoring includes a continuous ECG and measurements every hour or 2 hours. Supplementation should be started together with the insulin infusion in normokalaemic patients as well. The rate of potassium substitution varies from 10 to 30 mmol/hour. Phosphate and magnesium deficiencies are common in diabetic emergencies (Tables 260.2 and 260.3). Their concentrations should be measured at least daily. However, aggressive magnesium and phosphate supplementation are rarely required.

Hyperglycaemia

Hyperglycaemia is the presenting feature of diabetic hyperglycaemic emergencies [1,2,7,10], but it has developed over days, leaving the cells time to adapt to the hyperosmotic environment. If hyperglycaemia were to be corrected too rapidly without proper attention to volume and electrolyte status, insulin will not only drive glucose, but also water, potassium, magnesium, and phosphate into the cells. This may result in dangerous cell swelling with cerebral oedema, hypokalaemia, hypomagnesaemia, and hypophosphataemia [7]. Hence, management protocols of hyperglycaemic crises have shifted to low-dose insulin regimens and omission of the priming insulin bolus-administration (Fig. 260.1) [1]. The initial drop in blood glucose concentrations is related to the fluid resuscitation, which also restores the insulin sensitivity. Consequently, insulin requirements may change briskly during treatment. It cannot be sufficiently emphasized that blood glucose measurements should be performed hourly until a stable trend becomes obvious. As glucometers for home use are inaccurate in the low and high range, blood glucose measurements ought to be done by hospital grade blood glucose meters [11]. On site, blood gas analysers are preferred since they provide accurate blood glucose measurements, and allow the evaluation of potassium, bicarbonate, ionized calcium levels, and blood gases simultaneously.

Insulin therapy

Insulin therapy should be administered by intravenous, continuous infusion. It is essential to lower the insulin infusion rate when blood glucose levels fall below 11 mmol/L in DKA and below 16.5 mmol/L in HHS. In addition, these thresholds indicate that intravenous fluids should be switched to glucose 5% (Fig. 260.1). Subsequently, blood glucose levels should be maintained between 8 and 10 mmol/L until the resolution of the ketoacidosis or HHS by regular adjustment of insulin and/or glucose 5% infusion. Provided that DKA has resolved

Table 260.3 Electrolyte disorders upon admission and during treatment of hyperglycaemic crises: pitfalls and recommendations

	Upon admission	Response to treatment	Recommendations
Na^+	falsely ↓↓	risk ↑↑	Calculate 'effective' serum Na^+= measured serum Na^+ +1,6 mmol/l for every 5,6 mM glycaemia above 5,6 mM
Cl^-		risk transient metabolic acidosis after resolution of keto-acidosis	Avoid excessive use of isotonic saline: (1) chloride load (2) urinary loss of $NaHCO_3$
K^+	variable: ↓, normal, ↑/↑↑	↓/↓↓	1. Treat life-threatening hyperkalaemia (>6 mM) with bicarbonate 2. Correct severe hypokalaemia before initiation of insulin 3. Resolution of acidosis/insulinopenia will reveal true K^+ deficit: 50–250 mEq 4. Be aware of renal impairment and hyperkalaemia risk
Bicarbonate	↓/↓↓↓	normalization of pH, HCO_3^- and PCO_2	1. Consider bicarbonate only in patients with pH < 6,9 who may deteriorate or whom compensatory mechanisms are stretched to the limits: HCO_3^- < 10 mM or PCO_2 < 12 mmHg 2. Be aware of bicarbonate administration and hypokalaemia risk
Phosphate	normal, ↑/↑↑	↓/↓↓	1. Consider potassium phosphate suppletion: - to prevent cardiac and skeletal muscle weakness and rhabdomyolysis - to reduce Cl-load (1/3 potassium phosphate + 2/3 potassium chloride) 2. Be aware of phosphate therapy and hypocalcaemia risk

Table 260.4 Signs and symptoms according to severity of hypoglycaemia

	Neurogenic	Neuroglycopenic
Glycaemia	< 3, 7 mM	< 2, 5 mM
Pathogenesis	Autonomic response	Brain glucose deprivation
Symptoms	*Cholinergic:* hunger, nausea diaphoresis paresthesias	*Cognitive impairment:* difficult thinking difficult speaking difficult concentrating
	Adrenergic: tremor palpitations, anxiety	*Behavioral changes:* irritability confusion *Psychomotor abnormalities:* blurred vision *Seizures* *Coma*

and the patient is able to eat, a multiple dose subcutaneous insulin regimen can be started. Noteworthy, profound insulinopenia, causing the rare presentation of DKA in type 2 diabetics, is potentially reversible [10]. Hence, part of these patients may be managed with a noninsulin regimen after resolution of DKA [1,10].

As DKA and HHS are hypercoagulable states due to the dehydration and the inflammatory response, it is suggested to initiate prophylactic low molecular weight heparin administration, as in any other critically-ill patient without contraindications [1]. Full therapeutic anticoagulation in HHS is not supported by evidence.

Hypoglycaemia

When unrecognized or inappropriately treated, hypoglycaemia can be associated with increased morbidity and mortality. Most cases of hypoglycaemia are iatrogenic. Insulin and sulfonylurea/meglitinide administration and alcohol intake are the major culprits (Table 260.1) [12,13]. Organ failure can further amplify the risk with these medications or cause spontaneous hypoglycaemia.

Classification

Hypoglycaemia can clinically be classified into severe or mild hypoglycaemia. Severe hypoglycaemia requires third party assistance as the hypoglycaemia episode is associated with coma or seizures, warranting parenteral therapy (intramuscular (im) glucagon or intravenous (iv) glucose). In mild hypoglycaemia the symptoms can be resolved by self-administered ingestion of carbohydrates. It is of note the symptoms of hypoglycaemia, rather than the blood glucose levels are central in the definition (Table 260.4) [3]. This is clinically relevant. In sedated critically-ill patients one can only rely on blood glucose measurements to detect hypoglycaemia (biochemical hypoglycaemia). In the literature, there is a growing consensus that severe biochemical hypoglycaemia is a blood glucose level below 2.2 mmol/L. Mild biochemical hypoglycaemia is variably defined as below 3.3–3.9 mmol/L. In biochemical hypoglycaemia symptoms may or may not be present. In asymptomatic hypoglycaemia the patient has a blood glucose level of less than 3.5 mmol/L without symptoms. A patient with frequent asymptomatic hypoglycaemia episodes has hypoglycaemia unawareness. Hypoglycaemia unawareness largely parallels the hypoglycaemia-associated autonomic failure (HAAF), which is the lack of an appropriate counter-regulatory response during hypoglycaemia. HAAF is associated with a higher risk of severe hypoglycaemia and sudden death in diabetes [3,5]. Recurrent hypoglycaemia episodes shift the glycaemic threshold for neurogenic/autonomic responses to lower blood glucose concentrations (Table 260.4). Therefore, only the neuroglycopenic symptoms will appear when the blood glucose levels are dangerously low and without the counter-regulatory response that would normally increase blood glucose levels. These responses can be restored by rigorously avoiding hypoglycaemia.

Management

The management of hypoglycaemia starts with prevention. Recent guidelines by the Endocrine Society recommend that specific directions for hypoglycaemia avoidance and treatment should be incorporated in hospital glucose management protocols [11]. This includes clear definitions of hypoglycaemia and the implementation of a system to track the frequency of hypoglycaemic events. To prompt immediate therapy the guidelines advise a standardized, hospital-wide, nurse-initiated hypoglycaemia protocol. To minimize the risk for hypoglycaemia, therapy with sulphonylurea, meglitinide, GLP-1, or DPP-4 medication should be discontinued during hospitalization. Blood glucose values should be reviewed daily and insulin therapy should be reassessed when blood glucose levels fall below 5.6 mmol/L. Insulin dose reductions in necessary when blood glucose concentrations are lower than 3.9 mmol/L.

Blood glucose levels below 3.9 mmol/L require treatment. This treatment should be proportional to the depth and the duration of hypoglycaemia [5,11]. Overcorrection should be kept to a minimum as recent data suggest hyperglycaemia during correction, rather than hypoglycaemia causes brain damage. In a conscious patient, 15–20 g rapid-acting carbohydrates, such as glucose tablets or gels, non-diet fizzy drinks and fruit juices should be taken orally. When the glycaemia falls below 2.2 mmol/L in an alert patient, larger amounts of carbohydrates should be administered. If the patient cannot swallow or take oral liquid, iv glucose 50% should be administered (20 mL for mild hypoglycaemia and 25 mL for severe hypoglycaemia). In the case of unconsciousness, one has to administer iv 30–50 mL of glucose 50%. If no iv access is available, 1 mg of glucagon should to be given im immediately. The immediate therapy by bolus administration of glucose needs to be followed by a continuous glucose infusion and frequent blood glucose checks (every 15 minutes) until glycaemia is normalized. This is essential when the hypoglycaemia is caused by sulphonylureas and, to a lesser extent by meglitinide, as they are long acting. If the sulfonylurea-induced hypoglycaemia becomes refractory, the administration of octreotide/somatostatin can be considered.

References

1. Nyenwe EA and Kitabchi AE. (2011). Evidence-based management of hyperglycemic emergencies in diabetes mellitus. *Diabetes Research and Clinical Practice*, **94**(3), 340–51.
2. De Beer K, Michael S, Thacker M, et al. (2008). Diabetic ketoacidosis and hyperglycaemic hyperosmolar syndrome—clinical guidelines. *Nursing in Critical Care*, **13**(1), 5–11.

3. Cryer PE. (2008). The barrier of hypoglycemia in diabetes. *Diabetes*, **57**(12), 3169–76.
4. Turchin A, Matheny ME, Shubina M, Scanlon JV, Greenwood B, and Pendergrass ML. (2009). Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. *Diabetes Care*, **32**(7), 1153–7.
5. Choudhary P and Amiel SA. (2011). Hypoglycaemia: current management and controversies. *Postgraduate Medical Journal*, **87**(1026), 298–306.
6. Kitabchi AE, Umpierrez GE, Miles JM, and Fisher JN. (2009). Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*, **32**(7), 1335–43.
7. Kitabchi AE, Umpierrez GE, Fisher JN, Murphy MB, and Stentz FB. (2008). Thirty years of personal experience in hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Journal of Clinical Endocrinology & Metabolism*, **93**(5), 1541–52.
8. SAFE Study Investigators, Finfer S, Bellomo R, et al. (2006). Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study. *British Medical Journal*, **333**(7577), 1044.
9. Crystalloid versus Hydroxyethyl Starch Trial (CHEST) Management Committee. (2011). The Crystalloid versus Hydroxyethyl Starch Trial: protocol for a multi-centre randomised controlled trial of fluid resuscitation with 6% hydroxyethyl starch (130/0.4) compared to 0.9% sodium chloride (saline) in intensive care patients on mortality. *Intensive Care Medicine*, **37**(5), 816–23.
10. Smiley D, Chandra P, and Umpierrez GE. (2011). Update on diagnosis, pathogenesis and management of ketosis-prone Type 2 diabetes mellitus. *Diabetes Management (London)*, **1**(6), 589–600.
11. Umpierrez GE, Hellman R, Korytkowski MT, et al. (2012). Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism*, **97**(1), 16–38.
12. American Diabetes Association (2012). Standards of medical care in diabetes—2012. *Diabetes Care*, **35**(Suppl. 1), S11–63.
13. Huang Z and Sjöholm A. (2008). Ethanol acutely stimulates islet blood flow, amplifies insulin secretion, and induces hypoglycemia via nitric oxide and vagally mediated mechanisms. *Endocrinology*, **149**(1), 232–6.

PART 10.5

Endocrine disorders

CHAPTER 261

Pathophysiology and management of adrenal disorders in the critically ill

Bala Venkatesh and Jeremy Cohen

Key points

- The existence of the syndromes of relative adrenal insufficiency, or critical illness-related corticosteroid insufficiency, are debatable.
- In sepsis, there are alterations in plasma cortisol profiles, and corticotrophin responsiveness with marked variability in responses between patients.
- It is probable that the spectrum of plasma and tissue glucocorticoid changes may represent a 'sick euadrenal state' analogous to the sick euthyroid state and may not reflect adrenocortical insufficiency.
- Treatment of acute adrenal crisis should not be delayed for the results of adrenal testing, and should consist of immediate supportive measures, fluid resuscitation, and high-dose intravenous glucocorticoid therapy.
- Admission to intensive care with a primary diagnosis of hyperadrenalism is uncommon. Patients usually present uncontrolled hypertension, electrolyte abnormalities, or encephalopathy.

Introduction

Characterizing the pathophysiology of the adrenal cortex in critical illness has been fraught with controversy and confusion. Some reports suggest 'adrenal insufficiency' directly attributable to critical illness, particularly sepsis. The uncertainty in this area arises from the inability of current tests to identify who is truly glucocorticoid 'deficient' at a cellular level, and requires supplemental glucocorticoid administration. Reports of hyperadrenalism are less common in intensive care practice.

Normal adrenal physiology

Cortisol, the major glucocorticoid synthesized by the adrenal cortex plays a pivotal role in normal metabolism. Secretion is under the control of the hypothalamo-pituitary axis. There are a variety of stimuli to secretion, including stress, tissue damage, cytokine release, hypoxia, hypotension, and hypoglycaemia. These factors act upon the hypothalamus to favour the release of corticotrophin releasing hormone (CRH) and vasopressin. CRH is synthesized in the hypothalamus and carried to the anterior pituitary in portal blood, where it stimulates the secretion of adrenocorticotrophic hormone (ACTH), which in turn stimulates the release of cortisol, mineralocorticoids (principally aldosterone) and androgens from the adrenal cortex (Fig. 261.1).

Free cortisol diffuses passively through the cell membrane. Once inside the cell the actions are profoundly affected by the activity of the 11β-hydroxysteroid dehydrogenase (11β-HSD) enzyme system. This system has two isozymes that have been studied extensively. 11β-HSD1 acts in vivo primarily as a reductase, generating active cortisol from inactive cortisone. By contrast, 11β-HSD2 has dehydrogenase action, inactivating cortisol by conversion to cortisone. The isozymes have differing tissue distributions; 11β-HSD2 is found primarily in mineralocorticoid target tissues such as kidney, sweat glands, and colonic mucosa, where it serves to prevent illicit occupation of the mineralocorticoid receptor by cortisol. 11β-HSD1 has a wide distribution including liver, adipose, and vascular tissues, and while its primary action is reductase, there is some evidence its directionality may be tissue specific (Fig. 261.1) [1].

Cortisol is necessary for the synthesis of adrenergic receptors, normal immune function, wound healing, and vascular tone. The majority of circulating cortisol is bound to corticosteroid-binding globulin (CBG). At normal levels of total plasma cortisol (e.g. 375 nmol/L or 13.5 μg/dL) less than 5% exists as free cortisol in the plasma.

In sepsis and critical illness, the beneficial effects of corticosteroids are thought to be mediated through two mechanisms—immune modulation and cardiovascular modulation. Corticosteroids modulate the transcription of an array of, mainly, nuclear factor-κB (NF- κB) regulated genes that contribute to inflammation. The synthesis of interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor (TNF)-alpha is inhibited, as is inducible cyclo-oxygenase 2 (COX2) and inducible nitric oxide synthase (iNOS) [2].Corticosteroids also enhance the vasoconstrictor response to vasopressor drugs, in particular exogenous catecholamines. They mediate catecholamine release from neural cells and stimulate noradrenaline to adrenaline conversion by the enzyme phenylethanolamine-N-methyltransferase (PNMT) [3].

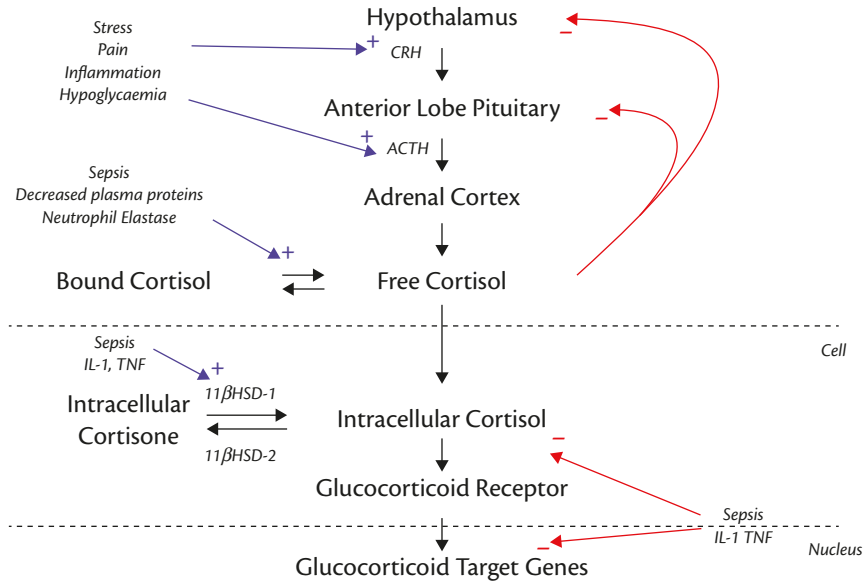


Fig. 261.1 Factors affecting secretion and effect of cortisol.

Normal adrenocortical response to stress

A functioning adrenocortical response appears to be essential for survival from significant stress. Adrenalectomized animals have 100% mortality from induced septic shock [4], and patients with non-functioning adrenal glands require supplemental glucocorticoid treatment during periods of severe illness [5]. Exposure to stress results in cortisol secretion that is transported to the tissues in three fractions. Approximately 80% is closely bound to CBG, 10–15% loosely bound to albumin, and 5–8% as a free fraction. Binding of cortisol to CBG is modulated by temperature, local tissue elastases, including neutrophil elastase, through which inflammatory cells may potentiate cortisol release, and through other tissue factors [6–8]. The relative proportions of cortisol present in these three fractions depend on cortisol levels; for example CBG is saturated at cortisol levels above 500nmol/L although, in sepsis, CBG levels are much reduced due to inhibition of synthesis by inflammatory cytokines such as IL-6 or increased consumption through CBG cleavage by elastases.

Adrenal insufficiency in critical illness

The pivotal role of the hypothalamo-pituitary adrenal axis in the response to critical illness has necessarily resulted in it becoming a focus of research. Structural disruption of the axis results in well recognized clinical sequelae, although the role of functional inadequacy of the system, particularly the need for glucocorticoid supplementation, remains controversial.

Structural inadequacy

The catastrophic consequences of destruction of the adrenal glands were first described by Thomas Addison in 1855. In the western world primary adrenal insufficiency, or Addison's disease, is an uncommon disorder, with an estimated prevalence of 120 per million. However, it remains an important differential diagnosis in the ICU as it can present as refractory circulatory shock, and failure to recognize it may be disastrous.

In adulthood, the commonest cause is autoimmune, but in the intensive care setting, possibilities of adrenal haemorrhage from coagulopathy, sepsis, and infiltration need to be considered. Tuberculosis is the commonest infective cause worldwide, but fungal infections, such as histoplasmosis, coccidiomycosis, and infections with cytomegalovirus (especially in patients with human immunodeficiency virus (HIV)) must be considered. Haemorrhage into the glands is associated with septicaemia, particularly meningococcal (Waterhouse–Friedrichsen syndrome). Secondary adrenal insufficiency is said to occur when there is damage or suppression of the hypothalamus or pituitary. This may occur secondary to tumours, trauma, or cranial irradiation, although the commonest cause is chronic exogenous glucocorticoid administration.

Addison's disease may present with gradual, ill-defined symptoms, including weight loss, anorexia, nausea, generalized weakness, myalgia, and postural hypotension. Hyperpigmentation may occur in areas of the skin exposed to friction, such as palmar creases and oral mucosa. This effect is caused by stimulation of the MC-1 receptor by ACTH and other pro-opiomelanocortin-related peptides, and is not seen in secondary disease.

Acute presentation of adrenal crisis may be precipitated by concurrent infection, surgery or trauma. The cardinal feature is circulatory shock that is refractory to both fluid resuscitation and vasoactive therapy. Diffuse abdominal pain or fever may also be present and this combination can mimic an acute surgical abdomen.

Suggestive features of adrenal crisis include a history of symptomatology consistent with the diagnosis, and demonstration of hyponatraemia, hyperkalaemia, and peripheral blood eosinophilia. A non-anion gap acidosis may be present. Random plasma total cortisol taken during a crisis will be low (below 80 nmol/L), and is diagnostic. Treatment should not be while awaiting the results of adrenal testing, and should consist of immediate supportive measures, fluid resuscitation, and high-dose intravenous glucocorticoid therapy. Hydrocortisone is the steroid of choice as in the doses recommended it also has mineralocorticoid activity A standard dose would be 100 mg hydrocortisone 6-hourly, or as an infusion.

Functional inadequacy

Functional inadequacy of the hypothalamo-pituitary adrenal axis occurring in the setting of critical illness is a more nebulous phenomenon. Pathophysiological changes induced by severe stress may result in a response that is not commensurate with the severity of the stimulus that evoked them. This syndrome is termed 'relative adrenal insufficiency (RAI)' or, more recently, critical illness-related corticosteroid insufficiency (CIRCI) [10,11]. A reduced incremental response to a standard short tetracosactride test performed during critical illness is associated with increased mortality. Additionally, exogenous glucocorticoid administration has been observed to reduce vasopressor requirements. In contrast to primary adrenal insufficiency, patients with CIRCI do not have obvious macroscopic evidence of adrenal gland damage or destruction, and often have high baseline circulating cortisol levels.

While the majority of the studies in this area have focused on patients with septic shock, CIRCI has been described in a wide variety of critical illnesses including liver disease, trauma, burns, and pancreatitis. Diagnosis of CIRCI is based upon the measurement of total plasma cortisol concentrations; either at baseline or following administration of synthetic ACTH. While numerous diagnostic criteria have been proposed in the literature, more recent consensus suggests a threshold of a cortisol increment under 250 nmol/l (9 μg/dL) in response to the short tetracosactride test indicates adrenal insufficiency.

Postulated mechanisms of glucocorticoid insufficiency in sepsis

Several mechanisms have been put forward to explain, why adrenal insufficiency might develop in sepsis [12]. These include impaired CRH and ACTH secretion from necrosis or haemorrhage in the hypothalamus or pituitary from hypotension, and coagulopathy in sepsis, inhibition of ACTH secretion through activation of opiate receptors by fentanyl a commonly used sedative agent, neuronal apoptosis, and cytokine mediated.

Primary adrenal failure from adrenal haemorrhage, adrenalitis from the primary pathogen and pharmacological suppression of cortisol synthesis by drugs used in critical illness are other mechanisms. Altered peripheral cortisol metabolism through the hydroxysteroid dehydrogenase enzyme systems, altered tissue delivery, and tissue glucocorticoid resistance are other mechanisms contributing to hypoadrenalism.

Controversy with the concept of CIRCI

The primary debate around the utility of the CIRCI diagnosis is whether it constitutes an appropriate indication for adjunctive glucocorticoid treatment [13,14]. Conceptually, the possibility of being able to identify and treat patients with a hypofunctioning adrenal axis is extremely appealing. However, studies of glucocorticoid treatment for patients in septic shock based upon the short tetracosactride test (SST) have returned conflicting results. Glucocorticoid treatment based upon the results of the short tetracosactride test has also been advocated in cirrhosis and multiple trauma, but the available studies are small scale and have not been replicated.

Diagnostic criteria

Many different diagnostic criteria based on cortisol responses have been proposed [13,14], the most common of which suggest either a minimum threshold random cortisol measurement during critical illness, or either a minimum peak or minimal response in plasma cortisol following a standard tetracosactride test. **The uncertainty in the diagnosis of RAI** is clearly evident from the widely varying observed incidence in the different studies depending upon which diagnostic criteria are used (Table 261.1) [13]. There are limitations in using total cortisol levels:

- Critically-ill patients appear to have wide plasma cortisol profiles irrespective of the severity of stress. The 'normal' range of cortisol in critical illness is not defined.
- There is marked variability in plasma cortisol profile, such that a random cortisol has limited diagnostic utility.
- There are gender differences in plasma cortisol response to stress.
- A high degree of variability exists between cortisol assays, which may potentially confound the diagnosis of RAI.
- There is marked dissociation between total and free cortisol (the 'bio-active fraction') with respect to 'response to stress'

There are also limitations in using the tetracosactride test:

- The standard 250 μg dose may result in supraphysiological concentrations of corticotrophin and may mask secondary adrenal insufficiency.
- There is marked dissociation between total and free cortisol with respect to tetracosactride stimulation.
- A number of other variables, such as plasma protein concentrations, adrenal blood flow, and body composition impact on the tetracosactride response.

Further issues that complicate the diagnosis of CIRCI have arisen from a greater insight into the changes that occur in glucocorticoid physiology in response to critical illness [13,14]. These include a relative increase in unbound cortisol concentrations, changes in intracellular cortisol metabolism through the activation of the 11β-HSD1 system, and alterations in glucocorticoid receptor expression and glucocorticoid target gene expression induced by the various inflammatory cytokines and stress. Reduced cortisol clearance, potentially as a result of a suppression of 11β-HSD2 activity also appears to be of importance [15]. These changes have the potential to substantially alter glucocorticoid activity in different tissues in a fashion that may not be reflected by circulating plasma cortisol concentrations. Therefore, the identification of patients who may be glucocorticoid deficient at a tissue level remains problematic.

Other dynamic tests for adrenal insufficiency

The insulin tolerance test (ITT) and the metyrapone tests are two other dynamic endocrine investigations which are used in the non-critically-ill patient. They are associated with significant adverse effects and thus have no place in the routine adrenal assessment in the ICU patient. Their role in the critically-ill patient remains to be determined. The glucagon stimulation test is another test of hypothalamo-pituitary adrenal axis integrity and thought to be equivalent to that of the ITT, but little data exist on its usefulness in critical illness.

The free cortisol fraction may represent a more valid measurement of circulating cortisolaemia than total cortisol. Standard

Table 261.1 Diagnostic criteria for adrenal insufficiency in critical illness

Study	Incidence of RAI	Study	Incidence of RAI
Corticotropin response criteria		Peak or baseline cortisol criteria	
Corticotrophin response < 250 nmol/L		**Peak cortisol < 700 nmol/L**	
Rothwell (1991)	40%	Bourne(2003)	40%
Bouachoar (1995)	75%		
Annane (2000)	54%	**Peak cortisol < 600 nmol/L**	
Annane (2002)	76%	Faber (1993)	20%
Ho (2006)	33%	**Peak cortisol <550 nmol/L**	
Bollaert (2002)	38%	Bourne (2003)	28%
Siraux (2005)	34%	Manglik (2003)	9%
Yildiz (2002)	35%	**Peak cortisol<500 nmol/L**	
Bourne (2003)	70%	Bouachoar (1995)	6.25%
Sprung (2008)	47%	Soni (1995)	25%
Jones (2006)	28%	Marik (2003)	8%
Corticotrophin response <200 nmol/L		**Baseline cortisol <690 nmol/L**	
Bouachoar (1995)	68%	Marik (2003)	61%
Briegel (1996)	50%	**Baseline cortisol <500 nmol/L**	
Oppert (2000)	55%	Moran (1994)	32%
Moran (1994)	66%	Aygen (1997)	16%
Hatherhill (1999)	52%		

Reproduced from *Intensive Care Medicine*, **33**(10), 2007, pp. 1746–53, 'Evidence of altered cortisol metabolism in critically ill patients: a prospective study', Venkatesh B et al. Copyright 2007 European Society of Intensive Care Medicine and the European Society of Paediatric and Neonatal Intensive Care. With kind permission from Springer Science and Business Media. Data from various studies. Please see original source for study references.

measurement techniques do not distinguish between the two, so in circumstances where plasma protein levels are abnormal, such as critical illness, measurement of total cortisol concentrations alone may be misleading. Data from trials in critically-ill patients suggest that plasma free cortisol may be superior to total cortisol in assessing adrenocortical function [16].

Hyperadrenalism

Admission to intensive care with a primary diagnosis of hyperadrenalism is uncommon. Moreover diagnosis of hypercortisolism during critical illness is complicated by the fact that patients frequently have raised plasma cortisol levels that are not suppressible by dexamethasone [17]. Patients usually present with one of the manifestations of a steroid storm requiring intensive care support, such as uncontrolled hypertension in pregnancy [18], electrolyte abnormalities, or encephalopathy [19]. Patients with hyperadrenalism may present to the ICU following a laparoscopic adrenalectomy for a cortical adenoma for peri-operative support.

Treatment of these conditions is largely supportive. Medical suppression of cortisol secretion may be undertaken with etomidate infusions; surgical excision of an adenoma, where present, may be the definitive procedure.

References

1. Tomlinson JW and Stewart PM. (2005). Cortisol metabolism and the role of 11beta-hydroxysteroid dehydrogenase. *Best Practice Research in Clinical Endocrinology & Metabolism,* **15**(1), 61–78.
2. Annane D. (2005). Glucocorticoids in the treatment of severe sepsis and septic shock. *Current Opinion in Critical Care*, **11**, 449–53.
3. Shi LJ, He HY, Liu LA, and Wang CA. (2001). Rapid nongenomic effect of corticosterone on neuronal nicotinic acetylcholine receptor in PC12 cells. *Archives of Biochemistry and Biophysics*, **394**, 145–50.
4. Hinshaw LB, Beller BK, Chang AC, et al. (1985). Corticosteroid/antibiotic treatment of adrenalectomized dogs challenged with lethal *E. coli*. *Circulatory Shock*, **16**, 265–77.
5. Lamberts SW, Bruining HA, and de Jong FH. (1997). Corticosteroid therapy in severe illness. *New England Journal of Medicine*, **337**, 1285–92.
6. Pemberton PA, Stein PE, Pepys MB, Potter JM, and Carrell RW. (1988). Hormone binding globulins undergo serpin conformational change in inflammation. *Nature*, **336**, 257–8.
7. Qi X, Loiseau F, Chan WL, et al. (2011). Allosteric modulation of hormone release from thyroxine and corticosteroid-binding globulins. *Journal of Biological Chemistry*, **286**, 16163–73.
8. Sumer-Bayraktar Z, Kolarich D, Campbell MP, Ali S, Packer NH, and Thaysen-Andersen M. (2011). N-glycans modulate the function of human corticosteroid-binding globulin. *Molecular & Cellular Proteomics*, **10**, M111 009100.
9. Marik PE. (2009). Critical illness-related corticosteroid insufficiency. *Chest*, **135**(1), 181–93.

10. Prigent H, Maxime V, and Annane D. (2004). Science review: mechanisms of impaired adrenal function in sepsis and molecular actions of glucocorticoids. *Critical Care*, **8**, 243–52.
11. Venkatesh B and Cohen J. (2011). Adrenocortical (dys)function in septic shock—a sick euadrenal state. *Best Practice Research in Clinical Endocrinology & Metabolism*, **25**, 719–33.
12. Cohen J and Venkatesh B. (2010). Relative adrenal insufficiency in the intensive care population.: background and critical appraisal of the evidence. *Anaesthesia and Intensive Care*, **38**, 425–36.
13. Venkatesh B, Cohen J, Hickman I, et al. (2007). Evidence of altered cortisol metabolism in critically ill patients: a prospective study. *Intensive Care Medicine*, **33**(10), 1746–53.
14. Boonen E, Vervenne H, Meersseman P, et al. (2013). Reduced cortisol metabolism during critical illness. *New England Journal of Medicine*, **368**, 1477–88.
15. Hamrahian AH, Oseni TS, and Arafah BM. (2004). Measurements of serum free cortisol in critically ill patients. *New England Journal of Medicine*, **350**, 1629–38.
16. Perrot D, Bonneton A, Dechaud H, Motin J, and Pugeat M. (1993). Hypercortisolism in septic shock is not suppressible by dexamethasone infusion. *Critical Care Medicine*, **21**, 396–401.
17. Choi WJ, Jung TS, and Paik WY. (2011). Cushing's syndrome in pregnancy with a severe maternal complication: a case report. *Journal of Obstetrics & Gynaecological Research*, **37**(2), 163–7.
18. Lutgers HL, Vergragt J, Dong PV, et al. (2010). Severe hypercortisolism: a medical emergency requiring urgent intervention. *Critical Care Medicine*, **38**(7), 1598–601.
19. Rothwell PM, Udwadia ZF, and Lawler PG. (1991). Cortisol response to corticotropin and survival in septic shock. *Lancet*, **337**, 582–3.

CHAPTER 262

Pathophysiology and management of pituitary disorders in the critically ill

Yves Debaveye and Greet Van den Berghe

Key points

- Prompt administration of hydrocortisone, in 'stress dosage', is the single most important acute medical intervention in patients with hypopituitarism.
- Pituitary surgery is often followed by transient abnormalities of antidiuretic hormone secretion and subsequent disorders of water balance (diabetes insipidus and syndrome of inappropriate antidiuretic hormone (SIADH)).
- Diabetes insipidus is hallmarked by an abrupt onset of polyuria, hypernatraemia, and urinary hypotonicity.
- Management of diabetes insipidus includes the correction of free water deficit and the reduction of polyuria with desmopressin.
- Restriction of fluid intake is the first-line treatment for SIADH in patients without hypovolaemia.

Introduction

The pituitary gland is sometimes called the 'master' gland of the endocrine system, because it controls the functions of all other endocrine glands. This makes the pituitary gland quite important, despite its small size.

Hypopituitarism

Hypopituitarism is the clinical syndrome that results from failure of the anterior pituitary gland to secrete one or more of its hormones adequately.

Hypopituitarism can result from intrinsic hypothalamic or pituitary lesions, or extrinsic extrasellar disease that impinges on, infiltrates, or destroys the hypothalamus, pituitary stalk, or pituitary gland [1,2]. All disorders can have an 'organic' or 'functional' origin; the latter has potential for reversibility (Box 262.1).

A critical care specialist may have to deal with hypopituitarism as a recognized pre-existing disease that requires appropriately continued treatment during intercurrent illness, acute exacerbation of an undiagnosed insufficiency evoked by surgery or disease, sequels of recent neurosurgery, cerebral trauma, infection, or shock, or temporary dysfunction induced by the stress of the critical condition itself and/or its therapy.

Clinical manifestations and diagnosis

Symptom presence and severity depends on the amount and rapidity of hormone depletion. Clinical manifestations of hypopituitarism are non-specific and closely match those of the primary deficiency or hypofunctioning of target glands [2]. The most acute clinical presentation occurs with pituitary apoplexy [3,4]. This is caused by sudden haemorrhage or infarction of a pituitary adenoma, and is characterized by headache, visual deficits, ophthalmoplegia, alterations in mental status, and circulatory collapse secondary to acute loss of ACTH with subsequent cortisol deficiency.

The endocrine assessment involves plasma ACTH, cortisol, T4 and T3, IGF-1, FSH, LH, oestradiol, testosterone, and prolactin. Note that TSH is not helpful in making the diagnosis of central hypothyroidism and that growth hormone is not typically measured as its secretion is pulsatile. Plasma electrolytes should also be measured in the initial evaluation as hyponatraemia is present in TSH and ACTH deficiencies, and hypernatraemia may suggest concomitant diabetes insipidus (DI) [2,5]. If visual disturbances occur prompt diagnostic imaging and neurosurgical consultation are mandatory.

Treatment

Acute decompensated patients with suspected hypopituitarism should be admitted to an intensive care unit (ICU) for immediate and adequate treatment that comprises:

- General supportive measures to ensure haemodynamic stability.
- Replacement of the missing hormones.
- Identification and treatment of the causative stressor.

After a diagnostic blood sample has been obtained prompt administration of hydrocortisone, in 'stress dosage', is the single most important acute medical intervention [3,4,6]. Replacement of other hormones is mostly not required in the hyperacute setting. If underlying infection is suspected broad-spectrum antibiotic coverage is advised pending culture results. During treatment, electrolyte and glucose levels must always be carefully monitored and corrected, particularly if concomitant DI is suspected. As absence of cortisol inhibits free water clearance in these patients, glucocorticoid administration may induce or aggravate diabetes insipidus (DI) [2,5].

Box 262.1 Aetiology of hypopituitarism

Hypothalamic

Hypothalamic or central nervous system disease

- Organic:
  - Developmental.
  - Traumatic.
  - Inflammatory.
  - Neoplastic.
  - Idiopathic.
- Functional:
  - Stress.
  - Anorexia nervosa.
  - Renal failure, hepatic failure, uncontrolled DM.
  - Prolonged critical illness.
  - Drugs (dopamine, somatostatin, glucocorticoids, etc.).

Stalk trauma or compression

Pituitary

- Organic.
  - Developmental aplasia or hypoplasia.
  - Traumatic or post-neurosurgical.
  - Inflammatory or infiltrative (infectious or systemic disease).
  - Ischaemic (Sheehan postpartum pituitary necrosis, DM, arteritis, eclampsia).
  - Pituitary apoplexy.
  - Neoplastic, miscellaneous.
- Functional.
  - Drugs (dopamine, somatostatin).

Extrasellar disease

Post-operative management following pituitary surgery

Pituitary surgery (PS), especially transsphenoidal PS, is a commonly performed neurosurgical procedure. All patients require a meticulous multidisciplinary pre-operative evaluation as many patients present with significant pre-operative systemic manifestations, especially patients with Cushing's disease and acromegaly. Ideally, serious systemic disease secondary to pituitary dysfunction should be controlled prior to surgery.

Adenoma specific comorbidities

Acromegalic patients often have macroglossia and hypertrophied soft tissue of the upper airway, making endotracheal intubation potentially difficult and obstructive sleep apnoea (OSA) common in this population [7]. Also, Cushing's disease is associated with OSA and predisposition to difficult intubation, so that narcotics and benzodiazepines should be used with caution.

In both patient groups, there is a high incidence of glucose intolerance or overt diabetes mellitus (DM), arterial hypertension, and ventricular hypertrophy with diastolic dysfunction. As the risk of thromboembolic complications is increased in Cushing's syndrome, peri-operative prophylaxis is warranted. Finally, one should avoid catheterizing the radial artery of an acromegalic patient, as blood flow through the ulnar artery is compromised in up to 50% of patients [8]. It is also imperative that hyperthyroidism is controlled before patients with thyrotropic (thyroid-stimulating hormone (TSH) producing) adenomas undergo surgical resection.

Post-neurosurgical follow-up

Although the majority of these patients do not experience complications, a significant component of post-operative care is devoted to vigilant monitoring for neuroendocrine abnormalities with initiation of appropriate intervention whenever necessary. In addition, awareness is required of other complications inherent to resection of pituitary tumours, such as visual loss, cerebrospinal fluid (CSF) leakage and meningitis (9–12).

All patients should undergo a thorough physical examination repetitively with special attention to cranial nerve function, including assessment of visual acuity, visual fields, and extra-ocular motility. The proximity of cranial nerves II–VI to the pituitary gland makes a post-operative cranial nerve palsy a feared complication. Any new post-operative neurological finding should be addressed with either immediate post-operative imaging or re-exploration in the operating room in case of visual field deficit (9–12).

In addition, patients should be questioned about rhinorrhoea or fluid leakage down the back of the throat. Although some nasal drainage is expected in the post-operative period, suspicious drainage should be further investigated. Drainage may be collected and analysed for the endogenous marker of CSF-leakage, beta-2 transferrin, to confirm or refute the diagnosis [9–12]. Post-operative CSF-leakage is best treated by operative repacking of the defect with autologous adipose tissue.

Meningitis is an infrequent complication of PS. When clinical suspicion is high, empiric broad-spectrum intravenous antibiotic coverage should be started immediately following lumbar puncture (LP). Duration of antibiotics is typically 14 days and adjustments are guided by LP cultures and sensitivity results. It is recommended that at least one repeat LP is performed to document clearing of CSF and appropriate response to antibiotic administration.

The most common post-PS complaint is headache, which may be treated with paracetamol, non-steroidal anti-inflammatory drugs and narcotics [12]. Narcotics should be used with care in patients with OSA.

Routine pharmacological post-operative nausea and vomiting (PONV) prophylaxis is advisable as nearly 40% of patients experience PONV and because of the detrimental effect of vomiting on intracranial pressure [12].

Peri-operative corticosteroid administration

At most centres, patients who undergo PS are given hydrocortisone 50–100 mg every 6–8 h intravenously for several days before being gradually weaned [9,11]. This is often not necessary and post-operative corticoid supplementation is rarely

required beyond the first 24 hours. In a more modern approach, patients receive peri-operative hydrocortisone, 50 mg every 6 hours, with the last peri-operative dose given on the morning of post-operative day 1. During the mornings of post-operative days 2 and 3, serum cortisol levels are assessed. Patients with two consecutive cortisol values ≤8 μg/dL should receive hydrocortisone replacement treatment. Patients who are already receiving corticosteroid replacement pre-operatively should have gradual dose reduction to their replacement dose during their hospitalization [10–12].

Patients with Cushing's disease are managed somewhat differently. Traditionally, dexamethasone is preferred because it does not interfere with post-operative endogenous cortisol assays [9]. However, recent publications advise avoiding all peri-operative corticosteroid administration [10–12]. Instead they obtain serum cortisol levels every 6 hours post-operatively to document laboratory evidence of disease remission. Patients should be monitored closely for clinical signs of hypocortisolaemia, including malaise, nausea, tachycardia, hypotension, and hypothermia, which in general does not appear until 24–36 hours post-operatively. Hydrocortisone is withheld until patients have hypocortisolaemia symptoms with low serum cortisol levels (usually <2μg/dL). If hypocortisolaemia does not develop, consideration is given to prompt surgical re-exploration. This approach is only possible if the hospital laboratory is able to report serum cortisol levels rapidly (<1 hour) [10–12].

Box 262.2 Causes of diabetes insipidus

Central

- Familial.
- Neurosurgery.
- Neurotrauma.
- Tumours: craniopharyngioma, hypothalamic glioma, metastatic carcinoma, meningioma, lymphoma.
- Intracranial hypertension.
- Brain death.
- Infections: cerebral abscess, meningitis, encephalitis, tuberculosis.
- Infiltrations: sarcoidosis, hystiocytosis X, haemochromatosis.
- Vascular: aneurysm, haemorrhage, thrombosis.
- Autoimmune disorder.
- Idiopathic.

Nephrogenic

- Familial.
- Hypercalcaemia.
- Hypokalaemia.
- Drugs: lithium, cidofovir, foscarnet, amphotericin, glibenclamide, demeclocycline.
- Amyloidosis, Sjögren syndrome.
- Sickle cell disease/trait.
- Post-obstructive polyuria.
- Pregnancy (placental production of vasopressinase).
- Idiopathic.

Other anterior hormone assessment

Although the pituitary thyroid axis may be disrupted at the time of PS, patients without pre-operative hypothyroidism should not be screened in the immediate post-operative period. Patients with known pre-operative hypothyroidism continue their pre-operative replacement therapy.

Post-operative assessment of growth hormone and gonadal function is also reserved for a later post-operative visit by the endocrinologist [9].

Disorders of water balance

Abnormalities of antidiuretic hormone (ADH) secretion and subsequent disorders of water balance are among the most common complications of patients undergoing PS [9–12].

Post-operative DI typically manifests in the first 24–48 hours after surgery. DI is observed in up to one-third of patients and is almost always transient. Since the majority of post-PS patients have an intact thirst mechanism, they are able to keep up with ongoing urinary losses and development of hypernatraemia is rather uncommon post-PS. When desmopressin is administered, a single dose may be sufficient and close monitoring of urine output and serum electrolytes is mandatory to avoid 'overshoot' hypernatraemia. For early detection of DI, it is recommended that urinary output and osmolality (or specific gravity) be measured routinely after PS [9–12].

It is important to distinguish DI from other causes of post-operative polyuria (Box 262.2). Note that acromegalic patients often have robust physiological diuresis after successful tumour resection, and early treatment with desmopressin should be avoided.

Hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) is observed in up to 25% of patients who underwent PS [9,10]. In SIADH, an injured posterior pituitary continues to secrete ADH regardless of plasma osmolality. If patients continue to drink or are administrated intravenous (iv) fluids, free water intake exceeds free water excretion while the kidney's ability to handle sodium remains intact. It is characterized by hyponatraemia (<135mmol/L), hypo-osmolality (<280mOsm/L), and inappropriately concentrated urine (> serum osmolality) in a setting of euvolaemia and normal renal, adrenal, and thyroid function [9,10,12].

The diagnosis of SIADH is mostly biochemical. However, symptoms such as headache, dizziness, nausea, vomiting, and altered mental status and seizures may arise if the onset of hyponatraemia is particularly rapid.

When making a diagnosis of SIADH, it is important to distinguish other causes of hyponatraemia, especially those associated with PS, such as hypocortisolism, hypothyroidism, and DM. Perhaps the most important clue to distinguish SIADH from other causes of hyponatraemia is the time frame in which it occurs. SIADH typically becomes manifest a week after surgery, which is much later than the other conditions described [5,9,10,12–15].

Restriction of fluid intake is the first-line treatment for SIADH in patients without hypovolaemia. In patients with severe (<120 mmol/L), symptomatic hyponatraemia hypertonic saline (3 or 1.8%) can be added to fluid restriction in order to restore serum sodium quickly, remembering only partial restoration is required. Excessive rapid correction (>0.5–1mmol/L/hour) should be avoided to prevent the rare, but serious complication of central pontine myelinolysis. In cases of severe or resistant hyponatraemia urea (iv or by mouth (po)) may be considered as adjunct therapy.

Diabetes insipidus

Vasopressin or ADH is secreted by the posterior pituitary. ADH increases water permeability in distal renal tubules and collecting ducts, resulting in an enhanced water reabsorption and urine concentration [5,13–16]. Consequently, insufficient production of ADH (central DI) or inadequate response of the renal tubules to ADH (nephrogenic DI) results in excretion of large volumes of hypotonic fluid (Box 262.3). This inability to conserve water is primarily reflected by polyuria (>2 mL/kg/hour), that does not decrease with reduction in fluid intake, and polydipsia. The main laboratory finding in critically-ill patients with DI is hypernatraemia.

In alert patients with an unimpaired thirst mechanism the polyuria and polydipsia are inconvenient, but not detrimental as these patients are able to drink sufficient amounts of water to maintain normal serum osmolality [5,13–16]. Most critically-ill patients, however, do not sense and/or cannot respond to thirst, and will rapidly develop dehydration, hyperosmolality, and hypernatraemia.

Clinical features and diagnosis

The hallmark of DI is an abrupt onset of polyuria. Because polyuria is not specific to DI, it is essential to exclude other causes of polyuria (Box 262.3) before treatment is initiated. Note that primary polydipsia, a classically cited possible cause of hypo-osmotic polyuria, is essentially excluded in the setting of hypernatraemia and plasma hyperosmolality.

Box 262.3 Causes of polyuria in the ICU

- Excessive fluid administration.
- Diuretic drugs.
- Primary polydipsia.
- Osmotic diuresis:
  - Mannitol.
  - Hyperglycaemia.
  - Intravenous contrast agent myogloburia.
  - Post-obstructive diuresis.
  - Recovery phase of acute kidney injury.
- Diabetes insipidus:
  - Central.
  - Nephrogenic.
- Post-tumour resection in acromegalic patients.

The classical diagnostic test of DI, the water deprivation test, should not be used in the ICU-setting as most critically-ill patients with DI are already hypernatraemic, and deliberate induction of hypovolaemia is potentially dangerous, since it may provoke haemodynamic instability. The diagnosis of DI in critically-ill patients can be made by demonstrating plasma hyperosmolality (≥295 mOsm/kg) and hypernatraemia (mostly ≥145 mmol/L) in the face of hypo-osmolar (usually ≤250 mOsm/kg) polyuria.

Treatment

Mild cases of DI can often be managed by adequate fluid replacement, in the form of glucose-containing water solutions to correct the loss of free water. Use of saline solutions is inappropriate as it represents an unnecessary solute load that further increases renal water loss. Careful routine monitoring of body weight, plasma sodium and osmolality, and fluid input and urinary output are essential. Collectively, these data provide serial information regarding fluid balance and allow adaptation of treatment when necessary.

Other electrolytes, such as potassium, magnesium, and phosphate, should be evaluated, since deficiencies can develop rapidly in polyuric patients and monitoring allows timely titrated replacement.

In patients with excessive polyuria administration of the synthetic ADH-analog desmopressin may be necessary to prevent the development of significant volume contraction and hyperosmolarity with severe hypernatraemia. Desmopressin, typically dosed at 1–2 μg subcutaneous or iv bd, is safer than vasopressin, as it lacks undesirable pressor effects.

Careful monitoring of fluid balance is essential because of the possibility of 'breakthrough' polyuria at a low desmopressin dose, and the risk of fluid overload and hyponatraemia at higher doses. Excessive infusion of hypotonic (5% glucose) fluid in the setting of demopressin-driven antidiuresis carries a high risk of profound hyponatraemia. An increase of urine output (hypo-osmotic polyuria) should be tolerated before administration of the next desmopressin dose. Maintenance of hypotonic fluid replacement should be switched from iv to po as soon as the patient is able to sense thirst and drink adequate amounts of water. Indeed, if the patient's thirst mechanism is intact, this is the best guide for adequate water replacement, while avoiding over-replacement.

Patients with nephrogenic DI do not, or only partially, respond to desmopressin [13,16]. In adults, a urinary concentrating disability severe enough to produce polyuria due to nephrogenic DI is most often due to hypercalcaemia or chronic lithium use. Therapy includes discontinuation of the causative drug and correction of the underlying disorder. Normalization of plasma calcium concentrations usually ameliorate polyuria in hypercalcaemic patients. In contrast, lithium-induced renal DI is frequently irreversible if the patient already has a notable renal concentrating defect.

Thiazide diuretics (such as hydrochlorothiazide 12.5–25 mg, od or bd) may diminish the degree of polyuria via volume contraction and enhanced tubular water reabsorption.

References

1. Dusick JR, Wang C, Cohan P, Swerdloff R, and Kelly DF. (2012). Pathophysiology of hypopituitarism in the setting of brain injury. *Pituitary*, **15**(1), 2–9.
2. Schneider HJ, Aimaretti G, Kreitschmann-Andermahr I, Stalla IK, and Ghigo E. (2007). Hypopituitarism. *Lancet*, **369**(9571), 1461–70.

3. Rolih CA and Ober KP. (1993). Pituitary apoplexy. *Endocrinology and Metabolism Clinics of North America*, **22**(2), 291–302.
4. Prescott H, Ellis E, and Soule S. (2011). Pituitary infarction: a potentially fatal cause of postoperative hyponatraemia and ocular palsy. *British Medical Journal*, **342**, 704–5.
5. Ober KP. (1991). Endocrine crises. Diabetes insipidus. *Critical Care Clinic*, **7**(1), 109–25.
6. Hazouard E, Piquemal R, Dequin PF, Tayoro J, Valat C, and Legras A. (1999). Severe non-infectious circulatory shock related to hypopituitarism. *Intensive Care Medicine*, **25**(8), 865–8.
7. Lombardi G, Galdiero M, Auriemma RS, Pivonello R, and Colao A. (2006). Acromegaly and the cardiovascular system. *Neuroendocrinology*, **83**(3–4), 211–17.
8. Campkin TV. (1980). Radial artery cannulation. Potential hazard in patients with acromegaly. *Anaesthesia*, **35**(10), 1008–9.
9. Ausiello JC, Bruce JN, and Freda PU. (2008). Postoperative assessment of the patient after transsphenoidal pituitary surgery. *Pituitary*, **11**(4), 391–401.
10. Dumont AS, Nemergut EC, Jane JA, and Laws ER. (2005). Postoperative care following pituitary surgery. *Journal of Intensive Care Medicine*, **20**(3), 127–40.
11. Vance ML. (2003). Perioperative management of patients undergoing pituitary surgery. *Endocrinology and Metabolism Clinics of North America*, **32**(2), 355–65.
12. Nemergut EC, Dumont AS, Barry UT, and Laws ER. (2005). Perioperative management of patients undergoing transsphenoidal pituitary surgery. *Anesthesia and Analgesia*, **101**(4), 1170–81.
13. Bagshaw SM, Townsend DR, and McDermid RC. (2009). Disorders of sodium and water balance in hospitalized patients. *Canadian Journal of Anaesthesia*, **56**(2), 151–67.
14. Buonocore CM and Robinson AG. (1993). The diagnosis and management of diabetes insipidus during medical emergencies. *Endocrinology and Metabolism Clinics of North America*, **22**(2), 411–23.
15. Verbalis JG. (2003). Disorders of body water homeostasis. *Best Practice & Research Clinical Endocrinology & Metabolism*, **17**(4), 471–503.
16. Garofeanu C. (2005). Causes of reversible nephrogenic diabetes insipidus: a systematic review. *American Journal of Kidney Disease*, **45**(4), 626–37.

CHAPTER 263

Pathophysiology and management of thyroid disorders in the critically ill

Michael O'Dwyer and David Watson

Key points

- Thyroid hormones act on most tissues via nuclear T_3 receptors.
- Thyroid hormones stimulate oxygen consumption and heat production, influence cell growth, and maturation (central nervous system, bone) and modulate metabolism (carbohydrates, lipids, proteins, drugs).
- Treatment for presumed thyroid disease frequently has to be initiated before the results of diagnostic tests are available.
- Treatment of hyperthyroidism should result in the reduction of serum thyroid hormone levels and their action on peripheral tissues with concurrent treatment of the precipitating event.
- In severe hypothyroidism the choice of thyroid hormone (thyroxine or triiodothyronine), optimal dosing, and the route of administration remain controversial.

Basic pathophysiology

The primary function of the thyroid gland is to produce tetraiodothyronine (T_4) and triiodothyronine (T_3) from iodide and tyrosine. While this pathway is the sole endogenous source of T_4, the majority of T_3 is derived from peripheral conversion of T_4 to T_3 in the liver and kidneys. This conversion is frequently inhibited by physiological stressors such as severe trauma and critical illness [1]. In addition, calcitonin produced by the thyroid parafollicular cells regulates calcium levels.

The half-life of T_4 is approximately 7 days and that of T_3 is approximately 24 hours. Both hormones are highly protein bound with the free hormones (FT_3 and FT_4) having physiological effect. The greater effect attributed to T_3 is largely explained by the relatively greater amount of FT_3 compared with FT_4 (0.4% versus 0.04% of the T_3 and T_4, respectively) [2]. The ultimate effect of free hormone binding to intracellular receptors is an increase in cellular energy output. These receptors are particularly abundant in cells of the heart, brain, and liver, where they are involved in the regulation of basal metabolism and heat production.

Thyroid-stimulating hormone (TSH), from the anterior pituitary, controls the production and release of thyroid hormones. Levels of TSH are in turn regulated by levels of FT_3 and FT_4 and also by hypothalamic thyrotropin-releasing hormone (TRH), which is itself regulated by higher neural centres and by feedback from circulating thyroid hormone levels [3].

The incidence of recognized thyroid disease remains under 5% in western populations. Thyroid crises are rarer still, yet untreated or poorly managed thyroid storm and myxoedema coma are frequently fatal.

Hyperthyroidism

Hyperthyroidism is a clinical syndrome caused by exposure of the body tissues to excess circulating levels of FT_3 and FT_4. Table 263.1 shows the cause of most cases.

Graves' disease

Graves' disease is an autoimmune condition associated with diffuse thyroid enlargement, opthalmopathy and proptosis, and pretibial myxoedema. The binding of IgG thyroid stimulating antibodies to the TSH receptor stimulates thyroid hormone production. The pathogenesis of the opthalmopathy and dermopathy is also believed to be immunologically mediated. Although the disease trigger has yet to be definitively identified, the frequent sudden presentation in middle age suggests an infective aetiology coupled with a genetic predisposition [4].

Toxic multinodular goitre and solitary nodule

In some patients a simple diffuse goitre may progress over decades, stimulated by thyroid-growth immunoglobulins, to a multinodular goitre with areas of autonomous function. Hyperthyroidism then develops in middle or old age.

A toxic solitary nodule is a follicular adenoma, which autonomously secretes thyroid hormones, while inhibiting TSH secretion, which causes subsequent atrophy of the rest of the gland [5].

Excess administration of iodide

While large amounts of available iodide usually inhibit hormone production through a negative feedback mechanism it may paradoxically induce hyperthyroidism, particularly in patients who are relatively iodide deficient. Iodide excess may come from dietary supplements or medication (e.g. antitussive agents, amiodorone, or radio-angiographic contrast agents). This paradoxical hyperthyroidism is termed the Jod–Basedow effect [6].

Table 263.1 Causes of hyperthyroidism

Common causes (>90% of cases)	Rare causes
◆ Graves' disease	◆ Excess pituitary secretion of TSH
◆ Toxic multinodular goitre	◆ Metastatic differentiated thyroid carcinoma
◆ Toxic solitary nodule	◆ Ovarian teratoma-containing thyroid tissue
◆ Overdose of thyroid hormones	◆ Intrinsic thyroid-stimulating activity of human chorionic gonadotropin in hydatid form mole and choriocarcinoma
	◆ Excess administration of iodide

Thyrotoxic crisis (thyroid storm)

A thyrotoxic crisis is a life-threatening increase in the severity of the clinical features of hyperthyroidism. This is most commonly precipitated by infection in a known hyperthyroid patient who is inadequately controlled by antithyroid drugs or alternatively has unrecognized Graves' disease. It may also be precipitated by surgery (particularly subtotal thyroidectomy in an inadequately prepared patient), trauma, labour, or iodine therapy. FT_3 and FT_4 are usually elevated although levels do not always correlate with severity of illness. TSH is usually undetectable.

Clinical presentation

Cardiorespiratory features

Thyroid hormones exert their cardiac effects directly via specific nuclear receptors and also through central activation of the sympathoadrenal system. The increased basal metabolic rate, frequently exacerbated by pyrexia due to impaired thermoregulation, is associated with an increase in oxygen consumption and carbon dioxide production, and a hyperdynamic circulation. Consequently, patients are at risk of developing arrhythmias and myocardial ischaemia, while concurrent respiratory muscle weakness may lead to respiratory failure.

Neuromuscular features

An excess of thyroid hormones affects the concentration and distribution of assorted neurotransmitters. The resultant neurological features include severe agitation, psychosis, irritability, tremor, delirium, stupor, and seizures.

Proximal muscle weakness is common and may be the dominant manifestation in some individuals.

When present, dysphagia is usually secondary to weakness of the striated muscles of the pharynx as a consequence of hyperthyroidism-induced myopathy. Ocular muscle involvement results in ophthalmoplegia.

Gastrointestinal features

Patients with hyperthyroidism have a high incidence of gastrointestinal hypermotility. Gastritis is frequent and associated with malabsorption. This may complicate management with oral medications.

Rarely, jaundice can be a sign of an associated fulminant hepatic necrosis.

Electrolyte and haematological abnormalities

Hypercalcemia is observed in up to 15% of cases and can be life-threatening. Similarly, hypomagnesaemia and hypokalaemia are frequently observed.

Haematological manifestations include anaemia, thrombocytopenia, and eosinophilia with lymphocytosis.

Management

Although the diagnosis of a thyrotoxic crisis is largely clinical, response to treatment can be monitored both clinically and by falling T_3 levels.

Treatment strategies involve the following principals:

- Control the effects of circulating T_3 and T_4.
- Acutely reduce the synthesis and secretion of thyroid hormones and prevent peripheral conversion of T_4 to T_3.
- Treat the precipitating cause.

General/supportive measures

Supplemental oxygen and intravenous fluids should be administered following principals common to all critically-ill patients.

Some medications, such as salicylates and furosemide, should be avoided. Salicylates, sometimes used to limit pyrexia, displace thyroid hormones from their binding proteins. Furosemide has a similar effect.

Gastric lavage and activated charcoal may be of use in cases of witnessed, recent thyroid hormone overdose [7]. Cholestyramine may increase faecal elimination of the hormone.

Plasma exchange, charcoal haemoperfusion and dantrolene are all reported treatment strategies, but remain controversial [8].

Specific antithyroid treatments

Both propylthiouracil and carmbimazole impede the formation of thyroid hormone and prevent peripheral conversion of T_4 to T_3 [9]. Disadvantages include the lack of a parenteral preparation for these drugs, and also the development of bone marrow depression and a transient leucopenia.

Oral potassium iodide or Lugol's iodine are effective treatments, but their administration should be delayed for approximately 1 hour following the first dose of propylthiouracil. This is to minimize the possibility of excessive hormone release following iodination. Intravenous iodine preparations can be easily prepared.

Recently, radiographic contrast dyes, such as sodium ipodate, which contains iodine have been suggested as superior agents as they may also directly diminish the cardiotoxic effects of thyroid hormones. In addition, they potently inhibit the peripheral conversion of T_4 to T_3 and it is now suggested these are the iodine preparations of choice [10].

If patients are known to be sensitive to iodine then lithium carbonate should be considered as it has a similar mechanism of action [11]. Therapeutic drug monitoring is essential.

Cardiovascular management

Propranolol blocks the β-adrenoreceptor effects of thyroxine, impairs conversion of T_4 to T_3 and also inhibits release of thyroid hormone. β1 adrenergic selective antagonists, such as atenolol or the ultrashort-acting β blocker esmolol may be indicated in cases of cardiac insufficiency or airflow limitation.

Digoxin may prove useful in the treatment of rapid atrial fibrillation, particularly in amiodorone-induced thyrotoxicosis, but should be preceded by the correction of hypokalaemia. Dosage is affected by the accelerated metabolism of digoxin in thyrotoxicosis. Conversely, these patients are more sensitive to warfarin because vitamin K-dependent clotting factors are metabolized more rapidly.

Although amiodorone can cause hyperthyroidism it can control the acute arrhythmias observed in this setting and can additionally inhibit the peripheral deiodination of T_4 to T_3 [12]. Verapamil may also be useful in this setting to reduce the ventricular rate.

Steroids are also usually administered since relative hypoadrenalism may be present in severe hyperthyroidism due to the accelerated metabolism of cortisol. Glucocorticoids can also reduce the conversion of T_4 to T_3.

Ongoing management

The response to treatment of a thyrotoxic crisis should be monitored by recording clinical vital signs of sympathetic drive as well as regular serum T_3 estimations. Hyperthyroidism is usually brought under control after approximately 10 days and the iodide preparations and β blockers may then be withdrawn. Patients may subsequently be maintained on oral carbimazole.

Sick euthyroid syndrome

In critical illness abnormal thyroid function tests are frequently reported in the setting of a non-thyroidal illness and patients are described as having sick euthyroid syndrome. Many abnormalities of thyroid hormones are described but the most prominent are low T_3 and elevated reverse T_3. TSH and T_4 are affected to varying degrees. As the severity of the illness increases T_3 and T_4 fall.

Treatment with exogenous thyroid hormones is controversial with little data to guide clinicians [13].

Hypothyroidism

Deficiency of thyroid hormones may result in a broad range of presentations with a spectrum of illness that varies from an asymptomatic disease process through to coma with multisystem involvement. Predominantly, it is a primary process whereby the thyroid gland fails to produce adequate thyroid hormone. The most common cause is autoimmune thyroid disease (Hashimoto thyroiditis). Although less common, it can also be secondary to inadequate production of TSH or TRH.

Clinical presentation

Cardiorespiratory features

Bradycardia results from a reduction in basal metabolism accompanied by loss of thyroid hormone stimulation of cardiac pacemaker cells. Catecholamine levels are usually normal but there is reduced sensitivity to their actions resulting in reduced myocardial contractility [14]. T_4 deficiency contributes to this as it is a myocardial growth factor. However, chronic peripheral vasoconstriction, necessary to maintain normal body core temperature, leads invariably to diastolic hypertension [15].

Pericardial effusion is commonly described and contributes to the low voltage observed on an ECG. Accompanying ECG abnormalities include long QT interval and flattened or inverted T waves.

Cardiac ischaemia, partially due to altered lipid metabolism, is frequent in hypothyroidism and may become clinically apparent during thyroid hormone replacement therapy [16].

Sleep apnoea syndrome, when present, is usually of mixed origin with a reduction of central drive in conjunction with tongue enlargement, which contributes to an obstructive picture.

Neurological features

Somnolence, lethargy, coma, and seizures are features of myxoedema coma. Associated hyponatraemia may exacerbate these features.

Gastrointestinal features

Hypothyroidism frequently slows gastric emptying and inhibits motor activity of the small intestine and colon. Intestinal absorption of drugs is not always preserved [17].

Haematological features and electrolyte abnormalities

Normocytic anaemia is common and may be due to decreased erythropoietin production.

The total leukocyte count rarely exceeds 10,000, even if infection is the precipitating event. The presence of band cells indicates probable sepsis.

Increased fibrinolytic activity with high plasminogen and reduced activation of the plasminogen inhibitor may play a role in haemorrhage associated with severe hypothyroidism.

Dilutional hyponatraemia is a constant feature of myxoedema coma as high plasma levels of vasopressin lead to water retention.

Musculoskeletal features

Muscle contraction and relaxation are slowed in hypothyroidism and high plasma levels of muscle derived enzymes (transaminases, creatine phosphokinase and lactic dehydrogenase) are frequently observed.

1,25-OH vitamin D concentrations are increased, leading to decreased calciuria, which may partly explain the hypercalcaemia occasionally described in severely hypothyroid patients.

Dermatological features

Peripheral vasoconstriction and decreased cutaneous metabolism result in a cold, dry, and pale skin. There is thinning of the epidermis and deep wrinkles are present. Hair is scarce and grows slowly. However, only 40% of hypothyroid patients display the typical cutaneous infiltration.

Carbohydrate metabolism

The risk of severe and prolonged hypoglycaemia is high in hypothyroidism. Insulin clearance is reduced, and sensitivity to endogenous or exogenous insulin is increased. Gluconeogenesis is also decreased.

Myxoedema coma/crisis

Myxoedema coma is a rare yet life-threatening medical emergency. It usually presents as altered mental status and defective thermoregulation with a precipitating event usually in an elderly patient. The precipitant is often infection, but climate-induced hypothermia and drug therapy are also well described [18].

Successful management requires early diagnosis and prompt appropriate therapeutic measures.

Diagnosis of myxoedema coma

Clinical suspicion should trigger initiation of specific treatment. Baseline blood samples should be obtained for assays of TSH, FT_3, FT_4, and cortisol. The diagnosis is confirmed in the presence of elevated plasma TSH, and dramatic reduction of both FT_3 and FT_4.

Hypothermia

Passive rewarming using blankets and warm ambient temperature is usual. If patients are rewarmed too aggressively peripheral vasodilatation can precipitate cardiovascular collapse.

Cardiovascular assistance

Hypotension indicates an unfavourable prognosis as hypothyroidism is usually associated with mild diastolic hypertension. Myocardial infarction, gastrointestinal blood loss, and aggressive rewarming should not be overlooked as causes of hypotension. Echocardiography and troponin levels may help to make a definite diagnosis of myocardial dysfunction as levels of muscular enzymes are increased in hypothyroid patients and ECG abnormalities are also common even in the absence of myocardial dysfunction.

Caution is needed in treating congestive heart failure. There is a substantial risk of overdose when administering digitalis, diuretics, and afterload-reducing agents in patients with hypothyroidism.

Vasoactive drugs are ineffective until thyroid hormone and possibly glucocorticoids are replaced. They may, in fact, prove to be disadvantageous by precipitating dangerous arrhythmias.

Fluids and electrolytes

Fluid status should be monitored closely and intravenous glucose or normal saline administered if appropriate. As a dilutional hyponatraemia is usually present water restriction should be instituted first. Hypertonic saline followed by furosemide may be necessary in severe hyponatraemia.

Antibiotic therapy

Infection is a common precipitating cause of myxoedema coma. Diagnosis is difficult because elevation of leukocyte count and fever is rare. However, left shift and band formation usually signify infection.

Hormonal therapy

Steroid therapy

The possibility of coexistent adrenal insufficiency (Schmidt's syndrome) mandates intravenous empiric hydrocortisone treatment until baseline cortisol results are reported [19].

Thyroid hormone therapy

Thyroid hormone replacement treatment must begin promptly, often before confirmatory test results. As impaired gastrointestinal absorption can potentially be a feature of the disease process intravenous therapy is usual but not universal.

Choice of thyroid hormone (T_4, T_3, or both) and optimal dosage remain controversial [20]. To exert full biological effect, T_4 must be converted into T_3 by an enzymatic step involving 5'-deiodinase. In critically-ill patients or those on medications, such as amiodorone T_3 administration, may be advisable due to reduced 5'-deiodinase activity. However, T_3 can induce too rapid an increase in oxygen consumption adversely affecting cardiovascular and respiratory functions [16]. Although inconsistent, some observational studies have described an association between large doses of T_3 and increased mortality.

One treatment regimen is to use an intravenous loading dose of T_4 followed by a maintenance intravenous dose until the patient is able to take oral medications. Additional intravenous T_3 may be considered. The benefits of a loading dose and ongoing high dosing of T_4 plus the concurrent use of T_3 should be weighed against the cardiovascular risk, particularly in elderly patients.

Monitoring serum concentrations of TSH, FT_3, and FT_4 is not clinically useful during ICU treatment, but demonstrates a rapid increase of plasma FT_4 and a slower increase of FT_3, whereas TSH levels decrease only after a few weeks. The goal of maintenance treatment is to normalize TSH levels, a process which may take several months.

References

1. Berger MM, Lemarchand-Beraud T, Cavadini C, and Chiolero R. (1996). Relations between the selenium status and the low T3 syndrome after major trauma. *Intensive Care Medicine*, **22**(6), 575–81.
2. Maberly GF, Waite KV, Cutten AE, Smith HC, and Eastman CJ. (1985). A reappraisal of the binding characteristics of human thyroxine-binding globulin for 3,5,3'-triiodothyronine and thyroxine. *Journal of Clinical Endocrinology and Metabolism*, **60**(1), 42–7.
3. Costa-e-Sousa RH and Hollenberg AN. (2012). Minireview: the neural regulation of the hypothalamic-pituitary-thyroid axis. *Endocrinology*, **153**(9), 4128–35.
4. Eschler DC, Hasham A, and Tomer Y. (2011). Cutting edge: the etiology of autoimmune thyroid diseases. *Clinical Reviews in Allergy & Immunology*, **41**(2), 190–7.
5. Tonacchera M, Chiovato L, Pinchera A, et al. (1998). Hyperfunctioning thyroid nodules in toxic multinodular goitre share activating thyrotropin receptor mutations with solitary toxic adenoma. *Journal of Clinical Endocrinology and Metabolism*, **83**(2), 492–8.
6. El-Shirbiny AM, Stavrou SS, Dnistrian A, Sonenberg M, Larson SM, and Divgi CR. (1997). Jod–Basedow syndrome following oral iodine and radioiodinated-antibody administration. *Journal of Nuclear Medicine*, **38**(11), 1816–17.
7. Ho J, Jackson R, and Johnson D. Massive levothyroxine ingestion in a pediatric patient: case report and discussion. *Canadian Journal of Emergency Medicine*, **13**(3), 165–8.
8. May ME, Mintz PD, Lowry P, Geller R, and Curnow RT. (1983). Plasmapheresis in thyroxine overdose: a case report. *Journal of Toxicology and Clinical Toxicology*, **20**(5), 517–20.
9. Liang M, Wang H, Tan L, Feng M, Shen Y, and Wang Q. (2012). Successful treatment of thyrotoxic crisis after esophagectomy in an elderly woman with hyperthyroidism. *Annals of Thoracic Surgery*, **93**(6), e141–2.
10. Ogiso S, Inamoto S, Hata H, Yamaguchi T, Otani T, and Koizumi K. (2008). Successful treatment of gastric perforation with thyrotoxic crisis. *American Journal of Emergency Medicine*, **26**(9), 1065.e3–4.
11. Nayak B and Burman K. (2006). Thyrotoxicosis and thyroid storm. *Endocrinology & Metabolism Clinics of North America*, **35**(4), 663–86, vii.
12. Martino E, Bartalena L, Bogazzi F, and Braverman LE. (2001). The effects of amiodarone on the thyroid. *Endocrine Reviews*, **22**(2), 240–54.
13. Pappa TA, Vagenakis AG, and Alevizaki M. (2011). The nonthyroidal illness syndrome in the non-critically ill patient. *European Journal of Clinical Investigations*, **41**(2), 212–20.
14. Silva JE and Bianco SD. (2008). Thyroid- adrenergic interactions: physiological and clinical implications. *Thyroid*, **18**(2), 157–65.
15. Cai Y, Ren, and Shi J. (2011). Blood pressure levels in patients with subclinical thyroid dysfunction: a meta-analysis of cross-sectional data. *Hypertension Research*, **34**(10), 1098–105.
16. McCulloch W, Price P, Hinds CJ, and Wass JA. (1985). Effects of low dose oral triiodothyronine in myxoedema coma. *Intensive Care Medicine*, **11**(5), 259–62.

17. Benvenga S, Bartolone L, Squadrito S, Lo Giudice F, and Trimarchi F. (1995). Delayed intestinal absorption of levothyroxine. *Thyroid*, **5**(4), 249–53.
18. Ballester JM and Harchelroad FP. (1999). Hypothermia: an easy-to-miss, dangerous disorder in winter weather. *Geriatrics*, **54**(2), 51–2, 55–7.
19. Gupta AN and Nagri SK. (2012). Schmidt's syndrome- case report. *Australasian Medical Journal*, **5**(6), 292–5.
20. Arlot S, Debussche X, Lalau JD, et al. (1991). Myxoedema coma: response of thyroid hormones with oral and intravenous high-dose L-thyroxine treatment. *Intensive Care Medicine*, **17**(1), 16–18.

CHAPTER 264

Pathophysiology and management of functional endocrine tumours in the critically ill

Sara Nikravan and Frederick Mihm

Key points

- Carcinoid tumours may secrete bioactive products that can lead to carcinoid syndrome and valvular heart disease with right heart failure.
- Carcinoid shock and bronchospasm can be precipitated or worsened by use of beta-adrenergic agents.
- Pheochromocytomas are rare and potentially lethal catecholamine secreting tumours. They mimic or co-exist with more common diseases making recognition challenging.
- Extreme blood pressure lability during pheochromocytoma manipulation and shock after removal can be dramatic.
- Neuroglycopenic patients with increased systemic insulin levels should be evaluated for insulinoma, while being aggressively treated for hypoglycaemia in a monitored setting.

Carcinoid tumours

Carcinoid tumours are rare, well-differentiated neuroendocrine tumours of the aerodigestive tract. They can produce as many as 40 different secretory amine and polypeptides including serotonin, histamine, tachykinins, kallikrein, and prostaglandins [1,2]. Tumours are classified based on their origins of embryonic division with most functional carcinoid tumours originating from the midgut.

Pathophysiology

Most patients are asymptomatic with tumours discovered incidentally, typically in the appendix. Carcinoid syndrome occurs in 20–30% of carcinoid patients [3]. The liver inactivates bioactive products in the portal system, so gastrointestinal carcinoid tumours only cause carcinoid syndrome with widespread liver metastases, unlike bronchial and extra-intestinal tumours. The syndrome includes flushing, mostly on the face, neck, and upper chest in a serpiginous pattern [4]. The facial flush can appear very similar to a lupus rash (see Fig. 264.1). Most events are spontaneous, but can be provoked by eating, alcohol, defaecation, liver manipulation, stress, exposure to catecholamines, cardiopulmonary bypass, and general anaesthesia. Severe flushing, generalized vasodilation, and capillary damage can cause profound hypotension and tachycardia. Moderate to severe bronchospasm may also occur. These episodic events can be life-threatening, resulting in carcinoid crisis and shock, particularly if mismanaged. Other serious problems can result from local tumour manifestations, such as bleeding, intestinal obstruction, and/or perforation [2].

Diagnosis

The diagnosis is usually well established before severe decompensation requiring intensive care unit (ICU) admission. Laboratory confirmation can be made with a 24-hour urine collection for 5-hydroxyindoleacetic acid (5-HIAA) secretion, the end product of serotonin metabolism. Chromogranin A is a glycoprotein stored in the secretory granules of neuroendocrine cells and is elevated in >80% of carcinoid syndrome patients. Levels of this marker correlate with disease activity and tumour burden [5].

About 50% of patients with carcinoid syndrome develop carcinoid heart disease, presumably related to the release of vasoactive substances (serotonin, substance P) into the venous circulation, ultimately affecting the right heart and right heart valves. Patients will present with significant dyspnoea and fatigue, lower extremity oedema, and other signs of right heart failure. Constant exposure of these substances has been correlated to plaque formation on the endocardial surfaces of the heart leading to right heart valvular lesions (tricuspid > pulmonary), restrictive cardiomyopathy, constrictive pericarditis, pericardial effusion, and hypoxia secondary to intra-atrial shunting in the presence of a patent foramen ovale, which can develop as the disease progresses. Left heart valve lesions are generally not observed because the lungs actively metabolize serotonin (70% first pass). However, left-sided valvular lesions can

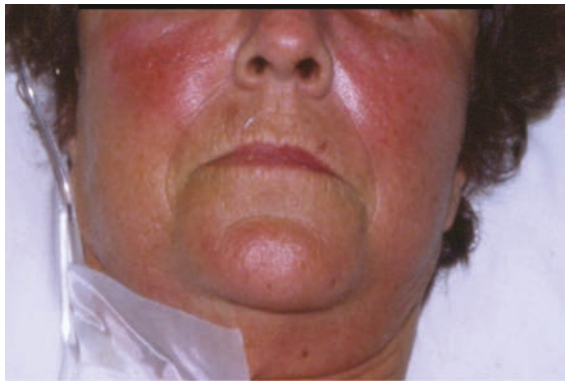


Fig. 264.1 Carcinoid rash associated with peri-operative carcinoid shock.

be observed with bronchial carcinoids and in patients who develop a patent foramen ovale, an independent mortality risk factor [5]. Median survival after diagnosis of carcinoid heart disease has improved from 1.5 to 4.4 years, and may be related to better selection of patients for valve surgery and better treatment strategies, particularly somatostatin [5].

Treatment

Somatostatin can be highly effective in treating carcinoid shock. It is a tetradecapeptide hormone, widely distributed throughout the CNS and peripheral nervous system, gastrointestinal tract, and pancreatic D cells. Somatostatin results in potent inhibition of hormone excretion (growth hormone (GH), thyroid-stimulating hormone (TSH), glucagon, insulin, prolactin, adrenocorticotropic hormone (ACTH), secretin, pancreozymin, vasoactive intestinal peptide (VIP), pancreatic polypeptide (PP), Gastrin), digestive enzymes (pepsin, pancreatic enzymes), while also decreasing intestinal motility and absorption (e.g. glucose). Analogs such as octreotide have a longer half-life and bind to somatostatin receptors on tumour cells, inhibiting the release of bioactive amines. They may also inhibit tumour growth [6]. Rare side effects include nausea, abdominal discomfort, and steatorrhoea. Most importantly, when given in acute settings, transient severe bradycardia and third degree heart block have been reported [7].

Pre- and intra-operative treatment with octreotide is crucial for protection against carcinoid crisis that can develop secondary to anaesthesia and/or tumour manipulation [8]. Intra-operative blood pressure lability can be supported by a 100 mg octreotide bolus or infusion (100 mg/hour). If carcinoid crisis does ensue, it is often refractory to fluid administration alone and, notably, can be exacerbated by administering beta-adrenergic agonists (including by inhalation) and/or calcium. The use of a pure alpha agonist, such as phenylephrine or a non-adrenergic drug like vasopressin, is recommended together with ongoing assessment of fluid requirements, as fluid sequestration may be dramatic. Since tricuspid regurgitation is common, beware of over-estimating CVP and subsequently under-resuscitating the patient. Drugs such as xylocaine and anti-cholinergic agents (ipratroprium) may be used for bronchospasm. If the patient is mechanically ventilated, it is vital to increase expiratory time to avoid breath-stacking and auto-PEEP.

Pheochromocytoma

Pheochromocytomas and catecholamine secreting paragangliomas (extra-adrenal pheochromocytomas) are rare tumours that arise from chromaffin cells of the adrenal medulla and sympathetic ganglia. If unrecognized and left untreated, they are almost certainly lethal. Approximately 95% of these tumours are located in the abdomen, 85–90% of which are intra-adrenal. About 10% are malignant. These tumours often go undiagnosed with vague paroxysmal symptoms. While they can occur at any age, pheochromocytomas most often develop in the 4th and 5th decades of life [9].

Pathophysiology

Pheochromocytomas can secrete a combination of norepinephrine, epinephrine, and very rarely, dopamine in a sustained or paroxysmal fashion. Patients can present with the classic triad of headaches, sweating, and tachycardia/palpitations. They most often have sustained or paroxysmal hypertension that can lead to hypovolaemia. This may cause orthostatic hypotension in some patients. Reflex bradycardia has also been described. Rarely, hypertension is absent, particularly in familial pheochromocytoma [9]. While symptoms can occur spontaneously, they can be precipitated by a number of factors, such as tumour palpation, trauma, exertion, valsalva, anxiety, pain, tyramine-containing foods or beverages, intubation, and induction of anaesthesia. Medications such as metoclopramide, phenothiazines, droperidol, amytriptiline, adrenocorticotropic hormone, glucagon, histamine, and illicit drugs, such as cocaine can also induce attacks. Hypercatecholaminaemia can cause significant weight loss, constipation or pseudo-obstruction, bowel ischaemia, all of the complications of severe sustained hypertension, and acute myocarditis (direct cardiac toxic effect of catecholamines) [9,10].

Diagnosis

The cumulative presence of headaches, sweating, and palpitations in the setting of hypertension makes the diagnosis likely. Patients with episodic symptoms may not be observed during catecholamine surges nor diagnosed with hypertension [11].

Besides clinical symptoms, certain routine laboratory findings raise the suspicion of pheochromocytoma. Hyperglycaemia in the absence of diabetes mellitus, hypertriglyceridaemia, and an unexplained elevated haematocrit (secondary to hypovolaemia and/or erythropoietin secretion from the tumour) may occur. Presence of lactic acidosis in the absence of shock may be noted as a result of persistent secretion of epinephrine. Pheochromocytoma may mimic many diseases, or rarely, co-exist with other disease processes (e.g. aortic dissection, thyrotoxicosis, etc.) [12]. Apparent hypotension occurs in the setting of extreme vasoconstriction. The patient is thought to be hypotensive because of an inability to measure blood pressure accurately when, in fact, they are experiencing a hypertensive crisis. Presenting features are varied and include, e.g. pulmonary oedema, congestive heart failure, angina or myocardial infarction, recurrent ventricular tachycardia, and lactic acidosis. There may be cardiomyopathy, peripheral vascular disease, gastrointestinal bleeding, hypertensive complications, or seizures.

Metanephrine and normetanephrine are formed by catecholamine metabolism inside the tumour. Diagnostic tests include plasma

fractionated metanephrines (normetanephrine and metanephrine) and catecholamines in addition to 24-hour urine excretion of free catecholamines, metanephrines, and vanillyl mandelic acid (VMA), the end product of catecholamine metabolism. Some recommend obtaining samples when patients are at a basal state, but this should not delay diagnosis in an unstable patient where pheochromocytoma is considered. Certain medications such as tricyclic antidepressants, levodopa, and other antipsychotics can interfere with laboratory interpretation. In many cases, these medications cannot be discontinued so diagnostic imaging should be used. Either CT or MRI is a reasonable first choice diagnostic imaging modality. Both suppression (clonidine) and provocative (histamine, metoclopramide, glucagon) testing have been used in the past, but are considered unnecessary and potentially dangerous. If diagnosis seems likely despite negative imaging, 123-I-metaiodobenzylguanidine (MIBG) scintigraphy can be used. MIBG is a norepinephrine-like compound that is taken up by adrenergic tissue, helping to detect presence of tumour(s). Diagnostic needle biopsy is dangerous and not recommended [13].

In pregnancy, pheochromocytoma can be distinguished from pre-eclampsia by tachyarrhythmias, hypertension before the 3rd trimester, and the lack of proteinuria.

Once diagnosed, it is important to evaluate the patient for evidence of catecholamine-induced cardiomyopathy, acute/chronic myocarditis, and/or any end organ damage. Appropriate diagnostics for heart disease include electrocardiogram (ECG), cardiac enzymes, and resting cardiography (not a stress/exercise study).

Treatment

Since resection of these tumours is high risk, patients must be diligently managed in the peri-operative period. Pre-operative preparation includes sufficient alpha-adrenergic blockage prior to surgery, allowing for hypertension control, organ recovery, and volume re-expansion. Current first line therapy is phenoxybenzamine, a long-acting, irreversible, non-selective alpha-adrenergic blocking agent that is usually initiated at 10–20 mg/day orally and increased in 10 mg divided intervals every 3–4 days as necessary for blood pressure control. Some patients might require >300 mg/day, and several weeks may be necessary to achieve proper blockade. The end points are resolution of episodic symptoms and hypertensive swings, with blood pressure in the normal to near normal range. Side effects include orthostasis, nasal stuffiness, and fatigue. Although there are different practice patterns, the conservative approach would place the timing of surgery 7–14 days after achieving proper blockade. One study suggests the risk of all peri-operative complications is reduced if pre-operative systolic BP ≤ 140 mmHg [14]. If the patient has any end organ damage (cardiomyopathy, myocarditis, renal failure, etc.), surgery should be delayed until organ recovery has occurred.

Beta-blockade is not necessary in most patients and should not be arbitrarily used. Since cardiovascular collapse is a major risk during the peri-operative period, avoiding unnecessary negative inotropic drugs is desirable. Additionally, pheochromocytoma patients with cardiomyopathy or myocarditis recover with the use of alpha-blockade alone, making the use of beta-blockade for myocardial remodeling unnecessary. Beta-blockade should be started for persistent tachycardia (not transient tachycardia with orthostasis). Most importantly, beta-blockade should not be used as part of the antihypertensive regimen. It has long been emphasized that beta-blockers should be avoided before adequate alpha-blockade, as inhibition of peripheral vasodilation, negative inotropy, inhibition of catecholamine metabolism, and subsequent unopposed alpha-adrenergic stimulation could lead to catastrophic vasoconstriction and morbidity/mortality. While this position is generally true, there are rare exceptions, e.g. if tachyarrhythmia is the primary problem.

Calcium channel blockers can also be used as adjuncts to control hypertension. They do not appear to completely prevent hemodynamic lability, but have been associated with low morbidity and mortality [15]. Catecholamine synthesis inhibition with metyrosine can effectively reduce catecholamine excretion by 50–80%. Unfortunately, it is not universally used for patients with resectable tumours because of significant side effects (sedation, diarrhoea, depression, confusion, crystalluria, extrapyramidal reactions) and dangerous rebound effects with abrupt drug cessation; cardiac arrest being the most extreme reported consequence.

Fluid management pre-operatively does not need to be aggressive. Placing the patient on high volume intravenous fluids 24 hours before surgery is no longer recommended. Instead, volume deficits are replaced gradually as blood pressure normalizes during the 2 or more weeks of pre-operative alpha-blockade. In addition, there is significant heterogeneity of blood volume deficits among pheochromocytoma patients and is such that further fluid resuscitation can be achieved more safely in the operating room, when the patient is invasively monitored and continuously assessed.

While laparoscopic resection of intra-adrenal tumours of less than 6 cm is usually preferred, paragangliomas, and tumours of larger size may need open resection. Unless the margins of disease are resectable, there is no definitive cure for the treatment of malignant pheochromocytoma. If possible, metastatic lesions should be removed. Surgical intervention in unresectable malignant tumours is undertaken for symptom improvement and prolonged survival [16].

In pregnancy factors such as tumour location, size of the fetus, and co-morbidities should be considered. Successful antepartum laparoscopic tumour removal has been reported in seven cases [17].

Understanding intra-operative management is key to post-operative care. Invasive monitoring during the surgical procedure is used for the risk of acute hypertensive crisis and arrhythmias secondary to induction, intubation, and tumour manipulation, as well as shock once the tumour is removed. Sudden cardiac arrest has been reported in 2–4% of patients, some cases occurring with induction of anaesthesia [14]. A 'central' arterial catheter (femoral or axillary) should be placed to measure blood pressure accurately during acute vasoconstriction, in addition to continuous $ScvO_2$/SvO_2 and cardiac output monitoring. Invasive catheters should be placed before induction of anaesthesia. Acute hypertensive episodes during direct tumour manipulation are expected despite adequate pre-operative preparation and proper anaesthetic technique, including adjunct epidural anaesthesia. Risk factors for intra-operative haemodynamic lability include tumour size >4 cm, higher pre-operative catecholamine concentrations, and >10 mmHg postural blood pressure drop after adequate alpha-blockade [18] and the magnitude of tumour manipulation that occurs during resection. Management of hypertensive crisis involves administration of rapidly-acting vasodilators through a central venous catheter.

Table 264.1 Treating hypertensive crisis. Titratable, short-acting medications (**bold**) are preferred

		Onset	Duration
Nitroprusside	NO donor	1	3–5 minutes
Nitroglycerin	NO donor	2–5	5–10 minutes
Fenoldopam	DA_1 agonist	4–5	<10 minutes
Clevidipine	Ca channel blocker	3–5	10 minutes
Esmolol	β_1 blocker	3–5	10 minutes
Phentolamine	α_1 α_2 blocker	15	1 hour
Nicardipine	Ca channel blocker	1–5	3–6 hours
Labetalol	β_1 β_2 α_1 blocker	≤5	3–6 hours
Urapidil	α_1 blocker	10	3–4 hours

Data from Cooper ZA and Mihm FG, 'Blood pressure control with fenoldopam during excision of a pheochromocytoma', *Anesthesiology*, 1999, **91**(2), pp. 558–60.

Nitroprusside, nitroglycerin, fenoldopam, and clevidipine share the desirable features of fast onset and offset (Table 264.1) [19]. Agents like phentolamine and nicardipine have been listed for comparison, but are not considered ideal agents for the rapidly changing physiology observed in the critical care setting. Esmolol is appropriate as an adjuvant to control tachycardia, but not hypertension. Magnesium sulphate has also been used to help control blood pressure, but there are limits to its use because of side effects (e.g. muscle relaxation). In some patients multiple agents may be necessary.

Box 264.1 Hypotension after pheochromocytoma tumour removal

- Reduced endogenous catecholamines.
- Receptor down regulation.
- Residual α receptor blockade.
- Residual β receptor blockade.
- Exogenous vasodilators.
- Vena caval compression (surgical retraction).
- Hypovolaemia.
- Adrenal insufficiency (in setting of bilateral adrenalectomy).
- Anaesthetic depth.
- Regional block (epidural-induced sympathectomy).
- Vasopressin deficiency.

Shock may develop immediately after removal of the tumour resulting in the need for post-operative vasopressors/inotropes. In some cases, hypotension develops less precipitously several hours after surgery. After adequate fluid resuscitation, if the patient appears vasoplegic (normal stroke volume/cardiac output, but low arterial pressure), vasopressin is recommended to avoid competing with residual alpha-blockade. If the patient has low cardiac output despite fluid resuscitation, epinephrine is recommended. Multiple causes of the hypotension may play a part in an individual patient (Box 264.1).

Patients should also be monitored post-operatively for hypoglycaemia, a complication noted after removal of catecholamine inhibition of insulin secretion. After tumour resection, it can take up to 1 week for normalization of catecholamine levels, as excess catecholamines leech out of storage granules throughout the body. Patients who remain hypertensive may have residual tumour (unlikely) or essential hypertension that will respond to conventional treatment.

Insulinoma

These rare, mostly benign pancreatic islet cell tumours can lead to profound hypoglycaemia. One cohort study reported a 6% incidence of insulinoma in the setting of multiple endocrine neoplasia (MEN) type I [20].

Patients present with neuroglycopenic symptoms such as confusion and amnesia, lethargy or loss of consciousness, and visual changes, in addition to palpitations, diaphoresis, and tremulousness. Most patients have fasting hypoglycaemia, but can also present with post-prandial hypoglycaemia [20]. They are often misdiagnosed with psychiatric or neurological disorders, such as seizures. If left untreated, patients face the risks of profound hypoglycaemia, coma, and death.

High serum insulin levels during episodes of hypoglycaemia confirms the diagnosis. Imaging techniques can be used to localize the tumour [20]. Initial treatment includes correction of hypoglycaemia with frequent glycaemic and neurological checks until surgical resection can be arranged. Up to 1200 mg of diazoxide in divided doses can be used to decrease insulin secretion while planning for tumour removal.

References

1. Kulke MH and Mayer RJ. (1999). Carcinoid tumors. *New England Journal of Medicine*, **340**(11), 858–68.
2. Modlin IM, Kidd M, Latich I, Zikusoka MN, and Shapiro MD. (2005). Current status of gastrointestinal carcinoids. *Gastroenterology*, **128**(6), 1717–51.
3. Anderson AS, Krauss D, and Lang R.(1997). Cardiovascular complications of malignant carcinoid disease. *American Heart Journal*, **134**(4), 693–702.
4. Braverman IM. (2002). Skin manifestations of internal malignancy. *Clinics in Geriatric Medicine*, **18**(1), 1–19.
5. Palaniswamy C, Frishman WH, and Aronow WS. (2012). Carcinoid heart disease. *Cardiology in Review*, **20**(4), 167–76.
6. Kvols LK, Moertel CG, O'Connell MJ, Schutt AJ, Rubin J, and Hahn RG. (1986). Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. *New England Journal of Medicine*, **315**(11), 663–6.
7. Dilger JA, Rho EH, Que FG, and Sprung J. (2004). Octreotide-induced bradycardia and heart block during surgical resection of a carcinoid tumor. *Anesthesia and Analgesia*, **98**(2), 318–20.
8. Kinney MA, Warner ME, Nagorney DM, et al. (2001). Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours. *British Journal of Anaesthesia*, **87**(3), 447–52.
9. Manger WM and Gifford RW. (2002). Pheochromocytoma. *Journal of Clinical Hypertension (Greenwich)*, **4**(1), 62–72.

10. Mihm FG. (1990). Catecholamines and myocardial damage. *Anesthesiology Review*, **17**, 25–35.
11. Jones AG, Evans PH, and Vaidya B. (2012). Phaeochromocytoma. *British Medical Journal*, **344**, e1042.
12. Mihm FG. (1998). Pheochromocytoma: decreased perioperative mortality. *Anesthesiology Clinics of North America*, **16**(3), 645–62.
13. Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, and Bornstein SR. (2004). The clinically inapparent adrenal mass: update in diagnosis and management. *Endocrine Reviews*, **25**(2), 309–40.
14. Plouin PF, Duclos JM, Soppelsa F, Boublil G, and Chatellier G. (2001). Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: analysis of 165 operations at a single center. *Journal of Clinical Endocrinology and Metabolism*, **86**(4), 1480–6.
15. Lebuffe G, Dosseh ED, Tek G, et al. (2005). The effect of calcium channel blockers on outcome following the surgical treatment of phaeochromocytomas and paragangliomas. *Anaesthesia*, **60**(5), 439–44.
16. Eisenhofer G, Bornstein SR, Brouwers FM, et al. (2004). Malignant pheochromocytoma: current status and initiatives for future progress. *Endocrine-related Cancer*, **11**(3), 423–36.
17. Zuluaga-Gomez A, Arrabal-Polo MA, Arrabal-Martin M, et al. (2012). Management of pheochromocytoma during pregnancy: laparoscopic adrenalectomy. *American Surgeon*, **78**(3), E156–8.
18. Bruynzeel H, Feelders RA, Groenland TH, et al. (2010). Risk factors for hemodynamic instability during surgery for pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism*, **95**(2), 678–85.
19. Cooper ZA and Mihm FG. (1999). Blood pressure control with fenoldopam during excision of a pheochromocytoma. *Anesthesiology*, **91**(2), 558–60.
20. Placzkowski KA, Vella A, Thompson GB, et al. (2009). Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007. *Journal of Clinical Endocrinology and Metabolism*, **94**(4), 1069–73.

SECTION 11

The haematological system

PART 11.1

Laboratory monitoring

CHAPTER 265

The blood cells and blood count

Tyler J. Albert and Erik R. Swenson

Key points

- A blood smear is a rapid, reliable, and inexpensive test to examine the functional status of the bone marrow during cytopenic states.
- Haematopoiesis originates from the pluripotent stem cell, which undergoes replication, proliferation, and differentiation, giving rise to cells of the erythroid, myeloid, and lymphoid series, as well as megakaryocytes, the precursors to platelets.
- Red blood cells (RBCs) have a normal lifespan of only 120 days, requiring constant erythropoiesis with the essential factors being iron, zinc, folate, and vitamin B12, under the influence of erythropoietin, thyroxine, androgens, cortisol, and catecholamines. Many aspects of critical illness reduce the circulating lifespan of red cells.
- The white blood count represents a summation of several circulating cell types that have independent kinetics and regulation, each deriving from the haematopoietic stem cell, and together form the critical components of both the innate and adaptive immune systems.
- Platelets are not only integral to haemostasis, but aid our inflammatory and immune responses, help maintain vascular integrity, and contribute to wound healing.

Normal physiology

Blood is a dynamic fluid consisting of cellular and plasma components undergoing constant regeneration and recycling. The cellular components, including red blood cells (RBCs), white blood cells (WBCs), and platelets, all originate from the bone marrow, with plasma proteins primarily being synthesized in the liver. In the steady state, the bone marrow has an enormous production capacity, with an estimated production of more than 200 billion RBC, 10 billion WBC, and 400 billion platelets each day. Like most physiological systems, the concentrations of these components are tightly regulated within narrow limits under normal conditions (Table 265.1). In the critically-ill population, however, the haematological abnormalities frequently recognized are predominantly quantitative, with qualitative defects being less common, but nonetheless important. Likewise, these haematological abnormalities are thought to be due to non-haematological single- or multiple-organ pathology. Acquired defects are much more common than congenital defects, and multiple abnormalities of both cellular and haemostatic components are more frequent than the single defects usually identified in routine haematological practice. A rapid, reliable and inexpensive method of examining haematological disorders is the peripheral blood smear, which allows practitioners to assess the functional status of the bone marrow, especially during cytopenic states [1].

Anatomically, the cellular components comprise cells in circulating blood, bone marrow, lymph nodes, and the spleen. RBCs are primarily concerned with oxygen and carbon dioxide transport, WBC with immunity and infection control, and platelets with maintaining vascular integrity and haemostasis. The haemostatic system is responsible for maintaining blood fluidity and, at the same time, prevents blood loss by initiating rapid, localized, and appropriate blood clotting at sites of vascular damage. This system is complex, comprising both cellular and plasma elements, i.e. platelets, coagulation, and fibrinolytic cascades, the natural intrinsic and extrinsic pathways of anticoagulation, and the vascular endothelium.

Haematopoiesis, the process by which RBCs, WBCs, and platelets are produced, occurs in adults within the marrow spaces of the bones of the axial skeleton. Haematopoiesis originates from the pluripotent stem cell, which has the capacity to maintain stem cell

Table 265.1 Normal haematological indices

Haemoglobin (g/dL)	M	13.0–16.5
	F	11.5–15.5
Haematocrit	M	0.40–0.50
	F	0.37–0.47
Red blood cells ($\times 10^{12}$/L)	M	3.8–5.6
	F	3.4–5.2
Mean corpuscular volume (fl)		84–99
Reticulocytes ($\times 10^{9}$/L)		20–70 (0.5–1.6%)
Red cell mass (mL/kg)	M	25–35
	F	20–30
Plasma volume (mL/kg)		35–45
White blood cells ($\times 10^{9}$/L)	Total	4.0–10.15
	Neutrophils	2.0–8.0
	Lymphocytes	1.0–4.0
	Monocytes	0.1–0.8
	Eosinophils	0.1–0.5
	Basophils	0.01–0.1
Platelets ($\times 10^{9}$/L)		150–400

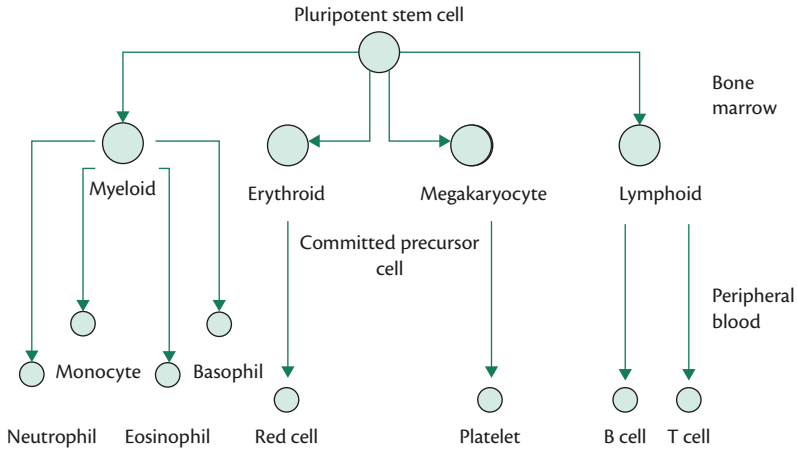


Fig. 265.1 Outline of haematopoietic development.

numbers through replication and proliferation. Furthermore, the stem cell is able to undergo differentiation, giving rise to cells of the erythroid, myeloid, and lymphoid series, as well as megakaryocytes, the precursors to platelets (Fig. 265.1).

Development and differentiation of haemopoietic stem cells is under the control of glycoprotein cytokines, which operate in a paracrine or endocrine fashion. These act at early, intermediate, and late stages of cell differentiation, target cell responsiveness depends upon both cytokine production, and expression of specific receptors on the target cells. Early-acting cytokines include stem cell factor and interleukin 3, while cytokines acting on more differentiated cells include granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), thrombopoietin, platelet growth factor, and erythropoietin, produced in the kidney and controlling erythropoiesis. Availability of human recombinant forms of these proteins has resulted in their usage in the treatment of anaemic and neutropenic states under some circumstances. There are also inhibitory cytokines (e.g. tumour necrosis factor, transforming growth factor, and probably, interleukin 2), which act in a negative regulatory manner to inhibit haematopoiesis. These are implicated in pathological conditions resulting in the suppression of haematopoiesis, in particular the anaemia of chronic disease.

Red blood cells

Erythrocytes are the most common circulating haemopoietic cells. The precursor forms within the marrow are nucleated, but when released into the peripheral blood, they no longer contain a nucleus or mitochondria. Red cells have a finite lifespan of around 120 days, at which time they are destroyed primarily in the reticuloendothelial system. Red cells recently released from the bone marrow contain trace amounts of ribonucleic acid (RNA) that can be stained with supravital stains and recognized as reticulocytes. The reticulocyte count can give a vital insight into the synthetic function of the marrow. Red cell numbers can be decreased by loss from the body (haemorrhage), failure of synthesis due to primary marrow disease or deficiency of iron, vitamin B12, and folate, depressed erythropoiesis in the anaemia of chronic disease, and premature red cell destruction (haemolysis). Measurement of haemoglobin concentration depends not only on the number of red cells present and their individual haemoglobin content, but also on the plasma volume in which they are distributed. A diminished plasma volume will spuriously elevate haemoglobin, and depletion of red cells and haemoglobin will be masked if there is concomitant loss of plasma volume. Consequently, measurement of plasma volume and red cell mass using isotopic techniques can sometimes be highly informative.

The efficient blood transport of oxygen and carbon dioxide is critically dependent upon the O_2, CO_2, and H^+ binding properties of haemoglobin (Hb). These are facilitated by the enzyme carbonic anhydrase, RBC specific membrane and cytoplasmic proteins, and by the unique intracellular RBC environment, including the modulation of Hb-O_2 affinity by 2,3-diphosphoglycerate (2,3-DPG) and maintenance of redox state stability. Packaging the majority of the blood's O_2 and CO_2 transport capacity in the RBC reduces the effective viscosity of blood by two-thirds in comparison to a cell-free medium of equivalent transport capacity and prevents loss of haemoglobin, carbonic anhydrase, and 2,3-DPG via glomerular filtration. RBCs also have potent anti-oxidant capacity, enhance haemostasis by directing platelets towards the vessel wall, and minimize haemoglobin–nitric oxide (NO) scavenging by sequestrating Hb away from direct contact with the endothelium of resistance arterioles. Finally, RBCs contribute to microcirculatory vasoregulation by both haemoglobin-independent and haemoglobin saturation-dependent vasodilator release [2].

RBC rheology contributes to vasoregulation, particularly at the microvascular level [3]. In addition to tissue and endothelial cell contributions to vascular tone, mediated in part by tissue oxygenation, rheology has an influence on vascular tone by altering wall shear stress and nitric oxide generation, as well as homogenizing flow distribution at capillary branch points. Local blood flow and metabolic demand are matched by three recently identified mechanisms involving RBCs and haemoglobin. First, bioactive NO is produced in proportion to the concentration of deoxyhaemoglobin acting as a nitrite reductase [4]. Secondly, NO is bound by oxyhaemoglobin in the lungs and released by deoxyhaemoglobin in the tissues, mediated by reversible allosteric S-nitrosylation of beta chain cystein-93 in haemoglobin [5]. Thirdly, mechanical deformation of RBCs and desaturation of haemoglobin initiates vasodilation by release of ATP, which binds to endothelial cell purinergic receptors and stimulates NO synthesis [6]. The redundancy of these mechanisms highlights the probable critical contribution of healthy

RBCs to active vasoregulation at the microvascular level. However, this function may be compromised both by anaemia and by pathological RBC changes occurring in critical illness and during storage of allogeneic blood [2].

With a lifespan of only 120 days, caused by accumulative radical oxygen species (ROS)-mediated damage and age-related loss of intrinsic antioxidant defences [7], there must be a constant production of new RBCs. The essential factors for erythropoiesis include iron, zinc, folate, and vitamin B12, under the influence of erythropoietin, thyroxine, androgens, cortisol, and catecholamines. RBC formation occurs at a basal rate of 15–20 mL/day under steady-state conditions, and upwards of 200 mL/day after haemolysis or heavy blood loss in iron-replete healthy persons [8]. Normal RBC ageing leads to changes in membrane characteristics (reduced fluidity and deformability), loss of volume and surface area, increased cell density and viscosity, and deleterious alterations in the intracellular milieu (decreased ATP and 2,3-DPG, and lowered hexokinase and glucose-6-phosphate dehydrogenase activity). These lead to a fall in cellular energy level, increased Hb-oxygen affinity, reduced repair of oxidant injury and diminished ability of cells to deform normally during microvascular transit [9]. These changes also mark RBCs for removal by the spleen and reticuloendothelial system (RES). Alterations in rheology with normal ageing may occur even sooner in the lifespan of the RBC in critically-ill patients, and have been shown to be associated with poor outcomes [10]. In many regards, these changes in red cell characteristics occur when red cells are stored for transfusion purposes and likely account for the markedly shorter lifespan of these cells when transfused [2].

Other determinants of RBC survival include the premature death of mature RBCs (eryptosis), and removal of RBCs just released from the marrow (neocytolysis). Eryptosis is thought to be partially triggered by excessive oxidant RBC injury, among other stressors, and is inhibited by EPO, which thus extends the life span of circulating RBCs [11]. This apoptosis-like process is characterized by a cascade of biochemical and biomechanical changes, leading to cell shrinkage, dysregulation of normal membrane asymmetry with exposure of normally sequestered phosphatidylserine on the outer membrane leaflet, and the formation of membrane blebs and microparticles. Phosphatidylserine marks cells for engulfment by macrophages and may carry important downstream effects related to inflammation, coagulation, cell signalling, and/or immune modulation. Conversely, excessive eryptosis may lead to the development of anaemia [12]. Neocytolysis is a physiological process first noted in the study of anaemia that develops during spaceflight (microgravity) and of polycythaemia correction with descent from high altitude; as both processes develop too rapidly to be solely accounted for by reduced erythropoiesis. This regulation of red cell mass by selectively removing young circulating erythrocytes is initiated by a sudden fall in EPO levels allows for fine control of the number of circulating erythrocytes under steady-state conditions and relatively rapid adaptation to new environments or conditions, where polycythaemia would no longer be advantageous [13]. Eryptosis and neocytolysis, negatively regulated by EPO and acting at different points in the life span of the RBC, provide flexibility in regulating total red cell mass [2].

White blood cells

The white blood count represents a summation of several circulating cell types that have independent kinetics and regulation, each deriving from the haematopoietic stem cell, together forming the critical components of both the innate and adaptive immune systems. WBC are divided into five groups—neutrophils, monocytes, eosinophils, basophils (collectively referred to as the myeloid cells), and lymphocytes.

Neutrophils, which form the majority of WBC, have a relatively short half-life of about 6 hours and function primarily as a defence mechanism against pathogenic bacteria. The differentiation of stem cells into mature neutrophils takes approximately 3 weeks, but this period can be compressed in the case of stress or under the influence of cytokines such as G-CSF. During this time the cell progresses through a number of identifiable stages: myeloblast, promyelocyte, myelocyte, metamyelocyte, band, and ultimately neutrophil. Throughout this progression there is condensation of the nucleus, with mature neutrophils having segmented nuclei (thus the origination of the term polymorphonuclear leukocyte (PMN) as a synonym for a neutrophil). Additionally, there is a concurrent reduction of the nuclear-to-cytoplasm ratio and increasing cytoplasmic granularity. A significant portion of neutrophils are in a marginated (loosely adherent to the vascular wall), rather than circulating pool, which can be rapidly mobilized, leading to the rapid development of a neutrophilic leukoyctosis following physiological stress, infection, trauma, burns, and any state of increased sympathetic nervous system or increased glucocorticoid activity.

Lymphocytes, the next most populous WBC, are an integral part of the body's humoral and cellular immune system. Lymphocytes are responsible for adaptive immunity, meaning the capacity to recognize foreign proteins and pathogens in the absence of prior exposure in order to amplify specific responses to those pathogens, retaining a memory so that subsequent challenges are met with a more rapid and vigorous response. Lymphocytes can be divided into three major sublineages—B cells, T cells, and natural killer cells, each of which can be readily identified by monoclonal antibodies to characteristic surface antigens. B cells are particularly important in the humoral immune response, producing immunoglobulin proteins, which serve as receptors for antigen on the cell surface and are secreted as antibodies. T cells are primarily involved in the cellular immune response, as they bear T cell antigen receptor proteins on their surface and play diverse roles in coordinating immune responses and directly killing virus-infected cells. It is becoming increasingly clear that B and T cells must act together for efficient functioning of the body's immune system. Natural killer (NK) cells, making up a small percentage of circulating lymphocytes and can destroy target cells without adaptive specificity for foreign antigens. About 70% of blood lymphocytes are T cells, 10–15% B cells, with the remaining cells being unidentifiable or NK cells. Lymphyocytosis, an increase in circulating lymphocytes, can be a reactive response as in the setting of a viral or bacterial infection, or a clonal process, such as with a lymphoproliferative malignancy.

Eosinophils, basophils, and monocyte/macrophages make up the remaining WBCs, each of which is differentiated from myeloid precursor cells as mentioned previously. Eosinophilic differentiation parallels that of neutrophils, although eosinophils can be easily recognized by their large, red-staining granules with minimally-segmented, bi-lobed nuclei. Normally present in small numbers (less than 5% of WBCs), eosinophila can occur with various allergic states and in response to many parasitic infections. Basophils, comprising less than 1% of total WBCs, have very large,

blue-staining granules covering the cell with receptors for IgE on their surface. When an antigen-IgE interaction takes place the basophil releases histamine from its granules, which can lead to rhinitis, bronchospasm and angioedema. Basophilic leukocytosis is a rare condition most often associated with myeloproliferative disorders. Monocytes, the largest cells normally seen in the blood, have a distinctive folded nucleus with a greyish-blue cytoplasm replete with vacuoles. They are known to participate in host defence at several levels, migrating into inflammatory sites where they are further differentiated into macrophages, which then phagocytize any opsonized organisms.

Platelets

Platelets are highly organized and structured anucleate cells of myeloid origin that circulate in a resting state in the blood. The cells themselves are small and discoid-shaped, with a diameter between 1.5 and 3 μm, although younger platelets tend to be much larger. In response to activating signals, the quiescent platelet phenotype changes and these versatile effectors of host defence perform major haemostatic, inflammatory, and reparative functions [14]. They express specific surface glycoproteins allowing them to bind to adhesive endothelial, subendothelial, and plasma proteins. They can undergo adhesion, aggregation, and subsequently a release reaction, which liberates the contents of granules contained within their cytoplasm, resulting in augmentation of the aggregation reaction. Activated platelets also provide a negatively charged phospholipid surface upon which proteins of the coagulation cascade can assemble. Although they are individually very small, aggregated platelets form a platelet plug, which can block vascular defects and precipitate a stabilizing fibrin mesh over the top. To perform this task efficiently, platelets need to be present in sufficient numbers and have normal function. The normal platelet count in an adult is 150,000–400,000/μL, with two-thirds of platelets circulating in the blood and one-third sequestered in the spleen. The lifespan of a platelet in the circulation is 9–10 days, but in cases of accelerated destruction this can be much shorter, in some cases only minutes to hours, leading to severe thrombocytopenia. Normal haemostasis, assuming normal platelet function, is maintained with platelet counts above 50,000/μL; diminution below this level results in a progressively prolonged bleeding time. At levels below 10,000–20,000/μL there is a much heightened risk of spontaneous haemorrhage.

While platelets are the chief effector cells in haemostasis, they are known to play important roles in other functions as well, including promoting inflammatory and immune responses, maintaining vascular integrity, and contributing to wound healing. Platelets have been shown to recruit leukocytes and progenitor cells to sites of vascular injury and inflammation. They store, produce, and release pro- and anti-inflammatory, and angiogenic factors and microparticles into the circulation, and they spur thrombin generation. In experimental models these function have been shown to contribute to atherosclerosis, sepsis, hepatitis, vascular restenosis, acute lung injury, and transplant rejection [15].

References

1. Bain BJ. (2005). Diagnosis from the blood smear. *New England Journal of Medicine*, **353**, 498–507.
2. Hayden SJ, Albert TJ, Watkins TR, and Swenson ER. (2012). Anemia in critical illness: insights into etiology, consequences, and management. *American Journal of Respiratory & Critical Care Medicine*, **185**, 1049–57.
3. Baskurt OK, Yalcin O, and Meiselman HJ. (2004). Hemorheology and vascular control mechanisms. *Clinical Hemorheology and Microcirculation*, **30**, 169–78.
4. Cosby K, Partovi KS, Crawford JH, et al. (2003). Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation. *Nature Medicine*, **9**, 1498–505.
5. Hess DT, Matsumoto A, Kim SO, Marshall HE, and Stamler JS. (2005). Protein S-nitrosylation: purview and parameters. *Nature Reviews Molecular Cell* Biology, **6**, 150–66.
6. Sprague RS, Ellsworth ML, Stephenson AH, and Lonigro AJ. (1996). ATP: the red blood cell link to NO and local control of the pulmonary circulation. *American Journal of Physiology*, **271**, H2717–22.
7. Kurata M, Suzuki M, and Agar NS. (1993). Antioxidant systems and erythrocyte life-span in mammals. *Comparative Biochemistry and Physiology, Part B*, **106**, 477–87.
8. Hillman RS and Henderson PA. (1969). Control of marrow production by the level of iron supply. *Journal of Clinical Investigations*, **48**, 454–60.
9. Staubli M, Ott P, Waber U, et al. (1985). Erythrocyte adenosine triphosphate depletion during voluntary hyperventilation. *Journal of Applied Physiology*, **59**, 1196–200.
10. Sakr Y, Dubois MJ, De Backer D, Creteur J, and Vincent JL. (2004). Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Critical Care Medicine*, **32**, 1825–31.
11. Myssina S, Huber SM, Birka C, et al. (2003). Inhibition of erythrocyte cation channels by erythropoietin. *Journal of the American Society of Nephrology*, **14**, 2750–7.
12. Lang F, Lang KS, Lang PA, Huber SM, and Wieder T. (2006). Mechanisms and significance of eryptosis. *Antioxidants & Redox Signaling*, **8**, 1183–92.
13. Rice L and Alfrey CP. (2005). The negative regulation of red cell mass by neocytolysis: physiologic and pathophysiologic manifestations. *Cellular Physiology and Biochemistry*, **15**, 245–50.
14. Bozza FA, Shah AM, Weyrich AS, and Zimmerman GA. (2009). Amicus or adversary: platelets in lung biology, acute injury, and inflammation. *American Journal of Respiratory Cell and Molecular Biology*, **40**, 123–34.
15. Smyth SS, McEver RP, Weyrich AS, et al. (2009). Platelet functions beyond hemostasis. *Journal of Thrombosis and Haemostasis*, **7**, 1759–66.

CHAPTER 266

Coagulation monitoring

Gerhardus J. A. J. M. Kuiper and Hugo ten Cate

Key points

- Knowledge of the coagulation and fibrinolysis cascade, and the interaction with and function of platelets is imperative for haemostasis monitoring and interpreting the laboratory results obtained.
- Primary haemostasis is dependent on platelet levels and function, while in secondary haemostasis fibrin formation is the ultimate goal with thrombin as its central controlling enzyme.
- Fibrinolysis is the breakdown of the fibrin mesh, a process regulated in part by thrombin.
- Point-of-care (POC) monitoring of haemostasis can be done with an array of devices each with its pros and cons. The main advantage over conventional laboratory assessment is that POC monitoring can be done at the bedside and with a shorter turnaround time.
- Acquired haemostasis disorders and the use of (oral) anticoagulants, antiplatelet, or prohaemostatic drugs are frequently seen in patients on the intensive care unit. Monitoring of these patients should be based on both classical and novel haemostasis monitoring techniques.

Haemostasis: platelets and the coagulation and fibrinolysis cascade

Haemostasis is a dynamic process between blood constituents and the vessel wall required to stop bleeding after vessel wall damage (Fig. 266.1). The involvement of platelets is classically described as primary haemostasis, while the coagulation proteins are responsible for secondary haemostasis. The breakdown of a blood clot is mediated by so-called fibrinolysis [1].

Platelets have several receptors for the activation of platelets, the adherence to collagen, and the aggregation with other platelets. In vivo, vessel wall damage exposes collagen to platelets, to which they can adhere through glycoproteins including the GPIb receptor with von Willebrand factor (vWF) as a co-factor. Other activators are thrombin, arachidonic acid, epinephrine, and adenosine diphosphate (ADP). Upon activation, platelets aggregate via GPIIb/IIIa receptors with other platelets through fibrinogen and vWF.

Vessel wall damage also exposes tissue factor (TF). Coagulation factor VII (FVII) is activated by TF and this complex can activate factor X (FX), with FV as its cofactor, in order to convert prothrombin into thrombin. This is classically described as the extrinsic route. Activation of the intrinsic route is achieved by contact activation via negatively charged surfaces in vitro and by compounds like polyphosphates in vivo. Activated FXII starts an intrinsic cascade through activation of FXI, which yields activated FIX. FIXa, with FVIIIa as its cofactor, activates FX and this again leads to prothrombin conversion. Thrombin stimulates fibrin and FXIIIa formation, which stabilizes fibrin via cross-links. Thrombin as the central coagulation enzyme has pro-, as well as anticoagulant properties, thereby balancing the haemostatic system. Thrombomodulin (TM), an endothelial receptor, binds thrombin and hereby inactivates thrombin's procoagulant properties. Protein C, activated via this thrombin–thrombomodulin complex, can inactivate FVa and FVIIIa. Circulating antithrombin attenuates thrombin formation by neutralizing FXa and thrombin, while tissue factor pathway inhibitor (TFPI) inactivates FXa when in complex with TF-FVIIa.

The fibrin mesh is degraded by plasmin, resulting from the action of tissue-type plasminogen activator (tPA), released from endothelial cells, on plasminogen. Likewise, urokinase is a potent fibrinolysis activator. Thrombin inhibits fibrinolysis via thrombin activatable fibrinolysis inhibitor (TAFI) when bound to TM, while platelets secrete plasminogen activator inhibitor (PAI)-1 and 2, which inhibit tPA and urokinase, respectively. Fibrin is degraded into fragments called fibrin degradation products (FDP's). D-dimer is an FDP in which the cross-link is still present.

Classical coagulation monitoring

In primary haemostasis testing various laboratory assays are adopted to reflect the function of platelets. In short, for effective primary haemostasis, a sufficient number of functional platelets need to be present in the body. First of all, a platelet count is indispensable, however, this does not adequately reflect the function of the respective platelets. Mean platelet volume (MPV) gives information on the volume of the platelets, reflecting the turnover of platelets and their reactivity. A high MPV could indicate a high platelet turnover due to increased production of platelets from bone marrow-derived megakaryocytes. A low MPV is usually an indication of less reactive platelets or due to splenic sequestration. The gold standard in platelet function testing is light transmission aggregometry (LTA). The test needs, however, a sufficient number of platelets to be reliable, while interpretation of the results is merely based on expertise, rather than specific cut-off values. The bleeding time test (the Ivy method), being the only in vivo platelet function test, is poorly reproducible. A prolonged bleeding time could indicate a platelet dysfunction. However, a normal test does not rule out a platelet disorder.

For monitoring secondary haemostasis the prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), and reptilase time (RT) reflect disorders in specific steps of the coagulation cascade. The PT is activated by adding TF, the aPTT

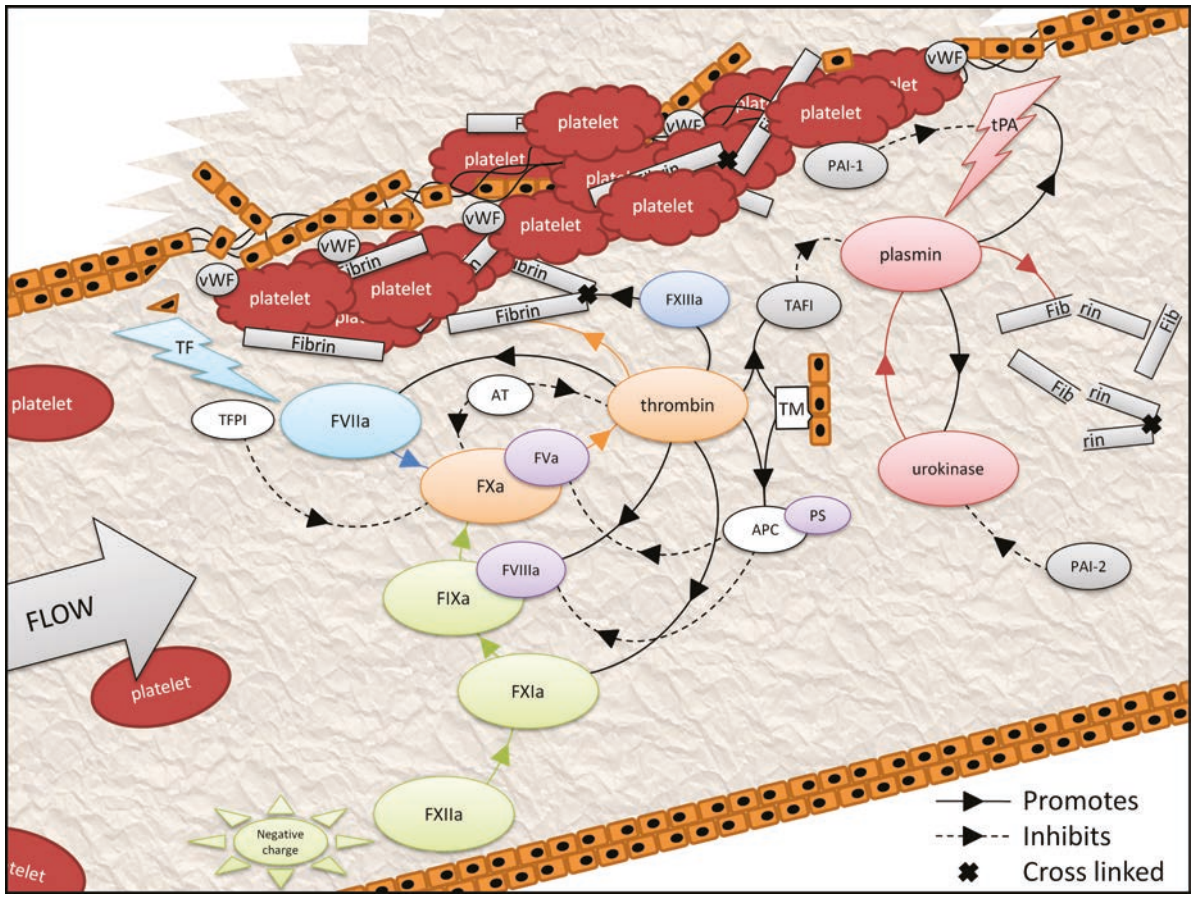


Fig. 266.1 Graphical representation of coagulation in vivo.

APC, activated protein C; AT, antithrombin; F[#]a, activated factor [#]; PAI-1/2, plasminogen activator inhibitor 1/2; PS, protein S; TAFI, thrombin activatable fibrinolysis inhibitor; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TM, thrombomodulin; tPA, tissue type plasminogen activator; vWF, von Willebrand factor.

Pathways: Light blue, extrinsic pathway; green, intrinsic pathway; orange, common pathway; red, fibrinolytic pathway; white, anticoagulant proteins; purple, cofactors; dark blue, fibrin cross-linking by FXIIIa; black lines and arrows, feedback loops.

by a contact activator. The international normalized ratio (INR) is a ratio of the PT of the local laboratory compared with a standardized reference PT. Prolonged PT and aPTT test are normally accompanied by a bleeding tendency (Table 266.1), although the presence of the lupus anticoagulant, which is an antibody, is paradoxically associated with a thrombotic tendency. An aPTT prolongation due to FXII deficiency does not exert in a bleeding or thrombotic tendency. The TT is measured by directly adding thrombin to plasma, which triggers fibrin formation. The TT is thus sensitive to fibrinogen, but also to FDP's (which themselves inhibit fibrin polymerization) and to heparin therapy. RT is similar to TT, but insensitive to heparin. Lastly, levels and activities can also be measured for each separate coagulation factor.

Fibrinolysis is frequently monitored by measuring d-dimer levels (or FDP's), fibrinogen levels, and the euglobulin clot lysis time. Excessive clot breakdown will result in low fibrinogen levels and high d-dimer or FDP levels. D-dimer has a low specificity, thereby making it only suitable to exclude (ongoing) fibrinolysis for the diagnosis in patients. Fibrinogen, as an acute phase protein, can be elevated in a wide variety of diseases. The euglobulin clot lysis time is an elaborate test in which the overall lysis potential of a formed clot can be quantified. A shortened euglobulin clot lysis time is an indication of potential hyperfibrinolysis.

Point-of-care coagulation monitoring

Point-of-care monitoring (POC) provides simple, rapid bedside testing for various laboratory tests. In coagulation monitoring the activated clotting time (ACT), a viscoelasticity measuring technique (TEG, ROTEM, or Sonoclot systems), and platelet function tests are widely-used, whole blood tests for coagulation monitoring.

In the ACT test, native whole blood is activated via the intrinsic pathway by either kaolin or celite. The time to form a clot is the ACT given in seconds. The ACT is used in cardiothoracic surgery to monitor unfractionated heparin therapy and its reversal by protamine sulphate. The ACT is less sensitive to therapy with low molecular weight heparins and insensitive to pentasaccharide therapy [2].

The TEG (thromboelastography) and ROTEM (rotational thromboelastometry) systems are the most widely used whole blood viscoelasticity devices, together with the Sonoclot [3]. The basic principle is that citrate anticoagulated whole blood is activated after recalcification with either an extrinsic or intrinsic activator in a measuring cuvette. While the blood starts to clot, the device measures the strength of the clot formed and plots the strength at each point in time in a graph. Each device has its own parameters, but all three display the time till the fibrin clot starts to form, the

Table 266.1 Causes of PT and aPTT test abnormalities

PT (extrinsic pathway)	aPTT (intrinsic pathway)	Possible cause
Prolonged	Normal	FVII deficiency or inhibitor
		Vitamin K deficiency or vitamin K antagonist therapy
		Liver disease
Normal	Prolonged	FVIII, FIX, and FXI deficiencies or inhibitors (haemophilia A/B/C)
		FXII, prekallikrein, or HMW kininogen deficiencies or FXII inhibitor
		Von Willebrand disease
		Heparin therapy
		Lupus anticoagulant
Prolonged	Prolonged	FX, FV, prothrombin, and fibrinogen deficiencies or inhibitors
		Disseminated intravascular coagulation, trauma-induced coagulopathy
		Combined VKA and heparin therapy

maximum clot strength achieved, and the time it takes to dissolve the formed clot [3]. For instance, the maximum clot strength is the resultant of both platelets and fibrin involved in the formed clot. The decline of the maximum clot strength is again influenced by both platelets (clot retraction) and fibrin (fibrinolysis) [4]. Each system has its own specific measuring principle, its own nomenclature, and (dis)advantages compared with the other two. The consequence is that, thus far, results cannot be interchanged between systems [3,5]. Correlations between some viscoelasticity parameters and standard coagulation tests are fairly good, making the need for standard coagulation tests redundant in certain scenarios [3].

Other POC tests are specially developed for platelet function measuring in whole blood [6]. All these operate according to the same basic principle—whole blood is put in a measuring cuvette and the platelet receptors are then activated by a reagent, aggregating the platelets. This alteration of the platelets is detected by the device. However, normal haematocrit and platelet levels are imperative for platelet function testing either by POC or LTA [7].

Coagulation monitoring in critical care diseases

Coagulation disorders seen in critical care are classically divided into bleeding, thrombosis, or a combination. Monitoring of the three disorders is highlighted in the following paragraphs.

Trauma-induced coagulopathy (TIC) is often referred to as consisting of a lethal triad. Massively bleeding trauma patients present with hypothermia and acidosis. Fluid resuscitation leads to a dilutional coagulopathy completing the triad [8]. This is further aggravated by endothelial damage, releasing tPA and thrombomodulin in abundance, resulting in anticoagulation and hyperfibrinolysis [9]. Classic laboratory coagulation tests for TIC include PT, aPTT, platelet count, and fibrinogen levels. The first coagulation factor to fall below a critical value is fibrinogen [8]. In colloid use fibrinogen levels are overestimated and platelet function is impaired [10]. Low platelet counts in TIC hinder platelet function testing. The use of viscoelasticity measurements in trauma or massive transfusion cases is advocated by many, although evidence for a favourable outcome is thus far scarce [11].

A mixed bleeding-thrombosis condition is DIC (disseminated intravascular coagulation). In overt DIC excess thrombin is produced, resulting in microvascular thrombosis due to failure of the natural anticoagulant mechanisms. This condition can be accompanied by bleeding due to a depletion of coagulation proteins and platelets [12]. In the early phase of DIC, fibrinolysis is often impaired due to high PAI-1 levels, while hyperfibrinolysis is present in late DIC. The diagnosis is based on classical coagulation tests incorporated in a scoring system [13]. Subsequent monitoring should focus on platelet levels and function over time, on the fibrinogen levels, and PT during DIC. Viscoelasticity measurements could help in monitoring hypo- or hyperfibrinolysis.

Haemolysis, **e**levated **l**iver enzymes and **l**ow **p**latelets (HELLP) is a syndrome complicating around 0.5% of all pregnancies. Monitoring for the presence of DIC and MPV, as a marker for platelet function and consumption, together with platelet levels and POC platelet function testing is advocated [14].

Coagulation monitoring in medication use

Antiplatelet and (oral) anticoagulant drugs are frequently used on the ICU or by patients at home. The effect of antiplatelet drugs can be monitored with platelet function tests, either by LTA or POC [6]. Vitamin K antagonist monitoring and dose-adjustment is done via the INR. Heparin treatment can be monitored by measuring anti-FXa levels for any type of heparin including pentasaccharides, while aPTT is only suitable in unfractionated heparin use [2]. A complication of heparin administration is HIT (heparin-induced thrombocytopenia). In HIT suspected patients, the 4T's scoring system followed by specialized laboratory analysis is applied [15]. New oral anticoagulants (NOACs) are emerging on the market targeted at inhibiting thrombin or FXa. It is advocated that monitoring is unnecessary, although in clinical practice there is growing demand for laboratory tests to monitor these NOACs, certainly in critical situations [16]. For screening in acute situations, some of the conventional coagulation tests may still be useful, provided that the reagents are sufficiently sensitive. For quantitative measurement, specific anti-FXa-based chromogenic assays (Xa-directed NOACs) or thrombin sensitive clotting methods (for thrombin-directed NOAC) should be used [17].

In TIC and in the peri-operative setting prohaemostatic therapy can be given in many forms [18]. Monitoring of prohaemostatic therapy is focused on platelet levels and function, fibrinogen levels, classical coagulation tests, and viscoelasticity measurements. Fibrinogen levels can decline rapidly due to thrombolytic therapy in stroke or venous embolism, resulting in an acquired bleeding tendency.

References

1. Tanaka KA, Key NS, and Levy JH. (2009). Blood coagulation: hemostasis and thrombin regulation. *Anesthesia and Analgesia*, **108**(5), 1433–46.
2. Linkins LA, Julian JA, Rischke J, Hirsh J, and Weitz JI. (2002). In vitro comparison of the effect of heparin, enoxaparin and fondaparinux on tests of coagulation. *Thrombosis Research*, **107**(5), 241–4.

3. Ganter MT and Hofer CK. (2008). Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. *Anesthesia and Analgesia*, **106**(5), 1366–75.
4. MacDonald SG and Luddington RJ. (2010). Critical factors contributing to the thromboelastography trace. *Seminars in Thrombosis and Hemostasis*, **36**(7), 712–22.
5. Venema LF, Post WJ, Hendriks HG, Huet RC, De Wolf JT, and De Vries AJ. (2010). An assessment of clinical interchangeability of TEG and RoTEM thromboelastographic variables in cardiac surgical patients. *Anesthesia and Analgesia*, **111**(2), 339–44.
6. Breet NJ, van Werkum JW, Bouman HJ, et al. (2010). Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *Journal of the American Medical Association*, **303**(8), 754–62.
7. Stissing T, Dridi NP, Ostrowski SR, Bochsen L, and Johansson PI. (2011). The influence of low platelet count on whole blood aggregometry assessed by Multiplate. *Clinical and Applied Thrombosis/Hemostasis*, **17**(6), E211–17.
8. Erber WN and Perry DJ. (2006). Plasma and plasma products in the treatment of massive haemorrhage. *Best Practice and Research Clinical Haematology*, **19**(1), 97–112.
9. Brohi K, Cohen MJ, and Davenport RA. (2007). Acute coagulopathy of trauma: mechanism, identification and effect. *Current Opinion in Critical Care*, **13**(6), 680–5.
10. Kozek-Langenecker SA. (2005). Effects of hydroxyethyl starch solutions on hemostasis. *Anesthesiology*, **103**(3), 654–60.
11. Afshari A, Wikkelso A, Brok J, Moller AM, and Wetterslev J. (2011). Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. *Cochrane Database of Systematic Reviews*, (3), CD007871.
12. Ten Cate H, Timmerman JJ, and Levi M. (1999). The pathophysiology of disseminated intravascular coagulation. *Thrombosis and Haemostasis*, **82**(2), 713–17.
13. Toh CH and Hoots WK. (2007). The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. *Journal of Thrombosis and Haemostasis*, **5**(3), 604–6.
14. Kuiper GJ, Lance MD, Smit-Fun VM, Peeters LL, and Marcus MA. (2011). Platelet monitoring follow-up in a pregnant patient with HELLP syndrome. *Platelets*, **22**(2), 160–3.
15. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, and Greinacher A. (2006). Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *Journal of Thrombosis and Haemostasis*, **4**(4), 759–65.
16. Ten Cate H. (2012). Monitoring new oral anticoagulants, managing thrombosis, or both? *Thrombosis and Haemostasis*, **107**(5), 803–5.
17. Tripodi A. (2013). The laboratory and the new oral anticoagulants. *Clinical Chemistry*, **59**(2), 353–62.
18. Levy JH and Tanaka KA. (2008). Prohemostatic agents to prevent perioperative blood loss. *Seminars in Thrombosis and Hemostasis*, **34**(5), 439–44.

PART 11.2

Haematological therapies

CHAPTER 267

Blood product therapy in the ICU

Lirong Qu and Darrell J. Triulzi

Key points

- Avoid unnecessary transfusion through adhering to the evidence-based transfusion guidelines. A restrictive red blood cell (RBC) transfusion strategy (haemoglobin < 7 g/dL) is recommended for haemodynamically stable patients in the critical care setting.
- Optimal haemoglobin threshold for patients with acute coronary syndrome has yet to be determined.
- Plasma transfusion for an invasive procedure has not been shown to be of benefit in patients with international normalized ratio <2.0.
- The target platelet count for a bleeding patient or for an invasive procedure is 50,000/dL.
- The risk of transfusion transmitted human immunodeficiency virus (HIV) and hepatitis C virus (HCV) or hepatitis B virus infections is less than 1 in a million; other risks such as transfusion-associated circulatory overload (TACO) and, to a lesser extent, transfusion-related acute lung injury (TRALI), are much more common.

Introduction

Blood transfusion is a frequent intervention in critically-ill patients. Major progress has been made in blood safety over the last two decades. This chapter will provide a brief updates on the evidence-based indications for blood product transfusion, as well as its attendant risks.

Anaemia in intensive care settings

Anaemia is prevalent in the critically ill patients. Its etiology is multifactorial including a shortened life span for the circulating RBC and diminished RBC production (1). The body responds to anaemia by employing compensatory mechanisms such as increase cardiac output, increased tissue oxygen extraction, right-shift of oxyhaemoglobin disassociation curve via increased 2,3 DPG in the red cells, and increased red cell production. Although there is an association between anaemia and poor outcomes in patient with various chronic diseases, it remains uncertain as to whether anaemia is an independent predictor of poor outcomes or merely a marker of severity of underlying condition (1). The optional management of anaemia in critically ill patients is a topic of much controversy and ongoing research.

Blood components

Currently, whole blood is processed into blood components (RBC, platelets, and plasma) so that each component can be stored at its optimal condition and patients receive only the specific blood components they need. Automatic cell separation (apheresis) technology can also be used to collect red cells, platelets, and/or plasma. A single apheresis platelets (single donor platelets) collection or 4–5 units of pooled platelets contains sufficient numbers of platelets for a therapeutic dose in an adult patient.

The shelf-life of RBC component is determined by the anticoagulant and preservative used. The most commonly used additive solution (ADSOL®) allows for up to 42 days of storage at 4°C (1–6°C) for RBC. The volume is approximately 350 mL of which 200 mL is red cells (haematocrit around 60%). In an average-size adult, transfusion of 1 unit RBC is expected to increase the haemoglobin by 1 g/dL or haematocrit by 3%. Platelets are stored at 20–24°C with constant agitation for a maximum of 5 days. Four to five units of whole blood-derived platelets or one apheresis platelets can increase platelet count by 20,000–40,000/μL in a stable patient. Fresh frozen plasma (FFP) is frozen and stored at –18°C within 8 hours of collection. Upon ordering, it is thawed at 37°C over 25 minutes and then stored at 4°C for 24 hours. FFP has a volume of 220 mL and contains 'normal' level of all coagulation factors. Thawed plasma is similar to FFP, but can be stored up to 5 days at 1–6°C and is clinically interchangeable with FFP. Cryoprecipitate is made from FFP and is a concentrated source of fibrinogen, each unit containing approximately 450 mg of fibrinogen.

Leukocyte-reduced blood components

White blood cells (WBCs) in the blood components can mediate adverse effects. White cells are removed primarily by filtration or apheresis processing. Leukocyte-reduction filters remove 3–5 logs (99.9–99.999%) of WBCs from whole blood-derived RBCs and platelet components. Leukoreduction can be performed before the component is stored (prestorage leukoreduction) or at the time blood is issued for transfusion (post-storage leukoreduction). Components collected by apheresis technology are leukoreduced as part of the collection. The benefits of leukocyte-reduced blood components include:

- Prevention or decrease of the incidence of HLA allo-immunization (and platelet refractoriness).
- Reduction of the incidence of febrile non-haemolytic transfusion reactions.

- Reduction of transfusion-transmitted WBC-associated viruses, such as cytomegalovirus and Epstein–Barr virus [1].

Other potential benefits, such as avoiding immunomodulatory effects of transfusion, remain controversial.

Evidenced-based blood component therapy

RBC transfusion

RBC should be transfused with the goal of improving tissue oxygenation in the context of anaemia or acute blood loss. Over one-third of all intensive care unit (ICU) patients receive transfusion; 70% if the ICU stay is longer than 1 week [2]. Many observational studies show an association between transfusion and poor clinical outcomes in hospitalized patients. In a systematic literature review of 45 observational studies including 272,596 critically-ill patients, RBC transfusion did not demonstrate efficacy in improving morbidity and mortality, although the study has the inherent limitations of an observational study, namely patient selection bias [3].

The best evidence for the threshold for RBC transfusion in the critical care setting is mainly based on the landmark randomized controlled trial (RCT) Transfusion Requirements in Critical Care (TRICC) trial in which patients assigned to a restrictive transfusion strategy (haemoglobin <7 g/dL) had similar mortality rates compared with patients assigned to a liberal transfusion strategy (haemoglobin <10 g/dL). The mortality was lower in the restrictive strategy group in patients who were younger than 55 years old and less ill (Acute Physiology and Chronic Health Evaluation score <20). The patients in the restrictive group also had lower multiple-organ-dysfunction scores, myocardial infarction, and pulmonary oedema [4]. In cardiac surgery patients, the RCT called the Transfusion Requirements After Cardiac Surgery (TRACS) trial compared a restrictive (haematocrit <24%) with a liberal (haematocrit <30%) transfusion strategy, and showed no difference in the composite 30-day mortality and morbidity (cardiogenic shock, acute respiratory distress syndrome, and acute kidney injury) between the two groups [5]. In the RCT FOCUS (Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair), patients with cardiovascular disease or cardiovascular risk factors who underwent repair of hip fracture were post-operatively randomly assigned to a liberal transfusion strategy (haemoglobulin threshold of 10 g/dL) or a restrictive transfusion strategy (symptomatic anaemia or haemoglobulin threshold of 8 g/dL) [6]. There was no difference in overall mortality and functional recovery. More recently, an RCT in 998 patients with septic shock compared a haemoglobin trigger of 7 g/dL versus 9 g/dL and found no difference in 90-day mortality [7].These RCTs support the safety of a restrictive transfusion policy and do not support the observational study findings of increased mortality in more heavily transfused patients compared with those transfused with a restrictive strategy. In a recently published Clinical Practice Guidelines for RBC transfusion from the AABB (formerly, the American Association of Blood Banks), four recommendations were made based on the quality of evidence from clinical trial data [8]. The clinical data were based on a systemic review of literature from 1950 to February of 2011 including the previously mentioned RCTs. The recommendations were:

- Strong recommendations for adhering to a restrictive transfusion strategy (7–8 g/dL) in hospitalized, stable patients (high-quality evidence).
- Suggests (weak recommendation) adhering to a restrictive strategy in hospitalized patients with pre-existing cardiovascular disease, and considering transfusion for symptoms or a haemoglobin of 8 g/dL or less (moderate-quality evidence).
- Cannot recommend for or against a liberal or restrictive transfusion threshold for patients with acute coronary syndrome (very low-quality evidence)
- Suggests (weak recommendation) that transfusion decisions be influenced by symptoms we well as haemoglobin level (low-quality evidence) [8].

RBC storage lesion

Stored RBC undergoes metabolic and structural changes including decrease in intracellular adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG), increase in extracellular concentration of potassium and changes in morphology. In the USA, the mean storage period for RBC transfused to ICU patients ranged from 16 to 21 days [2]. Recently, concerns over the age of transfused RBC have been raised as a contributing factor to morbidity and mortality [9]. A review of more than 20 studies in adult patients concluded that it is difficult to assign a causal relationship between the age of transfused RBC and adverse clinical outcomes [10]. Two large multicenter randomized clinical trials including the ABLE (**a**ge of **bl**ood **e**valuation) study in ICU patients in Canada and the RECESS (red cell storage duration) study of cardiac surgery patients in the USA have recently been reported [11,12]. Both studies failed to show a difference in patient outcomes between those transfused with fresher units versus those transfused with older units. These studies suggest that, although red cells show in vitro changes with storage, these changes are not associated with adverse clinical effects.

Platelet transfusion

Platelets are used to treat (therapeutic) or prevent (prophylaxis) bleeding due to deficiencies in platelet number or function. In patient with active bleeding or planned surgical procedures, platelet transfusions are indicated for platelet count of below 50,000/μL. Higher counts may be needed for bleeding at critical anatomic locations such as neurological or ophthalmological surgery. In non-bleeding stable patients with hypoproliferative thrombocytopenia, prophylactic transfusion for a platelet count of below 10,000/μl is indicated to prevent spontaneous bleeding [13]. In patients with high risk for spontaneous bleeding due to risk factors such as high fever, sepsis, disseminated intravascular coagulation (DIC), or splenomegaly, prophylactic transfusions for platelet count of below 20,000/uL is a reasonable approach.

The expected response to a platelet transfusion is an increment of 20-40,000/μL, 1–4 hours after the transfusion [13]. Patients with poor responses should be evaluated for immune refractoriness due to HLA-antibodies. HLA-matched or cross-match compatible platelets can achieve successful responses in the majority of patients who are HLA alloimmunized. Leukoreduction can be used to prevent platelet refractoriness due to HLA allo-immunization.

Plasma transfusion

Plasma transfusions are indicated for patients who are bleeding or undergoing invasive procedures with multiple coagulation factors deficiencies. Each unit of plasma is 220 mL and the recommended

dose is 15–20 mL/kg. Plasma transfusion for an invasive procedure has not been shown to be of benefit in patients with INR <2.0 and would probably have minimal or no effect on the INR [13].

Urgent and massive transfusion

Urgent transfusion refers to the administration of blood products before the pre-transfusion compatibility testing is completed. In patients with an unknown blood type, group O RBCs and group AB plasma products should be used. Rh-negative RBCs should be used for children and females with childbearing potential, to avoid the possible sensitization to the D antigen.

Massive transfusion refers to the replacement of more than one patient's blood volume within 24 hours. Transfusion of large amounts of cold, citrated blood products can lead to hypothermia, dilutional coagulopathy, and acid–base imbalance. Blood warmers may be used. The use of all blood components should be ideally guided by laboratory results. However, in trauma and massive transfusion setting, it may be necessary to empirically transfuse before laboratory results are available. Many hospitals have trauma transfusion protocols in which a predetermined plasma:RBC ratio is transfused. Platelet counts should be maintained >50,000/μl and cryoprecipitate should be given to maintain the fibrinogen level above 100 mg/dL. Whole blood clotting assays, such as thromboelastography (TEG) and rotational TEG (RoTEG) can be used to guide transfusion therapy in trauma and massive transfusion settings [13].

Adverse effects of blood transfusion

Major improvements have been made in blood safety over the last 20 years, particularly with the implementation of direct methods of viral detection using nucleic acid testing. The risk of HIV and HCV transmission through blood transfusion is less than 1 in a million [14,15]. (Table 267.1). While the risk of known viruses has become minimal, non-infectious risks are now the most common causes of transfusion related morbidity and mortality including TRALI, TACO, and acute haemolytic reactions.

Acute haemolytic transfusion reactions are caused by immune-mediated lysis of transfusion red cells via complement activation (intravascular haemolysis). Symptoms/signs include fever, chills, haemoglobulinaemia, haemoglobulinuria, shock, and DIC. The most common cause is infusion of ABO-incompatible blood due to human clerical error. Treatments include hydration, diuretics, blood pressure support, and treatment of DIC if present. Careful patient identification at the time of pretransfusion specimen collection and blood administration are keys in preventing acute haemolysis caused by ABO-incompatible transfusions [13]. With approximately 13.5 million RBC transfused each year in the USA, the estimated risk of death due to haemolysis is 1 in 1,250,000 (or 8 per 10 million RBC units) [6].

Febrile non-haemolytic transfusion reactions (FNHTR) are characterized by fever (≥1°C elevation), which may be accompanied by chills, rigors, hypertension, tachycardia, and dyspnoea without another clinical explanation. Leukocytes and cytokines released by leukocytes in the blood components are the primary cause of FNHTR, which has been reported to occur in approximately 0.5% of RBC or platelet transfusions. Leukoreduction (especially when performed prior to storage) has been shown to reduce the incidence of FNHTR to RBC and platelet transfusion. FNHTRs can be treated with antipyretics [13].

Allergic reactions to plasma proteins are characterized by a histamine-mediated urticarial rash occurring in 1–3% of transfused patients. In mild localized allergic reactions, transfusion can be temporarily stopped and the patient treated with antihistamines. If symptoms resolve, the transfusion can be restarted slowly with close observation. Future similar reactions can be prevented with pretransfusion medications using antihistamines and if the reaction was more severe, steroids 30–60 minutes before the start of the transfusion. Anaphylactic reactions to blood products are rare, occurring in patients with antibodies again plasma proteins such as IgA, haptoglobin, or complement (C4). Patients with severe allergic or anaphylactic reactions should be treated with fluid resuscitation, epinephrine, and steroids. Washed cellular blood components (RBCs and platelets) are indicated. Patients with anaphylactic reaction due to IgA deficiency should receive IgA deficiency plasma which can be obtained through rare-donor registry [13].

TRALI is manifested as new onset of dyspnoea, hypoxia, and non-carcinogenic bilateral pulmonary oedema associated with transfusion without another cause. It is an inflammatory process due to a proposed two-step mechanism:.

- Predisposing clinical event (including trauma or infection) leading to endothelial and neutrophil priming.
- Transfusion of biological response modifiers (including antibodies to human leukocytes and neutrophil antigens).

This leads to activation of neutrophils and complement in the pulmonary vasculature resulting in capillary leakage syndrome [13]. Treatment is supportive with oxygen and mechanical ventilation. With the recognition of the roles of donor HLA antibodies in the pathogenesis of TRALI, blood centres have implemented strategies to reduce TRALI risk using plasma from low risk donors. As a result, the incidence of TRALI has declined by more than 60%. The rate of TRALI in 2009 was 0.81 (95% CI: 0.44–1.49) per 10,000 transfused blood components according a large prospective study [16].

Transfusion-associated circulatory overload (TACO) is cardiogenic pulmonary oedema due to the rapid and/or excessive transfusion of blood products to a patient with limited/compromised cardiac reserve. Treatments include diuresis and supportive cardiopulmonary care. The estimated incidence of TACO is 1–4% [8].

Bacterial contamination of blood components is a rare, but serious complication. Patients may experience high fever, chills/rigors, and even shock. Aggressive therapy and broad-spectrum antibiotics

Table 267.1 Risks of transfusion-transmitted viral infections

Viruses	Estimated risk in USA
Human immunodeficiency virus (HIV)	1:1,467,000
Hepatitis C virus (HCV)	1:1,149,000
Hepatitis B virus (HBV)	1:843,000 to 1:1,208,000

Data from Carson JL et al., 2012, 'Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB', *Annals of Internal Medicine*, **157**, 49–58; Zou S et al., 2010, 'Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing', *Transfusion*, **50**, pp. 1495–504; and Vamvakas EC and Blajchman MA, 2009, 'Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention', *Blood*, **113**, pp. 3406–17.

should be started if a septic reaction is suspected. The implicated component should be sent for culture. Blood cultures should also be draw from the patient.

Alternative to blood transfusion

Several strategies can be used to reduce allogeneic blood product transfusions. Blood salvage during surgery and immediate post-post-operative period is gaining traction as a strategy for reducing blood transfusion. Strategies for reducing iatrogenic blood loss include the use of small-volume phlebotomy tube, elimination of redundant, and unnecessary laboratory testing, and the use of POC testing and non-invasive testing. Antifibrinolytic agents, such as tranexamic acid and epsilon-aminocaproic acid, have been used to decrease blood loss in cardiac surgery setting, control bleeding in patients on extracorporeal membrane oxygenation (ECMO), and in the management of thrombocytopenic bleeding. The available data on erythropoietin (EPO) indicates that it does not improve survival in critically-ill patients. There may be increased risk for thrombotic complications [13]. There are no safe and effective haemoglobin-based oxygen carriers to replace blood.

References

1. Clark P and Miller JP. (2011). Leukocyte-reduced and cytomegalovirus-reduced-risk blood components. In: Mintz PD (ed.) *Transfusion Therapy Clinical Principles and Practice*, pp. 665–98, 3rd edn. Bethesda, MD: AABB Press.
2. Hayden SJ, Albert TJ, Watkins TR, and Swenson ER. (2012). Anemia in critical illness: insights into etiology, consequences and management. *American Journal of Respiratory and Critical Care Medicine*, **185**(10), 1049–57.
3. Marik PE and Corwin HL. (2008). Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. *Critical Care Medicine*, **36**, 2667–74.
4. Hebert PC, Wells G, Blajchman MA, et al. (1999). A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *New England Journal of Medicine*, **340**, 409–17.
5. Hajjar LA, Vincent JL, Galas FR, et al. (2010). Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *Journal of the American Medical Association*, **304**, 1559–67.
6. Carson JL, Terrin ML, Noveck H, et al. (2011). Liberal or restrictive transfusion in high-risk patients after hip surgery. *New England Journal of Medicine*, **365**, 2453–62.
7. Holst LB, Haase N, Wettersley J, et al. (2014). Lower versus higher hemoglobin threshold for transfusion in septic shock. *New England Journal of Medicine*, **371**(15), 1381–91.
8. Carson JL, Grossman BJ, Kleinman S, et al. (2012). Red blood cell transfusion: a clinical practice guideline from the AABB. *Annals of Internal Medicine*, **157**(1), 49–58.
9. Koch CG, Li L, Sessler DI, et al. (2008). Duration of red-cell storage and complications after cardiac surgery. *New England Journal of Medicine*, **358**, 1229–39.
10. Triulzi DJ and Yazer MH. (2010). Clinical studies of the effect of blood storage on patient outcomes. *Transfusion and Apheresis Science*, **43**, 95–106.
11. Steiner ME, Ness PM, Assmann SF, et al. (2015). Effects of red-cell storage duration on patients undergoing cardiac surgery. *New England Journal of Medicine*, **372**, 1419–29.
12. Lacroix J, Hebert PC, Fergusson DA, et al. (2015). Age of transfused blood in critically ill adults. *New England Journal of Medicine*, **372**, 1410–18.
13. King KE. (2011). *Blood Transfusion Therapy: A Physician's Handbook.* Bethesda, MD: AABB.
14. Zou S, Dorsey KA, Notari EP, et al. (2010). Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. *Transfusion*, **50**, 1495–504.
15. Vamvakas EC and Blajchman MA. (2009). Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood*, **113**, 3406–17.
16. Toy P, Gajic O, Bacchetti P, et al. (2012). Transfusion-related acute lung injury: incidence and risk factors. *Blood*, **119**, 1757–67.

CHAPTER 268

Apheresis in the ICU

Marion Sternbach

Key points

- Apheresis means selective removal of either cellular or harmful molecular elements from blood.
- Instruments are based mostly on density centrifugation, less on specific column adsorption or membrane filtration.
- Plasmapheresis for noxious molecules uses albumin 5% most frequently. Fresh frozen plasma (FFP) is used therapeutically only in thrombotic micro-angiopathies.
- Critical care therapies may interfere or be interfered by plasmapheresis. Careful monitoring during and after apheresis cannot be over emphasized.
- Indication for plasmapheresis in haematological disorders proved as effective by RCT are only for thrombotic micro-angiopathies.

Definition

Apheresis is derived from Greek and means 'to remove'. Initially, it was used in situations like life-threatening neutropenia or hyperviscosity states. It involves separation of blood cellular elements or plasma from cellular elements, and occasionally removing harmful molecules from the plasma, returning purified plasma to the patient.

Instrumentation

Most apheresis machines are based on the principle of continuous or intermittent density centrifugation. Some instruments have attached devices for selective column adsorption or membrane filtration for specific molecules, like antibodies or antigen-antibody complexes.

Physical and biochemical principles of therapeutic plasma exchange

Plasma exchange removes harmful molecules from the circulation, but stimulates their resynthesis through feedback to lymphocytes and plasma cells. Therefore, plasma exchange has to be performed repeatedly. The rate of synthesis of some molecules can decrease if appropriate therapy is administered following plasma exchange. For steady equilibrium, 1 or 1.5 plasma volume removal will effectively deplete the body of ≥2/3 of the targeted molecule and 100% is removed by the fourth session [1]. Ions re-equilibrate very fast, while most non-immunoglobulin proteins recover within 72 hours [1].

Blood and plasma volume calculations

These can be calculated from a person's weight, gender, red cell volume, and muscle mass. Muscular people have a higher total blood volume (TBV) than obese persons.

During apheresis procedures extracorporeal blood volume should never exceed 15% of TBV to avoid hypovolaemia. Different instruments have different extracorporeal volumes varying between 150 and 500 mL. Therefore, small persons and children may not be able to tolerate a large extracorporeal volume. In such cases, the instruments can be primed with albumin 5% or a colloid solution.

Replacement fluids for plasma exchange

Albumin 5% with saline is the most common fluid. Fresh frozen plasma (FFP) or cryo-poor plasma are used only for thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS), and for hypofibrinogenaemia. Hypocalcaemia due to citrate and albumin infusion is an important consideration. Adverse effects of hypocalcaemia, depending on its level, are far reaching from inhibition of haemostasis to neuromuscular symptoms and signs up to seizures and cardiac arrhythmias [2]. Citrate levels will rise in addition to anticoagulation at ratios 1 part citrate to 10–14 parts of blood, by infusion of FFP containing citrate (CPD). On the other hand albumin will bind Ca^{2+} too. The body's parathormone will try to compensate by elevating Ca^{2+} levels. It rises fast, levels off, and decreases later during the procedure [3,4]. Higher concentration of citrate, as well as rate of its infusion and duration of the procedure will worsen hypocalcaemia.

Pathophysiology of apheresis

Therapeutic plasma exchange (TPE) depletes the body of immunoglobulins and coagulation factors. However, rapid resynthesis occurs due to negative feedback.

During thrombapheresis lymphocyte depletion also occurs because of their vicinity during density centrifugation. Lymphocytes that are long lived are not easily replaced by the lymphatic system.

For vascular access, peripheral antecubital veins are preferred as they typically permit a blood flow of 60–120 mL/min and completion of a TPE in about 3 hours. Major cell collections take longer and require more invasive access, such as subclavian or jugular vein with rigid double lumen catheters. Central venous catheters are considered potentially dangerous because of possible clotting and septic complications.

Bleeding due to apheresis is rare, unless one is facing underlying DIC with septicaemia, hepatic coagulopathies, or vitamin K

depletion due to broad spectrum antibiotics and starvation. In such cases, replacement fluid may have to include FFP and vitamin K.

During and immediately following the procedure, the prothrombin time (PT) and partial thromboplastin time (PTT) may be prolonged, and platelets and fibrinogen may fall, but clinical haemorrhage is rare, and abnormalities usually resolve in 24 hours.

Adverse effects

Adverse events occur in 4–5% of cases, especially in first time procedures, as shown in a large US review [1]. These events include fluid overload or hypovolaemia, unintentional removal of drugs from the circulation, citrate-induced hypocalcaemia and alkalosis, vaso-vagal reactions, allergic reactions, and some specific drug interactions. Careful monitoring of fluid status and consideration of drug redosing are therefore important. To avoid hypocalcaemia, consider using the lowest ratio of citrate to blood that prevents clotting. With early signs or symptoms of hypocalcaemia, consider reducing the blood flow to 50 mL/min. Treatment with oral calcium may be useful, but more severe cases require intravenous (iv) calcium gluconate, and aphersis should be put on hold. Allergic reactions are typically to hydroxyethyl starch (HES), plasma or the ethylene dioxide in the tubing. Typical drug interactions relate to the blunting of physiological responses to volume shifts by drugs, such as beta blockers or calcium channel blockers.

Therapeutic plasma exchange in haematological disorders

TPE is most commonly indicated, and most clearly demonstrated to be efficacious, in select haematological disorders, such as thrombotic thrombocytopenic purpura (TTP)/haemolytic uraemic syndrome (HUS) [5]. Thrombotic micro-angiopathies present with micro-angiopathic haemolytic anaemia, thrombocytopenia, and microthrombi due to platelet aggregation in small arterioles in kidneys, brain, heart, and in pregnancy even in the liver.

They comprise TTP, HUS, and HELLP (haemolysis, elevated liver enzymes, low platelets in pregnancy). Depending on the predominance of the brain versus kidney, the disease is coined either TTP or HUS. In overlap symptomatology it is called TTP/HUS [6]. A similar micro-angiopathy occurs in pregnancy, usually in the third trimester, known as HELLP, life-threatening to both mother and fetus. Immediate delivery is here indicated. If the condition does not resolve spontaneously post-partum, TPE is indicated with FFP or cryo-poor plasma.

The pathogenesis of thrombotic micro-angiopathies has been elucidated to be due in part to deficiency of ADAMTS 13, a metalloprotease cleaving ultra large von Willebrand multimers, originating in the endothelium, causing microthrombi through platelet aggregation. This deficiency may be either congenital or acquired due to antibodies to ADAMTS 13. TPE with FFP replaces at least in part the deficient enzyme. TPE with cryo-poor FFP is devoid of von Willebrand multimers, which ought to make it more efficacious. This has not been proven unequivocally to date.

Moshkovwitz's classic 'pentad' of haemolysis, low platelets, neurological symptoms and signs (from headaches to palsies and seizures), renal failure, and fever is not always present. The presence of micro-angiopathic haemolytic anaemia and thrombocytopenia establish the likely diagnosis of TTP/HUS and justify the start of TPE, since this disease has a very high mortality in the absence of plasma exchange. If TPE cannot be started right away, infusion of FFP should be considered. Renal involvement may start with proteinuria, haemoglobinuria and haematuria and may end up with dialysis dependent uraemia. Early TPE may prevent this latter. *E. coli* with enterotoxin or *Shigella* are frequent aetiologies of HUS. Laboratory features are schistocytes and fragmented red blood cells, thrombocytopenia, elevated lactate dehydrogenase and unconjugated bilirubin, elevated creatinine. Usually PT, PTT, fibrinogen, and thrombin time are within normal limits. Direct antiglobulin test (Direct Coombs') is negative. These parameters need to be monitored before and after daily TPE of 1–1.5 volume.

The average number of apheresis procedures to achieve lasting remission is 16. Mortality has dropped from 80% to less than 20%, but relapses after 1 month to years amount to 20% [7]. There are also cases with refractory TTP/HUS in 10–22% of patients. They will require repeat plasma exchanges and may benefit from anti-platelet drugs and splenectomy [8], as well as immune suppressant drugs, like vincristine, cyclosporin A, cyclophosphamide and rituximab (anti-CD20 monoclonal antibody), most successful [9].

Platelet transfusions may be harmful in TTP, 'fuelling the fire' of thrombotic micro-angiopathy. However, red cell transfusions may become necessary in severe haemolytic anaemias, either during or following plasmapheresis. Rock et al. showed in a randomized controlled trial (RCT) [5] comparing TPE with FFP infusion, the superiority of TPE with survivals of 78 versus 63%, respectively. The response rate was also faster in the TPE group by day 9, 82 versus 49% in the FFP infusion group. The average number of TPE required was 15.8, including tapering with five treatments over 2 weeks.

Adult HUS is more severe than the paediatric, epidemic variety associated with *E. coli* verotoxin (O-157 H:7) or *Shigella* with diarrhoea at the outset. Adults may suffer from enterocolitis, neurological manifestations, liver impairment, pancreatitis, and even cardiac ischaemia with severe renal failure, requiring dialysis. Histology of renal biopsies in these patients show platelet aggregates, with von Willebrand Factor, thrombin in the glomeruli with fibrin deposits and widening of the glomeruli. HUS has usually somewhat higher platelets, over 31,000/μl. TPE has not been established as the most efficacious treatment. ADAMTS 13 may be normal or somewhat reduced in HUS.

HELLP occurs in 10% of women with severe pre-eclampsia, but may appear also post-partum or continue after delivery. Presenting symptoms are abdominal pains, nausea, oedemas with haemolysis, thrombocytopenia, liver dysfunction. Maternal mortality is about 1%, infant mortality goes as high as 10–20% due to placental ischaemia and possible abruption. Delivery should be performed as soon as possible. Post-partum recovery occurs usually within 6 days. In the presence of severe ongoing thrombocytopenia and organ dysfunctions plasma exchange may be helpful and, occasionally, all abnormalities have reverted to normal after a couple of procedures. ADAMTS 13 is usually reduced in the third trimester of pregnancy and no useful marker.

Autoimmune haemolytic anaemia with warm antibodies

Plasma exchange is rarely first line therapy in this disease. Autoimmune haemolytic anaemia (AIHA) may be 'idiopathic',

due to underlying autoimmune disease, like systemic lupus erythematosus or lymphoproliferative disorders. Its symptoms are fatigue and dyspnoea, conspicuous signs pallor, icterus, and splenomegaly. The peripheral blood film shows anaemia with spherocytosis, polychromasia, and investigations detect a positive direct antiglobulin test (DAT) or Direct Coombs' test often directed against an Rh system component and an elevated unconjugated (indirect) bilirubin. Since warm antibodies (IgG = immunoglobulin G) are widely distributed intra- and extravascular, TPE is not very helpful and should only be used in cases of fulminant AIHA, where conventional therapy with steroids given intravenous immunoglobulin (IVIg), cyclophosphamide, and splenectomy have failed.

Cold antibody haemolytic anaemia

This may be also 'idiopathic', associated with lymphoproliferative disorders, *Mycoplasma* pneumonia, viral diseases, like Hepatitis B, infectious mononucleosis or *Varicella*. Symptoms and signs are due to red blood cell (RBC) sludging coated by IGM antibodies with acral cyanosis of fingers, toes, ears and nose. Haemolysis occurs largely intravascularly, since IGM fixes complement. The specificity of the antibody is usually anti-I, occasionally IH or IGM dissociates itself in a warmer environment at 37°C from the RBC. The C3b-coated RBCs flowing through the liver, fix C3d (which is a C3b inhibitor), emerging more resistant to haemolysis. Thermal amplitude of these IGM antibodies determines the severity of the clinical manifestations. Cold antibody haemolytic anaemia CAHA respond poorly or not at all to steroids. Immune suppression by cyclophosphamide, azathioprine recently to rituximab (anti-CD20 monoclonal Antibody) [4,10] have been more successful.

IGM, a very large molecule is mostly intravascular and lends itself to very efficient removal by plasma exchange. One to one-and-a-half plasma volume removed, will remove up to 90% of the circulating IGM, provided the blood and fluids are maintained at 37°C, using a blood warming coil.

Immune thrombocytopenia

Is in adults a similar autoimmune disease to AIHA, starting out insidiously—in children it may follow viral infections. The auto-antibody is directed against the membrane glycoproteins on the platelet GIIb IIIa and less to GIb9. It presents with haemorrhagic symptoms of different degrees, petechiae, purpura, ecchymoses, and often active bleeding. The blood film shows scant platelets, but large, often giant young ones. The bone marrow is replete of megakaryocytes, young, and hypoploid with no pathology. TPE is not included in the newest guidelines of the American Society of Hematology (ASH) being currently developed for immune thrombocytopenia (ITP). Correct therapy of ITP in adults includes steroids, followed by IVIg 1.0 g/kg. If that fails, immune suppression with rituximab before or after splenectomy has shown success. If all fails TPE has been used by Bussell followed by large dose IVIg in a few refractory cases [11].

Post-transfusion purpura

This is a rare syndrome, more frequently seen in females, presenting as severe thrombocytopenia, 10,000–20,000/μl within 5–14 days usually following red cell transfusion. The pathogenesis is due to previous sensitization to a specific platelet antigen PLA1 during pregnancy, which persists in the recipient. The antigen, absent in the recipient is being transfused with the red cells, adsorbed to the recipient's platelets and then reacting with the specific (Immunoglobulin G (IgG) antibody to PLA1. Thus the platelets are destroyed as 'innocent bystanders'. Post-transfusion purpura PTP responds usually dramatically to IVIg [4]. TPE has been used successfully in cases of failure due to IVIg [12]. Haemostasis should be closely monitored during and after plasmapheresis, since dilutional coagulopathies may occur and FFP may have to be used as replacement fluid.

Coagulation factor inhibitors (allo- and autoantibodies)

Allo-antibodies against Factor VIII in haemophiliacs occur in 15–20% of this population. Autoantibodies against this appear spontaneously in SLE, pregnancy, and may be a presenting symptom or sign in lymphoproliferative disorders. Immune suppressive therapy with corticosteroids, cyclophosphamide, and rituximab have been used for eradication of the autoantibody. 'Bypassing coagulation factors' with activated Factor VII, have been used in severe, life-threatening haemorrhage. Porcine Factor VIII can be used successfully, though cross-reacting antibodies with the porcine Factor VIII may also develop.

Slocombe described successful plasma exchange in a haemophiliac with alloantibodies to Factor VIII and post-operative haemorrhage: fourteen daily 4.0 l. exchanges reduced the antibody by 90% [13]. TPE followed by immune suppression with steroids, and cyclophosphamide and Factor VIII infusion resulted in good control of haemorrhage [14]. Central catheters in such bleeding patients should be, if possible, avoided. Currently anti-Factor VIII inhibitors can be successfully treated by column adsorption.

Hyperviscosity syndromes

Occur in lymphoproliferative disorders with IGM monoclonal antibody hyperproduction. These are large molecules of 900,000 Dalton present in 50–70% of patients with Waldenstrom's macroglobulinaemia. These large, intravascular molecules cause hypervolaemia due to their colloid osmotic pressure. They also surround and coat the red cells lowering their 'zeta' (electro-negative repealing) potential, thus causing sludging in the microcirculation in the brain and eyes. Symptoms consist of headaches, dizziness, somnolence, nystagmus, stupor, and if untreated, lead to coma. Eye grounds show sausage-shaped veins, poor pulsations, haemorrhages, and retinal exudates. When plasma viscosity reaches four times that of water (Ostwald units), symptoms may appear, over 8 Ostwald units, manifestations become severe. Impaired platelet function and fibrin polymerization may result in a coagulopathy. TPE results in immediate and dramatic improvement of symptoms, since one volume exchange removes 90% of the intravascular immunoglobulin. Chemotherapy is very important as mainstay, since TPE stimulates through its IGM removal 'feedback' resynthesis of IGM by lymphocytes. ASFA and AABB classify hyperviscosity as category II indication for TPE.

Myeloma with renal failure

Myeloma is classified by the WHO as a lymphoplasmacytoid lymphoproliferative disease, often evolving from a monoclonal gammopathy at a rate of 1% per year. Its characteristics are a monoclonal immunoglobulin expansion due to neoplastic plasma cell proliferation, which cause through osteoclastic activity very painful osteolytic lesions. Anaemia due mostly to bone marrow infiltration by plasma cells, but often, in part, also due to the accompanying renal failure.

Renal impairment progressing to severe renal failure requiring haemodialysis is multifactorial. Good hydration and occasional haemodialysis may be required to reverse or improve renal failure to enable appropriate chemotherapy. TPE has been used in myeloma renal disease in RCT with variable success. Where TPE was compared with its absence, but where one arm consisted of TPE, chemotherapy, and haemodialysis, while the control arm had no TPE, but peritoneal dialysis the outcomes were good favouring TPE significantly with improved renal function (creatinine < 2.5 mg/dL), marked decrease of light chain proteinuria and significantly improved survival, 66% in the TPE group, versus 28% in the control arm [15]. TPE was not shown to be superior to conventional chemotherapy in a small study of patients with multiple myeloma [16].

Cryoglobulinaemia

Encompasses diverse groups of immunoglobulins with a low thermal amplitude, which causes their precipitation at even room temperature:

- **Type 1**: monoclonal proteins seen with myeloma.
- **Type 2**: mixed cryoglobulins, monoclonal IGM, and polyclonal IGG, as seen in autoimmune diseases, like rheumatoid arthritis, scleroderma, or leucocytoclastic vasculitis.
- **Type 3**: antigen-polyclonal immunoglobulin complexes, associated with glomerulonephritis, polyarthralgias, and skin ulcerations.

Pathogenetic therapy comprises steroids, (except in hepatitis C) and immune suppression [17]. TPE as adjuvant therapy has a salutary effect on symptoms, clinical signs and a protective effect on renal function [18].

Cytapheresis in the critical care setting

Cytapheresis implies selective removal of blood cell types from the buffy coat, separable by density centrifugation. This has become possible over the years through highly sophisticated cell separators, electronic cell size recognition and computerized programming. Centrifugal force and speed in the separation chamber allows for collection of platelets from the upper most layer of the buffy coat, mononuclear cells (MNC): lymphocytes, blasts, monocytes from the lower layer and polymorphonuclears (PMN) from the deepest layer of the buffy coat. This latter can be enhanced by hydroxyethyl starch (HES), causing rouleaux formation of red cells, thus separating the PMN more visibly from the RBCs and harvesting larger numbers.

The intended number of cells to be removed is not easily predictable:

- Blood volumes calculated may be underestimated.
- Cells may be recruited also from bone marrow and large spleens.
- Leukaemic blasts may have different sedimentation density than expected [19].

Therefore it is recommended to monitor harvested cell numbers during cytapheresis procedures until the desired number has been collected. In therapeutic cell depletions one should achieve optimally 30–50% collection of the harmful elements.

Therapeutic plateletpheresis (thrombapheresis)

Is indicated in rare cases of myeloproliferative neoplasias (MPN), such as chronic myelogenous leukaemia (CML) and essential thrombocythaemia (ET) with platelet counts of 100–10^{-9}/L (over 1 million per µl) with clinical evidence of haemorrhagic or thrombosing tendency, and only until chemotherapeutic agents (e.g. hydroxyurea or anagrelide) have started to lower platelets. Thrombosis may be venous like in Budd–Chiari syndrome or arterial in stroke, gastrointestinal haemorrhages can be severe and life-threatening.

Therapeutic leukapheresis

This is performed in leukaemia with high blast counts of over 100,000/µl because of leucostasis, impending or ongoing tumour lysis syndrome and high mortality.

Table 268.1 ASFA and AABB indication categories for therapeutic apheresis in hematologic diseases and dysproteinemias

Disease	ASFA/AABB Category
ABO-incompatible marrow transplant	II
Aplastic Anemia	III
Autoimmune hemolytic anemia	III
Coagulation Factor Inhibitor	II
Cryoglobulinemia	II
HELLP syndrome (postpartum)	NR
Hemolytic uremic syndrome	III
Hyperviscosity syndrome/multiple myeloma	II
Immune Thrombocytopenic Purpura	II*
Posttransfusion purpura	I
Pure red cell aplasia	III
Red cell alloimmunization	III
Thrombotic thrombocytopenic purpura	I

*This disorder is only ranked in context of staphylococcal protein A immune adsorption. NR, Disorder not ranked by AABB or ASFA; HELLP, hemolysis, elevated liver enzymes, low platelets; Category I, standard acceptable therapy; Category II, available evidence suggests efficacy; Category III, available evidence inconclusive; Category IV, ineffective in controlled trials.

From: THERAPEUTIC APHERESIS, A Physician's Handbook 1-st Edition 2005 AABB and ASFA,Editor: Bruce C. McLeod, MD. Reproduced with permission of the Editor and Publishers.

Clinical leucostasis manifestations are microvascular sludging in brain and eyes, as well as in the pulmonary circulation in acute leukaemia. In CML priapism has been seen on occasion. The causes of leucostasis are multifactorial, of which hyperviscosity is the least important, while reduced deformability, cytokine secretion, inter-adherence of mostly myeloblasts are essential [19,20]. Hyperleucocytosis has a poor prognosis at presentation. It parallels hyperuricaemia and unless treated promptly, leads to tumour lysis syndrome. Therefore, it should be dealt with by apheresis, before initiating definitive chemotherapy, thus making it an urgent indication.

The risk of introducing a central venous line in patients with severe thrombocytopenia or even coagulopathies in acute promyelocytic leukaemia and acute monocytic leukaemia has to be weighed against the benefits of leukapheresis. The extent and number of leukapheresis procedures to prevent tumour lysis syndrome is unknown. Removal of large number of blasts, will also remove significant amounts of plasma, therefore fluid replacement is essential. Efficiency of cell removal is increased by HES addition as sedimenting agent and volume expander. Cell counts should be monitored, during procedures, as well as volume status and urinary output.

References

1. McLeod BC. (2005). *Therapeutic Apheresis: a Physician's Handbook*. Bethesda MD: AABB and ASFA.
2. Strauss RG and McLeod BC. (2001). Complication of therapeutic apheresis In: Popovsky MA (ed.) *Transfusion Reactions*, 2nd edn, pp. 315–38. Bethesda MD: AABB Press.
3. Bolan CD, Greer SE, Cecco SA, et al. (2001). Comprehensive analysis of citrate effects during platelet pheresis in normal donors. *Transfusion*, **41**, 1165–71.
4. Weinstein R. (2001). Hypocalcemic toxicity and atypical reaction in therapeutic plasma exchange. *Journal of Clinical Apheresis*, **16**, 210–11.
5. Rock GA, Shumak KH, Buskard NA, et al. (1991). Comparison of plasma exchange and plasma infusion in the treatment of thrombotic thrombocytopenic purpura. *New England Journal of Medicine*, **325**, 393–7.
6. Moake JL. (2002). Thrombotic micro-angiopathies. *New England Journal of Medicine*, **347**, 589–600.
7. Bondarenko N and Brecher ME. (1998). United States thrombotic thrombocytopenic purpura apheresis study group (US TTP ASG): multicenter survey and retrospective analysis of current efficacy of therapeutic plasma exchange. *Journal of Clinical Apheresis*, **13**, 133–41.
8. Crowther MA, Heddle N, Hayward CP, et al. (1996). Splenectomy done during hematologic remission to prevent relapse in patients with thrombotic thrombocytopenic purpura. *Annals of Internal Medicine*, **125**, 294–6.
9. Yomtovian R., Niklinski W, Silver B, et al. (2004). Rituximab for chronic recurring thrombotic thrombocytopenic purpura: a case report and review of the literature. *British Journal of Haematology*, **124**, 787–95.
10. Zaja F, Russo D, Fugo G, et al. (2001). Rituximab in a case of cold agglutinin disease. *British Journal of Haematology*, **115**, 232–4.
11. Bussel JB, Saal S, and Gordon B. (1998). Combined plasma exchange and intravenous gammaglobulin in the treatment of patients with refractory immune thrombocytopenic purpura. *Transfusion*, **28**, 38–41.
12. Cimo PL and Aster RH. (1972). Post-transfusion purpura: successful treatment by exchange transfusion. *New England Journal of Medicine*, **287**, 290–2.
13. Slocombe GW, Newland AC, Colvin MP, et al. (1981). The role of intensive plasma exchange in the prevention and management of haemorrhage in patients with inhibitors to factor VIII. *British Journal of Haematology*, **47**, 577–85.
14. Pintado T, Taswell HF, and Bowie EJW. (1975). Treatment of life threatening hemorrhage due to acquired factor VIII inhibitor. *Blood*, **46**, 435–41.
15 Zucchelli P, Pasquali S, Cagnoli L, and Ferrari G. (1988). Controlled plasma exchange trial in acute renal failure due to multiple myeloma. *Kidney International*, **33**, 1175–80.
16 Clark WF, Stewart K, Rock GA, et al. (2005). Plasma exchange when myeloma presents as acute renal failure. *Annals of Internal Medicine*, **143**, 777–84.
17. Berkman EM and Orlin JB. (1980). Use of plasmapheresis and partial plasma exchange in the management of patients with cryoglobulinemia. *Transfusion*, **20**, 171–8.
18. Geltner D, Kohn RW, Gorevic PD, et al. (1981). The effect of combination chemotherapy (steroids, immunosuppressives and plasmapheresis) on 5 mixed cryoglobulinemia patients with renal, neurologic and vascular involvement. *Arthritis & Rheumatology*, **24**, 1121–7.
19. Hester J. (2003). Therapeutic cell depletion. In: McLeod BC, Price TA, Weinstein R (eds) *Apheresis: Principles and Practice*, 2nd edn, 283–94. Bethesda MD: AABB Press.
20. Porcu P, Cripe LD, Ng EW, et al. (2000). Hyperleukocytic leukemias: a review of pathophysiology, clinical presentation and management. *Leukemia & Lymphoma*, **39**, 1–18.

PART 11.3

Disordered coagulation

CHAPTER 269

Pathophysiology of disordered coagulation

Simon Stanworth and Stuart McKechnie

Key points

- The integrity of haemostasis is maintained by complex interactions between the vascular endothelium, the coagulation cascade, anticoagulant mechanisms, the fibrinolytic system, platelets, leucocytes, inflammatory mediators, and blood flow dynamics.
- Dysregulation of haemostasis is common in critically-ill patients, and may result from infection, trauma, haemorrhage, inflammation, organ dysfunction or drug therapy.
- Dysregulation of haemostasis may present as bleeding or thrombosis, although complex patterns of coagulopathy, where both bleeding and pro-thrombotic tendencies co-exist, are well recognized in critical illness.
- The laboratory tests of APTT and PT were developed to investigate coagulation factor deficiencies in patients with a known bleeding history, and their limited significance and applied clinical value in predicting bleeding (or thrombotic) risk in critically-ill patients is well recognised.
- The diversity of mechanisms and interactions between coagulation pathways and inflammation is considered with reference to two different clinical settings, sepsis, and trauma.

Normal haemostasis

Haemostasis *in vivo* results from the complex interplay of vascular endothelium, platelets, a series of soluble coagulation factors known as the coagulation cascade, anticoagulation mechanisms and the fibrinolytic system. The key points of haemostasis are summarized in the following sections and in Fig. 269.1.

Primary haemostasis

This refers to the generation of a platelet plug. Injury of the vascular endothelium results in vascular endothelial contraction and exposure of underlying collagen. Circulating platelets bind to the exposed collagen via collagen-specific glycoprotein surface receptors. Von Willebrand factor (vWF), released from endothelial cells and platelets, also attaches to the exposed subendothelium. This is followed by interactions between platelets and vWF mediated by specific glycoprotein receptors (e.g. gpIIb/IIIa) on the platelet surface. Platelet activation then occurs. Platelets change shape and start to secrete a variety of pro-coagulant factors (e.g. adenosine diphosphate (ADP), calcium, serotonin, fibrinogen, lysosomal enzymes, and platelet factor 4) at the site of injury. The arachidonic acid pathway is also stimulated by platelet activation resulting in formation of thromboxane A_2 (TXA_2). The interaction of platelets with vWF, released enzymes, ADP, and TXA_2 promote platelet aggregation and the formation of a platelet plug. This temporarily seals the breach in the endothelium at the site of injury and provides a surface for the procoagulant reactions of secondary haemostasis.

Secondary haemostasis

This refers to the formation of a stable fibrin clot by activation of an integrated cascade of enzymatic reactions. Initiation of coagulation occurs when circulating factor VII (FVII) is exposed to tissue factor (TF) in subendothelial tissues, resulting in formation of a TF-FVIIa complex. Through its action on Factors IX and X, and the formation of the tenase (FIXa and its cofactor FVIIIa) and prothrombinase (FXa and its cofactor FVa) complexes, the TF-FVIIa complex leads to the generation of thrombin. Thrombin cleaves fibrinogen to fibrin, the ultimate step in the coagulation chain reaction. Fibrin monomers link together, polymerizing to form fibrils that are then cross-linked by Factor XIIIa-mediated covalent bond formation to form a stable fibrin clot.

Thrombin

The protease **thrombin** plays a key role in haemostasis, including activation of platelets and clotting factors (V, VIII, and XIII), activation of anti-coagulant factors (protein C) and interaction with pathways of fibrinolysis (in particular by activation of plasminogen activator inhibitor type 1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI)).

Anticoagulant control

Natural **anticoagulants** control thrombin generation and other steps of the clotting cascade. Principal anticoagulant pathways include tissue factor pathway inhibitor (TFPI), which inhibits the FVIIa-TF complex, antithrombin (AT, also known as antithrombin III), which inhibits thrombin (and other activated clotting factors) and activated protein C, which, with its co-factor protein S, inhibits activated factors V and VIII. Protein C also attenuates tPA inhibition, increasing plasmin generation and fibrinolysis.

Fibrinolysis

This is a normal homeostatic mechanism following vascular injury, ensuring that fibrin clot formation remains localized to the site of injury. The fibrinolytic system contains an inactive pro-enzyme,

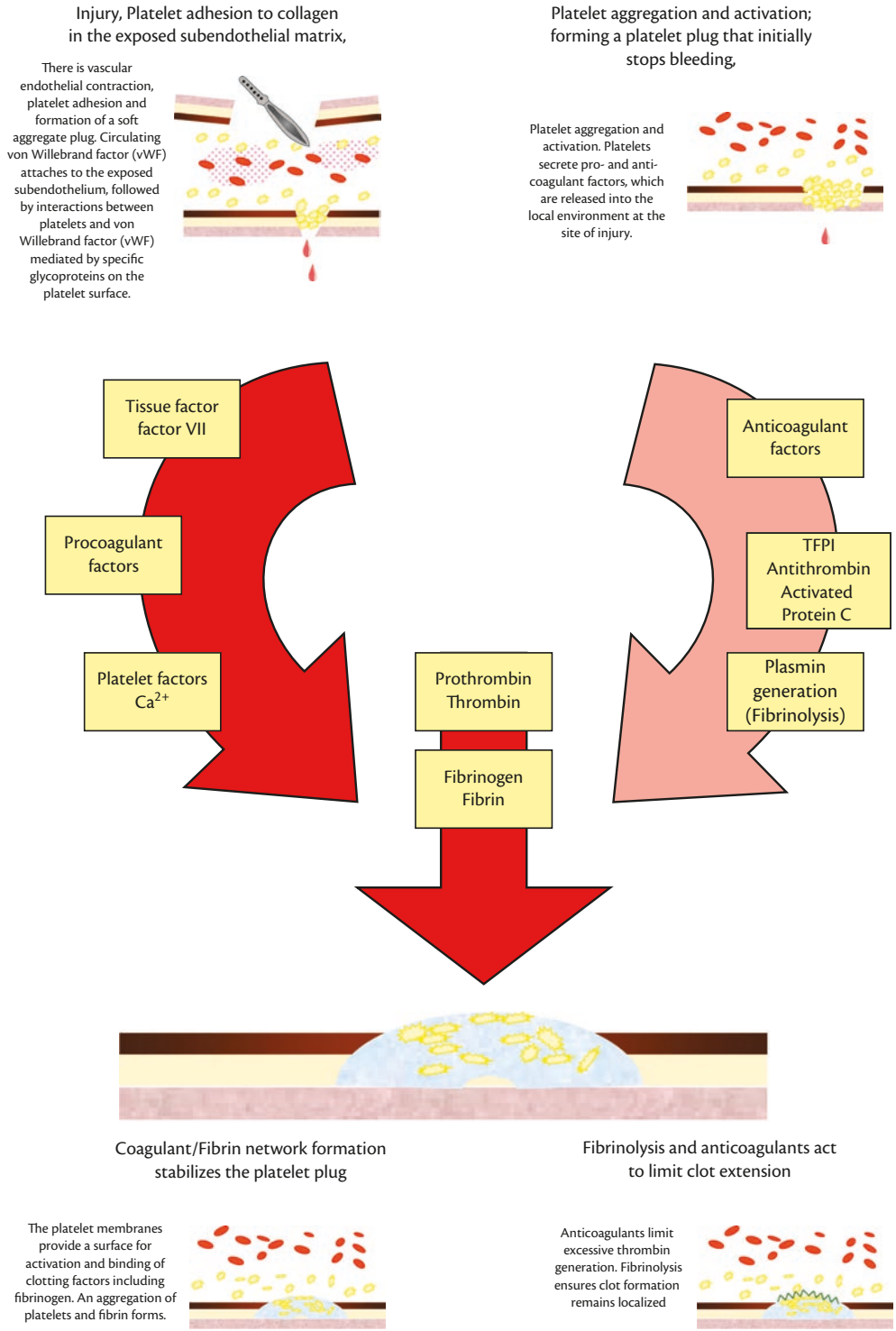


Fig. 269.1 An illustration of the pathways of haemostasis *in vivo*.

plasminogen, which is converted to plasmin by tissue plasminogen activator (tPA). tPA is released from the endothelium in response to a variety of stimuli including trauma, thrombin, and venous stasis. tPA binds to fibrin and converts clot-bound plasminogen to plasmin. Plasmin degrades fibrin and fibrinogen into a number of soluble fibrin degradation products. Plasmin activity is inhibited by α_2-antiplasmin and the therapeutic agent tranexamic acid. Fibrinolysis is also inhibited by thrombin-activatable fibrinolysis inhibitor (TAFI).

Vascular endothelium

The **vascular endothelium** plays an important role in maintaining haemostasis. Under normal conditions, endothelial cells form a regulated antithrombotic interface between the blood and tissues

by synthesizing a number of anticoagulants, including nitric oxide, thrombomodulin, prostacyclin, and glycosoaminoglycans. Injury exposes subendothelial collagen leading to the local expression of tissue factor and the localized sequence of haemostatic events described. However, widespread changes in endothelial cell function and tissue factor expression can occur in response to circulating cytokines (e.g. IL-8, TNF, IL-1, and IL-6) and/or bacterial endotoxin rendering the endothelial surface procoagulant.

Molecular pathophysiology

The structural domains of many proteins involved in haemostasis have been characterized. These typically include multiple functional units, presumably derived from common ancestral genes, which are responsible for key steps of synthesis, post-translational processing (vitamin K dependent procoagulant factors), membrane binding, and enzyme function. The first coagulation factor gene to be cloned and characterized in the early 1980s was Factor IX, the deficiency of which leads to haemophilia. Factor IX is a much smaller gene than factor VIII, and this is one reason why gene transfer has been reported and tested first for Factor IX deficiency, including the recent documentation that dose-dependent increases in FIX can be achieved and sustained in humans by gene therapy [1]. Von Willebrand disease is the commonest inherited bleeding disorder causing primary haemostatic defects, with a gene prevalence of around 1%. Many different mutations have been identified across the large number of exons of the vWF gene.

While inherited causes of bleeding appear to be often related to single gene abnormalities, thrombotic tendencies appear to reflect more complex interactions between acquired factors and multiple genes. Inherited thrombophilia describes patients with genetic defects that predispose them to thrombosis. The hereditary thrombotic disorders include deficiencies of anticoagulants (anti-thrombin, protein C, protein S), and mutations in selected genes, such as factor V Leiden, and a prothrombin gene mutation. Although the prevalence of some of these thrombophiliac mutations is common in populations, the relative risk for venous thrombosis is often not significantly increased. The co-inheritance of other genetic factors (some as yet unidentified), or contributions of acquired, or environmental risk factors (e.g. advancing age, atherosclerosis, malignancy, and trauma) is likely to be highly relevant and this will particularly apply for admissions to critical care.

Laboratory tests of disordered coagulation

The term disordered coagulation or coagulopathy is often used synonymously with abnormalities in standard laboratory coagulation test results, most frequently the platelet count, activated partial thromboplastin time (APTT) and prothrombin time (PT). Abnormalities of these tests (**laboratory-defined** coagulopathy) are common in hospital practice. In some patients, the abnormal results are largely incidental to the reason for admission to critical care (e.g. mild inherited 'deficiencies' of coagulation factors or the presence of lupus anticoagulant). However, the clinical significance of abnormal laboratory tests often remains unclear. The laboratory tests of APTT and PT were developed to investigate coagulation factor deficiencies in patients with a known bleeding history, and their significance and applied clinical value in predicting bleeding (or thrombotic) risk in critically-ill patients remains debatable [2]. Both PT and APTT results are dependent on reagent and laboratory quality controls and may be abnormal for a number of reasons not associated with bleeding risk, including normal variation of coagulation factor levels, or the presence of a lupus anticoagulant, or as part of an acute phase response. Coagulation results also vary in sensitivity with reduced levels of different coagulation factor levels. For example, the APTT will be significantly prolonged with only small reductions in the levels of some intrinsic coagulation factors, and the PT, in particular, is sensitive to mild (but not clinically significant) deficiencies of multiple pro-coagulants, as is often seen in clinical practice, for example liver disease [3].

Many laboratories report the international normalized ratio (INR), but the INR was developed to monitor warfarin therapy by standardizing PT results to account for different sensitivities of thromboplastins in the laboratory. The extrapolation of PT to INR is really only valid for those patients stably anticoagulated with vitamin K antagonists, and may not be a valid measure of coagulation for many patients in critical care. An INR of 1.5 is not equivalent to a PT of 1.5× midpoint of reference range, although it may approximate to this measure as the ISI value (a measure of 'quality' of the laboratory coagulant reagents) moves closer to a standard of 1.0. A study by Deitcher (2002) showed that over the INR range of 1.3–1.9 inclusive, mean factor levels ranged from 31 to 65% (FII), 40 to 70% (FV), and 22 to 60% (FVII). All of these levels are consistent with adequate concentrations of factors to support haemostasis in most clinical settings.

Newer global tests of haemostasis may provide a more clinically meaningful assessment of overall haemostatic competence. These include tests to assess endogenous thrombin generation potential (e.g. thrombin generation tests) or visco-elastic techniques such as thromboelastography (TEG) and thromboelastometry (TEM).

Features of disordered coagulation in critical care

Disordered coagulation in critical illness occurs as a consequence of multiple haemostatic abnormalities (Table 269.1), and may present clinically as bleeding or thrombosis [5]. Clinical bleeding ranges from minor localized bleeding (e.g. bleeding from vascular access sites), to microvascular bleeding, major haemorrhage (e.g. gastrointestinal haemorrhage resulting in shock) or bleeding in a critical site (e.g. intracranial haemorrhage). Using a structured bleeding assessment tool, a group in Canada reported rates of bleeding in 100 consecutive patients admitted to ICU [6]. Bleeding, often minor, occurred in the majority (90%) of patients, with one in five patients experiencing a major bleed. A decrease in platelet count and prolonged PT were independent risk factors for major bleeding in this observational study, the use of prophylactic anticoagulation was not.

In a prospective multicentre study (ISOC-1), of all sequentially admitted patients to UK general intensive care units (ICUs), around 30% of patients had or developed a prolonged PT (defined pragmatically as an INR >1.5) [7,8]. Most INR abnormalities appeared minor and short-lived, with ~70% of worst INR values in the range 1.6–2.5. Patients with PT prolongation in this study were more likely to have sepsis, be older, female, have higher APACHE II scores, chronic liver disease, and dialysis-dependent renal failure. PT prolongation was also associated with increased risk of death. For the purposes of this study, clinically significant haemorrhage during a 24-hour period was defined as estimated total cumulative blood loss >300 mL (one unit of red blood cells) or bleeding from a critical site, e.g. intracranial bleed. Clinically significant

Table 269.1 Haemostatic abnormalities in critically-ill patients

Disease	Haemostasis
Liver disease	◆ All clotting factors decreased except factor VIII and vWF ◆ Decreased AT, PC, PS ◆ Decreased platelet count ◆ Platelet dysfunction ◆ Dysfibrinogenaemia ◆ Increased fibrinolysis (rare) ◆ DIC (in patients with acute hepatic failure)
Renal failure	◆ Major abnormality is platelet dysfunction ◆ Decreased clotting factors rare in the absence of uremic enteritis, liver disease, or DIC ◆ AT deficiency in nephrotic syndrome
Cardiopulmonary bypass surgery	◆ Platelet function defect (the most common and relates to duration of surgery) ◆ Over-heparinization is common; this causes increased APTT but bleeding is rare ◆ Decreased fibrinogen ◆ Decreased factors II, V, VII, X, XI ◆ DIC
Severe head injury	◆ Increased FDPs ◆ DIC
Massive transfusion	◆ Decreased procoagulant factors (see text) ◆ Acute traumatic coagulopathy ◆ Iatrogenic dilutional coagulopathy ◆ DIC
Warfarin	◆ Decreased factors II, VII, IX, X ◆ Decreased PS, PC
Heparin	◆ LMWH Inhibits action of Xa; heparin inhibits other factors ◆ Thrombocytopenia (rare, unless HITT)
Thrombolytic agents	◆ Increased plasmin, FDPs ◆ Decreased fibrinogen
DIC	◆ Decreased pro and anti-coagulant factors ◆ Decreased fibrinogen ◆ Decreased platelets ◆ Increased FDPs

vWF, von Willibrand factor; AT, Antithrombin; PC, Protein C; PS, Protein S; DIC, Disseminated intravascular coagulation; APTT, Activated partial thromboplatin time; FDP, Fibrin degradation product; LMWH, Low molecular weight heparin; HITT, Heparin induced thrombocytopoenia and thrombosis.

haemorrhage was recorded most frequently affecting the gastrointestinal tract, chest, and abdominal cavity, and occurred in 258 out of 1923 (13%) patient admissions. There was no association with the degree of INR derangement and the occurrence of haemorrhage (10.2 versus 9.2%), including major haemorrhage (6.4 versus 6.8%) in this study.

Haemostatic disturbance should not be considered in terms of coagulation pathways in isolation. Thrombocytopenia in critically-ill patients is a well-recognized independent risk factor for death, and the prevalence of mild ($<150 \times 10^9$/L) and severe ($<50 \times 10^9$/L) thrombocytopenia in adult ICU patients is reported at around 40 and 8%, respectively. In the ISOC-1 study, the period prevalence of severe thrombocytopenia ($<50 \times 10^9$/L) for the entire ICU stay was 13.7% when the 24 hours prior to admission was also included [9]. 35.4% of patients who experienced severe thrombocytopenia died in ICU. During their ICU stay, patients with severe thrombocytopenia were more likely to experience an episode of clinically significant bleeding. There was wide variation in platelet transfusion use, and patients commonly received platelet transfusions on days without clinically significant haemorrhage.

Thromboembolism, most notably deep vein thrombosis (DVT) and pulmonary embolus (PE), is an important cause of morbidity and mortality in critically-ill patients. In addition to clot formation in the macrocirculation, the development of a prothrombotic tendency and thrombosis in the microcirculation is increasingly recognized as central to the pathogenesis of organ dysfunction in several conditions, including sepsis, trauma, and DIC, for example. Whilst bleeding is often (but not always) clinically apparent, thrombosis (particularly in the microcirculation) may be clinically occult. Compounding this, standard laboratory tests of coagulation (PT, APTT, platelet count, D-dimers) have less value in defining thrombotic risk. Significant thrombosis is likely to be under-diagnosed as a result. Although observational studies report a large range of incidence (1–31%), DVT is present in around 2% of admissions to critical care and thought to occur in 5–10% of patients following admission, even those on prophylactic anticoagulation. The most significant risk factors associated with DVT appear to be a previous history of DVT, renal failure and vasopressor therapy. Pulmonary embolus was radiologically confirmed in 0.5% of critically-ill patients in one large multicentre observational study, but post-mortem examination suggests the incidence of PE may be significantly higher (20–27%).

Pathophysiology of disordered coagulation in critical care

The pathophysiology of the coagulopathy occurring in sepsis and trauma, is considered here in more detail. Disseminated intravascular coagulation is described elsewhere.

Inflammation and sepsis

Studies of specific markers of coagulation activity, such as activated clotting factor assays, suggest that systemic inflammation triggers widespread activation of coagulation, with pro-inflammatory cytokines activating procoagulant pathways and downregulating anticoagulant pathways [10]. The net result of this interaction between inflammatory and coagulation pathways in sepsis are widespread thrombin generation, intravascular fibrin deposition, and a consumptive coagulopathy. Reduced levels of coagulation factors and thrombocytopenia may result in increased bleeding risk in patients with systemic inflammation [11], whilst microvascular fibrin deposition and thrombosis has been implicated in the pathogenesis of organ dysfunction.

Pro-inflammatory cytokines (notably IL-6) markedly increase the expression of tissue factor (TF) by circulating monocytes and this appears to play a central role in inflammation-induced activation of coagulation. Exposure of TF to blood results in the formation of the TF-FVIIa complex, activation of Factor X, and the conversion of prothrombin to thrombin. In animal models, inhibition of both IL-6 and TF has been shown to inhibit inflammation-induced

thrombin generation, as has infusion of recombinant tissue factor pathway inhibitor (TFPI) to achieve TFPI concentrations above physiologically normal levels in humans.

Three important anticoagulant pathways regulate procoagulant activity—antithrombin (AT), protein C, and TFPI. Systemic inflammation has an inhibitory effect on all three anticoagulant pathways.

Antithrombin inhibits thrombin, with AT activity significantly enhanced under normal conditions by heparin-like glycosaminoglycan cofactors on the endothelial surface. Circulating AT levels are significantly reduced in severe inflammation as a result of increased consumption (secondary to ongoing thrombin generation), degradation by neutrophil elastase, and reduced synthesis. Pro-inflammatory cytokines also inhibit endothelial glycosaminoglycan synthesis, reducing AT activity.

Activated protein C has antithrombotic (inactivation of Factors Va and VIIIa), antifibrinolytic (inhibition of plasminogen activator inhibitor type 1 (PAI-1)) and anti-inflammatory properties (reduced inflammatory and endothelial cell release of IL-1, IL-6, and TNF-α; downregulation of vascular adhesion molecules). Diminished activity in the protein C pathway has long been implicated as having a central role in the coagulopathy and pathogenesis of microvascular injury in sepsis. The circulating zymogen protein C is converted to activated protein C when it binds to thrombin. Protein C activation is greatly enhanced by endothelial protein C receptors (EPCRs) and thrombomodulin. Levels of protein C are reduced in sepsis as a result of increased degradation and reduced synthesis. Additionally, activation of protein C is inhibited by pro-inflammatory mediator (IL-1β, TNF-α) induced downregulation of thrombomodulin and EPCRs. Anti-coagulant activity of the protein C pathway is further decreased by reduced levels of protein S, a cofactor of protein C in the inactivation of Factors Va and VIIIa.

Increased understanding of the haemostatic changes in sepsis, most notably deficiencies in the activated protein C and AT anti-coagulant pathways, has informed the design of several recent clinical studies. To date, there is little evidence that administration of recombinant activated protein C or antithrombin to correct deficiencies improves outcome in severe sepsis. These studies are discussed in more detail in other chapters.

Trauma

In 2003, large observational studies reported that approximately one-quarter of all trauma patients had a coagulopathy on hospital admission [12]. Coagulopathy was evident in patients who had received little or no intravenous fluid therapy, and has subsequently been reported 'on-scene' (within 45 minutes) following injury. There is little current consensus about a definition of acute traumatic coagulopathy (ATC), but identifying patients with ATC is clinically important, because these patients have poorer outcomes.

In the past, trauma-induced coagulopathy was considered to be largely caused by dilution of coagulation factors (following administration of intravenous fluids or red blood cells), and exacerbated by consumption, acidosis, and hypothermia. The prevention of the 'lethal triad' of coagulopathy, acidosis, and hypothermia has become central to the management of military trauma in recent years emphasizing this interrelationship.

Several broad models may mechanistically explain traumatic coagulopathy [13]. One proposes that ATC results from the combined effects of tissue injury and hypoperfusion leading to protein C activation. Activated protein C causes the breakdown of Factors Va and VIIIa resulting in reduced thrombin generation and systemic anticoagulation. Activated protein C also inhibits PAI-1, thereby promoting fibrinolysis. Recent observational patient data confirm low clotting factor values, including low protein C values, in coagulopathic trauma patients, with the lowest values seen in Factor V. The second model suggests that tissue damage per se leads to excess tissue factor exposure, activation of coagulation, and consumption of clotting factors in a DIC-like manner. Fibrinolysis occurs not by PAI-1 inhibition, but by release of t-PA from the endothelium as a direct result of hypoxia and cell activation. However, unlike true DIC, pathological evidence of inappropriate widespread thromboses is not evident in traumatic injury.

Both hypotheses highlight the important role of fibrinolysis in ATC. Further evidence for the clinical significance of fibrinolysis comes from CRASH-2, a large multi-centre randomized controlled trial, which indicated that administration of the anti-fibrinolytic tranexamic acid within 3 hours of injury reduced mortality in patients with or at risk of significant bleeding following trauma.

References

1. Nathwani AC, Tuddenham EGD, Rangarajan S, et al. (2011). Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *New England Journal of Medicine*, **365**(25), 2357–65.
2. Segal JB and Dzik WH (2005). Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion*, **45**, 1413–25.
3. Tripodi A and Mannucci PM. (2011). The coagulopathy of chronic liver disease. *New England Journal of Medicine*, **365**, 147–56.
4. Deitcher SR. (2002). Interpretation of the international normalised ratio in patients with liver disease. *Lancet*, **359**, 47–8.
5. Hunt BJ. (2014). Bleeding and coagulopathies in critical care. *New England Journal of Medicine*, **370**, 847–59.
6. Arnold D, Donahoe L, Clarke FJ, et al. (2007). Bleeding during critical illness: a prospective cohort study using a new measurement tool. *Clinical & Investigative Medicine*, **30**(2), E93–102.
7. Walsh TS, Stanworth SJ, Prescott RJ, Lee RJ, Watson DM, and Wyncoll D. (2010). Writing Committee of the Intensive Care Study of Coagulopathy (ISOC) Investigators. Prevalence, management, and outcomes of critically ill patients with prothrombin time prolongation in United Kingdom intensive care units. *Critical Care Medicine*, **38**(10), 1939–46.
8. Stanworth SJ, Walsh TS, Prescott RJ, Lee RJ, Watson DM, and Wyncoll D. (2011). The Intensive Care Study of Coagulopathy (ISOC) investigators: a national study of plasma use in critical care: clinical indications, dose and effect on prothrombin time. *Critical Care*, **15**(2), R108.
9. Stanworth SJ, Walsh TS, Prescott RJ, et al. (2012). Thrombocytopenia and platelet transfusion in UK critical care: a multicentre observational study. *Transfusion*, **53**(5), 1050–8.
10. Levi M, van der Poll T, and Schultz M. (2012). Systemic versus localized coagulation activation contributing to organ failure in critically ill patients. *Seminars in Immunopathology*, **34**(1), 167–79.
11. Goerge T, Ho-Tin-Noe B, Carbo C, et al. (2008). Inflammation induces hemorrhage in thrombocytopenia. *Blood*, **111**, 4958–64.
12. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, and Pittet J-F. (2007). Acute traumatic coagulopathy: Initiated by hypoperfusion: Modulated through the protein C pathway? *Annals of Surgery*, **245**, 812–18.
13. Curry NS, Davenport RA, Hunt BJ, and Stanworth SJ. (2012). Transfusion strategies for traumatic coagulopathy. *Blood Review*, **26**(5), 223–32. [Review.]

CHAPTER 270

Disseminated intravascular coagulation in the critically ill

Marcel Levi and Marcus J. Schultz

Key points

- Disseminated intravascular coagulation (DIC) is a syndrome characterized by a systemic activation of coagulation leading to the intravascular deposition of fibrin in the (micro)vasculature, and the simultaneous consumption of coagulation factors and platelets.
- The relevance of the occurrence of microvascular thrombosis as a consequence of DIC is underscored by pathological, experimental, and clinical findings, demonstrating a link between DIC and organ dysfunction.
- DIC is not a disease in itself, but a complication of a variety of disorders, including sepsis, severe trauma, pregnancy complications, cancer, and systemic inflammatory states.
- The diagnosis of DIC can be made using a combination of widely available tests and may be helpful in guiding the selection of patients that require specific interventions in the coagulation system.
- The cornerstone of DIC treatment is treatment of the underlying disorder. Supportive strategies are tailored on the current insight in the pathogenesis of DIC and include anticoagulant strategies (e.g. directed at tissue factor) and strategies to restore physiological anticoagulant pathways (such as activated protein C concentrate).

Introduction

In virtually all critically-ill patients some degree of coagulation activation may be detected. In many cases, this activation of coagulation will not lead to clinical complications and will not even be detected by routine laboratory tests, but can only be measured with sensitive molecular markers for activation of coagulation factors and pathways [1]. However, if activation of coagulation is sufficiently strong, the platelet count may decrease and global clotting times may become prolonged. In its extreme form, systemic activation of coagulation is known as disseminated intravascular coagulation (DIC). DIC is characterized by the simultaneous occurrence of widespread (micro)vascular thrombosis, thereby compromising blood supply to various organs, which may contribute to organ failure [2,3]. Because of ongoing activation of the coagulation system and other factors, such as impaired synthesis and increased degradation of coagulation proteins and protease inhibitors, consumption of clotting factors and platelets may occur, resulting in bleeding from various sites.

Epidemiology and diagnosis

In clinical studies DIC has shown to be an independent predictor of organ failure and mortality [4]. In addition to microvascular thrombosis and organ dysfunction, coagulation abnormalities may have other harmful consequences. Critically-ill patients with a platelet count of $<50 \times 10^9$/L have a 4–5-fold higher risk for bleeding as those with higher platelet counts [5]. Although the overall risk of intracerebral bleeding in patients in the ICU is less than 0.5%, up to 88% of patients with this complication have platelet counts less than 100×10^9/L. In particular, thrombocytopenia that persists more than 4 days after ICU admission, or 50% of greater decrease in platelet count during the ICU stay is associated with a 4–6-fold increase in mortality.

Thrombocytopenia or a rapidly declining platelet count is an important diagnostic hallmark of DIC. However, the specificity and sensitivity of thrombocytopenia for the diagnosis of DIC is limited [5]. A platelet count of $<100 \times 10^9$/L is seen in 50–60% of DIC patients, whereas 10–15% of patients have a platelet count $<50 \times 10^9$/L. In surgical or trauma patients with DIC, over 80% of patients have platelet counts less than 100×10^9/L. On the other hand, in consecutive critically-ill patients with thromboctypenia, only 35% had DIC [5].

Consumption of coagulation factors leads to low levels of coagulation factors in patients with DIC. In addition, impaired synthesis, for example, due to impaired liver function or a vitamin K deficiency, and loss of coagulation proteins, due to massive bleeding, may play a role in DIC as well. The low level of coagulation factors is reflected by prolonged coagulation screening tests, such as the prothrombin time (PT) or the activated partial thromboplastin time (APTT). A prolonged PT or APTT occurs in 14–28% of intensive care patients, but is present in more than 95% of patients with DIC.

Measurement of fibrinogen has been widely advocated as a useful tool for the diagnosis of DIC, but is not in fact very helpful in the diagnosis of DIC in most cases. Fibrinogen acts as an acute-phase reactant and despite ongoing consumption plasma levels can remain well within the normal range for a long period of time. In a consecutive series of patients the sensitivity of a low fibrinogen level for the diagnosis of DIC was only 28% and hypofibrinogenaemia was detected in very severe cases of DIC only.

Plasma levels of fibrin split products (such as D-dimer) are frequently used for the diagnosis of DIC. Fibrin split products are detectable in 42% of a consecutive series of intensive care patients, in 80% of trauma patients and in 99% of patients with sepsis and

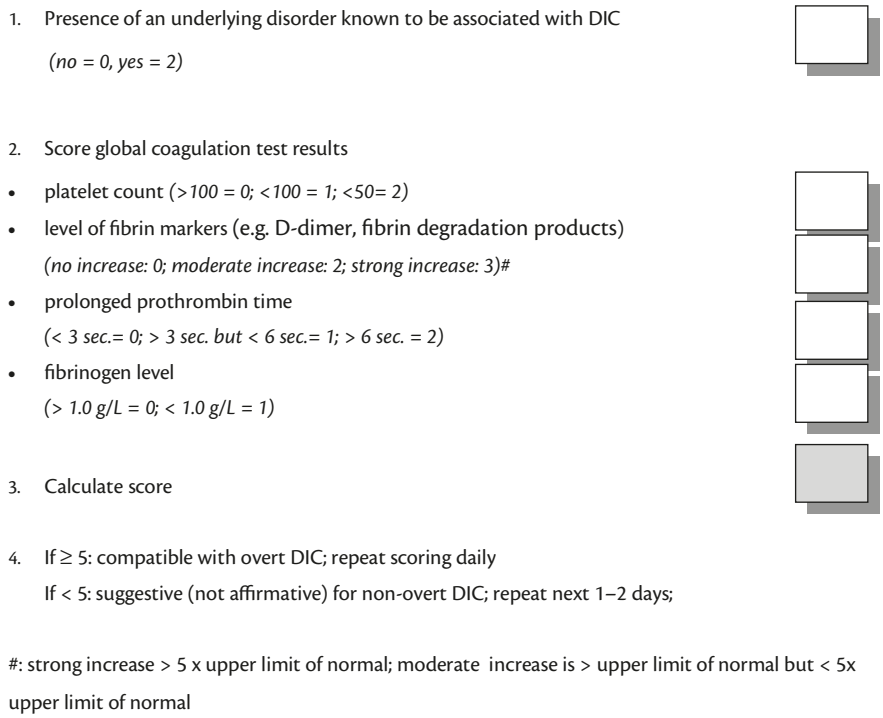


Fig. 270.1 Diagnostic algorithm for the diagnosis of overt DIC.
Reproduced from Taylor FB et al., 'Towards Definition, Clinical and Laboratory Criteria, and a Scoring System for Disseminated Intravascular Coagulation* On behalf of the Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the ISTH', *Thrombosis and Haemostasis*, **86**(5), pp. 1327–30, with permission from Schattaeur Publishers.

DIC. Most of the available assays for fibrin degradation products (FDP's) poorly discriminate between degradation products of cross-linked fibrin and fibrinogen degradation, which may cause spuriously high results. The specificity of high levels of fibrin degradation products is limited and many other conditions, such as trauma, recent surgery, inflammation or venous thromboembolism, are associated with elevated FDP's or D-dimer.

Plasma levels of physiological coagulation inhibitors, such as protein C or antithrombin may be useful indicators of ongoing coagulation activation [6]. Low levels of these coagulation inhibitors are found in 40–60% of critically-ill patients and in 90% of DIC patients.

Thromboelastography (TEG) is a method that has been developed decades ago and provides an overall picture of ex vivo coagulation. Modern techniques, such as rotational thromboelastography (ROTEM), enable bedside performance of this test and has become popular recently in acute care settings [7]. The theoretical advantage of TEG over conventional coagulation assays is that is provides an idea of platelet function, as well as fibrinolytic activity. There are no systematic studies on the diagnostic accuracy of TEG for the diagnosis of DIC, although the test may be useful for assessing the global status of the coagulation system in critically-ill patients.

For the diagnosis of overt DIC a simple scoring system has been developed (Fig. 270.1) [8]. The score can be calculated based on routinely available laboratory tests, i.e. platelet count, prothrombin time (or international normalized ratio), a fibrin-related marker (usually D-dimer), and fibrinogen. Tentatively, a score of 5 or more is compatible with DIC. Prospective studies show that the sensitivity of the DIC score is 93%, and the specificity is 98%. Studies in series of patients with specific underlying disorders causing DIC (e.g. cancer patients or patients with obstetric complications) show similar results. The severity of DIC according to this scoring system is related to the mortality in patients with sepsis [4].

Underlying causes of DIC

DIC is always secondary to an underlying disorder (Box 270.1).

Infection and sepsis

Severe systemic infections and/or sepsis are among the most common causes of DIC. Immunocompromised patients, asplenic patients whose ability to clear bacteria (particularly pneumococci) is impaired, and newborns whose anticoagulant systems are immature are particularly prone to infection-induced DIC. Infections may be superimposed on trauma or malignancies, which themselves are potential triggers of DIC. Clinically overt DIC occurs in 30–50% of patients with Gram-negative or Gram-positive sepsis, but also in infections with non-bacterial pathogens, such as viruses, protozoa (malaria), and fungi. An extreme form of DIC is represented by purpura fulminans, a severe, often lethal form of DIC in which extensive areas of the skin over the extremities and buttocks undergo haemorrhagic necrosis.

DIC in trauma and burns

Extensive exposure of damaged tissue (including tissue factor (TF)) to the blood circulation and haemorrhagic shock probably are the most immediate triggers of DIC in trauma. An alternative hypothesis is that cytokines play a pivotal role in the occurrence of DIC in trauma patients [9]. Bleeding, laboratory tests indicative of DIC, and vascular microthrombi in biopsies of undamaged skin have been described in patients with extensive burns. Kinetic studies with labelled fibrinogen and labelled platelets disclosed that, in

Box 270.1 Clinical conditions that are most frequently complicated by DIC

- Sepsis/severe infection.
- Trauma/burn/heatstroke.
- Malignancy:
  - Solid tumours.
  - Acute leukaemia.
- Obstetrical conditions:
  - Amniotic fluid embolism.
  - Abruptio placentae.
  - HELLP (haemolysis, elevated liver enzymes, low platelet) syndrome.
- Vascular abnormalities:
  - Kasabach–Merrit syndrome.
  - Other vascular malformations.
  - Aortic aneurysms.
- Severe allergic/toxic reactions.
- Severe immunological reactions (e.g. transfusion reaction).

Reproduced from Taylor FB et al., 'Towards Definition, Clinical and Laboratory Criteria, and a Scoring System for Disseminated Intravascular Coagulation* On behalf of the Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the ISTH', *Thrombosis and Haemostasis*, **86**(5), pp. 1327–30, with permission from Schattaeur Publishers.

addition to systemic consumption of haemostatic factors, significant local consumption occurs in burned areas.

DIC in obstetric calamities

Placental abruption is a leading cause of perinatal death [10]. The severe haemostatic failure accompanying abruptio placentae is the result of acute DIC emanating from the introduction of large amounts of TF into the blood circulation from the damaged placenta and uterus. Amniotic fluid has been shown to be able to activate coagulation in vitro, and the degree of placental separation correlates with the extent of DIC, suggesting that leakage of thromboplastin-like material from the placental system is responsible for the occurrence of DIC.

DIC in malignancy

Patients with solid tumours are vulnerable to risk factors and additional triggers of DIC that can aggravate thromboembolism and bleeding. Solid tumour cells can express different procoagulant molecules including tissue factor and cancer procoagulant (CP), a cysteine protease with factor X activating properties. Numerous reports on DIC and fibrinolysis complicating the course of acute leukaemias have been published. In 161 consecutive patients presenting with acute myeloid leukaemia, DIC was diagnosed in 52 (32%). In acute lymphoblastic leukaemia, DIC was diagnosed in 15–20% [11]. Some reports indicate that the incidence of DIC in acute leukaemia patients might further increase during remission induction with chemotherapy. In patients with acute promyelocytic leukaemia (APL), DIC is present in more than 90% of patients at the time of diagnosis or after initiation of remission induction.

DIC with vascular disorders

Rarely, vascular anomalies can trigger DIC. With some large aortic aneurysms, localized consumption of platelets and fibrinogen can produce coagulation abnormalities and bleeding. In a series of patients with aortic aneurysms, 40% had elevated levels of FDPs, but only 4% had laboratory evidence of DIC or bleeding. Kasabach and Merritt were the first to describe bleeding in association with giant cavernous haemangiomas, benign tumours found in newborns or children, and can evolve into convoluted masses of abnormal vascular channels that sequester, and consume platelets and fibrinogen.

DIC with toxic reactions or snake bites

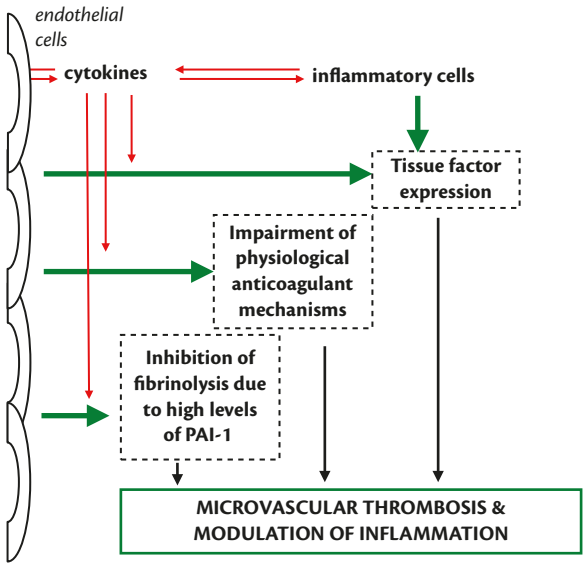
The venom of certain snakes, particularly vipers and rattlesnakes, can produce a coagulopathy similar to that of DIC [12]. Interestingly, victims of snake bites rarely have excessive bleeding or thromboembolism despite the abnormal coagulation tests and DIC-like picture.

Pathophysiology

In recent years, the molecular mechanisms of coagulation pathways have been defined (Fig. 270.2). The most important mediators that orchestrate the imbalance of the coagulation system in DIC are cytokines [13]. The initiation of coagulation activation leading to thrombin generation in DIC is mediated exclusively by the tissue factor/factor VII(a) pathway. Despite the potent initiation of coagulation by tissue factor, the activation of coagulation cannot be propagated if physiological anticoagulant pathways function properly. However, in DIC all major natural anticoagulant pathways (i.e. antithrombin III, the protein C system, and tissue factor pathway inhibitor (TFPI)) appear to be impaired [14]. Plasma levels of antithrombin III, the most important inhibitor of thrombin, are markedly reduced during DIC, due to a combination of consumption, degradation by elastase from activated neutrophils, and impaired synthesis. A significant depression of the protein C system may further compromise an adequate regulation of activated coagulation. This impaired function of the protein C system is caused by a combination of impaired protein synthesis, cytokine-mediated downregulation of endothelial thrombomodulin, and a fall in the concentration of the free fraction of protein S (the essential co-factor of protein C), resulting in reduced activation of protein C [15]. There seems to be an imbalance of TFPI function in relation to the increased tissue factor-dependent activation of coagulation. Finally, and importantly, experimental and clinical studies indicate that during DIC the fibrinolytic system is largely suppressed at the time of maximal activation of coagulation. This inhibition of fibrinolysis is caused by a sustained rise in the plasma level of plasminogen activator inhibitor-1 (PAI-1), the principal inhibitor of the fibrinolytic system.

Management

Adequate management of patients with DIC depends on vigorous treatment of the underlying disorder to alleviate or remove the inciting injurious cause. In addition of intensive support of vital



Pathways involved in the activation of coagulation in DIC. Both perturbed endothelial cells and activated mononuclear cells may produce proinflammatory cytokines that induce tissue factor expression, thereby initiating coagulation. In addition, downregulation of physiological anticoagulant mechanisms and inhibition of fibrinolysis promotes intravascular fibrin deposition. PAI-1: plasminogen activator inhibitor, type 1.

Fig. 270.2 Pathogenesis of disseminated intravascular coagulation.

functions, supportive treatment aimed at the coagulopathy may be helpful.

Platelet and plasma transfusion

Low levels of platelets and coagulation factors may increase the risk of bleeding. However, plasma or platelet substitution therapy should not be instituted on the basis of laboratory results alone; it is indicated only in patients with active bleeding and in those requiring an invasive procedure or are at risk for bleeding complications. The presumed efficacy of treatment with plasma, fibrinogen concentrate, cryoprecipitate, or platelets is not based on randomized controlled trials, but appears to be rational therapy in bleeding patients or in patients at risk of bleeding who have a significant depletion of these haemostatic factors. Replacement therapy for thrombocytopenia should consist of 5–10 U platelet concentrate to raise the platelet count to 20–30 $\times$ 10^9/L and, in cases in patients who need an invasive procedure, to 50 $\times$ 10^9/L.

Anticoagulant treatment

Heparin therapy in patients with DIC remains controversial. Experimental studies have shown that heparin can at least partly inhibit the activation of coagulation in DIC. However, a beneficial effect of heparin on clinically important outcome events in patients with DIC has not definitively been demonstrated in controlled clinical trials. Also, the safety of heparin treatment is debatable in DIC patients who are prone to bleeding. A large trial in patients with severe sepsis showed a slight, but non-significant benefit, of low dose heparin on 28-day mortality in patients with severe sepsis who were also treated with activated protein C and no major safety concerns [16]. There is general consensus that administration of heparin is beneficial in some categories of DIC, such as metastatic carcinomas, purpura fulminans, and aortic aneurysm (prior to resection). Heparin also is indicated for treating thromboembolic complications in large vessels and before surgery in patients with chronic DIC. Apart from all these considerations, current guidelines dictate the universal use of prophylactic doses of heparin or low molecular weight heparin to prevent venous thromboembolic events in critically-ill patients [17].

Recombinant human soluble thrombomodulin binds to thrombin to form a complex that inactivates thrombin's coagulant activity and activates protein C, and thus, is a potential drug for the treatment of patients with DIC. In a phase III randomized double-blind clinical trial in patients with DIC, administration of the soluble thrombomodulin had a significantly better effect on bleeding manifestations and coagulation parameters than heparin. Currently, ongoing trials with soluble thrombomodulin focus on DIC, organ failure, and mortality rate.

Physiological anticoagulant factor concentrates

Restoration of the levels of physiological anticoagulants in DIC may be a rational approach. In several small clinical trials, use of very high doses of AT concentrate showed even a modest reduction in mortality, however, without being statistically significant. A large-scale, multicenter, randomized controlled trial also showed no significant reduction in mortality of patients with sepsis [18]. Interestingly, post-hoc subgroup analyses of the latter study indicated some benefit in patients who did not receive concomitant heparin, but this observation needs validation.

A randomized controlled phase III trial of recombinant human activated protein C (APC) in patients with severe sepsis was prematurely stopped because of efficacy in reducing mortality in these patients [19]. Interestingly, patients who had DIC according to international criteria benefited more from the therapy with APC than patients who did not have overt DIC [4]. However, meta-analyses of published literature concluded that the basis for treatment with APC, even in patients with a high disease severity, was not very strong. A recently completed placebo-controlled trial in patients with severe sepsis and septic shock was prematurely stopped due to the lack of any significant benefit of APC. Subsequently, the manufacturer of APC has decided to withdraw the product from the market.

Fibrinolytic inhibitors

Most guidelines recommend against the use of anti-fibrinolytic agents, such as ε-aminocaproic acid or tranexamic acid, in patients with DIC. This is because these drugs block already suppressed endogenous fibrinolysis, and may further compromise tissue perfusion. However, in patients with DIC accompanied by primary fibrino(geno)lysis, as in some cases of acute promyelocytic leukaemia, giant cavernous haemangioma, heat stroke, and metastatic carcinoma of the prostate, the use of fibrinolytic inhibitors can be considered if the patient has profuse bleeding that does not respond to replacement therapy.

- Presence of an underlying disorder known to be associated with DIC (**no = 0, yes = 2**).
- Score global coagulation test results:
  - Platelet count (**>100 = 0; <100 = 1; <50 = 2**).
  - Level of fibrin markers (e.g. D-dimer, fibrin degradation products) (**no increase: 0; moderate increase: 2; strong increase: 3**)#.

- Prolonged prothrombin time (**<3 seconds = 0; >3 seconds, but <6 seconds = 1; >6 seconds = 2**).
- Fibrinogen level (> **1.0 g/L = 0;** < **1.0 g/L = 1**).

◆ Calculate score.

◆ If ≥5: compatible with overt DIC; repeat scoring daily.

If <5 is suggestive (not affirmative) for non-overt DIC, repeat next 1–2 days; # indicates strong increase >5× upper limit of normal; moderate increase is > upper limit of normal but <5× upper limit of normal.

Pathways involved in the activation of coagulation in DIC. Both perturbed endothelial cells and activated mononuclear cells may produce pro-inflammatory cytokines that induce tissue factor expression, thereby initiating coagulation. In addition, downregulation of physiological anticoagulant mechanisms and inhibition of fibrinolysis promotes intravascular fibrin deposition.

References

1. Levi M and Seligsohn U. (2010). Disseminated intravascular coagulation. In: Kaushansky K, Lichtman M, Beutler E, Kipps T, Prchal J, and Seligsohn U (eds) *Williams Hematology*. Philadelphia: McGraw Hill, 2593–2618.
2. Levi M and ten Cate H. (1999). Disseminated intravascular coagulation. *New England Journal of Medicine*, **341**, 586–92.
3. Levi M (2007). Disseminated intravascular coagulation. *Critical Care Medicine*, **35**, 2191–5.
4. Dhainaut JF, Yan SB, Joyce DE, et al. (2004). Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. *Journal of Thrombosis and Haemostasis*, **2**, 1924–33.
5. Levi M and Opal SM. (2006). Coagulation abnormalities in critically ill patients. *Critical Care*, **10**, 222.
6. Levi M and Meijers JC. (2010). DIC: which laboratory tests are most useful. *Blood Review*, **25**(1), 33–7.
7. Dempfle CE and Borggrefe M. (2008). Point of care coagulation tests in critically ill patients. *Seminars in Thrombosis & Hemostasis*, **34**, 445–50.
8. Taylor FBJ, Toh CH, Hoots WK, Wada H, and Levi M. (2001). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thrombosis and Haemostasis*, **86**, 1327–330.
9. Gando S, Nakanishi Y, and Tedo I. (1995). Cytokines and plasminogen activator inhibitor-1 in posttrauma disseminated intravascular coagulation: relationship to multiple organ dysfunction syndrome. *Critical Care Medicine*, **23**, 1835–42.
10. Levi M. (2009). Disseminated intravascular coagulation (DIC) in pregnancy and the peri-partum period. *Thrombosis Research*, **123**(Suppl. 2), S63–4.
11. Barbui T and Falanga A. (2001). Disseminated intravascular coagulation in acute leukemia. *Seminars in Thrombosis & Hemostasis*, **27**, 593–604.
12. Isbister GK. (2010). Snake bite doesn't cause disseminated intravascular coagulation: Coagulopathy and thrombotic microangiopathy in snake envenoming. *Seminars in Thrombosis & Hemostasis*, **36**(4), 444–51.
13. Levi M and van der Poll T (2010). Inflammation and coagulation. *Critical Care Medicine*, **38**, S26–34.
14. Levi M, de Jonge E, van der Poll T. (2001). Rationale for restoration of physiological anticoagulant pathways in patients with sepsis and disseminated intravascular coagulation. *Critical Care Medicine*, **29**(7 Suppl.), S90–429.
15. Esmon CT. (2001). Role of coagulation inhibitors in inflammation. *Thrombosis and Haemostasis*, **86**(1), 51–56.
16. Levi M, Levy M, Williams MD, et al. (2007). Prophylactic heparin in patients with severe sepsis treated with drotrecogin alfa (activated). *American Journal of Respiratory and Critical Care Medicine*, **176**, 483–90.
17. Levi M, Toh CH, Thachil J, and Watson HG. (2009). Guidelines for the diagnosis and management of disseminated intravascular coagulation. *British Journal of Haematology*, **145**, 24–33.
18. Warren BL, Eid A, Singer P, et al. (2001). Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *Journal of the American Medical Association*, **286**, 1869–78.
19. Bernard GR, Vincent JL, Laterre PF, et al. (2001). Efficacy and safety of recombinant human activated protein C for severe sepsis. *New England Journal of Medicine*, **344**(10), 699–709.
20. Lowenberg EC, Meijers JC, and Levi M. (2010). Platelet-vessel wall interaction in health and disease. *Netherlands Journal of Medicine*, **68**, 242–51.

CHAPTER 271

Prevention and management of thrombosis in the critically ill

Chee M. Chan and Andrew F. Shorr

Key points

- The incidence of venous thromboembolism (VTE) in the critically-ill patient is extremely high and ranges between 13 and 24% in the general medical ICU patient.
- Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) significantly decreases incidence of deep vein thrombosis (DVT) in critically-ill patients.
- Chemical thromboprophylaxis is preferred over mechanical DVT prophylaxis in the intensive care unit.
- LMWH is more effective at reducing the incidence of DVT among trauma and ischaemic stroke patients.
- The primary modality for managing VTE is prevention.

Introduction

Critically-ill patients face a heightened risk of venous thromboembolism (VTE) for multiple reasons. Typically, they suffer from conditions that lead to the features that encompass all three principles of Virchow's triad relative to thromboembolic disease. For example, they have disturbed blood flow because they are immobile, they have injured vascular endothelium due to multiple procedures, and they have alterations in the constitution of their blood (i.e. sepsis, inflammation). Furthermore, the underlying condition, itself leading to critical illness, can also represent an independent risk factor for VTE. These syndromes include, but are not limited to, acute respiratory failure, trauma, sepsis, and congestive heart failure.

More concerning, critically-ill patients necessarily lack the cardiopulmonary reserve required to tolerate a VTE, particularly a pulmonary embolus (PE). Conversely, since these patients are often both at increased risk for bleeding and are less tolerant of bleeding should it occur, the intensivist must carefully weigh the risk:benefit ratio regarding use of full dose anticoagulation.

Epidemiology of VTE in the ICU

The incidence of DVT varies among the heterogeneous ICU population and depends upon the reason for admission. Among the general medical ICU population, the incidence of DVT ranges between 13 and 24% in the first week of admission when using various imaging modalities to screen for DVT [1,2]. Moser and colleagues performed a prospective observational study among 34 patients admitted to a respiratory ICU [2]. Of the 23 subjects who had screening radiofibrinogen leg scans within the first week, 13% were found to have a DVT. In a similar study evaluating the incidence of DVT in a mixed medical-surgical critical care population, approximately 30% of subjects developed a DVT during the course of critical illness as determined using screening lower extremity Doppler examinations [1]. Of the 261 subjects enrolled, 2.7% were found to have a DVT within 48 hours of admission to the ICU, which demonstrates the hypercoagulability of these subjects. In trauma patients, the incidence of DVT is even more worrisome. Geerts documented the presence of DVT in 58% of 716 major trauma patients with the use of serial impedance plethysmography and lower extremity contrast venography [3]. Finally, among acute stroke patients, the incidence of DVT is as high as 70% with 1–2% succumbing to a fatal PE [4–6].

The incidence of PE is difficult to assess in the ICU. The current diagnostic modalities pose a challenge for screening and quantifying the incidence of disease. The inability of the intubated patient to make a conscious inspiratory effort limits the utility of ventilation-perfusion scintigraphy (V/Q scan). The increased risk of contrast nephropathy from computed tomography (CT) of the chest with PE protocol in a population already at higher risk for renal impairment hampers the ability to screen for PE in the ICU. Therefore, most knowledge regarding the prevalence of PE in the ICU derives from autopsy data. In post-mortem studies of ICU subjects, incidental PEs are found in approximately 7–27% with 1–3% of these PE felt to have caused demise [7]. However, autopsy data has substantial flaws and are subject to selection bias. Autopsies are mostly performed when the aetiology of death is unknown and, as such, only about 6–8% of critically-ill patients who die will have an autopsy [8]. Without knowing the cause of death in all subjects who die in the ICU, it is difficult to estimate the true mortality rate from PE in this patient population. Furthermore, since there is a high discrepancy rate between pre- and post-mortem diagnoses (20–40%) among critically-ill patients, one must be sceptical about diagnostic accuracy in this setting [7]. Specifically, PE remains one of the top three misdiagnosed diseases in the ICU, which re-emphasizes the need to prevent the condition.

Management of VTE among critical care subjects

The use of and choice for thromboprophylaxis in critical care patients is a complex topic. The heterogeneity of the ICU population with regards to the risk for thrombosis must be carefully

weighed against the risk of bleeding associated with anticoagulant options for prevention. There are two broad categories for thromboprophylaxis—mechanical and chemical. Mechanical VTE prophylaxis is generally reserved for those who are at high risk of VTE, but chemical prophylaxis is contraindicated. These individuals include those who are actively bleeding, those considered high risk for bleeding, and those with profound thrombocytopenia. Since the literature base for the efficacy of mechanical thromboprophylaxis in the ICU setting is particularly narrow, the initiation of pharmacological therapies must constantly be re-evaluated.

Five randomized controlled trials (RCTs) have been performed to assess the use of mechanical DVT prophylaxis in the critical care population [9–13]. Four of the five studies involved trauma patients, while the last study involved subjects with acute myocardial infarctions. In a pooled analysis of these five studies, 811 subjects were randomized to mechanical thromboprophylaxis versus another form of prophylaxis (placebo, another mechanical device, or a chemical agent, low molecular weight heparin (LMWH)) [14]. Due to these varying comparison groups, only two studies were pooled in a recent meta-analysis. To summarize, 562 subjects were randomized to pneumatic compression devices versus LMWH. LMWH was found to be superior and patients given mechanical prophylaxis were more than twice as likely to suffer a DVT (odds ratio: 2.37; 95% confidence interval [CI]: 0.57–9.9). In the study involving patients with acute myocardial infarctions ($n = 80$), graduated compression stockings had better efficacy at preventing DVT compared with placebo (0 versus 10%, $p = 0.003$) [9]. Given the scarcity of quality data supporting the use of mechanical thromboprophylaxis in the critically-ill patient, the preferred modality for VTE prophylaxis remains chemical options [15].

Several pharmacological therapies are recommended for the use of VTE prophylaxis in the critically ill; these include unfractionated heparin (UFH) and LMWH. While other agents are available for VTE prophylaxis, such as fondaparinux, rivaroxaban, and dabigatran, these agents have not yet been studied in the ICU patient population. Only a few randomized controlled trials have been performed to assess the safety and efficacy of chemical thromboprophylaxis in the ICU. About 223 mechanically-ventilated patients with chronic obstructive pulmonary disease were randomized to nadoparin, a LMWH, versus placebo [16]. Doppler ultrasonography was performed upon enrolment into the study, weekly, and when clinically indicated. All subjects also had a venography study performed at completion, after early discontinuation, or as confirmatory testing after a positive or indeterminant Doppler ultrasound study. The incidence of DVT was significantly lower for nadoparin compared to placebo (15.5 versus 28.2%, $p = 0.045$). There was no difference in the rate of adverse events, which included major and minor bleeding, and thrombocytopenia. In another RCT, 3746 critically-ill medical-surgical patients were randomized to either dalteparin 5000 U od or UFH 5000 U bd [17]. The incidence of DVT served as the primary outcome and was assessed within 2 days after admission and then twice weekly using Doppler ultrasonography. Secondary outcomes included the incidence of symptomatic PE and the development of major bleeding. Within the first two days of admission, 3.5% of subjects who received dalteparin already had a DVT, while 3.4% in the UFH group had a DVT. The incidence of DVT was also similar between groups (5.2% for dalteparin versus 5.8% for UFH, $p = 0.57$) using bi-weekly testing. However, those in the dalteparin group had fewer clinically significant PE compared with the UFH group (1.2 versus 2.0%, $p = 0.02$). Major bleeding was similar between groups (5.5% for dalteparin and 5.6% for UFH, $p = 0.98$). There was no correlation between renal function and bleeding with either agent. Thus, the rate of VTE is low in the presence of thromboprophylaxis for medical-surgical critical care patients. These studies demonstrate that chemical thromboprophylaxis is efficacious and safe in decreasing the incidence of DVT when compared with placebo. Overall, UFH and LMWH were similarly effective and safe in preventing VTE as a combined endpoint.

One must be cautious, however, about the interpretation of these studies. Screening for DVT with the use of Doppler ultrasonography has never been validated in the critical care setting and may therefore lead to over- or underdiagnosis of DVT. Additionally, there is uncertainty regarding the clinical significance of DVTs that are found incidentally. Patel and colleagues determined that the rate of symptomatic DVT and PE were only 1.0% (95% CI: 0.8–1.2) and 0.5% (95% CI: 0.4ƨ0.6%), respectively [18]. These incidence rates are substantially lower compared with the rate of asymptomatic VTE diagnosed when using screening tests. This study illustrates that VTE is underdiagnosed in the ICU and clinicians must be vigilant in identifying signs and symptoms of VTE in the ICU.

In combination, this data demonstrates that pharmacological therapy for VTE prophylaxis is safe and efficacious. Given the risks associated with the development of DVT and the risks associated with full dose anticoagulation in the ICU patient population, the best current management for DVT remains prevention. For these reasons, the American College of Chest Physicians recommends that early, thoughtful initiation of thromboprophylaxis upon admission to the ICU is imperative and that chemical prophylaxis is preferred to mechanical when the risk of bleeding is tolerable [15].

VTE prophylaxis in trauma patients

Trauma patients are at substantial risk for DVT with an incidence of 25–65% [19]. One RCT of 344 consecutive trauma patients randomized to the LMWH, enoxaparin 30 mg bd, versus UFH 5000 U bd for thromboprophylaxis has been performed to assess the efficacy and safety of these agents [3]. Leg venography was performed between 10 and 14 days after enrolment and when clinically indicated. The primary outcome was the incidence of DVT. The use of LMWH decreased the incidence of DVT compared to UFH (31 versus 44%, $p = 0.014$) with a relative risk reduction of 30% (95% CI: 4–50%). The incidence of proximal DVT was also lower in the LMWH group (6%) compared with UFH (15%) with a 58% risk reduction (95% CI: 12–87%). The risk for major bleeding was similar between groups. Thus, the high rate of DVT in this patient population mandates the consideration of chemical thromboprophylaxis when the risk of bleeding is acceptable.

VTE prophylaxis in ischaemic stroke

The risk for VTE in patients with acute ischaemic stroke can be as high as 70% [4–6]. Few studies have assessed the efficacy and safety of VTE prophylaxis in this patient population. In a meta-analysis pooling 2028 ischaemic stroke patients, the efficacy and safety of LMWH was compared to UFH for VTE prophylaxis [20]. Based on this meta-analysis, LMWH reduced the occurrence of DVT compared with UFH with an odds ratio of 0.54 (95% CI: 0.41–0.70). There were no differences in major bleeding, intracranial haemorrhage, and overall mortality between groups.

Conclusion

Prevention is the primary modality for managing VTE in the ICU. Although data are sparse, there is clear evidence that chemical thromboprophylaxis is the most effective means of preventing VTE. Newer evidence demonstrates that these agents are also safe with minimal to no increased risk for bleeding. In patients at particularly high risk for DVT in the ICU, mechanical devices should be used to prevent DVT until pharmacological agents can be initiated.

References

1. Cook D, Crowther M, Meade M, et al. (2005). Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. *Critical Care Medicine*, **33**(7), 1565–71.
2. Moser KM, LeMoine JR, Nachtwey FJ, and Spragg RG. (1981). Deep venous thrombosis and pulmonary embolism. Frequency in a respiratory intensive care unit. *Journal of the American Medical Association*, **246**(13), 1422–4.
3. Geerts WH, Jay RM, Code KI, et al. (1996). A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *New England Journal of Medicine*, **335**(10), 701–7.
4. McCarthy ST, Turner JJ, Robertson D, Hawkey CJ, and Macey DJ. (1977). Low-dose heparin as a prophylaxis against deep-vein thrombosis after acute stroke. *Lancet*, **2**(8042), 800–1.
5. McCarthy ST and Turner J. (1986). Low-dose subcutaneous heparin in the prevention of deep-vein thrombosis and pulmonary emboli following acute stroke. *Age and Ageing*, **15**(2), 84–8.
6. Kelly J, Rudd A, Lewis R, and Hunt BJ. (2001). Venous thromboembolism after acute stroke. *Stroke*, **32**(1), 262–7.
7. Blosser SA, Zimmerman HE, and Stauffer JL. (1998). Do autopsies of critically ill patients reveal important findings that were clinically undetected? *Critical Care Medicine*, **26**(8), 1332–6.
8. Perkins GD, McAuley DF, Davies S, and Gao F. (2003). Discrepancies between clinical and postmortem diagnoses in critically ill patients: an observational study. *Critical Care (London)*, **7**(6), R129–32.
9. Kierkegaard A and Norgren L. (1993). Graduated compression stockings in the prevention of deep vein thrombosis in patients with acute myocardial infarction. *European Heart Journal*, **14**(10), 1365–8.
10. Elliott CG, Dudney TM, Egger M, et al. (1999). Calf-thigh sequential pneumatic compression compared with plantar venous pneumatic compression to prevent deep-vein thrombosis after non-lower extremity trauma. *Journal of Trauma*, **47**(1), 25–32.
11. Murakami M, McDill TL, Cindrick-Pounds L, et al. (2003). Deep venous thrombosis prophylaxis in trauma: improved compliance with a novel miniaturized pneumatic compression device. *Journal of Vascular Surgery*, **38**(5), 923–7.
12. Ginzburg E, Cohn SM, Lopez J, Jackowski J, Brown M, and Hameed SM. (2003). Randomized clinical trial of intermittent pneumatic compression and low molecular weight heparin in trauma. *British Journal of Surgery*, **90**(11), 1338–44.
13. Kurtoglu M, Yanar H, Bilsel Y, et al. (2004). Venous thromboembolism prophylaxis after head and spinal trauma: intermittent pneumatic compression devices versus low molecular weight heparin. *World Journal of Surgery*, **28**(8), 807–11.
14. Limpus A, Chaboyer W, McDonald E, and Thalib L. (2006). Mechanical thromboprophylaxis in critically ill patients: a systematic review and meta-analysis. *American Journal of Critical Care*, **15**(4), 402–10; quiz/discussion, 11–12.
15. Kahn SR, Lim W, Dunn AS, et al. (2012). Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th edn, American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, **141**(2 Suppl.), e195S–226S.
16. Fraisse F, Holzapfel L, Couland JM, et al. (2006). Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. *American Journal of Respiratory and Critical Care Medicine*, **161**(4 Pt 1), 1109–14.
17. Cook D, Meade M, Guyatt G, et al. (2011). Dalteparin versus unfractionated heparin in critically ill patients. *New England Journal of Medicine*, **364**(14), 1305–14.
18. Patel R, Cook DJ, Meade MO, et al. (2005). Burden of illness in venous thromboembolism in critical care: a multicenter observational study. *Journal of Critical Care*, **20**(4), 341–7.
19. Attia J, Ray JG, Cook DJ, Douketis J, Ginsberg JS, and Geerts WH. (2001).Deep vein thrombosis and its prevention in critically ill adults. *Archives of Internal Medicine*, **161**(10), 1268–79.
20. Shorr AF, Jackson WL, Sherner JH, and Moores LK. (2008). Differences between low-molecular-weight and unfractionated heparin for venous thromboembolism prevention following ischemic stroke: a metaanalysis. *Chest*, **133**(1), 149–55.

CHAPTER 272

Thrombocytopenia in the critically ill

Jaimal Kothari and Marie Scully

Key points

- Sepsis and disseminated intravascular coagulation are the commonest causes of thrombocytopenia in the intensive care unit.
- Always assess the platelet count in combination with laboratory clotting parameters.
- Consumption, sequestration, impaired production, increased destruction, and haemodilution are the primary pathological mechanisms for thrombocytopenia, and in practice, a number of the mechanisms overlap and are implicated in critically-ill patients.
- Heparin-induced thrombocytopenia is a rare, but highly thrombogenic condition that needs prompt diagnosis and action.
- There are standardized platelet thresholds that should generally be followed when considering the need for platelet transfusions.

Introduction

The multiple co-morbidities of patients in intensive care make thrombocytopenia very common. It is typically, but essentially arbitrarily defined as a platelet count of $<150 \times 10^9$/L, with severe thrombocytopenia being $<50 \times 10^9$/L.

It is estimated that 35-45% of ICU patients have thrombocytopenia with between 5-20% severely thrombocytopenic [1–3]. The prevalence of thrombocytopenia is 20–30% of ICU admissions and a similar number of patients develop thrombocytopenia during their ICU admission. It is rarer for patients to be severely thrombocytopenic at admission to ICU, with one recent series showing it to be approximately 6% [4].

An understanding of the aetiology is crucial, allowing specific interventions as required, together with a global appreciation of how thrombocytopenia interacts with the multiple other haemostatic and mechanisms that define the bleeding risk, which is a daily consideration in many ICU patients.

Platelet count dynamics in ICU

The bone marrow produces approximately 150 billion platelets per day, and the average lifespan of a single unit is 7–10 days. In any disease process, the balance between production and consumption is altered, and this is especially notable in acutely sick patients. It is not uncommon to see a decrease in the platelet count on the first few days after admission to the ICU, especially in patients who have undergone surgery. The platelet nadir tends to occur 1–4 days post-surgery, with the count then tending to increase to the presurgery level, before a rebound thrombocytosis is often seen. This is in keeping with an initial consumptive/dilutional effect and subsequent increases above the normal range due to the normal physiological response to reduced platelet counts, where an increased thrombopoeitin leads to stimulation of megakaryocytes. In medical patients, a complex interplay of factors can lead to more unpredictable and labile counts, and are more likely to be thrombocytopenic on admission.

Thrombocytopenia and platelet dynamics as a prognostic factor

There is evidence that thrombocytopenia per se is associated with adverse outcomes. This is understandable as severely-ill patients have multifactorial mechanisms underlying their thrombocytopenia and critically unwell patients with thrombocytopenia who are admitted to the ITU have higher values on validated scoring systems used to stratify disease severity (e.g. MODS and APACHE) [5], compared with patients who are admitted with normal platelet counts. It has also been shown that the dynamics of platelet recovery—i.e. a blunted or absent rise in the platelet count after the initial decrease is associated with prolonged ICU stays and excess mortality. One series has shown that mortality in patients with thrombocytopenia ($< 150 \times 10^9$/L) at day 4 was 33%, compared with 66% at day 14 and mortality in normal counts [6].

Causes

There are five main mechanisms contributing to thrombocytopenia. Typically, in the intensive care unit (ICU) setting there is interplay of more than one:

- Haemodilution.
- Increased consumption.
- Increased platelet destruction.
- Reduced production.
- Increased sequestration.

Haemodilution (associated with bleeding) and consumption (typically associated with disseminated intravascular coagulation (DIC)/tissue trauma and sepsis) are the commonest reasons

for a low platelet count in the ICU, and it is normal to have at least two or three of the mechanisms involved at any particular time. Major haemorrhage can often lead to a partly dilutional and partly consumptive thrombocytopenia if product replacement does not include the judicious use of fresh frozen plasma and platelets.

Pseudothrombocytopenia

Pseudothrombocytopenia should also always be considered as a potential confounding factor. This is an in vitro phenomenon typically caused by either activation of the sample in the tube with clots or aggregates in ethylenediaminetraacetic acid (EDTA)-anticoagulated blood. Pseudothrombocytopenia is especially common in patients treated with GPIIb/IIIa antagonists, and this phenomenon is almost as frequently seen as true thrombocytopenia [7].

Sepsis and DIC

Sepsis and DIC are by the far the commonest causes of thrombocytopenia seen in the ICU, with significant overlap between both pathologies. The severity of sepsis does correlate with the magnitude of the platelet drop, and from a recent series, approximately 75% of septic episodes are associated with thrombocytopenia, and that as the count drops, the mean platelet volume (MPV) increases [8]. It is not uncommon for a moderate thrombocytopenia to be caused by sepsis alone, but when the count drops to less than 50×10^9/L, disseminated intravascular coagulation (DIC) is often present [9].

In the septic state, consumption, impaired production, and sequestration are all involved to a greater or lesser extent. They can all be involved at the endothelial cell surface as result of extensive and well understood interaction between platelets and the endothelium. Increased consumption can be associated with the sepsis itself, together with haemophagocytosis and, importantly, DIC. DIC is a frequent clinical problem in the acutely-ill patient—a syndrome caused by the systemic intravascular activation of the clotting system that leads to the generation of thrombin (the most potent in vivo activator of platelets) and formation of microvascular thrombi. Platelet counts in DIC can rapidly drop in association with the characteristic other abnormalities in laboratory clotting tests (raised prothrombin time (PT), raised activated partial thromboplastin time (APTT), raised D-dimers and fibrin degradation products (FDPs). Laboratory evidence of DIC is not always associated with bleeding, and an isolated thrombocytopenia can be the first evidence of impending DIC. The key mantra of managing DIC is to treat the underlying cause.

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia is an important aetiology not to miss, but can be difficult to pin-point as patients are often on multiple medications, and there are so many alternative explanations for thrombocytopenia in this patient group. Drugs can cause thrombocytopenia via a number of mechanisms, but the commonest cause is an immune-mediated idiosyncratic reaction. Typically with the immune form, the thrombocytopenia only occurs in the presence of the drug, and the timing is highly significant. On removal of the drug, the rapid recovery of the count is evidence for the drug being the cause. Drug induced thrombocytopenia may also be a direct myelosuppressive action on the bone marrow.

Rarer causes of thrombocytopenia in the intensive care unit

Post-transfusion purpura

This is an immune condition, most commonly caused by platelet allo-antibodies against the human platelet antigen HPA-1a. Post-transfusion purpura (PTP) should be considered if the patient received blood transfusions in the previous two weeks. Typically, PTP affects woman who during pregnancy, developed an antibody against the HPA-1a. Transfusion then leads to an immune response, which boosts anti-HPA-1a, which then destroy the patient's own platelets. Treating with intravenous immunoglobulin is effective.

Heparin-induced thrombocytopenia

Commonly tested for, but rarely found, this is a diagnosis not to be missed. It has an incidence of approximately 0.5% in ICU patients [10]. Heparin-induced thrombocytopenia (HIT) is caused by an immune-mediated adverse drug reaction caused by the development of IgG antibodies directed against platelet factor 4/heparin complexes that form on the surface of platelets. The antibody/antigen interaction leads to the activation of platelets, and vascular endothelium, leading to thrombin generation, and the development of potentially devastating venous/arterial thromboses and thrombocytopenia. HIT is at least 10 times more common in patients taking unfractionated heparin and more common in women who have undergone surgery, typically orthopaedics or cardiothoracic. Thrombocytopenia and thromboembolism are common in intensive care units without HIT, and therefore diagnosis of HIT requires a combination of appropriate clinical suspicion and the use of sensitive laboratory tests when appropriate. The '4Ts' scoring system, introduced by Warkentin and Heddle, gives a validated probability score on the basis of the nature of the thrombocytopenia (the percentage drop, and nadir), the timing of the thrombocytopenia, whether a thrombosis has formed and whether there is a potential alternative cause for thrombocytopenia. Following a confirmed case of HIT/or a high clinical suspicion prior to confirmation (even in the absence of new thrombosis)—all heparin must be stopped **immediately**. Anticoagulation is required to counteract the highly thrombogenic environment with alternative agents.

Micro-angiopathic haemolysis

Patients with thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS) are characterized by the presence of severe thrombocytopenia, micro-angiopathic haemolytic anaemia and end organ damage (typically brain/heart in TTP) and more kidney related damage in HUS, which can often require renal replacement therapy. These patients are often admitted to ITU for organ support and for the initiation/continuation of definitive treatment. In TTP the dysfunction/absence of the cleaving metalinoproteinase ADAMTS 13 (via an immune autoantibody, or in some cases the congenital absence of enzyme) leads to the accumulation of ultra-large von Willebrand multimers, and the activation of the clotting system with a consumptive coagulopathy and the development of intravascular thrombi, leading to the end organ damage. The mainstay of treatment is plasma exchange, with new evidence for immune suppression by Rituximab (a monoclonal anti-CD20 antibody) in acquired TTP [11]. Platelet transfusions are contraindicated in TTP, with exogenous platelets merely feeding the thrombogenic environment. Drugs are rarely implicated in the development of a TTP-like state, and in these cases, cessation

of the drug is key intervention. Laboratory findings that are suggestive of TTP/HUS are anaemia with a reticulocytosis, raised LDH, thrombocytopenia and a blood film showing evidence of red cell fragments, sometimes described as schistocytes. It should be noted that red cell fragments are also seen on the blood film of patients with DIC, and one of the key discriminating laboratory features being normal clotting times in TTP/HUS.

Immune thrombocytopenia

This is not typically seen as an isolated cause of thrombocytopenia in intensive care, but remains on the differential—an immune mediated peripheral destruction of platelets not associated with production failure. First-line treatments include corticosteroids or intravenous immunoglobulins.

Platelet counts, bleeding, and transfusions

ICUs are amongst the highest users of platelet pools in hospitals. Transfusion practice is widespread with marked variation in triggers and targets. This is partly explained by the lack of a convincing evidence base in this area, and a lack of appreciation of what a 'safe' platelet count is. The absolute platelet count is an independent risk factor for bleeding, however, impaired platelet function is also implicated, together with the other multiple interacting factors that control bleeding risk at any point in time—intervention type, local anatomical factors, hyperfibrinolysis, and DIC. It is rare for patients with platelet counts >10×10^9/L to bleed because of their thrombocytopenia alone and factors above are likely to be involved. The complexity of individual cases in the ICU together with the constant need for interventions (e.g. central lines, tracheostomies) and anticoagulation (for haemofiltration, prophylaxis, or treatment of thromboembolic disease) require a higher threshold and may lead to numerous platelet transfusions. There is not a good evidence base for transfusion triggers in this population, and what is deemed 'safe' varies. However, clinicians need a pragmatic guide to how and when platelet transfusions should be given. A single adult pool of platelets generally contains 240×10^9 platelets, and an increment of at least 10×10^9/L is expected, although the actual increment can be very variable. Multiply transfused patients can develop HLA-antibodies, and the transfusion of HLA-matched platelets helps ensure that immune-mediated destruction does not occur. National and international guidelines exist to guide clinicians, and one such guideline is highlighted in Table 272.1.

Table 272.1 Platelet thresholds and transfusion

Intervention type/clinical problem	Transfuse platelets if count below
Bone marrow failure/following chemotherapy, without bleeding	10×10^9/L
Active sepsis/low risk procedure (e.g. endoscopy/bronchoscopy)	20×10^9/L
Major surgery or procedure with high risk of bleeding (e.g. tracheostomy), lumbar puncture	50×10^9/L
Neurosurgery or high risk of bleeding into critical sites	100×10^9/L

Data from British Committee for Standards in Haematology and Blood Transfusion Taskforce, 'Guidelines for the use of platelet transfusions', *British Journal of Haematology*, 2003, **122**(1), pp.10–23.

Further well designed, randomized trials examining the risks of bleeding and platelet thresholds are needed to improve the evidence base in this area, and such studies are already being carried out in neonates [13]. Another area of uncertainty and variation within platelet transfusion practice is within dysfunctional platelets—acquired abnormalities usually due to antiplatelet agents. When these patients bleed, platelet transfusion is often of value in providing functional ability.

Anti-coagulating patients with thrombocytopenia

Superimposed thrombocytopenia can make formal anticoagulation risky, with differing practice to what platelet count is safe for full anticoagulation. Practice is generally not evidence based, with some units preferring an absolute platelet count of 50×10^9/L, below which all anticoagulation is withheld. Using unfractionated heparin allows a more rapid 'switch-off' of anticoagulation effect, but in practice there tends to be greater use of split-dose low molecular weight heparin, with dosing adjusted in relation to the absolute platelet count.

Conclusion

The multifactorial nature of thrombocytopenia in critically-unwell patients means that a logical approach is required to diagnose the cause(s), allowing timely aetiology-specific interventions, specifically to treat underlying pathologies and minimize bleeding risk.

References

1. Strauss R, Wehler M, Mehler K, et al. (2002). Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. *Critical Care Medicine*, **30**, 1765–771.
2. Stephan F, Hollande J, Richard O, et al. (1999). Thrombocytopenia in a surgical ICU. *Chest*, **115**, 1363–70.
3. Crowther MA, Cook DJ, Mead MO, et al. (2005). Thrombocytopenia in medical-surgical critically ill patients: prevalence, incidence, and risk factors. *Journal of Critical Care*, **20**, 348–53.
4. Marco-Schulke CM, Sánchez-Casado M, Hortigüela-Martín VA, et al. (2012). Severe thrombocytopenia on admission to the intensive care unit in patients with multiple organ failure. *Medicina Intensiva*, **36**(3), 185–92.
5. Vanderschueren S, De Weerdt A, Malbrain M, et al. (2000). Thromboc ytopenia and prognosis in intensive care. *Critical Care Medicine*, **28**, 1871–6.
6. Akca S, Haji-Michael P, de Mendonca A, et al. (2002). Time course of platelet counts in critically ill patients. *Critical Care Medicine*, **30**(4), 753–6.
7. Said SM, Hahn J, Schleyer E, et al. (2007). Glycoprotein IIb/IIIa inhibitor-induced thrombocytopenia: diagnosis and treatment. *Clinical Research in Cardiology*, **96**(2), 61–9.
8. Aydemir H, Piskin N, Akduman D, Kokturk F, and Aktas E. (2015). Platelet and mean platelet volume kinetics in adult patients with sepsis. *Platelets*, **26**(4), 331–5.
9. Neame PB, Kelton JG, Walker IR, et al. (1980). Thrombocytopenia in septicaemia: the role of intravascular disseminated coagulation. *Blood*, **56**, 88–92.
10. Crowther MA, Cook DJ, Albert M, et al. (2010). The 4Ts scoring system for heparin-induced thrombocytopenia in medical-surgical intensive care unit patients. *Journal of Critical Care*, **25**, 287–93.
11. Scully M. (2012). Rituximab in the treatment of TTP. *Hematology*, **17**(Suppl. 1), S22–4.
12. British Committee for Standards in Haematology, Blood Transfusion Task Force. (2003). Guidelines for the use of platelet transfusions. *British Journal of Haematology*, **122**, 10–23.
13. Planet-2. Available at: http://www.planet-2.com/

PART 11.4

Disorders of the blood cells

CHAPTER 273

Pathophysiology and management of anaemia in the critically ill

Timothy Walsh

Key points

- Anaemia is prevalent among the critically ill, especially during prolonged critical illness.
- Aetiology is multifactorial, including iatrogenic blood loss (especially blood sampling), reduced red cell lifespan, and impaired erythropoiesis.
- Most patients tolerate a haemoglobin concentration as low as 70–80 g/L without adverse effects on clinical outcome.
- Red cell transfusions have an uncertain risk-to-benefit profile in the critically ill, and should be restricted to bleeding patients, or non-bleeding patients requiring transfusion to maintain a haemoglobin concentration >70 g/L.
- Recombinant erythropoietin is not licensed for treating the anaemia of critical illness; parenteral iron therapy requires further evaluation before introduction into routine care.

Definition of anaemia

Anaemia is a haemoglobin concentration (Hb) below expected population values, when age, gender, pregnancy, and certain environmental factors, such as altitude, are taken into account. It results in a reduction in red cell mass and a decrease in the oxygen-carrying capacity of the blood. The World Health Organization (WHO) defines anaemia as a haemoglobin <130 g/dL (haematocrit <39%) for adult males and < 120 g/L (haematocrit <36%) for adult non-pregnant females. The WHO has further classified anaemia as mild (95–109 g/L), moderate (80–94 g/L), severe (65–79 g/L), and life-threatening (<65 g/L).

Prevalence of anaemia during critical illness

The prevalence of anaemia among critically-ill patients is high, but depends on patient case mix and the blood transfusion practice employed. More consistent use of restrictive Hb transfusion triggers, typically 70–90 g/L since publication of the Transfusion Requirements In Critical Care (TRICC) study [1], have enabled prevalence attributable to critical illness to be more accurately estimated. At ICU admission 10–15% of patients have a history of chronic anaemia, but typically the first Hb measured indicates anaemia in 60–70% of patients and 20–30% have a Hb <100 g/L [2]. Anaemia is associated with greater illness severity and older age.

During early ICU stay Hb decreases progressively in many patients, typically by 0.1–5 g/L/day in ICU, until clinicians intervene with blood transfusions. Consequently, the prevalence of anaemia increases with duration of ICU stay and typically 70–80% of patients are anaemic at ICU discharge, with 20–30% having Hb values <90 g/L [3]. Local blood transfusion policies will strongly influence anaemia severity in longer stay patients, but typically mean Hb concentrations among ICU populations are 90-100 g/L. Longer ICU stay and greater organ dysfunction are associated with more severe anaemia at ICU discharge.

Anaemia frequently persists for many weeks following ICU discharge and is often present when patients are discharged from acute care facilities [3]. Recovery occurs much slower than in otherwise healthy individuals suffering acute anaemia following blood loss and 10–30% of patients remain anaemic for at least 3 months [4]. The importance of anaemia to functional recovery is unknown.

Anaemia and outcome

Anaemia is associated with adverse outcomes during critical illness, including failure of liberation from mechanical ventilation, myocardial ischaemia and infarction, and increased risk of death. As anaemia is most prevalent in patients with greatest illness severity and longest intensive care unit (ICU) stays, it is uncertain whether this association is causative or simply an epiphenomenon. Importantly, the association does not imply that interventions to modify anaemia will improve outcomes and the risk to benefit profile of interventions to treat anaemia requires further evaluation. The heterogeneity of critical care populations also means that similar treatment effects cannot be assumed for all patient groups.

Aetiology of anaemia during critical illness

Important factors contributing to anaemia during critical illness are summarized in Fig. 273.1.

Haemodilution

Haemodilution contributes to the rapid decrease in Hb described during early ICU treatment, as a result of resuscitation with fluids

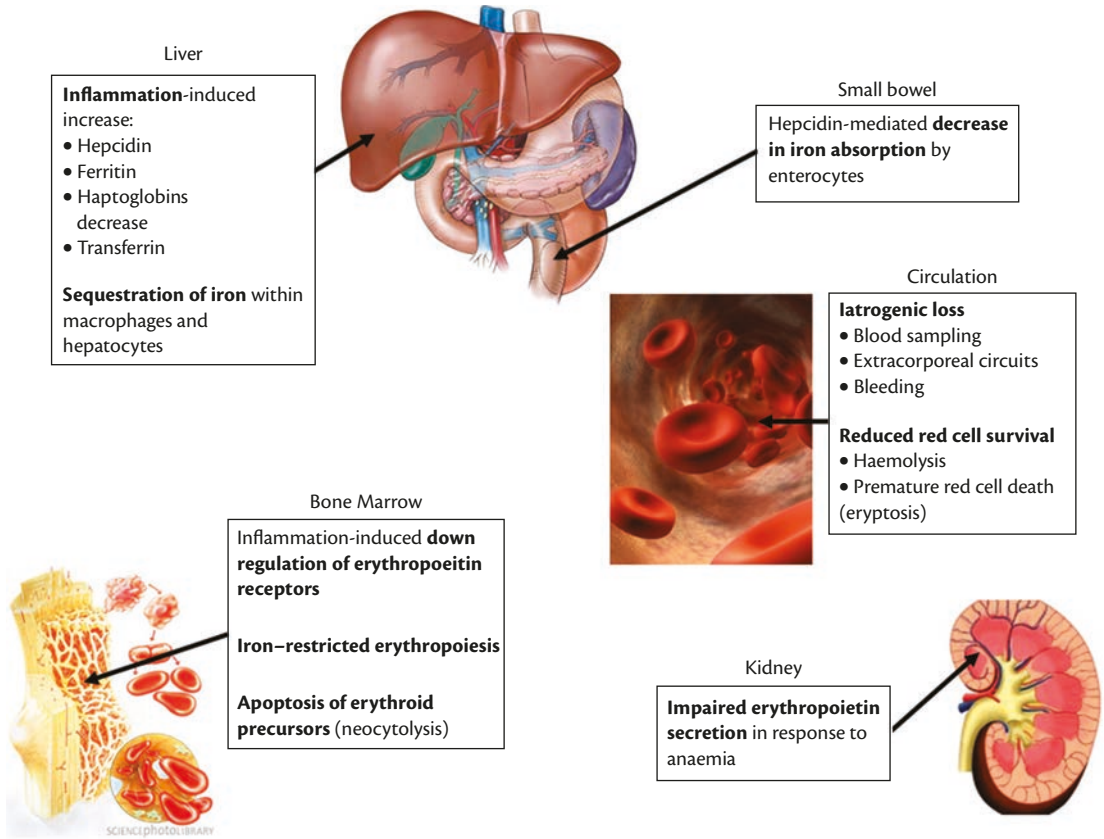


Fig. 273.1 Pathogenesis of anaemia during critical illness.

to expand intravascular volume. Modest haemodilution can cause anaemia without decreasing red cell mass or, importantly, oxygen carrying capacity.

Red cell loss

Iatrogenic blood loss

Blood loss is a significant cause of anaemia in ICU patients. Diagnostic blood sampling typically amounts to 30–40 mL/day, and accounted for approximately 30% of blood transfusion requirements prior to the introduction of blood conservation measures [2]. Sampling volumes are highest for sicker patients, such as those requiring advanced respiratory support or renal replacement therapy who require frequent monitoring of gas exchange or blood coagulation. Several strategies are effective at reducing blood sampling, including the use of paediatric sampling tubes [5] and collection systems that enable the return of dead space volumes from arterial sampling lines [6]. Local protocols to limit sampling frequency will also significantly decrease iatrogenic blood loss. Other sources of iatrogenic blood loss include haemofiltration circuits and other extracorporeal systems.

Haemorrhage

There are many potential sources of bleeding in critically-ill patients. The contribution of stress ulceration is probably small with modern resuscitation and stress ulcer prophylaxis. About 20% of ICU patients experience at least one episode of significant bleeding during ICU stay, and between 20 and 50% of all blood transfusions administered during ICU treatment are associated with clinically significant bleeding [7].

Reduced red cell survival

It is likely that critical illness, and sepsis in particular, reduces RBC lifespan [2]. Premature death of mature RBCs (termed eryptosis, a type of cellular apoptosis) is thought to be triggered, in part, by oxidant injury and other inflammatory processes, which are features of most critical illnesses. Inflammatory mediators, such as TNF-α and IL-1, decrease erythrocyte survival time in other settings, and induce premature apoptosis among RBCs. Cell injury causes changes including phosphatidylserine exposure on RBC membranes, which marks cells for engulfment by macrophages. Another process, neocytolysis, is the selective removal of young circulating RBCs, and is associated with rapid reductions in plasma levels of erythropoietin (EPO). Although a pathophysiological rationale exists for both eryptosis and neocytolysis their relative importance to critical illness anaemia is currently unknown.

Increased haemolysis is also likely during critical illness, especially in association with extracorporeal circuits, but is difficult to demonstrate clinically. Serum haptoglobins are positive acute phase proteins; consequently, their utility as biomarkers of haemolysis is limited unless severe haemolytic anaemia is present.

Reduced red cell production

The essential factors for normal erythropoiesis include iron, zinc, folate, and vitamin B12, under the influence of erythropoietin (EPO), thyroxine, androgens, cortisol, and catecholamines. Metabolism of all of these is affected by critical illness. In health RBC formation occurs at a basal rate of 15–20 mL/day under

steady-state conditions, increasing to >200 mL/day after haemolysis or heavy blood loss in iron-replete healthy individuals.

Anaemic critically-ill patients typically have a normochromic normocytic anaemia [7]. Reticulocyte counts are low compared with the healthy response to anaemia suggesting impaired erythropoiesis. This pattern is similar to the anaemia of chronic disease, which is frequently associated with inflammatory illness [8]. The typical biochemical parameters observed in anaemic critically-ill patients are shown in Table 273.1.

Iron metabolism

ICU patients typically have a low serum iron, total iron binding capacity, serum transferrin, transferrin saturation, and serum iron/total iron binding capacity ratio [7]. Serum ferritin concentration is usually normal or increased, a pattern typical of inflammatory conditions. Ferritin synthesis increases and transferrin decreases, because these are, respectively, positive and negative acute phase proteins. The net result is a transfer of iron into storage form (ferritin) within macrophages and hepatocytes, which reduces plasma transferrin saturation and serum iron. The iron regulatory protein hepcidin plays a key role in these processes [8]; it is upregulated when body iron stores are replete and downregulated during iron deficiency. Hepcidin decreases duodenal iron uptake and release of iron into the circulation by enterocytes, and prevents release of storage iron from macrophages and hepatocytes. Inflammation induces upregulation of hepcidin irrespective of iron status, which effectively reduces the availability of iron for RBC production. This iron-restricted erythropoiesis, also sometimes termed functional iron deficiency, results in impaired RBC production despite adequate total body iron stores. Several parameters are associated with functional iron deficiency, including a reduced reticulocyte haemoglobin concentration (CHR) and increased percentage hypochromic red cells in peripheral blood, both of which have been demonstrated in the critically ill [6]. Transferrin receptors are shed into the circulation as soluble molecules (sTFR) when erythropoiesis is increased or during significant iron deficiency, but concentrations of sTFR are normal in most anaemic critically-ill patients [4,7]. Taken together, these data indicate that the most critically-ill patients do not have an absolute iron deficiency, but many have a functional iron deficiency resulting from inflammation-mediated sequestration of iron within macrophages and hepatocytes. The resulting iron-restricted erythropoiesis may contribute to anaemia, especially when the duration of critical illness is prolonged. The difficulties diagnosing iron deficiency during critical illness make an accurate estimation of prevalence challenging, but is estimated to affect 10–20% of anaemic patients. It has been suggested that a reduced hepcidin concentration can be used to identify iron-deficiency during critical illness [9].

Table 273.1 Biochemical characteristics of anaemia in critically-ill patients

	Change in relation to healthy state
Serum iron	↓
Total iron binding capacity	↓
Serum iron/total iron binding capacity ratio	↓
Ferritin	↑
Transferrin	↓
Transferrin saturation	↓
Soluble transferrin receptor concentration	N
Percentage hypochromic red cells	N/↑
Vitamin B12 and folate	N
Erythropoietin concentration	N/slight increase
Hepcidin concentration	↑

N, normal range.

B12 and folate metabolism

Vitamin B12 or folate deficiency is rare in critically-ill patients, and has been demonstrated in <5% of ICU patients [2,7].

Endogenous erythropoietin response

The normal response to anaemia is to increase EPO release from the kidneys. Critically-ill patients have inappropriately low EPO concentrations for their degree of anaemia [2,7]. The blunted EPO response probably results from inhibition of the *EPO* gene by inflammatory cytokines and direct renal injury. Some drugs commonly used in critical care also reduce EPO release in response to anaemia, such as angiotensin-converting enzyme inhibitors and beta-blockers. Downregulation of EPO receptors on marrow red cell precursor cells may also contribute to blunted erythropoiesis.

Abnormal red blood cell maturation

Inflammatory cytokines such as tumour necrosis factor α, interleukin-1 and interleukin-6 directly inhibit red cell formation, and other circulating factors such as interferon γ can induce apoptosis of erythroid precursors, which could be important during critical illness [2,7]. These factors, together with a relative EPO deficiency, downregulation of EPO receptors, and decreased iron availability are likely explanations for the poor erythroid response during critical illness.

Management of anaemia

Reduction of red cell loss

Decreasing iatrogenic blood loss by reducing sampling frequency, sample volumes, and systems that allow re-infusion of dead space from lines can reduce anaemia severity [2,5,6].

Red cell transfusion

The treatment with greatest efficacy for increasing haemoglobin concentration is red cell transfusion. However, evidence from physiological studies and randomized trials indicates that anaemia is well-tolerated by the majority of critically-ill patients, despite the risk of inadequate oxygen delivery, increased tissue oxygen requirements, and impaired oxygen extraction [2,7]. Stored red cell transfusions have potential risks, including pro-inflammatory effects, immunomodulation, and increased infection [10,11]. Decreased deformability, greater endothelial adherence, and impaired oxygen release also mean that stored red cells are less effective oxygen transporters than circulating autologous cells [10,11]. These factors may explain the association between red cell transfusion and adverse patient outcomes in many cohort studies, and in some randomized trials, and questions the risk-to-benefit balance of red

cell transfusion to treat anaemia during critical illness [12]. Based on available evidence a default haemoglobin transfusion trigger of 70 g/L is justified in haemodynamically-stable non-bleeding patients [13,14]. Factors that support using higher transfusion triggers include the presence of tissue hypoxia (elevated lactate concentration), chronic ischaemic heart disease, acute coronary syndromes, delayed liberation from mechanical ventilation, and acute neurological injury. The quality of evidence to guide practice in these situations is poor. The lack of high quality evidence or physiological measures to assess adequacy of organ perfusion within individual patients mean clinician judgement strongly influences clinical decision-making in these situations. Most guidelines suggest a haemoglobin transfusion trigger of between 70 and 90 g/L for critically-ill anaemic patients, reassessing patients after each red cell unit [13,14]. Recently published trials have found no evidence to support a transfusion trigger >70 g/L for patients with septic shock [15], but some evidence of benefit from more liberal transfusion triggers after cardiac surgery [16]. A large trial using clinician-determined transfusion decisions found no evidence of benefit from using exclusively fresher RBCs (stored on average 6.1 days) with standard issue RBCs (stored on average 22 days) for critically ill patients [17].

EPO therapy

Relative EPO deficiency and impaired erythropoeisis provide a physiological rationale for pharmacotherapy with exogenous EPO during critical illness. Epoetin alfa (or any erythropoiesis stimulating agents) is not currently licensed for use to treat the anaemia of critical illness, but several trials have evaluated its efficacy and effectiveness [18]. The three largest trials were industry sponsored (EPO-1, EPO-2, and EPO-3), and had varying sample size, inclusion criteria, and intervention regimens (dose of erythropoietin; dose and route of iron therapy) [18,19]. A key difference was the progressive adoption of more restrictive haemoglobin transfusion triggers with each trial, decreasing from a mean of 90 g/L (EPO-1) to 80 g/L (EPO-3). Although EPO-1 and EPO-2 showed a small reduction in transfusion requirements, there was no transfusion-sparing effect in EPO-3 (the largest trial). Thrombotic events also occurred more frequently with EPO therapy in EPO-3, possibly in association with failure to provide thromboprophylaxis. Based on this evidence EPO therapy is not recommended to treat the anaemia of critical illness. A sub-group analysis of the EPO-3 trial indicated an association between EPO therapy and improved survival in trauma patients [19]. It is hypothesized that EPO might have cytoprotective effects, but these are likely mediated through different receptors (EPO-BCR receptor) rather than any link to anaemia (erythropoietic effect mediated via EPO-R receptors) [2].

Iron therapy

Evidence from animal and experimental studies suggests that greater iron availability may promote infection and exogenous therapy may induce oxidative stress [20]. There is no high quality evidence to support this association in humans, but it is a possible evolutionary explanation for iron sequestration within reticulo-endothelial cells, reduced intestinal iron absorption, during inflammatory illnesses and infections. Increased hepcidin concentrations during inflammatory illness decrease intestinal iron absorption, suggesting that parenteral iron therapy is required to effectively treat functional iron deficiency. Parenteral iron preparations vary, and each has documented risks, including anaphylaxis. The risk to benefit profile of enteral and parenteral iron in anaemic critically-ill patients has not been investigated in large clinical trials in critically-ill humans. The difficulty diagnosing iron-deficient erythropoiesis during critical illness also makes this challenging. Routine administration of iron therapy to treat anaemia is not currently recommended by any route during critical illness. Ongoing and future trials may provide evidence to guide practice.

Conclusion

Anaemia is a prevalent feature of critical illness, with multiple aetiology. During long-term critical illness anaemia results mainly from iatrogenic blood loss and impaired erythropoiesis. Anaemia is well-tolerated by most critically-ill patients, and blood transfusions in non-bleeding patients are rarely indicated if the Hb is greater than 80–90 g/L. EPO is not licensed for use to treat the anaemia of critical illness; parenteral iron therapy requires further evaluation before introduction into routine practice.

References

1. Hébert PC, Wells G, Blajchman MA, et al. (1999). A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *New England Journal of Medicine*, **340**, 409–17.
2. Hayden SJ, Albert TJ, WatkinsTR, and Swenson ER. (2012). Anemia in critical illness insights into etiology, consequences, and management. *American Journal of Respiratory and Critical Care Medicine*, **185**, 1049–57.
3. Walsh TS, Lee RJ, Maciver CR, et al. (2006). Anemia during and at discharge from intensive care: the impact of restrictive blood transfusion practice. *Intensive Care Medicine*, **32**, 100–9.
4. Bateman AP, McArdle F, and Walsh TS. (2009). Time course of anemia during six months follow up following intensive care discharge and factors associated with impaired recovery of erythropoiesis. *Critical Care Medicine*, **37**, 1906–12.
5. Sanchez-Giron F and Alvarez-Mora F. (2008). Reduction of blood loss from laboratory testing in hospitalized adult patients using small-volume (pediatric) tubes. *Archives of Pathology & Laboratory Medicine*, **132**, 1916–19.
6. Mukhopadhyay A, Yip HS, Prabhuswamy D, et al. (2010). The use of a blood conservation device to reduce red blood cell transfusion requirements: a before and after study. *Critical Care*, **14**, R7.
7. Walsh TS and Saleh EE. (2006). Anaemia during critical illness. *British Journal of Anaesthesia*, **97**: 278–91.
8. Weiss G and Goodnough LT. (2005). Anemia of chronic disease. *New England Journal of Medicine*, **352**, 1011–23.
9. Lasocki S, Baron G, Driss F, et al. (2010). Diagnostic accuracy of serum hepcidin for iron deficiency in critically ill patients with anemia. *Intensive Care Medicine*, **36**, 1044–8.
10. Zimrin A and Hess J. (2009). Current issues relating to the transfusion of stored red blood cells. *Vox Sanguinis*, **96**, 93–103.
11. Tinmouth A, Fergusson D, Yee IC, and Hebert PC. (2006). Clinical consequences of red cell storage in the critically ill. *Transfusion*, **46**, 2014–27.
12. Marik PE and Corwin HL. (2008). Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. *Critical Care Medicine*, **36**, 2667–74.
13. Napolitano LM, Kurek S, Luchette FA, et al. (2009). Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care. *Critical Care Medicine*, **37**, 3124–57.

14. Walsh TS, Wyncoll DL, and Stanworth SJ. (2010). Managing anaemia in critically ill adults. *British Medical Journal*, **341**, c4408.
15. Holst LB, Haas N, Wetterslev J, et al. (2014). Lower versus higher haemoglobin threshold for transfusion in septic shock. *New England Journal of Medicine*, **371**, 1381–91.
16. Murphy GJ Pike K, Rogers CA, et al. (2015). Liberal or restrictive transfusion after cardiac surgery. *New England Journal of Medicine*, **372**, 997–1008.
17. Lacroix J, Hébert PC, Fergusson DA, et al. (2015). .Age of transfused blood in critically ill adults. *New England Journal of Medicine*, **372**, 1410–18.
18. Zarychanski R, Turgeon AF, McIntyre L, and Fergusson DA. (2007). Erythropoietin-receptor agonists in critically ill patients: a meta-analysis of randomized controlled trials. *Canadian Medical Association Journal*, **177**, 725–34.
19. Corwin HL, Gettinger A, Fabian TC, et al. (2007). Efficacy and safety of epoetin alfa in critically ill patients. *New England Journal of Medicine*, **357**, 965–76.
20. Shander A and Javidroozi M. (2012). Resurrecting the iron age. *Critical Care Medicine*, **40**, 2252–3.

CHAPTER 274

Pathophysiology and management of neutropenia in the critically ill

Benoit Champigneulle and Frédéric Pène

Key points

- Neutropenia is a common side-effect of most chemotherapy regimens and is defined by an absolute neutrophil count <500/mm^3.
- Profound (<100 neutrophils/mm^3) and prolonged (>7 days) neutropenia carry the highest risk for severe bacterial and invasive fungal infections.
- Febrile neutropenia imposes urgent empirical antibiotic therapy.
- The choice of the initial antimicrobial regimen should involve the presence of complications such as pneumonia or severe sepsis as well as the risk assessment of Gram-positive and fungal infections.
- The outcome of critically-ill cancer patients including neutropenic patients has markedly improved over the last two decades.

Introduction

Neutropenia is defined as an absolute neutrophil count <500 cells/mm^3, but also includes situations when neutrophil count is predicted to drop within a few days. The spectrum of infections encountered during neutropenia relies on the critical role of phagocytic cells in host defence against bacteria and fungi. Therefore, neutropenia, especially when profound and prolonged, represents a major risk factor for severe bacterial and invasive fungal infections. Common sources of infections include the lung, the gastrointestinal tract, soft tissues, and indwelling catheters. In addition, some patients may experience respiratory status deterioration at the time of neutropenia recovery due to pulmonary influx of activated neutrophils. Whatever the initial clinical presentation, the risk for rapid clinical deterioration of febrile neutropenic patients underlies the concept of urgent antimicrobial empirical treatment. The present chapter aims at discussing the particularities of neutropenic patients in the intensive care unit (ICU).

Aetiologies and mechanisms of neutropenia in the ICU

The leading mechanism of neutropenia is related to chemotherapy- and radiotherapy-induced myelotoxicity that also often accounts for thrombocytopenia and anaemia. The type and dosing of cytostatic drugs as well as the extent of radiation field and dosimetry determine the depth and duration of neutropenia. Patients with solid tumours usually exhibit moderate and short (<7 days) neutropenia. In contrast, patients with acute leukaemia, high-grade lymphoma and haematopoietic stem cell transplantation (HSCT) exhibit profound (<100 neutrophils/mm^3) and prolonged neutropenia. In this setting, the mechanism of neutropenia is obvious and does not require additional investigations. However, bone marrow explorations may provide useful prognostic information in critically-ill patients for whom neutropenia recovery is urgently expected. Bone marrow may exhibit granulocytes progenitors suggestive of neutropenia recovery within a few days, or may conversely appear empty or invaded by malignant cells.

Neutropenia can also result from bone marrow involvement by haematological malignancies or by solid tumour metastasis or from associated mechanisms such as haemophagocytosis or bone marrow necrosis. Non-malignant disorders can also present with neutropenia, including aplastic anaemia, drug-induced agranulocytosis, auto-immune neutropenia or vitamin deficiency. Various infections can be responsible for neutropenia, either by bone marrow involvement (dengue virus, leishmaniosis), haemophagocytic lymphohistiocytosis (tuberculosis), or by granulopoiesis exhaustion with maturation blockade that typically occurs in severe pneumococcal infections. Diagnosis relies on the presence of associated cytopenias, cytological examination of blood smears and most often bone marrow exploration by sternal puncture or biopsy. Neutropenia may occasionally result from peripheral mechanisms, such as auto-immune destruction of neutrophils.

Epidemiology of infections in neutropenic patients

The depth and duration of neutropenia are the critical factors that determine the development of infections. Profound and prolonged neutropenia observed during acute leukaemia induction and intensive conditioning regimen of HSCT carry the highest risk of bacterial and invasive fungal infections. The risk of febrile neutropenia is increased by disruption of anatomical barriers, such as indwelling catheters, mucositis, and enterocolitis. Herpes simplex virus reactivation may also contribute to oral mucosal damage in this setting.

In addition, many anticancer treatments affect B- and T-cell immunity, and lymphopenia represents an independent risk factor of infections during neutropenia.

Numerous interventional studies and observational surveys have delineated the trends in microbiological epidemiology of febrile neutropenia over time. Of note, these data are based on blood cultures that are retrieved positive in less than one-third of febrile episodes, owing to low bacterial inocula or early administration of broad-spectrum antibiotics. Until the mid-eighties, Gram-negative bacilli including enterobacteriaceae and *Pseudomonas aeruginosa* were the most frequent pathogens encountered in febrile neutropenic episodes. Since then, Gram-positive cocci have become predominant as a consequence of severe mucosal damage induced by intensive chemotherapy, the increasing use of indwelling vascular access, gut decontamination with absorbable or non-absorbable antibiotics and treatment with anti-acid drugs [1,2]. Coagulase-negative staphylococci are the most frequent isolates in febrile neutropenic patients, although the distinction between infection and blood culture contamination is often unclear. Importantly, virulent pathogens, such as Gram-negative bacilli, streptococci, and *Staphylococcus aureus* account for most documented episodes of severe sepsis and septic shock in neutropenic patients [3,4]. Furthermore, polymicrobial infections represent a significant proportion of documented infections in neutropenic patients with gastrointestinal and soft tissue infections.

Invasive fungal infections also concur to severe complications in neutropenic patients [4]. The common clinical presentation of invasive candidiasis in neutropenic patients is candidaemia from digestive or cutaneous origin. Alternatively, hepatosplenic candidiasis may occur after neutropenia recovery as a manifestation of immune reconstitution syndrome towards previous occult candidaemia. Invasive aspergillosis typically affects patients with prolonged neutropenia or long-term corticosteroid treatment. The diagnosis of pulmonary aspergillosis is most often presumptive and based on retrieval of the fungus in respiratory samples, positive galactomannan antigen and CT-scan findings with nodules surrounded by the round-glass opacities, also known as the halo sign. Screening by galactomannan antigen assay is limited by false-positive results induced by beta-lactams or food, but retains a good performance in neutropenic patients [5]. Finally, neutropenia is also a risk factor for emergent fungal infections such as mucormycosis that are not covered by recent antifungal drugs such as echinocandins and voriconazole.

Outcome of neutropenic patients in the ICU

Over the last two decades, a number of studies reported an improvement in the outcome of cancer patients in the ICU including those with neutropenia. Several factors accounted for this trend through advances in both antitumoural treatments and supportive care. Close collaborations between haematologist/oncologists and intensivists resulted in better selection of patients likely to benefit from intensive care, early detection of organ failures, and early admission to the ICU in order to prevent further deterioration. Specifically, recent advances in care of severe sepsis and septic shock were associated with a dramatic improvement in survival of non-neutropenic and neutropenic patients [3,4,6].

Although neutropenia was previously associated with poor outcome, recent data suggest it is no longer a risk factor of mortality in critically-ill cancer patients [4,7,8]. Conversely, some neutropenic patients with recent intravenous chemotherapy or allogeneic HSCT recipients during engraftment period may even fare better than non-neutropenic counterparts [9,10]. As an explanation, infections that largely account for organ failures in neutropenic patients are likely to be controlled by antimicrobials treatment and forthcoming reversal of immunosuppression through neutropenia recovery. Therefore, admission to the ICU of neutropenic patients should no longer be considered as a terminal event, but as an integral part of supportive care in the curative process of the underlying disease.

Antimicrobial treatments in neutropenic patients

Principles of antibiotic treatment

The principles ruling antimicrobials management in febrile neutropenia have been formally summarized by the recently updated guidelines of the Infectious Diseases Society of America [11]. Early initiation of empirical antibiotic therapy represents the cornerstone of the treatment of febrile neutropenia. However, practical modalities may differ according to the clinical presentation and to the risk assessment for specific pathogens. High-risk patients include those with anticipated prolonged and profound neutropenia and/or significant co-morbid conditions, including hypotension, pneumonia, new-onset abdominal pain, and neurological changes, and therefore include virtually all neutropenic patients in the ICU. Therefore, the initial antibiotic regimen in critically-ill neutropenic patients should provide a broad coverage against Gram-negative and -positive bacteria through antibiotic combination.

The initial antibiotic regimen is based on broad-spectrum beta-lactams with anti-pseudomonal activity, including piperacillin-tazobactam, ceftazidime, cefepime, and carbapenems, and should take into account the presumed source of infection, the presence of risk factors for Gram-positive cocci, previous drug-induced allergy, and local patterns of antibiotic resistance. The widespread emergence of multiresistant bacteria is also a matter of concern in neutropenic patients as a consequence of multiple courses of antibiotics prior to ICU admission. Digestive colonisation or previous infections caused by extended-spectrum beta-lactamase enterobacteriaceae, multiresistant *Pseudomonas aeruginosa*, meticillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococci* should be carefully tracked in the medical file.

Addition of other antimicrobials (aminoglycosides, fluoroquinolones, and/or vancomycin) has been recommended in order to broaden the antibiotic spectrum and/or to improve bactericidal activity in patients with pneumonia or haemodynamic instability. Aminoglycosides are highly bactericidal antibiotics, which display synergism with beta-lactams. Although a number of studies did not retrieve any overall benefit to aminoglycosides in febrile neutropenia, antibiotic combination with beta-lactams, and aminoglycosides may improve outcome in Gram-negative bacteraemia and severe sepsis [3,12]. Most beta-lactams provide excellent coverage against viridans streptococci or meticillin-susceptible *Staphylococcus aureus*. However, suspicion of resistant Gram-positive cocci or the use of ceftazidime or aztreonam, which retain poor activity against Gram-positive bacteria may indicate empirical treatment with vancomycin. Linezolid

represents a valuable alternative to vancomycin, although delayed recovery of neutropenia may be of concern in these patients [13]. Step-down of antibiotic regimen should be considered after 48 hours in the light of bacterial documentation. However, maintenance of a broad spectrum beta-lactam is advocated until neutropenia recovery in order to prevent sepsis recurrence with Gram-negative bacteria. Gram-negative bacteraemia, most especially those related to *Pseudomonas aeruginosa*, may indicate a combination antibiotic therapy with aminoglycosides [12]. Specific coverage for Gram-positive organisms may be stopped if no evidence of such infection [14].

Antibiotic pharmacokinetics

Neutropenic patients display some pharmacokinetic particularities of beta-lactams, aminoglycosides and glycopeptides that should be taken into account in order to optimize the efficacy of antibiotic treatment [15]. Beta-lactams are time-dependent antibiotics requiring that serum concentrations exceed the minimal inhibitory concentration (MIC) of the causative bacteria for most of the dosing interval. In neutropenic patients, increased volumes of distribution and the risk of too low trough levels require shorter dosing intervals or even continuous infusion for short-life beta-lactams in order to prevent bacterial regrowth. Glycopeptides are also time-dependent antibiotics with increased volume of distribution and shorter elimination half-life. The use of higher doses of glycopeptides is recommended more highly in neutropenic patients than in non-neutropenic ones, as is monitoring of trough levels. Alternatively, efficient and durable concentrations of vancomycin are better achieved with continuous infusion. Aminoglycosides are highly bactericidal concentration-dependent antibiotics for which the efficacy is dependent on a high ratio between concentration peak and MIC of the causative pathogen. Pharmacokinetic changes of aminoglycosides in neutropenic patients include increased distribution volumes and increased clearance rates. Therefore, several studies documented that achievement of high aminoglycoside concentrations required once-daily dosing regimen that also appeared to be less nephrotoxic than multiple daily schedules.

Antifungal treatments

Prolonged and profound neutropenia is a major risk factor of invasive fungal infections. High-risk neutropenic patients with persistent or recurrent fever after 5–7 days of antibiotics should be considered for investigation of invasive fungal infection and empirical antifungal treatment. Echinocandins and amphotericin are currently approved for empirical treatment of febrile neutropenia [16,17]. Lipid formulations of amphotericin are preferred to amphotericin deoxycholate in critically-ill neutropenic patients owing to the frequency of renal dysfunction and/or concurrent use of nephrotoxic drugs [16].

Special features of ICU management in neutropenic patients

Protective measures

The prevention of acquisition of exogenous bacteria or fungi is a major challenge in hospitalized neutropenic patients, especially in the ICU environment, where the risk of transmission of multiresistant micro-organisms is high. In haematology units, data from the literature support the simultaneous application of isolation in a single room, standard barrier precautions (cap, gown, gloves, mask), high-efficiency particulate air filtration, and clean or even sterile food. In addition, antibacterial and antifungal digestive decontamination has been used in very high risk patients with HSCT or acute leukaemia induction. In the ICU, the need for stringent protective measures should be balanced with the necessity of a close watch being kept on critically-ill patients. Neutropenic patients should be applied simple preventive measures including geographic isolation and standard barrier precautions. Air filtration is recommended, but remains restricted to recent units.

Source control measures

In addition to antibiotic treatment, some sources of infections may require surgical treatment, such as extensive debridement of infected tissues in cellulitis. Management of neutropenic enterocolitis is preferentially conservative, but uncontrolled septic shock or evidence of intestinal perforation or obstruction indicates surgical resection of necrotic or perforated bowel. Without any doubt, the expected benefits of source control on septic shock overcome the potential risks of surgery in neutropenic patients.

Central lines are major sources of bloodstream infections in neutropenic patients. Causing micro-organisms include coagulase-negative staphylococci, *Staphylococcus aureus* and *Candida* species, but also aerobic Gram-negative bacilli. A catheter-related infection is suggested by shorter time-to-positivity >120 minutes of blood cultures drawn from the device as compared with simultaneous blood cultures drawn from peripheral vein. Bloodstream infections due to virulent pathogens such as *S. aureus*, fungi or Gram-negative bacilli usually impose urgent catheter removal. Nevertheless, catheters may represent an occult source of infection despite negative blood cultures. Accordingly, systematic removal of catheters has been independently associated with improved survival in neutropenic patients with severe sepsis without evidence of alternative source of infection [3].

Management of organ failures

Management of organ failures in neutropenic patients is generally similar to that of non-neutropenic ones. Nonetheless, the ventilatory management of acute respiratory failure may differ with respect to specific indications of non-invasive ventilation (NIV) in this population. Indeed, NIV has been shown to decrease the intubation rate and the eventual ICU mortality in non-neutropenic and neutropenic immunocompromised patients with hypoxaemic respiratory failure [18]. Of note, NIV is best applied in non-terminal respiratory failure, implicating early detection of patients likely to benefit from it. However, the reluctance to intubate such high-risk patients should not lead to disregard the contraindications for NIV such as end stage acute respiratory failure or extra-respiratory failures.

Immune defence restoration

The poor outcome of severely-infected neutropenic patients prompted some therapeutic strategies aimed to restore the number and functions of neutrophils, including treatment with granulopoiesis-stimulating agents and granulocyte transfusion. Granulocyte colony-stimulating factor (G-CSF) is a haematopoietic growth factor that promotes the production of neutrophils

from bone marrow progenitors and enhances their antimicrobial activity. Prophylactic use of G-CSF has been able to shorten duration of neutropenia with an eventual decrease in the risk of febrile episodes, and is now considered for chemotherapy-treated patients with a high risk (>20%) of febrile neutropenia. The use of G-CSF as an adjunctive therapy of febrile neutropenia did not result in improved outcomes although a meta-analysis reported a possible decrease in infection-related mortality [19]. The use of G-CSF in critically-ill neutropenic patients neither reduced the time to neutrophil recovery nor improved survival [7], nor has been associated with deterioration of respiratory status at the time of neutropenia recovery related to lung infiltration by activated neutrophils [20]. Transfusion of granulocytes collected by leukapheresis from G-CSF-stimulated healthy donors has been proposed as a supportive treatment in patients with neutropenia or neutrophil dysfunction experiencing severe infections. The efficacy of this procedure remains questionable, and it is associated with side effects such as transfusion-associated lung injury and anti-HLA immunization. Whenever indicated, it should anyway be restricted to patients with forthcoming neutropenia recovery and progressive infections clearly linked to defective pathogen clearance (necrotic cellulitis, invasive fungal infections). To date, uncertainties about the real efficacy and the potential adverse side effects of G-CSF and granulocytes transfusion argue against their routine application in critically ill neutropenic patients.

References

1. Wisplinghoff H, Seifert H, Wenzel RP, and Edmond MB. (2003). Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. *Clinical Infectious Diseases*, **36**, 1103–10.
2. Cordonnier C, Buzyn A, Leverger G, et al. (2003). Epidemiology and risk factors for Gram-positive coccal infections in neutropenia: toward a more targeted antibiotic strategy. *Clinical Infectious Diseases*, **36**, 149–58.
3. Legrand M, Max A, Peigne V, et al. (2012). Survival in neutropenic patients with severe sepsis or septic shock. *Critical Care Medicine*, **40**, 43–9.
4. Zuber B, Tran TC, Aegerter P, et al. (2012). Impact of case volume on survival of septic shock in patients with malignancies. *Critical Care Medicine*, **40**, 55–62.
5. Cordonnier C, Botterel F, Ben Amor R, et al. (2009). Correlation between galactomannan antigen levels in serum and neutrophil counts in haematological patients with invasive aspergillosis. *Clinical Microbiology and Infection*, **15**, 81–6.
6. Pène F, Percheron S, Lemiale V, et al. (2008). Temporal changes in management and outcome of septic shock in patients with malignancies in the intensive care unit. *Critical Care Medicine*, **36**, 690–6.
7. Darmon M, Azoulay E, Alberti C, et al. (2002). Impact of neutropenia duration on short-term mortality in neutropenic critically ill cancer patients. *Intensive Care Medicine*, **28**, 1775–80.
8. Soares M, Caruso P, Silva E, et al. (2010). Characteristics and outcomes of patients with cancer requiring admission to intensive care units: a prospective multicenter study. *Critical Care Medicine*, **38**, 9–15.
9. Vandijck DM, Benoit DD, Depuydt PO, et al. (2008). Impact of recent intravenous chemotherapy on outcome in severe sepsis and septic shock patients with hematological malignancies. *Intensive Care Medicine*, **34**(5), 847–55.
10. Pène F, Aubron C, Azoulay E, et al. (2006). Outcome of critically ill allogeneic hematopoietic stem-cell transplantation recipients: a reappraisal of indications for organ failure supports. *Journal of Clinical Oncology*, **24**, 643–9.
11. Freifeld AG, Bow EJ, Sepkowitz KA, et al. (2011). Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clinical and Infectious Diseases*, **52**, e56–93.
12. The EORTC International Antimicrobial Therapy Cooperative Group. (1987). Ceftazidime combined with a short or long course of amikacin for empirical therapy of Gram-negative bacteremia in cancer patients with granulocytopenia. *New England Journal of Medicine*, **317**, 1692–8.
13. Jaksic B, Martinelli G, Perez-Oteyza J, Hartman CS, Leonard LB, and Tack KJ. (2006). Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. *Clinical and Infectious Diseases*, **42**, 597–607.
14. Cometta A, Kern WV, De Bock R, et al. (2003). Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. *Clinical and Infectious Diseases*, **37**, 382–9.
15. Lortholary O, Lefort A, Tod M, Chomat AM, Darras-Joly C, and Cordonnier C, (2008). Pharmacodynamics and pharmacokinetics of antibacterial drugs in the management of febrile neutropenia. *Lancet Infectious Diseases*, **8**, 612–20.
16. Walsh TJ, Finberg RW, Arndt C, et al. (1999). Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *New England Journal of Medicine*, **340**, 764–71.
17. Walsh TJ, Teppler H, Donowitz GR, et al. (2004). Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *New England Journal of Medicine*, **351**, 1391–402.
18. Hilbert G, Gruson D, Vargas F, et al. (2001). Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *New England Journal of Medicine*, **344**, 481–7.
19. Clark OA, Lyman GH, Castro AA, Clark LG, and Djulbegovic B. (2005). Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. *Journal of Clinical Oncology*, **23**, 4198–214.
20. Karlin L, Darmon M, Thiery G, et al. (2005). Respiratory status deterioration during G-CSF-induced neutropenia recovery. *Bone Marrow Transplantation*, **36**, 245–50.

CHAPTER 275

Sickle crisis in the critically ill

Shilpa Jain and Mark T. Gladwin

Key points

- Sickle cell disease (SCD) crises are precipitated by an acute occlusion of microvessels, which can lead to end organ ischaemia reperfusion injury and acute haemolysis.
- Acute fat emboli syndrome, acute lung injury (the acute chest syndrome), acute pulmonary hypertension and cor pulmonale, haemorrhagic and occlusive stroke, and systemic infection represent the most common life-threatening complications observed in current ICU practice.
- General principles of management in all patients admitted to the critical care unit are hydration, antibiotics, pain control, and maintenance of oxygenation and ventilation.
- Red blood cell transfusion therapy is the treatment of choice for most complications of sickle cell disease requiring intensive care management. Transfusion of sickle negative, leukoreduced red blood cells, phenotypically matched for Rhesus and Kell antigens is the minimum standard of care in sickle cell disease patients as they have a high incidence of red blood cell alloimmunization.
- SCD poses an increased risk of sudden death in patients, probably related to the high incidence of chronic pulmonary hypertension and haemodynamic deterioration in the acute setting.

Introduction

Sickle cell disease (SCD) is the most common haemoglobinopathy in the world, affecting nearly 275,000 babies born annually [1]. It is caused by a single nucleotide substitution in the beta-globin gene, valine for glutamic acid, resulting in a mutant haemoglobin S (HbS) molecule. When deoxygenated, HbS has an exposed hydrophobic valine residue that binds to other HbS molecules leading to the formation of insoluble polymers within the red blood cells (RBCs). This causes a structural damage to the membrane of the RBCs, which become sickle-shaped, rigid, hyperadhesive, and prone to haemolysis. It also impairs their passage through the microvessels causing end organ ischaemia and necrosis. Sickling is precipitated by hypoxia, acidosis, hypothermia, dehydration, and inflammatory adhesive events between RBCs, white blood cells (WBCs), and the endothelium.

Sickle cell disease is inherited as an autosomal recessive disorder with homozygotes (SS) or compound heterozygotes (haemoglobin SC, and Sbeta thalassaemia) demonstrating haemolytic anaemia and low levels of vaso-occlusion at steady state. Individuals with one sickle cell gene (AS or sickle trait) are usually asymptomatic. Acute occlusion of microvessels results in events called vaso-occlusive crises (VOC), represented by severe pain and acute organ injury. These further exacerbate already present end-organ complications which are becoming common with the increasing lifespan of the SCD patients. The most frequent problems for which a SCD patient is seen in a critical care setting are listed below, and reviewed subsequently:

- Acute chest syndrome.
- Haemolytic transfusion reactions.
- Sepsis (most commonly related to central line infections).
- Pulmonary hypertension and right heart failure.
- Multi-organ failure.

Acute chest syndrome

Acute chest syndrome (AChS) frequently develops in SCD patients post-operatively, and after hospitalization for acute VOC [2]. Diagnosis is established by the finding of a new segmental pulmonary infiltrate, excluding atelectasis, along with some or all of the following symptoms: cough, chest pain, fever (>38.5°C), hypoxia, and dyspnoea (Fig. 275.1) [3]. Laboratory findings include leukocytosis (mean WBC, 23,000 cells/μl), increased haemolysis, and drop in Hb and platelet counts (~1 g/dL and <200,000/mm^3, respectively) [3]. Risk factors identified for respiratory failure are decreased platelet count, multilobar disease, cardiac disease likely representing pulmonary hypertension (PH), and neurologic complications [3].

Acute chest syndrome is essentially a form of acute lung injury similar to ARDS, which results from a vicious cycle of lung infarction by bone marrow fat emboli and *in situ* sickle cell vaso-occlusion, infection, and atelectasis that produce ventilation–perfusion mismatch, hypoxaemia, and often acute increases in pulmonary and right ventricular pressures. The major identifiable aetiologies of AChS that promote the above-listed mechanisms are listed below in order of frequency [2]:

- Respiratory infections from chlamydia, mycoplasma, respiratory syncytial virus, *Staphylococcus aureus, Streptococcus pneumoniae*, and other pathogens in decreasing order of frequency [2]. Influenza also produces severe seasonal outbreaks of AChS .
- Pulmonary fat embolism syndrome caused by bone marrow necrosis following severe vaso-occlusion in the bone marrow. Fat emboli in the lung vasculature are metabolized to free fatty acids, including secretory phospholipase A2, which mediate alveolar inflammation and endothelial injury [4]. Oil red O-positive

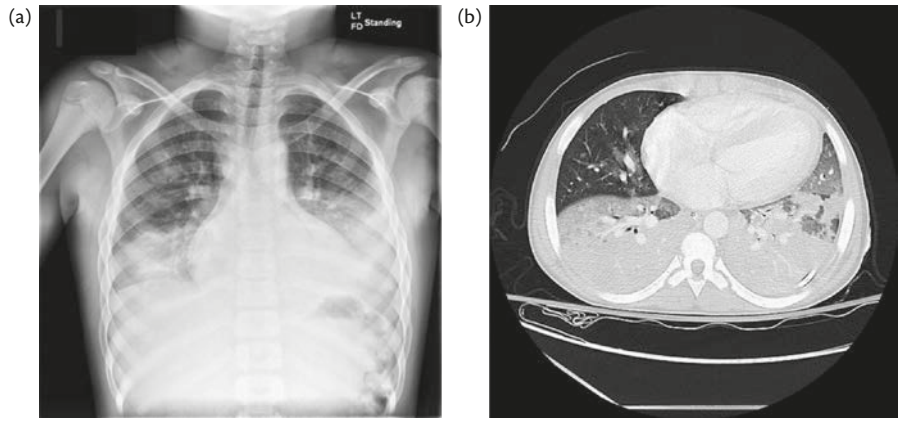


Fig. 275.1 A 14-year-old boy with sickle cell disease and acute chest syndrome. (a) Chest X-ray bilbasilar infiltrates and a moderate-sized left pleural effusion. (b) Chest CT of the same patient showing multifocal bilateral consolidations.

fat-laden macrophages in bronchoalveolar lavage (BAL) or induced sputum are diagnostic [2].

- Costal or sternal infarction resulting in splinting and consequently hypoventilation and atelectasis, and pooling of secretions at lung bases which predisposes to ventilation-perfusion mismatch and hypoxia.
- Pulmonary infarction from in situ sickle cell vaso-occlusion as a result of increased adhesion of sickled RBCs to the endothelium.
- Pulmonary embolism (PE) or in situ thrombosis may also occur in small subset of patients [5].

Haemolytic transfusion reactions

Haemolytic transfusion reactions (HTR) occur as a complication of RBC allo-immunization following blood transfusions, and is reported to occur in 19–47% of SCD adults in USA [6]. The high risk of allo-immunization is related to the differences in RBC antigen expression between African-American SCD patients, and the predominantly Caucasian blood donor pool, leading to antibody formation against Rh (C,E), Kell (K1), Kidd (Jk^b), MNSs (S), and Duffy (Fy^a). Rarely, HTR in SCD can occur in the absence of detectable antibodies from other mechanisms, such as macrophage mediated erythrophagocytosis [7].

Haemolytic transfusion reactions can result in severe life-threatening anaemia and can present acutely or delayed (2 days to 2 weeks). Delayed HTR is caused by re-exposure to red cell alloantigens, producing an anamnestic immune response. This stimulates the formation of previously low-titre antibodies which were below the limits of detection during standard cross-matching procedures. In extreme cases, a hyperhaemolytic crisis may ensue as a result of delayed HTR and is defined by development of more severe anaemia than was present prior to transfusion. This occurs as a result of 'bystander haemolysis' of self and transfused RBCs, suppressed erythropoiesis, and autoantibody formation.

Diagnosis is a challenge, and requires a high degree of suspicion as symptoms are similar to those of acute VOC. Laboratory evaluation shows evidence of haemolysis, haemoglobinuria, and marked reticulocytopenia initially, with reticulocytosis heralding recovery. Direct antiglobulin test (DAT) is positive unless the antibody titres have decreased to undetectable levels between transfusions. Serial CBC with reticulocyte count and Hb electrophoresis to look for disappearance of transfused HbA donor RBCs may aid in diagnosis.

Sepsis

Sepsis in SCD occurs secondary to impaired immunity from splenic, complement, and neutrophil dysfunction. Patients are particularly susceptible to encapsulated organisms (*Streptococcus pneumoniae, Salmonella* species, *Haemophilus influenza*), although their incidence has decreased markedly with the use of vaccinations and penicillin prophylaxis. Effects of infection such as fever, hypoxia, acidosis, dehydration, and increased WBC counts, can trigger a cascade of events leading to vaso-occlusive events. Pathological effects of SCD correlate to the following sources and specific pathogens:

- The most common source of infection is intravenous catheters placed for antibiotic infusions, erythrocytapheresis, chronic blood transfusion, or haemodialysis. Commonly isolated organisms are *Staphylococcus aureus* and skin flora.
- **Osteomyelitis**: haematogenous spread of *Salmonella typhimurium* and less frequently *Staphylococcus* aureus and enteric Gram-negative bacilli. This complication is seen almost exclusively in children.
- **Biliary tract**: anaerobes.
- **Urinary tract infections**: *Escherichia coli* and other Gram negative enteric organisms.
- **Lung**: typical and atypical bacteria.
- **Iron overload**: *Yersinia enterocolitia* causing fever, diarrhoea, and symptoms mimicking acute appendicitis.
- **Recurrent hospitalizations and exposure to multiple antibiotics**: nosocomial infections and colonization with resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA).

Pulmonary hypertension

Pulmonary hypertension (PH) is an emerging cause of morbidity and mortality, associated with a 10-fold increased risk for early death [8,9].The prevalence of PH is approximately 10% in adult SCD patients, based on right heart catheterization screening

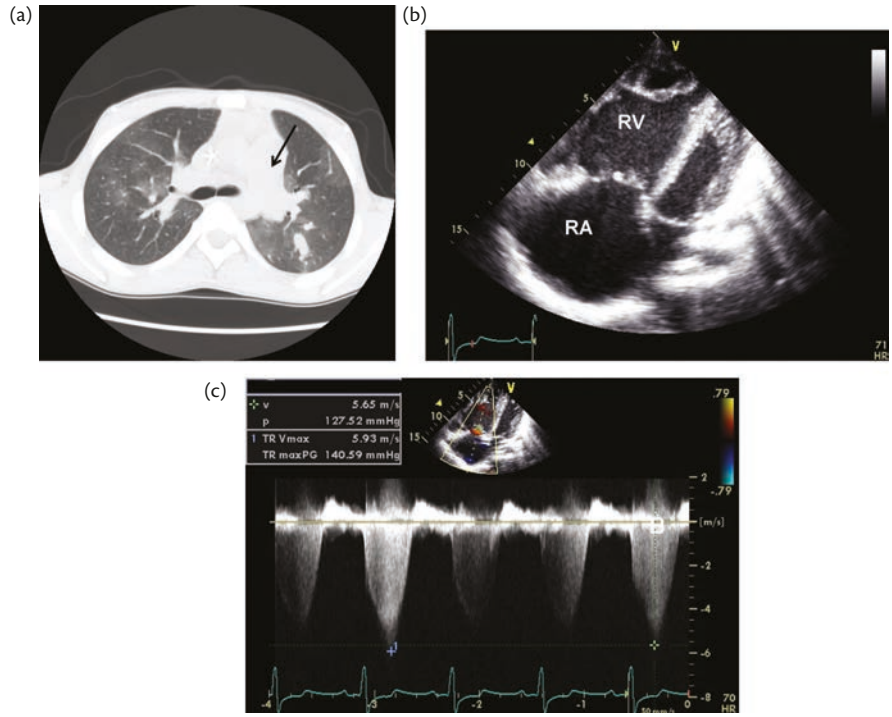


Fig. 275.2 Patient with Sickle Cell Disease and Pulmonary Hypertension. (a) CT of the chest showing dilation of main pulmonary artery (black arrow) and mosaic perfusion in both lobes of the lungs. (b) A four-chamber view of the heart shows right ventricular (RV) and right atrial (RA) dilatation. Right ventricular wall thickness is increased consistent with right ventricular hypertrophy. There is flattening of the interventricular septum indicative of pulmonary hypertension. (c) A Doppler echocardiographic tracing shows peak tricuspid regurgitant-jet-velocity to be 5.9 m/second. With an assumed right atrial pressure of 15 mmHg, the estimated pulmonary artery systolic pressure is 154 mmHg. This constitutes severe pulmonary hypertension.

studies, and is defined by a mean pulmonary artery pressure greater than or equal to 25 mm Hg [10–12]. A central event in the pathogenesis of PH is acute and chronic haemolytic anaemia. Chronic vascular exposure to haemolysate and cell free plasma haemoglobin scavenges nitric oxide (NO) and generates reactive oxygen species that contributes to the development of a progressive systemic and pulmonary vasculopathy. Risk factors for PH include increased lactate dehydrogenate (capturing increased intensity of haemolytic anaemia), liver and renal dysfunction, increasing age, iron overload, systolic hypertension, and left ventricular diastolic dysfunction [13].

Echocardiographic assessments of tricuspid regurgitant (TR) jet velocity and right heart function are convenient and non-invasive screening assessments for PH and should be performed in all patients admitted to the ICU, since pulmonary pressures can rise acutely during severe VOC or AChS [14,15]. Pulmonary hypertension and right heart failure (cor pulmonale) complicates approximately 13% of patients with the acute chest syndrome and portends a worse prognosis [15] (Fig. 275.2).

Acute multi-organ failure syndrome

Acute Multi-organ failure syndrome (AMOFS) involves severe dysfunction of at least two major organ systems (kidney, lung, liver) during an acute painful VOC. It is diagnosed when the following criteria are present: serum creatinine >2 mg/dL; ALT and total bilirubin >5× normal; direct bilirubin >2× normal; prothrombin time >3 seconds; acute pulmonary infiltrate and hypoxia [16]. Patients can present with fever, rapid fall in Hb and platelet count, non-focal encephalopathy, rhabdomyolysis, and sudden syncope. Necrosis of bone marrow can result in fat emboli, and rarely myocardial ischaemia. Thrombotic thrombocytopenic purpura (TTP) can mimic AMOFS in its presentation, but is difficult to diagnose in SCD because of higher von Willebrand antigen levels as compared with ADAMTS13 levels at baseline, with the latter further decreasing during VOC [17]. In TTP, coagulation studies are usually normal and if abnormal should raise the suspicion of disseminated intravascular coagulation (DIC).

General principles of management of SCD complications

The ultimate goal of treatment of SCD-related complications is to prevent HbS polymerization or to remove and replace sickle RBCs. Major approaches to general management, applicable to most patients, are primarily supportive and based on the pathophysiology of the disease as listed in Table 275.1.

Guidelines for transfusion

A SCD patient admitted to an ICU for almost any reason requires a blood transfusion, simple or exchange, and the following guidelines should be followed:

- Sickle negative, leukocyte reduced, at least Rh (ABO, C, D, E), and Kell matched
- Extended phenotype matching in patients with history of allo-immunization

Table 275.1 General management principles to prevent haemoglobin S (HbS) polymerization in sickle cell disease based on pathophysiology

Pathophysiology	Goal	Therapy
Limit HbS deoxygenation	Reduce tissue hypoxia	◆ Supplemental oxygen ◆ Incentive spirometry (10 puffs every 2 hours while awake), BiPAP or assisted breathing to improve ventilation
	Increase HbS oxygen affinity	◆ Prevent acidosis with adequate ventilation ◆ Antipyretics for fever
Limit erythrocyte-leukocyte adhesion in the microvasculature	Reduce inflammation	◆ Treat infections (encapsulated organisms, atypical, viral) ◆ Analgesia (NSAIDs + opioids, patient-controlled)
Reduce red cell HbS concentration	Reduce RBC dehydration and vaso-occlusion	Hydration with hypotonic iv fluids: (dextrose 5% + ½ normal saline at 1 – 1.5 × maintenance); reduce to 0.75 × maintenance in AChS to avoid pulmonary oedema
	Increase HbA concentration	Transfusion of normal red blood cells
	Increase HbF concentration	Pharmacological therapy (hydroxyurea)

HbS, sickle haemoglobin; HbA, adult haemoglobin; HbF, fetal haemoglobin; RBC, red blood cell; NSAIDs, non-steroidal anti-inflammatory drugs; AChS, acute chest syndrome.

- Goal is to increase the Hb concentration to 10–11 g/dL or decrease HbS <30% with exchange.
- Post-transfusion Hb to not exceed 11 g/dL to avoid hyperviscosity, and more vaso-occlusion.
- Exchange transfusion if baseline Hb >10g/dL, AMOFS, AChS with severe respiratory distress, concurrent stroke or a worsening clinical condition despite simple transfusion.

A recommended and straight forward approach is to rapidly transfuse to a post-transfusion Hb target of 10–11 g/dL and then maintain it at that level with daily simple transfusions of 1–2 units as needed. This will maintain haemoglobin S levels at less than 20–30% while the patient recovers from multi-organ injury.

Management of specific complications

In addition to instituting supportive care (Table 275.1), specific guidelines pertaining to each of the complications are discussed in the following sections.

Acute chest syndrome

- Empiric coverage for typical and atypical bacteria with third-generation cephalosporins or quinolones, macrolides, and vancomycin especially for MRSA in severely-ill patients. In the influenza season, empiric treatment with antiviral medication oseltamivir should be included.
- Early and aggressive RBC transfusions result in immediate improvements in arterial Hb oxygen saturations and in the A-a O_2 gradient. It has been noted in observational trials that simple transfusion of 2–4 units is as effective as performing exchange transfusion [18]. However, the goal should be to reduce Hb S levels rapidly to less than 20–30%.
- If a patient does not improve with supportive care and empiric antibiotics, consider diagnostic bronchoscopy with BAL, CT imaging to evaluate for other sources of infection and possible pleuracentesis if large effusions present.
- Management of PE follows the guidelines for the general population although the role of anticoagulation for in situ thrombosis is unknown.
- The effectiveness of vasodilators such as inhaled nitric oxide has not been fully ascertained, but clearly does not reduce the severity of VOC [19].
- Two major comorbidities, asthma and PH, are highly prevalent in SCD patients with AChS and can worsen the outcome.
  - **Airway hyperreactivity**: use of bronchodilator therapy every 4 hours. Routine corticosteroid therapy is controversial in SCD patients as its use has been associated with rebound pain crisis and hospitalization. It is our practice to only use corticosteroids in patients that have received transfusion therapy.
  - **Pulmonary hypertension**: Doppler-echocardiogram should be performed in every patient admitted to the ICU with AChS to diagnose right ventricular failure.

Haemolytic transfusion reactions

It is important to avoid additional transfusions as they may exacerbate the ongoing haemolysis, unless there is evidence of haemodynamic compromise from the acute anaemia. In this case transfusions should be given along with immune modulators to suppress the activity of macrophages. There is anecdotal evidence that high dose corticosteroids and intravenous (iv) immunoglobulins (IVIg) are beneficial in this setting, although both treatments have SCD-specific relative contraindications. Particular attention should be made to maintenance of hydration with iv fluids to avoid haemoglobinaemia-associated renal damage. Complete RBC phenotyping should be undertaken in case of an emergency, but it is important to highlight that during hyperhaemolytic crises, haemolysis may occur in spite of the infusion of fully cross-matched compatible blood.

There are anecdotal reports of the successful use of rituximab, a monoclonal antibody against the CD20 antigen on B-cells, prior to subsequent transfusions to reduce auto-antibody formation and further hyperhaemolytic reactions.

Sepsis

Supportive care for septic shock follows the same guidelines instituted for the general population. Central lines should be removed, broad-spectrum antibiotics administered, and sources of infection determined with therapy tailored accordingly.

Pulmonary hypertension

Detailed management of PH is discussed elsewhere. Patients with right heart failure (cor pulmonale) should receive exchange transfusion to increased mixed venous oxygen saturations and prevent pulmonary vaso-occlusion. Right heart catheterization, therapy with inotropes to increase right heart function, and iv epoprostenol

may be required to increase cardiac output and acutely lower pulmonary vascular resistance, and pressures. A multicenter, placebo-controlled trial of treatment of PH in SCD using oral sildenafil, phosphodiesterase 5-inhibitor was prematurely stopped because of increased hospitalization rate from pain in the sildenafil group. This drug is no longer considered a first-line therapy for PH in SCD [20]. Other agents used for PH include endothelin receptor antagonists, bosentan, and ambrisentan.

Acute multi-organ failure syndrome

Prompt initiation of transfusion therapy or exchange transfusion should be undertaken to improve tissue oxygenation and perfusion, and to aid in recovery of organ function. If TTP is strongly suspected, plasmapheresis should be promptly instituted in tandem with exchange transfusion, for rapid resolution of symptoms.

References

1. Modell B and Darlison M. (2008). Global epidemiology of haemoglobin disorders and derived service indicators. *Bulletin of the World Health Organization*, **86**(6), 480–7.
2. Vichinsky EP, Neumayr LD, Earles AN, et al. (2000). Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *New England Journal of Medicine*, **342**(25), 1855–65.
3. Vichinsky EP, Styles LA, Colangelo LH, Wright EC, Castro O, and Nickerson B. (1997). Acute chest syndrome in sickle cell disease: clinical presentation and course. Cooperative Study of Sickle Cell Disease. *Blood*, **89**(5), 1787–92.
4. Styles LA, Schalkwijk CG, Aarsman AJ, Vichinsky EP, Lubin BH, and Kuypers FA. (1996). Phospholipase A2 levels in acute chest syndrome of sickle cell disease. *Blood*, **87**(6), 2573–8.
5. Mekontso Dessap A, Deux JF, Abidi N, et al. (2011). Pulmonary artery thrombosis during acute chest syndrome in sickle cell disease. *American Journal of Respiratory and Critical Care Medicine*, **184**(9), 1022–9.
6. Vichinsky EP. (2001). Current issues with blood transfusions in sickle cell disease. *Seminars in Hematology*, **38**(1 Suppl. 1), 14–22.
7. Chadebech P, Habibi A, Nzouakou R, et al. (2009). Delayed hemolytic transfusion reaction in sickle cell disease patients: evidence of an emerging syndrome with suicidal red blood cell death. *Transfusion*, **49**(9), 1785–92.
8. Castro O, Hoque M, and Brown BD. (2003). Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. *Blood*, **101**(4), 1257–61.
9. Gladwin MT, Sachdev V, Jison ML, et al. (2004). Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *New England Journal of Medicine*, **350**(9), 886–95.
10. Fonseca GH, Souza R, Salemi VM, Jardim CV, and Gualandro SF. (2012). Pulmonary hypertension diagnosed by right heart catheterisation in sickle cell disease. *European Respiratory Journal*, **39**(1), 112–18.
11. Mehari A, Gladwin MT, Tian X, Machado RF, and Kato GJ. (2012). Mortality in adults with sickle cell disease and pulmonary hypertension. *Journal of the American Medical Association*, **307**(12), 1254–6.
12. Parent F, Bachir D, Inamo J, et al. (2011). A hemodynamic study of pulmonary hypertension in sickle cell disease. *New England Journal of Medicine*, **365**(1), 44–53.
13. Sachdev V, Machado RF, Shizukuda Y, et al. (2007). Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. *Journal of the American College of Cardiologists*, **49**(4), 472–9.
14. Machado RF, Mack AK, Martyr S, et al. (2007). Severity of pulmonary hypertension during vaso-occlusive pain crisis and exercise in patients with sickle cell disease. *British Journal of Haematology*, **136**(2), 319–25.
15. Mekontso Dessap A, Leon R, Habibi A, et al. (2008). Pulmonary hypertension and cor pulmonale during severe acute chest syndrome in sickle cell disease. *American Journal of Respiratory and Critical Care Medicine*, **177**(6), 646–53.
16. Hassell KL, Eckman JR, and Lane PA. (1994). Acute multiorgan failure syndrome: a potentially catastrophic complication of severe sickle cell pain episodes. *American Journal of Medicine*, **96**(2), 155–62.
17. Schnog JJ, Hovinga JA, Krieg S, et al. (2006). ADAMTS13 activity in sickle cell disease. *American Journal of Hematology*, **81**(7), 492–8.
18. Vichinsky EP, Haberkern CM, Neumayr L, et al. (1995). A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. The Preoperative Transfusion in Sickle Cell Disease Study Group. *New England Journal of Medicine*, **333**(4), 206–13.
19. Gladwin MT, Kato GJ, Weiner D, et al. (2011). Nitric oxide for inhalation in the acute treatment of sickle cell pain crisis: a randomized controlled trial. *Journal of the American Medical Association*, **305**(9), 893–902.
20. Machado RF, Barst RJ, Yovetich NA, et al. (2011). Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity. *Blood*, **118**(4), 855–64.

SECTION 12

The skin and connective tissue

PART 12.1

Skin and connective tissue disorders

CHAPTER 276

Assessment and management of dermatological problems in the critically ill

Richard Groves

Key points

- Important primary dermatological conditions that require intensive care management include erythroderma, toxic epidermal necrolysis/Stevens Johnson syndrome, widespread drug eruptions and blistering disorders with extensive skin involvement.
- Drug reaction with eosinophilia and systemic symptoms may affect multiple organ systems and death may ensue from hepatic necrosis. Treatment of severe cases includes steroids and/or immunosuppression.
- Acute generalized exanthematous pustulosis occurs rapidly following exposure to causative drugs and is generally self-limiting, although associated with secondary infection.
- Toxic epidermal necrolysis, Stevens–Johnson syndrome and widespread erythema multiforme represent a continuum of severe skin reactions associated with significant mortality and morbidity.
- Treatment of extensive skin disease requires expert nursing care in order to mitigate the consequences of skin failure.

Introduction

Although dermatology is generally considered to be an outpatient specialty, relating to conditions of low acuity, a wide array of skin problems can present in the critically-ill patient. Some may reflect pre-existing disease (psoriasis, for example, affects 2% of the general population and so will be seen in many acutely unwell patients and be unconnected with their acute illness); some may occur as a consequence of treatment, for example, drug eruptions, and a small fraction will represent severe or extensive primary skin disease that is best managed in a critical care setting.

The spectrum of dermatological disease in critical care

A number of studies have reviewed dermatological presentations in critical care settings in different countries [1–3]. A survey in the UK suggested that primary dermatological diagnoses account for around 0.5% of ICU admissions [3], although dermatological conditions were present in 9.3% ICU patients identified in a recent prospective study [4] and reviews of dermatological consults in ICU suggest that many were for infectious complications of ICU admission (candida intertrigo, cellulitis, herpes simplex/zoster) [1].

Important primary dermatological conditions that require intensive care management include erythroderma, toxic epidermal necrolysis/Stevens–Johnson syndrome (TEN/SJS), widespread drug eruptions and blistering disorders with extensive skin involvement.

General approach to the assessment and management of the patient with skin disease in intensive care

Skin disease diagnosis and management can be confusing for the non-specialist and, in the critical care context, will be best achieved by a team-based approach with input from medical dermatologists, dermatology specialist nurses and colleagues in critical care.

A methodical approach will often provide useful pointers, and taking a good history is the first step. Does the patient have a history of skin problems? Are they currently using any prescribed topical medication? Is there a family history of skin problems? What is the chronology of the skin problem in relation to the patients other medical problems? Has any new medication been started recently? If it has, when exactly?

When examining the patient, a number of factors will require evaluation in order to define the potential severity of the eruption. Estimation of the extent of the skin involvement can conveniently be done using the rule of 9s. Evaluation of the integrity of the skin is also crucial—are there blisters or erosions? Is there mucosal involvement? Thinking about the principal lesion (papules, pustules, vesicles, bullae) will aid in identifying the potential pathology and in communication with dermatological colleagues.

All patients with extensive skin disease will require expert nursing care in order to mitigate the consequences of skin failure. Thus, low-friction beds, non-adherent primary dressings, careful attention to prevention of infection, temperature regulation, fluid management, and so on are critical.

Erythroderma

Erythroderma is generally defined as a state in which there is >90% skin area involvement with an inflammatory process. The

skin is typically red (erythematous), and may be scaly or exudative. Remember that in black skin erythema can be hard to assess. Erythroderma should be regarded as a situation of general skin failure, where the skin fails to perform its normal functions of protection against infection (barrier and immunological), temperature control and fluid regulation (preventing and regulating losses). Therapy is primarily supportive and intensive care is often required. Although erythroderma has traditionally been associated with a high mortality, with modern intervention mortality is low [5].

Erythroderma is a final common pathway for various inflammatory dermatoses including psoriasis, eczema (of all sorts), drug eruptions and cutaneous T-cell lymphoma (see Table 276.1). Associated clinical features (for example, psoriatic nail dystrophy) or the patient's past dermatological history may point to the underlying diagnosis, but erythroderma due to any of the potential underlying diagnoses may appear remarkably similar clinically.

Histopathology of the skin may be helpful in the elucidation of some causes of erythroderma, most particularly pemphigus foliaceus and cutaneous T-cell lymphoma. Diagnostic features may be seen in patients with eczema (spongiosis) or psoriasis (papillomatosis, thinning of the suprapapillary plate), but often only non-specific changes are seen. Repeat biopsies may eventually show features more typical of the underlying diagnosis and should be considered if an underlying cause remains elusive. Blood investigations are generally unhelpful in identifying the cause (for example, eosinophilia can be seen in atopic eczema, drug eruptions, and in acute psoriasis) though Sezary cells are suggestive of a cutaneous lymphoma.

Initial assessment of the erythrodermic patient should focus on the general state of the patient, including electrolyte balance, nutritional status and signs of infection. Management is supportive, with liberal bland topical applications in the early stages of therapy. Topical steroids and tar are, in general, avoided as they may destablize psoriasis and provoke a pustular flare. Once a diagnosis is established, and the initial acute inflammatory state improves, specific systemic therapy can be introduced according to the underlying diagnosis. Thus, in eczematous states, systemic steroids may be of benefit and in psoriasis agents such as ciclosporin, acitretin or anti-TNF therapy can be considered.

Table 276.1 Causes of erythroderma

Condition	Prevalence (%)
Eczema of various types	40.0
Psoriasis	25.0
Drugs	10.0
Lymphoma and leukaemias	15.0
Hereditary disorders	1.0
Other skin diseases: ◆ Lichen planus, dermatophytosis ◆ Crusted scabies, Pemphigus foliaceus ◆ Dermatomyositis	1.0
Unknown	8.0

Drug eruptions

Drug eruptions can be seen either as a coincidental finding in patients in an intensive care setting or as the primary reason for admission. Numerous morphological changes can occur, although most drug eruptions seen in ICU are relatively trivial, generally exanthematous and frequently secondary to antibiotic drugs. These reactions are self-limiting, as long as the offending drug is withdrawn. Toxic epidermal necrolysis is generally drug-induced and is considered later in this chapter. Two additional reactions can be more severe and are dealt with in more detail here.

Drug reaction with eosinophilia and systemic symptoms

Drug reaction with eosinophilia and systemic symptoms (DRESS) [6,7] is a potentially life-threatening adverse drug reaction with a mortality rate of around 10%. It is characterized by skin changes, most usually a morbilliform (measles-like) rash, in association with liver, renal, and other systemic organ involvement. Mortality occurs particularly as a result of liver involvement.

DRESS represents a severe hypersensitivity reaction and has been described in association with a wide variety of medication, especially anticonvulsant drugs [8]. Immunosuppression may play a role, and recent evidence suggests that human herpes virus-6 (HHV-6) infection may predispose to the eruption [9]. Interestingly, some human leukocyte antigen (HLA) types are over-represented in DRESS patients suggesting a potential genetic predisposition [9].

Onset of DRESS is typically delayed following first exposure to the drug, generally by 2–6 weeks. Patients are often febrile and develop a morbilliform rash typically initially affecting the face, sometimes with significant associated oedema. The eruption may take differing morphological forms, and an erythema multiforme-like change has been associated with a poorer outcome [8]. Mucositis may occur in ~30% patients [6].

Multiple organ systems may be affected in DRESS, with lymphadenopathy, haematological changes (eosinophilia, leukocytosis), kidney, lung, endocrine, neurological and cardiac involvement reported. The principal cause of mortality is hepatic involvement, initially transaminitis, which may progress to fulminating hepatic necrosis requiring hepatic transplantation.

Once DRESS is recognized, immediate withdrawal of the probable offending drug is required. Mild cases may resolve spontaneously, but where there is evidence of internal organ involvement, systemic steroids are generally required, typically oral prednisolone 1 mg/kg/day or intravenous (iv) methylprednisolone [7,10]. Prolonged tapering may be required over several months in order to prevent relapse. In patients resistant to the effects of steroids other interventions have been used including ciclosporin, IVIg, cyclophosphamide, as well as antivirals such as valganciclovir in order to prevent or minimize complications relating to HHV-6 reactivation. Patients may require multi-organ support and intensive skin care nursing in the acute phase.

In some patients it may be unclear which of a number of drugs is responsible. In this situation challenge patch testing or lymphocyte stimulation assays following recovery can provide pointers to the potential culprit. Unfortunately false negative results are recognized with both approaches and thus positive results tend to be of more help than negative ones.

Acute generalized exanthematous pustulosis

Acute generalized exanthematous pustulosis (AGEP) [11] is a relatively uncommon reaction characterized by fever and pruritus followed by the appearance of multiple tiny sterile pustules, often most marked in the flexures. Women seem to be more often affected than men. Internal organ involvement is uncommon, although renal and hepatic dysfunction have been reported. Associated mortality of 5% seems to relate particularly to secondary infection in the elderly. Some patients with DRESS will present with pustulation and this differential diagnosis must be borne in mind.

Unlike DRESS, AGEP occurs rapidly following exposure to the causative drug, typically within 48 hours. Many drugs have been reported to cause the eruption with penicillins, antimalarials, terbinafine, and diltiazem being amongst the most frequent.

The principal differential diagnosis is acute pustular psoriasis. Skin histology in AGEP shows subcorneal pustule formation, but the typical features of psoriasis are absent. Following resolution, epicutaneous patch testing to the offending drug may provoke inflammation and, in some patients, pustule formation at the site of application.

AGEP is generally self-limiting (assuming withdrawal of the causative drug) and it remains to be established whether topical or systemic steroid therapy hastens resolution.

Toxic epidermal necrolysis/Stevens–Johnson syndrome

TEN, SJS, and widespread erythema multiforme represent a continuum of severe skin reactions in which there is extensive keratinocyte cell death in the epidermis leading to blistering, erosion, and skin failure. TEN and SJS in particular are associated with significant mortality and morbidity.

Definition

Erythema multiforme major, SJS, and TEN are all characterized by similar pathological changes, with necrosis/apoptosis of epidermal keratinocytes, either individually or affecting the full thickness of the epidermis, in association with a perivascular inflammatory cell infiltrate in the dermis. Histological features vary depending on the site of biopsy and it's timing in relation to the evolution of a lesion.

Erythema multiforme lesions are typically a concentric circular erythema, but as the name implies, may take multiple forms. Lesions are typically acral or over extensor prominences. In SJS, there is generally mucosal involvement (mouth, eyes, genitalia) together with EM-type lesions affecting less than 10% body surface area (BSA). TEN is defined as more than 30% BSA involvement and TEN/SJS overlap having 10–30% BSA affected.

Causes

The overwhelming majority of cases of TEN occur as a result of drug hypersensitivity, although infection (for example, mycoplasma) may also precipitate the reaction. SJS is more commonly related to infection, most notably herpes simplex and mycoplasma. All patients with suspected TEN or SJS should undergo forensic analysis of recent drug exposure: the ALDEN algorithm has been developed to assist with this [12]. TEN typically occurs 1–8 weeks following drug exposure, with mean time of onset between 6 days and 2 weeks. Common drug culprits are listed in Box 276.1.

Box 276.1 Drugs commonly implicated in TEN

- **Allopurinol**
- **Aminopenicillins**
- **Carbamazepine**
- **Cephalosporins**
- **Cotrimoxazole**
- **Lamotrigine**
- **Nevirapine**
- **Oxicam**
- **NSAIDs**
- **Phenobarbital**
- **Phenytoin**
- **Quinolones**
- **Sulfasalazine**

Clinical features

The characteristic feature of TEN is the development of widespread denudation of the dermis with sheets of epidermal separation. There is frequently a prodrome of general malaise, fever, and rash, which may be morbilliform or with features of erythema multiforme. The skin is typically tender and pain is prominent. Mucosal ulceration occurs in the majority of patients with TEN, affecting the mouth, eyes, and genitalia. It is important to remember that the erosive process may also affect the respiratory mucosa, and ARDS has been documented, with lung function abnormalities in up to 25% patients.

Pathophysiology

The key pathological change in TEN and SJS is apoptosis within the epidermis, potentially mediated by granzyme B, perforin, granulysin, and fas/fas ligand interactions [13]. There is increasing evidence for involvement of CD8+ve cytotoxic T-cells, which can be found in blister fluid and in the dermis of affected skin. Interestingly, a number of recent studies have demonstrated a relationship between MHC class I status and drug hypersensitivity reactions. Thus in some populations (notably Han Chinese) a strong relationship exists between anticonvulsant reactions and the presence of HLA B*1502, whereas patients with TEN secondary to allopurinol have a higher frequency of HLA-B*5801. Because of the potential severity of skin reactions such as TEN, genetic testing should be considered prior to commencing treatment in those groups where strong genetic relationships have been demonstrated [14].

Prognosis

TEN is associated with a mortality of ~25% at 6 weeks and 34% at 1 year [15]. Principal causes of death are sepsis, respiratory failure, and gastrointestinal bleeding. In order to guide prognosis the severity of illness **score** for **TEN** (SCORTEN) scale has been developed and validated in a number of studies [16,17]. Seven variables (see Box 276.2 and Table 276.2) are scored for presence or absence and the number of positive variables relates directly to outcomes. SCORTEN values on the third day of hospital admission seem to have the best predictive value.

Patients who survive the acute phase of TEN are at risk of multiple sequelae, including cutaneous scarring and dyspigmentation, eye, respiratory, genitourinary, and psychological problems. Multidisciplinary involvement at an early stage may minimize these and provide a framework for subsequent management.

Management

General measures and wound care

The most important therapeutic intervention in TEN is identification and withdrawal of the precipitating drug. Identification is not

Box 276.2 SCORTEN variables

- **Age >40 years**: heart rate >120 bpm.
- **Bicarbonate <20 mmol/L**: comorbid malignancy.
- **Epidermal detachment > 10%**: urea > 10 mmol/L.
- Glucose >14 mmol/L.

Data from Bastuji-Garin S et al., 'SCORTEN: a severity-of-illness score for toxic epidermal necrolysis', *Journal Investigative Dermatology*, 2000, **115**(2), pp. 149–53.

always easy and withdrawal of all potentially culprit drugs is mandatory. Unfortunately, diagnostic sensitivity testing (for example, by lymphocyte proliferation or cytokine release assays) is of little value in the acute situation.

TEN represents a situation of acute skin failure, with loss of most of the normal functions of the skin and consequent risks of infection, fluid loss, loss of temperature control, and so-on. Expert nursing care, such as will be available in a specialized dermatological or burns centre is advisable. Most patients will require nursing in an ICU setting. Non-adherent primary dressings such as silicone mesh will minimize damage to newly re-epithelialized skin at dressing changes. Many absorbent secondary dressings are available, some in garment-shaped configurations that give increased patient comfort. Liberal use of emollients will minimize shearing damage to the skin and patients should be nursed on a friction-reducing mattress.

Systemic therapy

Corticosteroids have been used to variable effect. Although for many years their use was thought to be associated with adverse outcomes, particularly from infection, some recent studies have suggested a possible beneficial effect [18]. At present however there is no consensus as to how or when they may be of benefit.

Intravenous immunoglobulin has been widely used in the management of TEN, initially because of its inhibitory effect on fas/fas ligand interactions [19]. Since then, many studies have been reported [20], with variable benefit. Unfortunately none of these has been controlled and, as with steroids, there is no consensus on appropriate use. Whilst IVIG might not have the potential adverse effects on healing or infection of steroids, it is expensive and in short supply.

Table 276.2 SCORTEN mortality

Number of positive variables	Mortality
0–1	3.2%
2	12.2%
3	35.5%
4	58.3%
5–7	90%

Data from Bastuji-Garin S et al., 'SCORTEN: a severity-of-illness score for toxic epidermal necrolysis', *Journal Investigative Dermatology*, 2000, **115**(2), pp. 149–53.

Other interventions have been reported in small numbers of patients, including ciclosporin, plasmapheresis and TNF inhibitors, but there is currently insufficient evidence to recommend their routine use.

Conclusion

Dermatological problems occur frequently in the critical care setting. Many are minor and relate to drug sensitivities that resolve following drug withdrawal. Others however are life-threatening but, with a carefully coordinated multidisciplinary approach involving dermatologists, intensivists, organ specialists and specialist nurses should now have a much improved long-term outcome.

References

1. Emre S, Emre C, Akoglu G, Demirseren DD, and Metin A. (2013). Evaluation of dermatological consultations of patients treated in intensive care unit. *Dermatology*, **226**(1), 75–80.
2. Fischer M, William T, and Wohlrab J. (2009). Skin diseases in intensive care medicine. *Journal der Deutschen Dermatologischen Gesellschaft*, **7**(2), 108–15.
3. George SMC, Harrison DA, Welch CA, Nolan KM, and Friedmann PS. (2008). Dermatological conditions in intensive care: a secondary analysis of the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme database. *Critical Care*, **12**(Suppl. 1), S1.
4. Badia M, Serviá L, Casanova JM, et al. (2013). Classification of dermatological disorders in critical care patients: a prospective observational study. *Journal of Critical Care*, **28**(2), 220.e1–8.
5. Sigurdsson V, Toonstra J, Hezemans-Boer M, and van Vloten WA. (1996). Erythroderma. A clinical and follow-up study of 102 patients, with special emphasis on survival. *Journal of American Dermatology*, **35**(1), 53–7.
6. Husain Z, Reddy BY, and Schwartz RA. (2013). DRESS syndrome: Part I. Clinical perspectives. *Journal of American Dermatology*, **68**(5), 693.e1–14; quiz 706–8.
7. Husain Z, Reddy BY, and Schwartz RA. (2013). DRESS syndrome: Part II. Management and therapeutics. *Journal of American Dermatology*, **68**(5), 709.e1–9; quiz 718–20.
8. Walsh S, Diaz-Cano S, Higgins E, et al. (2012). Drug reaction with eosinophilia and systemic symptoms (DRESS): is cutaneous phenotype a prognostic marker for outcome? A review of clinicopathological features of 27 cases. *British Journal of Dermatology*, **168**(2), 391–401.
9. Camous X, Calbo S, Picard D, and Musette P. (2012). Drug reaction with eosinophilia and systemic symptoms: an update on pathogenesis. *Current Opinion in Immunology*, **24**(6), 730–5.
10. Cacoub P, Musette P, Descamps V, et al. (2011). The DRESS syndrome: a literature review. *American Journal of Medicine*, **124**(7), 588–97.
11. Fernando SL. (2012). Acute generalised exanthematous pustulosis. *Australasian Journal of Dermatology*, **53**(2), 87–92.
12. Sassolas B, Haddad C, Mockenhaupt M, et al. (2010). ALDEN, an algorithm for assessment of drug causality in Stevens–Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. *Clinical Pharmacology and Therapeutics*, **88**(1), 60–8.
13. Tohyama M and Hashimoto K. (2012). Immunological mechanisms of epidermal damage in toxic epidermal necrolysis. *Current Opinion in Allergy and Clinical Immunology*, **12**(4), 376–82.
14. Phillips EJ, Chung W-H, Mockenhaupt M, Roujeau J-C, and Mallal SA. (2011). Drug hypersensitivity: pharmacogenetics and clinical syndromes. *Journal of Allergy and Clinical Immunology*, **127**(3 Suppl.), S60–6.
15. Sekula P, Dunant A, Mockenhaupt M, et al. (2013). Comprehensive survival analysis of a cohort of patients with Stevens-Johnson

syndrome and toxic epidermal necrolysis. *Journal of Investigative Dermatology*, **133**(5), 1197–204.
16. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, and Wolkenstein P. (2000). SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *Journal of Investigative Dermatology*, **115**(2), 149–53.
17. Guégan S, Bastuji-Garin S, Poszepczynska-Guigné E, Roujeau J-C, and Revuz J. (2006). Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. *Journal of Investigative Dermatology*, **126**(2), 272–6.
18. Kardaun SH and Jonkman MF. (2007). Dexamethasone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis. *Acta Dermato-Venereologica*, **87**(2), 144–8.
19. Viard I, Wehrli P, Bullani R, et al. (1998). Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science*, **282**(5388), 490–3.
20. Schwartz RA, McDonough PH, and Lee BW. (2013). Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. *Journal of the American Academy of Dermatology*, **69**(2), 187.e1–16; quiz 203–4.

CHAPTER 277

Vasculitis in the critically ill

Karina A. Keogh

Key points

- The vasculitic syndromes are a heterogeneous group of rare disorders characterized by degrees of inflammation and necrosis of blood vessels with a wide variety of clinical manifestations.
- These syndromes were previously associated with a very high mortality, but significant gains in mortality have been seen with current immunosuppressive therapy.
- Vasculitis is frequently diagnosed for the first time during an intensive care unit (ICU) admission.
- Vasculitis in the ICU is most commonly an anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis.
- ICU admission may be for end-organ damage from the disease process itself, or may be for a treatment complication, most commonly severe infection in an immunocompromised host.

Introduction

The vasculitic syndromes are a heterogeneous group of rare disorders characterized by degrees of inflammation and necrosis of blood vessels with a wide variety of clinical manifestations. The pathological process may affect the arteries, veins, and capillaries of any organ. The majority of primary vasculitis syndromes have no known aetiological factors. Secondary vasculitis can be seen in collagen vascular disease, immunological disorders, and infections, e.g. hepatitis B and C.

A number of nomenclature systems have been developed, primarily for research purposes. The American College of Rheumatology (ACR) 1990 diagnostic criteria, classifies the primary vasculitides based on the size of blood vessels involved (aorta and major branches, and equivalent veins) [1]. The Chapel Hill Consensus Conference (CHCC) definitions [2], similarly divide on the basis of blood vessel size. Unlike the ACR criteria, CHCC definitions define microscopic polyangiitis (MPA) as a distinct entity. The European Medicines Agency algorithm [3] also incorporates ANCA, and the latest iteration of the CHCC definition takes into account the recent move away from 'honorific' names for syndromes, towards more descriptive names. These recently accepted more descriptive names for vasculitic syndromes are used throughout this chapter, and an updated list of the primary vasculitides is outlined in Box 277.1. Differential diagnoses typically consists of infection, collagen vascular disease, sarcoidosis, and malignancy.

Intensive care admission is most commonly required for vasculitis involving small blood vessels, including capillaries. The three most common forms of systemic small vessel vasculitides are granulomatosis with polyangiitis (GPA) (Wegener's), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss syndrome). These three conditions are associated with antineutrophil cytoplasmic antibodies (ANCA) and are referred to as the ANCA-associated vasculitides [4,5]. Non-vasculitic manifestations may also be present, such as pulmonary nodules secondary to necrotizing granulomatous inflammation in GPA.

Standard treatment consists of corticosteroids and cytotoxic drugs [6]. ICU admission is typically for end organ damage secondary to inflammation, or because of side effects from the cytotoxic therapies, particularly infection. Overall, there has been a dramatic improvement in prognosis for these conditions since the introduction of cyclophosphamide in the late 1970s, previously rapidly fatal diseases now have 5-year survivals of 80%. ICU admission is associated with a worse prognosis. In one French cohort of 210 patients with primary vasculitides there were 26 ICU admissions over a 20-year period [7]. In 77% the reason for admission was active vasculitis, and in almost half, this was the initial presentation of the disease. The in-ICU mortality was 15% (n = 4), primarily from infectious complications. After a mean follow-up of 31.4 ± 29.2 months, the overall mortality rate was 39% (n = 10).

Small vessel vasculitis

Granulomatosis with polyangiitis (Wegener's)

GPA is a systemic vasculitis characterized by necrotizing granulomatous vasculitis of the respiratory tract, kidneys, and other organs. Alveolar haemorrhage and renal involvement with focal segmental glomerulonephritis are severe manifestations of GPA. The term 'limited Wegener's granulomatosis' has been used to describe disease that is not life- or organ-threatening. Morphological characteristics of GPA include necrotizing granulomas, fibrinoid necrosis, micro-abscesses, focal vasculitis, and thrombosis. GPA, the most common form of vasculitis to involve the lung has a prevalence of up to 63 per million, and an annual incidence of 10 per million

The mean age at onset of symptoms of Wegener's granulomatosis is approximately 45 years; the male to female ratio is 2:1. Patients may initially present with non-specific symptoms including fever, malaise, weight loss, arthralgias, and myalgias. Other frequent disease manifestations are: skin (40–50%), eyes (43%), arthralgias (58%), and arthritis (28%), and neurological involvement in (25%). The cardiovascular system may also be involved.

Upper airway disease, which is present in over 85% of patients, manifests as rhinorrhoea with purulent or bloody nasal discharge,

Box 277.1 Classification of the primary systemic vasculitides based on the size of the blood

- Vessel involvement.
- **Large vessel:**
  - Takayasu's arteritis.
  - Giant cell arteritis.
- **Medium-sized vessel**:
  - Kawasaki's disease.
  - Polyarteritis nodosa (PAN).
- **Small vessel—ANCA-associated vasculitis**:
  - Granulomatosis with polyangiitis (GPA) (Wegener's).
  - Microscopic polyangiitis (MPA).
  - Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss syndrome).
- **Small Vessel—Immune Complex Small Vessel Vasculitis**:
  - Anti-glomerular basement membrane (anti-GBM) disease.
  - Cryoglobulinaemic vasculitis.
  - IgA vasculitis (Henoch–Schönlein purpura).
  - Hypocomplementemic urticarial vasculitis.
- **Variable vessel vasculitis**: Behcet's disease.

nasal mucosal drying, and crust formation, epistaxis. Paranasal sinus involvement leading to deep facial pain, nasal septal perforation, and ulceration of the vomer are important signs. Destruction of the nasal cartilages resulting in 'saddle-nose deformity' is usually a subacute or chronic complication.

Laryngeal and tracheal ulcerated lesions which are present in 30% of untreated patients Subglottic stenosis develops in 5–8% of treated patients. The symptoms caused by subglottic stenosis are usually insidious in onset. Inspiratory and expiratory flow-volume loops may be useful in assessing the impairment of upper airway function, as well as in the follow-up of these patients. Laryngeal involvement may lead to a more difficult intubation, often requiring a smaller endobronchial tube. Surgical dilatation and less commonly tracheostomy may be required.

Microscopic polyangiitis

MPA is a separate entity, with similar vasculitic manifestations to GPA—pauci-immune necrotizing and crescentic glomerulonephritis, and alveolar haemorrhage. By definition there is no granulomatous inflammation, and the upper airway complications seen in Wegener's granulomatosis are not seen. Both GPA and MPA have similar clinical courses and therefore in clinical trials are typically grouped together. They respond similarly to immunosuppressive treatment.

Investigation

Both GPA and MPA are associated with ANCA [8]. These antibodies react with antigens in neutrophil granules, resulting in two staining patterns on indirect immunofluorescence. The C-ANCA pattern demonstrates granular staining in the cytoplasm while the P-ANCA pattern is staining in a perinuclear distribution. The target antigen for cANCA is almost always protease 3 (PR-3). This C-ANCA/PR3 pattern is found in 80–95% of patients with GPA, and up to 40% of patients with MPA. P-ANCA most commonly targets MPO (myeloperoxidase), however, there are a large number of other antigens with which it reacts including many different neutrophil granule and cytoplasmic components, as well as infection-related antigens, (e.g. bactericidal permeability increasing protein (BPI)). The P-ANCA/MPO pattern is seen in 40–80% of patients with MPA (and also Churg–Strauss syndrome), but is less specific for the ANCA-associated vasculitidies. P-ANCA positivity may also be seen in rheumatoid arthritis, ulcerative colitis, Crohn's disease, autoimmune chronic active hepatitis, primary biliary cirrhosis, and sclerosing cholangitis.

Laboratory testing in GPA and MPA may also reveal the following non-specific findings—normochromic normocytic anaemia, mild leukocytosis, mild thrombocytosis, elevated erythrocyte sedimentation rate (often above 100 mm/hour). On urinalysis, abnormalities such as haematuria, proteinuria, and red cell casts are observed in 80% of patients. Pulmonary function tests, particularly flow-volume curves, are helpful in assessing major airway involvement in GPA. In the setting of neurological symptoms an electromyogram may suggest a vasculitic aetiology. Ideally, the diagnosis would be confirmed with a biopsy, although in cases with classical symptomatology, particularly when supported by appropriate serology, it is not always necessary. A tissue diagnosis is not required to fulfil either the ACR criteria or the definitions of the CHCC. When a biopsy is necessary, it should be taken from the most accessible involved organ, such as the skin. In GPA an upper airway biopsy is often diagnostic. The role of transbronchial biopsy in the diagnosis of pulmonary vasculitis is limited, whereas open lung biopsy has a much higher yield.

Treatment

The primary treatment of severe GPA or MPA vasculitis is a combination of corticosteroids and cytotoxic agents [9]. Corticosteroids are typically initially given as methylprednisolone 1 g/day × 3 days, followed by 1 mg/kg/day of prednisone until the disease is controlled, then a slow taper over 3–6 months. The standard induction agent for severe disease over the last 40 years has been oral cyclophosphamide (standard dose 2 mg/kg/day orally, maximum 200 mg/day) [10], followed by a less toxic remission maintenance agent, typically azathioprine or methotrexate, continued for 2 years [11]. This regimen induces remission in >90%, however, is associated with significant toxicity. In one study, 54% of patients treated, developed a serious infection. Other side effects are bladder toxicity, malignancy, and infertility. In an attempt to limit this toxicity, intermittent pulsed (intravenous) dosing has been studied. This leads to a lower total dose of cyclophosphamide administered, with comparable efficacy of inducing remission, but presumably less toxicity [12]. An alternative, distinctly different agent rituximab has also recently been approved for the treatment of severe ANCA-associated vasculitis, on the basis of multicentre randomized trials indicating that rituximab is as efficacious as cyclophosphamide in inducing remission [13,14]. The standard vasculitis rituximab treatment regimen is 375 mg/m^2 weekly × 4 weeks. Rituximab likely has a more favourable side effect profile than cyclophosphamide, in particular it does not have the same negative effects on fertility. There

is, however, a risk with rituximab use of multifocal progressive leukoencephalopathy, a very rare irreversible dementia, thought to be secondary to the reactivation of the John Cunningham (JC) virus in the brain. Major relapses necessitate a return to an induction therapy regimen.

A large multicentre randomized study has also supported a role for plasma exchange in patients with acute renal failure secondary to ANCA-associated vasculitis, with a creatinine greater than 4 mg/dL [15]. Plasma exchange is also often considered in alveolar haemorrhage, requiring mechanical ventilation. A large multicentre study is currently underway to address the efficacy of plasma exchange in this setting.

Patients receiving long-term steroids should also receive prophylaxis against osteoporosis including calcium, vitamin D, and bisphosphonates, as indicated. Prophylaxis against pneumocystis jiroveci should be considered in any patient on chronic immunosuppressive therapy or corticosteroids in excess of 20 mg/day. Active vasculitis is also associated with a greater risk of thromboembolic disease, thus DVT prophylaxis should ideally be given in the ICU, balancing the risk of clot with the potential risk of severe bleeding in this patient population.

Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)

EGPA, also previously known as allergic granulomatosis and angiitis, is the third ANCA-associated vasculitis, although ANCA positivity is typically only seen in 50% of patients. EGPA vasculitic manifestations are typically not as severe as those seen in GPA and MPA, and EGPA has distinct eosinophilic manifestions, therefore EGPA has typically been studied separately in clinical trials. Greater than 95% of patients have asthma. Nasal symptoms such as allergic rhinitis, nasal polyps, nasal mucosal crusting, and septal perforation are seen in over 70% of patients. Hypereosinophilia in peripheral blood, tissue eosinophilia, and elevation of serum IgE are common. Other causes of hypereosinophlia need to be ruled out, including hypereosinophlic syndrome secondary to a bone marrow disorder, and parasitic infection. The classic pathological findings are granulomatous or non-granulomatous angiitis and extravascular necrotizing granulomas, usually with eosinophilic infiltrates

Chest radiographic abnormalities are present in over 60% of patients, and include patchy and occasionally diffuse alveolar-interstitial infiltrates in the perihilar area. Pulmonary nodules +/– cavitation may be seen. Alveolar haemorrhage is very uncommon. Renal involvement is seen in 25%, but the need for renal replacement therapy is rare. One of the leading causes of morbidity/mortality is cardiac involvement with eosinophilic infiltration of the myocardium. These patients may require intensive care for vasculitic manifestations, eosinophilic manifestations (particularly cardiac, eosinophilic pneumonia), or for asthma management. The use of several medications has been associated with the development of EGPA, most notably the leukotriene-modifying agents, although it may be simply, that the use of these agents lead to a reduction in system corticosteroid use, which allows for the 'unmasking' of forme fruste Churg–Strauss syndrome (CSS).

Severity has classically been defined based on a five factor score (FFS), based on the presence or absence of five clinical features—cardiac involvement, gastrointestinal involvement, renal insufficiency (creatinine >1.58 mg/dL), proteinuria (>1 g/day), central nervous system involvement.

The primary therapy for EGPA is corticosteroids. If severe manifestations, typically denoted by a five factor score >1, treat as for the other ANCA-associated vasculitis. There are no large randomized treatment trials in EGPA, but small non- randomized studies support the use of cyclophosphamide in severe disease. There is also some evidence suggesting efficacy of rituximab in EGPA. The anti-IL 5 agent mepolizumab has also shown promise [16].

Anti-glomerular basement membrane (anti-GBM) disease

Anti-glomerular basement membrane (anti-GBM) disease was previously known as Goodpasture's disease. This is a rarer cause of 'pulmonary-renal syndrome' with alveolar haemorrhage and glomerulonephritis associated with autoantibodies that target the glomerular and pulmonary basement membranes. Treatment consists of prednisone and cyclophosphamide, similar to the ANCA-associated vasculitides, in conjunction with plasmaphoresis. The use of plasmaphoresis is based on a small randomized trial of 17 patients (where the best correlation with outcome was the severity of renal disease on entry, rather than treatment group), biological plausibility regarding benefit of rapid reduction in anti-GBM levels, and the improved morbidity and mortality with plasmaphoresis, compared to historic rates [17].

Medium vessel vasculitis

Polyarteritis nodosa

This medium vessel vasculitis, affecting primarily medium-sized muscular arteries, and occasionally small muscular arteries, is rare with a prevalence of 2–33/million, and may be associated with hepatitis B or C infection, or hairy cell leukaemia. Many patients who would previously been classified as having polyarteritis nodosa (PAN) are now classified as having MPA. While any organ may be affected, pulmonary involvement is rare. If a diagnostic biopsy cannot easily be obtained. Angiography can be helpful in making the diagnosis; multiple micro-aneurysms may be seen in the renal, hepatic, or mesenteric circulation. Severe manifestations such as renal insufficiency, mesenteric artery ischaemia, and mononeuritis multiplex, are treated with high dose corticosteroids and cyclophosphamide, as outlined for GPA. When there is underlying hepatitis, it is important that antivirals are used in conjunction with immunosuppression.

Large vessel vasculitis

Giant cell arteritis

Giant cell arteritis, also known as temporal arteritis, cranial arteritis, and granulomatous arteritis is a large vessel vasculitis. The characteristic histological findings are lymphocytic infiltration with fragmentation of the internal elastic lamina, granulomatous inflammation, histiocytes, and multinucleated giant cells. The classic pathological features of giant cell arteritis are seen in approximately 60% of temporal artery biopsies. Giant cell arteritis may be seen in association with polymyalgia rheumatica, the relationship between these two entities remains uncertain. Giant cell arteritis usually affects persons in middle age or older individuals. There are no specific laboratory tests available to diagnose giant cell arteritis,

even though moderate elevation of erythrocyte sedimentation rate is common.

The onset of arteritis and blindness may be sudden, but usually the clinical illness is gradual in onset, with the development of non-specific systemic symptoms, such as low grade fever, malaise, and weight loss. Headache, variable, but often severe, is the most common symptom in giant cell arteritis. These may be followed by more specific symptoms like jaw claudication and sudden loss of vision. Amaurosis fugax is observed in 20% and visual loss in 10%.

Pulmonary complications of giant cell arteritis occur in approximately 10% of patients, and may be the presenting symptoms. They included cough, sore throat, and hoarseness. A population-based study of patients with giant cell arteritis noted respiratory symptoms in up to 30%. It should be considered in any older patient with a new cough or throat pain without obvious cause. Small airways disease has been observed in 46.2% of patients with giant cell arteritis, although the abnormalities have not been significantly different from controls. Chest radiograph abnormalities consist of pulmonary nodules, interstitial infiltrates, occlusion, and aneurysms of pulmonary artery.

Virtually all patients respond favourably to systemic corticosteroids at an initial dose of 1 mg/kg/day. Chronic low-dose therapy is required to maintain remission in most patients.

Takayasu's arteritis

Takayasu's arteritis, is a term synonymous with pulseless disease, aortic arch syndrome, or reversed coarctation. The aorta and its main branches are primarily involved. Histological features include continuous or patchy panarteritis with plasma cells, histiocytes and multinucleated giant cells.

Takayasu's arteritis is more common in Asia. The female to male ratio is 8.5:1, and 80% of patients are between 11 and 30 years of age. Initial or acute clinical features of temporal arteritis include fever, malaise, weight loss, arthralgias, and night sweats lasting for 4–6 works. Chronic disease is the result of ischemia of affected organs.

Pulmonary artery involvement is present in up to 50% of all patients with Takayasu's arteritis. Pathological lesions are generally localized to medium and large pulmonary arteries. Panarteritis with plasma cells, histiocytes and multinucleated giant cells lead to pulmonary arterial occlusion and stenoses A retrospective study of perfusion lung scans, revealed abnormalities in 76% of 120 patients with Takayasu's arteritis. Initially, the changes appeared in the upper lobes, and then progressed to involve arteries of the middle and lower lobes. In another study of 42 patients, in whom a respiratory problem was not clinically suspected, intravenous digital subtraction angiography in 42 patients with temporal arteritis showed involvement of pulmonary artery in 14.3% of patients even though chest radiographs were abnormal in only two patients. A comparison study of 59 patients with temporal arteritis showed that, although chest radiograms were abnormal in 68%, pulmonary angiography revealed arterial occlusions in 86%. A poor correlation has been noted between angiographic changes, and the results of spirometry and arterial blood gas analysis. Other thoracic complications described include aneurysms of pulmonary arteries. Takayasu arteritis presenting as idiopathic adult respiratory distress syndrome with a pathological diagnosis of acute interstitial pneumonia has been described.

Corticosteroids therapy results in symptomatic remission in within days to weeks, but approximately 50% of patients will require an additional agent because of relapsing disease. There are small open-label studies supporting the use of methotrexate and azathioprine. Patients with significant pulmonary artery occlusions may require surgical bypass. Death is usually the result of vascular complications such as rupture of aneurysm, myocardial infarction, congestive cardiac failure, or cerebrovascular accident. Pulmonary involvement signifies a poor prognosis.

Variable vessel vasculitis

Behçet's disease

Behçet's disease is a chronic recurring vasculitic syndrome, most prevalent in Turkey, followed by other countries along the ancient silk route from Asia to the Mediterranean. It is characterized by aphthous stomatitis together with two or more of the following: aphthous genital ulcerations, uveitis, cutaneous nodules, or pustules, synovitis, or meningoencephalitis. The histological features of mucocutaneous lesions are non-specific, and exhibit with various degrees of lymphocytic and plasma cell infiltration, and deposition of IgM and C_3 in the dermal vessels. Both arteries and veins, of variable sizes are involved by the vasculitis. Fever, elevated erythrocyte sedimentation rate, and anaemia are common. Obstruction of major vessels and aneurysms occurs in 10–37% of patients. Thrombosis of superficial and deep veins of both upper and lower extremities, and superior and inferior vena cava develop in 7–37% of patients.

Massive haemoptysis is the most serious respiratory complication in Becet's disease. Life-threatening haemoptysisis is common and is the cause of death in more than 1/3 of patients with pulmonary disease. Serious haemoptysis, initially sensitive to corticosteroid therapy, demonstrates a propensity to reoccur. A review of 28 patients with Behçet's disease with respiratory complications noted haemoptysis, fever, chest pain, and dyspnoea in all 28 patients, and the lung involvement was associated with extrapulmonary disease. Another report on 49 patients with lung involvement observed that recurrent dyspnoea, cough, chest pain, and haemoptysis were the primary clinical signs, particularly in young men, and appeared 3.6 years after the onset of Behçet's disease. Chest radiographs may show pulmonary infiltrates, pleural effusions, and prominent pulmonary arteries. The reasons for haemoptysis include aneurysms of the pulmonary artery, pulmonary artery-bronchus fistula, and mucosal ulcerations. Pulmonary angiography may reveal amputation of the branches of the pulmonary artery and aneurismal dilatations. Immunopathological studies have indicated that pulmonary vasculitis is a result of circulating immune complexes.

Pulmonary embolism occurs with greater frequency because of the high incidence of deep vein thrombosis of the extremities and the vena cavas. Other complications include formation of the fistulas between the coronary and pulmonary arteries, and between the bronchial and pulmonary arteries, pulmonary hypertension, pulmonary haemorrhage, thromboembolism of the superior vena cava and/or other mediastinal or hilar lymphadenopathy, and interstitial pulmonary fibrosis.

Corticosteroids suppresses, but seldom controls all manifestations of the disease. Sudden deaths in corticosteroid-treated patients have indicated that corticosteroid alone may be inadequate. Other drugs namely colchicine, chlorambucil, methotrexate, azathioprine, and cyclosporin have been utilized, but there is very little supporting data for any particular agent. Anticoagulant

therapy is contraindicated. Patients with significant haemoptysis or diffuse pulmonary infiltrates carry a poor prognosis; a mortality of 80% within 2 years after the onset of lung disease has been noted.

References

1. Hunder GG, Arend WP, Bloch DA, et al. (1990). The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. *Arthritis and Rheumatology*, **33**, 1065–7.
2. Jennette JC, Falk RJ, Bacon PA, Basu N, and Cid MC. (2012). Revised international Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis and Rheumatology*, **65**, 1–11.
3. Watts R, Lane S, Hanslik T, et al. (2007). Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Annals of Rheumatic Disease*, **66**(2), 222–7.
4. Semple D, Keogh J, Forni L, and Venn R. (2005). Clinical review: vasculitis on the intensive care unit—part 1: diagnosis. *Critical Care*, **9**, 92–7.
5. Watts R, Lane S, Hanslik T, et al. (2007). Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Annals of Rheumatic Diseases*, **66**, 222.
6. Semple D, Keogh J, Forni L, and Venn R. (2005). Clinical review: vasculitis on the intensive care unit—part 2: treatment and prognosis. *Critical Care*, **9**, 193–7.
7. Cruz BA, Ramanoelina J, Mahr A, et al. (2003). Prognosis and outcome of 26 patients with systemic necrotizing vasculitis admitted to the intensive care unit. *Rheumatology*, **42**, 1183–8.
8. Hoffman GS and Specks U. (1998). Anti-neutrophil cytoplasmic antibodies. *Arthritis and Rheumatology*, **41**, 1521–37.
9. Hoffman GS, Kerr GS, Leavitt RY, et al. (1992). Wegener's granulomatosis: an analysis of 158 patients. *Annals of Internal Medicine*, **116**, 488–98.
10. Fauci AS, Katz P, Haynes BF, and Wolff BM. (1979). Cyclophosphamide therapy of severe systemic necrotizing vasculitis. *New England Journal of Medicine*, **301**, 235–8.
11. Jayne D, Rasmussen N, Andrassy K, et al. (2003). A randomised trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *New England Journal of Medicine*, **349**, 36–44.
12. De Groot K, Harper L, Jayne DR, et al. (2009). Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Annals of Internal Medicine*, **150**, 670–80.
13. Stone JH, Merkel P, Spiera R, et al. (2010). Rituximab versus cyclophosphamide for ANCA associated vasculitis. *New England Journal of Medicine*, **363**, 221–32.
14. Jones RB, Tervaert JW, Hauser T, et al. (2010). Rituximab versus cyclophosphamide in ANCA- associated renal vasculitis. *New England Journal of Medicine*, **363**, 211–20.
15. Jayne DR, Gaskin G, Rasmussen N, et al. (2007). Randomized trial of plasma exchange or high dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *Journal of the American Society of Nephrology*, **18**, 2180–8.
16. Vaglio A, Moosig F, and Zwerina J. (2012). Churg–Strauss syndrome: update on pathophysiology and treatment. *Current Opinion in Rheumatology*, **24**, 24–30.
17. Levy JB, Turner AN, Rees AJ, and Pusey CD. (2001). Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. *Annals of Internal Medicine*, **134**, 1033–42.

CHAPTER 278

Rheumatoid arthritis in the critically ill

Rodrigo Cartin-Ceba and Udaya B. S. Prakash

Key points

- Rheumatoid arthritis is a progressive chronic inflammatory disease of autoimmune aetiology that predominantly affects the joints.
- Rheumatoid arthritis frequently affects non-articular systems, most commonly the cardiopulmonary, gastrointestinal, and haematological systems.
- Treatment of rheumatoid arthritis includes corticosteroids and disease-modifying anti-rheumatic drugs, such as methotrexate, that reduce the inflammatory activity as well as inhibit joint destruction.
- Over the last years, the use of biologicals, such as infliximab, etanercept, adalimumab, anakinra, rituximab, and abatacept has dramatically enhanced the success of rheumatoid arthritis management.
- The main reasons for intensive care unit admission for patients with rheumatic autoimmune diseases include infections, life-threatening manifestations of the underlying disease, adverse effects of the treatment, and unrelated acute medical or surgical illness that are aggravated by the autoimmune disease.

Introduction

Rheumatoid arthritis (RhA) is a progressive chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality. RhA predominantly affects the sinovium of diarthrodial joints, with frequent involvement of tendons, ligaments, fascia, muscle, and bone [1]. Many extraskeletal systems are frequently affected and, indeed, may be the presenting manifestations of RhA. The prevalence of RhA has been estimated at 0.5–1% of the adult population and is the most common form of inflammatory joint disease. It affects women about three times as frequently as men. RhA can occur at any age, although its peak incidence is during the fourth and the sixth decade of life. Given the presence of autoantibodies, such as rheumatoid factor and anti-cyclic citrullinated peptide, which can precede the clinical manifestation of RhA by many years, RhA is considered an autoimmune disease [1]. Over the last years, the optimal use of disease-modifying anti-rheumatic drugs (DMARD), in particular methotrexate, and the availability of several new biological agents, have dramatically enhanced the success of RhA management.

A quarter of patients with autoimmune diseases are admitted to the hospital after presenting to the emergency department and a third of those individuals will require management in the intensive care unit (ICU), of whom a significant percentage are patients with RhA (between 25 and 36% of all autoimmune disease patients managed in the ICU). The main reasons for ICU admission for patients with rheumatic autoimmune diseases are infections resulting from the immunosuppressive therapy, flare or a new life-threatening manifestation of the underlying autoimmune disease, adverse effects of the treatment, and usual unrelated acute medical or surgical illness that are usually aggravated by the autoimmune disease [2,3].

Systemic manifestations of rheumatoid arthritis

RhA is a systemic disease that frequently affects many non-articular systems as outlined in Table 278.1.

Respiratory system

The respiratory system is the most commonly non-skeletal system affected by the disease itself or by severe infections. The pulmonary complications are more common in males with RhA. Pleuropulmonary complications may precede the onset of arthritic symptoms. Many of the intrathoracic manifestations have the potential to cause critical illness and respiratory distress. Acute respiratory failure can occur in RhA patients from a wide variety of causes, but most commonly is related to infections [4–6].

Pleural involvement

Pleural involvement is the commonest intrathoracic manifestation of rheumatoid arthritis [4–6]. Chest X-ray evidence of pleural involvement has been noted in 24% of males and 16% of females. Post-mortem analyses have observed pleural involvement in nearly 50% of individuals. Clinically, massive pleural effusion with the potential to cause respiratory distress is uncommon. Indeed, one-third of patients with rheumatoid pleural involvement are relatively asymptomatic. The pleural effusion is generally unilateral, small, persistent, or recurrent. Occasionally, effusions become chronic and persist for months to years. Pleural involvement is more common in those with active and seropositive rheumatoid

Table 278.1 Systemic complications in rheumatoid arthritis

System	Complication
Pulmonary	◆ Pleurisy and pleural effusion ◆ Pneumothorax ◆ Interstitial pneumonitis and fibrosis ◆ Obliterative and follicular bronchiolitis ◆ Obstructive airway disease ◆ Necrobiotic (rheumatoid) nodules ◆ Caplan's syndrome ◆ Pulmonary arterial hypertension ◆ Pulmonary vasculitis with diffuse alveolar haemorrhage ◆ Bronchiectasis ◆ Apical fibrobullous disease ◆ Pulmonary amyloidosis ◆ Drug-related pulmonary toxicity
Upper airway	◆ Cricoarytenoid joint inflammation ◆ Laryngeal nodules ◆ Upper airway obstruction
Cardiovascular	◆ Pericarditis and pericardial effusion ◆ Constrictive pericarditis ◆ Myocarditis ◆ Valvular disease ◆ Aortitis and aortic dissection
Central nervous system	◆ Rheumatoid pachymeningitis ◆ Cord compression from atlanto-axial dislocation
Haematological	◆ Anaemia of chronic disease ◆ Leukopenia (Felty's syndrome)
Gastrointestinal	Gastrointestinal bleeding (drug-associated: NSAIDS and corticosteroids)

arthritis than those with inactive disease. It is, however, important to recognize that rheumatoid effusions may become complicated by empyema. One complication that may lead to respiratory distress is the sudden occurrence of pneumothorax following transthoracic needle aspiration of rheumatoid lung nodules.

Analysis of pleural fluid typically shows exudative level of total protein (>3.0 g/dL). The fluid is usually pale yellow but occasionally bloody although it may assume opalescent green colour due to the high cholesterol content ('pseudochylothorax'). Typically, the glucose level in pleural fluid is very low (<30 mg/dL) in over 80% of patients and could be confused with an empyema. This is the result of selective blockage of glucose transport into the pleural space as well as the increased glucose utilization by the inflamed and metabolically active pleural mesothelial cells. Analysis of the fluid for its pH may reveal an acidotic fluid (pH <7.30) in acute rheumatoid effusions. The low pH is the result of localized acidosis caused by blockage to the efflux of the end products (lactate and CO_2) of glucose metabolism in the pleural space.

Interstitial lung disease

The term, 'rheumatoid lung' is used to describe the diffuse interstitial pneumonitis and fibrosis that occurs as a complication of RhA [4–6]. The rheumatoid lung disease is among the most serious complications. The estimated prevalence of this condition using high resolution computed tomography (HRCT) is 20–44%. A restrictive pattern of pulmonary dysfunction can be documented by pulmonary function testing in over one-third of patients. The clinical, physiological, and histopathological features of rheumatoid lung disease are analogous to those in idiopathic interstitial pneumonia and include usual interstitial pneumonia (the commonest pattern in RhA), non-specific interstitial pneumonia, organizing pneumonia, lymphocytic interstitial pneumonia, and desquamative interstitial pneumonia. Cough and dyspnoea on exertion are common symptoms [7]. Physical examination reveals fine late inspiratory crackles, more pronounced in the lung bases, and clubbing occurs in over two-thirds of the patients. The chest X-ray usually exhibits a bibasilar interstitial process or micronodules, with progression to other regions as the disease progresses. Late stage disease may show generalized honeycombing. HRCT of the chest in early stages of the disease may show 'ground-glass' infiltrates and as the disease progresses, interstitial process, and honeycombing appear.

Pulmonary function testing in patients with rheumatoid lung disease typically demonstrate restrictive lung dysfunction manifested by decreased lung volumes, relatively normal airflow, and diminished diffusing capacity of the lungs for carbon monoxide diffusing capacity of the lungs for carbon monoxide (DLCO); the latter being the earliest physiological abnormality. Exercise-induced hypoxia is common in patients with advanced disease.

Invasive diagnostic procedures are rarely indicated in patients with rheumatoid lung. Diagnostic bronchoalveolar lavage has demonstrated abnormalities identical to those in idiopathic pulmonary fibrosis, namely increased neutrophils at times lymphocytes, although diagnostic bronchoalveolar lavage and lung biopsy may be indicated in complicated situations, particularly in patients with immunocompromised status as a result of therapy of rheumatoid arthritis. A lung biopsy is rarely required to document rheumatoid lung disease. Moreover, the morphological features are non-specific without clinical correlates because the observed abnormalities are dependent on the stage of the disease.

The occurrence of rapidly progressive lung disease, respiratory failure, and cor pulmonale as the result of rheumatoid lung is rare. Occasionally, a rapid progression of the lung disease occurs when the arthritic features flare. Clinically, the respiratory disease in such patients demonstrates the course exhibited by patients with rapidly progressive idiopathic pulmonary fibrosis. The mortality from pulmonary disease in RhA patients is twice that of the general population.

Obstructive lung disease

Obstructive airway disease is a well-recognized complication of RhA [4–6]. More than 20% of patients with active rheumatoid lung disease develop obstructive airway disease secondary to obliterative bronchiolitis, follicular bronchiolitis, bronchiectasis, and bronchitis. Pulmonary function testing in patients (non-smokers) with rheumatoid arthritis has demonstrated obstructive lung dysfunction in nearly one-third of patients. A much higher prevalence of obstructive lung disease has been noted in patients with rheumatoid arthritis who smoke. The combination of rheumatoid arthritis and smoking is associated with a higher prevalence of airway disease than either of the factors alone.

Bronchiectasis has been described as a complication of rheumatoid arthritis. Bronchiolitis may predispose to this complication. Bronchiectasis is uncommon in earlier stages of the disease. In many reported cases, the occurrence of bronchiectasis has been in patients with advanced and severe rheumatoid arthritis. Progressive rheumatoid airway disease with rapid progression may lead to respiratory failure.

Laryngeal involvement

Cricoarytenoid involvement is an important complication of rheumatoid arthritis because it may present with inspiratory and expiratory difficulty caused by fixed obstruction at the level of larynx. Inflammation of the cricoarytenoid joint is a common finding [8,9]. Cricoarytenoid arthritis is recognized clinically in one-third of cases, even though its presence has been noted in most of the necropsy studies in patients with RhA. Clinical manifestations are episodic and include laryngeal pain, dysphonia, and occasionally pain on swallowing, all of which may be accentuated in the morning. Chronic persistent sore throat and hoarseness may be seen in some patients. Laryngoscopy may show erythema and oedema of the vocal apparatus, abnormal motion of vocal cords, and dysfunction of the arytenoids. Laryngeal obstruction rarely occurs, but may be seen in the few hours following extubation for endotracheal ventilation. Occurrence of rheumatoid nodule in the larynx may present with hoarseness, cough, and dyspnoea. It is of importance for specialists in critical care and anaesthesia to recognize that laryngeal nodules may remain asymptomatic and pose problems at the time of tracheal intubation.

Other complications

Pulmonary hypertension has been described in several patients with rheumatoid arthritis, although it rarely causes significant complications. Another uncommon complication of rheumatoid arthritis is pulmonary vasculitis. Anecdotal cases with description of vasculitic lesions within the pulmonary capillaries may explain the alveolar haemorrhage encountered in some of these patients.

Pericarditis secondary to rheumatoid arthritis has been identified in nearly 50% of autopsied patients. Symptomatic pericarditis and haemodynamic alterations caused by it are rare. Acute flares of rheumatoid pericarditis coincide with the activity of rheumatoid arthritis. Constrictive pericarditis, myocardial involvement, valvular dysfunction, conduction defects, and cardiomyopathy are also rare. A serious complication is unusual the occurrence of rheumatoid aortitis associated with aortic insufficiency and aortic rupture.

Cervical spinal involvement with resultant instability of the affected spinal column is an important complication to be reckoned by specialists in critical care and anaesthesia. Subluxation and instability of the atlanto-axial joint may preclude extension of the neck for purposes of laryngoscopic tracheal intubation. The temporomandibular joints can also be affected limiting the oral opening during intubation. The tracheal intubation in such patients should be accomplished with a flexible bronchoscope.

Treatment and prognosis

The general concept in the management of these patients in the ICU is to recognize the presence of a complicating infection, other side effects of the medications use for its treatment (particularly lung toxicity) or to recognize a flare of the disease. Most of the patients with RhA use non-steroidal anti-inflammatory drugs (NSAIDs) in the initial stages of their disease. NSAIDS are pivotal in the treatment of symptomatic pericarditis. Unfortunately, NSAIDs use is a common cause of upper gastrointestinal bleeding. Systemic corticosteroid therapy is generally used in the presence of systemic disease. In the earlier stages of rheumatoid interstitial lung disease, the use of corticosteroids may reverse the acute inflammatory process, and slow or stop progression to irreversible fibrotic lung disease. As the lung disease becomes chronic, the ability to reverse it with corticosteroid and other therapies diminishes. Poor prognosis is associated when the interstitial process is advanced. Such patients have shown a median survival of 3.5 years and a 5-year survival of 39%. Poor prognosis is also associated with rheumatoid bronchiolitis. Immunotherapy consisting of corticosteroid and cytotoxic agents has been reported, but the response has been unsatisfactory in chronic or advanced cases. It is important to recognize that certain cytotoxic agents used in the treatment of rheumatoid arthritis can produce pulmonary toxicity. The agents with known pulmonary toxicity include gold, methotrexate, and cyclophosphamide [4,5]. Prospective studies have shown that methotrexate has no major effect on pulmonary function in the majority of patients with rheumatoid arthritis and that there is no evidence that patients with pre-existing pulmonary disease are at increased risk for further deterioration of lung function.

Recently, the use of biological agents has changed significantly the management of RhA. Multiple studies have demonstrated the efficacy of anti-TNF therapy (infliximab, etanercept, adalimumab, anakinra), as well as other targeting agents such as rituximab and abatacept in reducing inflammatory activity, as well as inhibiting joint destruction in patients with active RhA. Today, these drugs play an important role in the treatment of RhA, particularly in patients whose disease is not responding to treatment with conventional DMARDs. Patients treated with biological agents have a higher risk of infection, particularly opportunistic infections. Severe deterioration of pulmonary function may occur with the use of anti-TNF therapy in RhA patients with underlying interstitial lung disease.

The studies evaluating the outcome of RhA patients admitted to the ICU have included other rheumatological conditions. However, they all have identified a high mortality ranging from 17 to 55%. In addition, the overall observed ICU mortality in these studies have found a considerably higher than predicted mortality when using the APACHE II and SAPS II score systems [10–12]. The main variables associated with mortality include a higher critical illness score, such as APACHE (II and III), SOFA, and SAPS; comorbidities, use of steroids, infection as the cause of admission, and older age [13,14].

References

1. Dedhia HV and DiBartolomeo A. (2002). Rheumatoid arthritis. *Critical Care Clinics*, **18**(4), 841–54, ix.
2. Janssen NM, Karnad DR, and Guntupalli KK. (2002). Rheumatologic diseases in the intensive care unit: epidemiology, clinical approach, management, and outcome. *Critical Care Clinic*, **18**(4), 729–48.
3. Quintero OL, Rojas-Villarraga A, Mantilla RD, and Anaya JM. (2013). Autoimmune diseases in the intensive care unit. An update. *Autoimmunity Review* **12**(3), 380–95.
4. Anaya JM, Diethelm L, Ortiz LA, et al. (1995). Pulmonary involvement in rheumatoid arthritis. *Seminars in Arthritis and Rheumatology*, **24**(4), 242–54.

5. Gauhar UA, Gaffo AL, and Alarcon GS. (2007). Pulmonary manifestations of rheumatoid arthritis. *Seminars in Respiratory and Critical Care Medicine*, **28**(4), 430–40.
6. Amital A, Shitrit D, and Adir Y. (2011). The lung in rheumatoid arthritis. *La Presse Médicale*, **40**(1 Part 2), e31–48.
7. Hacking JC and Flower CD. (1995). Causes and investigation of increasing dyspnoea in rheumatoid arthritis. *Annals of Rheumatic Disease*, **54**(1), 17–19.
8. Geterud A, Bake B, Berthelsen B, Bjelle A, and Ejnell H. (1991). Laryngeal involvement in rheumatoid arthritis. *Acta Otolaryngologica*, **111**(5), 990–8.
9. Voulgari PV, Papazisi D, Bai M, Zagorianakou P, Assimakopoulos D, and Drosos AA. (2005). Laryngeal involvement in rheumatoid arthritis. *Rheumatology International*, **25**(5), 321–5.
10. Kollef MH and Enzenauer RJ. (1992). Predicting outcome from intensive care for patients with rheumatologic diseases. *Journal of Rheumatology*, **19**(8), 1260–2.
11. Moreels M, Melot C, and Leeman M. (2005). Prognosis of patients with systemic rheumatic diseases admitted to the intensive care unit. *Intensive Care Medicine*, **31**(4), 591–3.
12. Camargo JF, Tobon GJ, Fonseca N, et al. (2005). Autoimmune rheumatic diseases in the intensive care unit: experience from a tertiary referral hospital and review of the literature. *Lupus*, **14**(4), 315–20.
13. Godeau B, Mortier E, Roy PM, et al. (1997). Short and longterm outcomes for patients with systemic rheumatic diseases admitted to intensive care units: a prognostic study of 181 patients. *Journal of Rheumatology*, **24**(7), 1317–23.
14. Cavallasca JA, Del Rosario Maliandi M, Sarquis S, et al. (2010). Outcome of patients with systemic rheumatic diseases admitted to a medical intensive care unit. *Journal of Clinical Rheumatology*, **16**(8), 400–2.

PART 12.2

Wound and pressure sore management

CHAPTER 279

Principles and prevention of pressure sores in the ICU

Laura Crawford and Ruth Kleinpell

Key points

- A number of factors contribute to pressure ulcer development including the intensity and duration of pressure, tissue tolerance, shear, and friction.
- The elderly are at greater risk because of physiological changes that occur to the skin and tissue with age, such as dermal thinning and the inability of tissue to distribute the mechanical load.
- The most common anatomical sites for pressure ulcers to occur are the sacrum and heels.
- Hospitalized patients, especially the critically ill, should be evaluated for the risk of pressure ulcer development upon admission.
- A risk assessment should be performed to identify the vulnerability of pressure ulcer development and to provide guidance for the implementation of preventative interventions.

Principles and prevention of pressure ulcer

Pressure ulcers are a troubling complication of a hospital stay, especially for acute and critically-ill patients. Pressure ulcers can increase the length of hospitalization, recovery time and the risk of infection, increases the costs of care, and can cause pain and suffering for patients. Of significance for clinicians is that pressure ulcers are thought to be preventable in most cases and are seen as a reflection of the quality of care provided.

A pressure ulcer is defined by the National Pressure Advisory Panel and European Pressure Ulcer Advisory Panel (NPUAP and EPUAP) [1] as localized injury to the skin and/or underlying tissue usually over a bony prominence, as the result of pressure, or pressure in combination with shear. When a person is immobile the soft tissue is compressed between the skin and bone. This leads to ischaemia and later tissue death. Typically, a pressure ulcer occurs over a bony prominence, but can occur anywhere soft tissue is compressed. Pressure ulcers are characteristically rounded with regular edges.

Pressure ulcer prevalence rates range from 88 to 53.2%, and incidence rates vary from 7 to 71.6%, depending on associated risk factors. The most common anatomical sites for pressure ulcers to occur are the sacrum and heels [2]. The NPUAP and EPUAP [1] define pressure ulcers in six stages according to the degree of tissue damage present in the wound. There are a number of factors that contribute to pressure ulcer development. The intensity and duration of pressure, as well as tissue tolerance play a role. If the intensity of the pressure exerted exceeds the pressure that it takes to hold open a capillary to allow blood flow, tissue ischaemia, and subsequent necrosis will result. The duration of the pressure is also an important component [3]. High pressure over a short period of time is as damaging as low pressure over a long period of time. The last factor that influences the effect of pressure is tissue tolerance. This is the ability of the skin and underlying structures to undergo pressure without experiencing adverse effects. This tolerance is lower in some patients such as the elderly and those with spinal cord injuries [4].

There are a number of extrinsic or external factors that affect the tissue tolerance. Shear force is concept that plays a part in pressure ulcer development [3]. Shear occurs when parallel forces are exerted on the skin, for example, if a patient's head of bed is elevated greater than 30°, gravity pulls the skeleton downward, but the skin is held in place by friction. This force impairs blood at the fascial level causing ischaemia and necrosis. The 'knee gatch' position, (elevating the knees in bed), helps reduce sliding, and should be practiced in cases where the head of bed must be at 30° or higher, i.e. ventilated patients. Friction works synergistically with gravity and this results in shear. Friction is a significant factor in pressure ulcer development. It often occurs when patients are pulled up in bed or slid across a gurney or procedure table. It is best to use a lift device or transfers sheet to reduce the risk of dermal abrasion from the surface of the sheet rubbing on the skin. If patients have good upper body strength a trapeze also reduces their risk of friction injury and encourages independence. Moisturizing or applying a dressing can help to protect the skin on the elbows, heels, and sacrum. Friction can occur without pressure, and therefore, if it is the exclusive aetiology of injury it should not be labelled as a pressure ulcer, but as a partial thickness wound. Excessive moisture is an additional element that predisposes a patient to pressure ulcer development. When skin is persistently wet, through urine and/or faecal incontinence or wound drainage, the dermal integrity is at greater risk of injury. The combine assault of urine and faecal incontinence is very caustic to the skin; it raises the pH of the skin producing an alkaline environment that leads to further breakdown and dermatitis. Skin breakdown related to moisture should be classified according the underlying aetiology, i.e. incontinence-associated dermatitis should not be confused with a pressure

Table 279.1 Pressure ulcer classification: a brief guide

Category/Stage I pressure ulcer	Non-blanchable erythema. Intact skin
Category/Stage II pressure ulcer	Partial thickness tissue loss. Wound bed is pink/red
Category/Stage III pressure ulcer	Full thickness tissue loss extending into the subcutaneous tissue, slough/eschar may be present in the wound bed, but does not obscure depth of the wound
Category/Stage IV pressure ulcer	Full thickness tissue loss, the muscle, bone, or tendon may be present in the wound bed. Slough/eschar may be present in the wound bed, but does not obscure depth of the wound
Unstageable: Unknown depth	Full thickness tissue loss. Unable to visualize base of the wound due to slough or eschar
Deep tissue injury	Purple or maroon coloured. Intact skin

Data from National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance. Prevention and Treatment of Pressure Ulcers: Clinical Practice Guideline. Emily Haesler (Ed.). Cambridge Media: Osborne Park, Western Australia; 2014.

ulcer. There is the chance of having the presence of both aetiologies. When moisture cannot be controlled it is important to protect the skin by using a barrier or skin protectant ointment. Underpads that draw away moisture should be used. The absorbent material in the pad helps reduce the risk of trapping the moisture against the skin and prevents maceration. For large volumes of faecal incontinence consider the use of a faecal containment device of a faecal management system. Immediately after each episode of incontinence clean skin gently and apply a skin barrier [4].

There are a number of intrinsic or internal factors related to the risk of pressure ulcer development. Poor nutrition and dehydration contribute to pressure ulcer development because these conditions make tissue more vulnerable to damage [3]. The elderly are at greater risk because of physiological changes that occur to the skin and tissue with age, such as dermal thinning and the inability of tissue to distribute the mechanical load. Low blood pressure is thought to divert blood away from the skin to more essential organs during critical times. Additionally stress, smoking, surgery, elevated body temperature are other conditions are understood to contribute to pressure ulcer development [4].

According to the NPUAP [5] the six stages of pressures are classified as the following (Table 279.1 gives a brief summary of this guideline).

Pressure ulcer stages

Suspected deep tissue injury

Purple or maroon localized area of discoloured intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer, or cooler compared with adjacent tissue. Deep tissue injury may be difficult to detect in individuals with dark skin tones. Evolution may include a thin blister over a dark wound bed. The wound may further evolve and become covered by thin eschar. Evolution may be rapid exposure of additional layers of tissue even with optimal treatment.

Stage I

Intact skin with non-blanchable redness of a localized area, usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area. The area may be painful, firm, soft, warmer, or cooler, compared with adjacent tissue. Stage I may be difficult to detect in individuals with dark skin tones. May indicate 'at risk' persons (a heralding sign of risk).

Stage II

Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled blister. Presents as a shiny or dry shallow ulcer without slough or bruising. This stage should not be used to describe skin tears, tape burns, perineal dermatitis, maceration, or excoriation. Bruising indicates suspected deep tissue injury

Stage III

Full thickness tissue loss. Subcutaneous fat may be visible, but bone, tendon, or muscle are not exposed. Slough may be present, but does not obscure the depth of tissue loss. May include undermining and tunnelling. The depth of a stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput, and malleolus do not have subcutaneous tissue, and stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep stage III pressure ulcers. Bone/tendon is not visible or directly palpable.

Stage IV

Full thickness tissue loss with exposed bone, tendon, or muscle. Slough or eschar may be present on some parts of the wound. Often include undermining and tunnelling. The depth of a stage IV pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput, and malleolus do not have subcutaneous tissue and these ulcers can be shallow. Stage IV ulcers can extend into muscle and/or supporting structures (e.g. fascia, tendon, or joint capsule) making osteomyelitis possible. Exposed bone/tendon is visible or directly palpable.

Unstageable

Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, grey, green, or brown) and/or eschar (tan, brown, or black) in the wound bed. Until enough slough and/or eschar is removed to expose the base of the wound, the true depth, and therefore stage, cannot be determined. Stable (dry, adherent, intact without erythema, or fluctuance) eschar on the heels serves as 'the body's natural (biological) cover' and should not be removed [1].

Pressure ulcers should not be staged when located on a mucous membrane. The pressure ulcer staging system classifies ulcers according to the tissue type, i.e. partial or full thickness. The histology of the tissue on a mucous membrane is different than the histology of the skin and, therefore, cannot be used to classify this type of ulcer. It should be classified as a 'mucosal pressure ulcer'.

Pressure ulcers should never be 'reversed or back' staged. The classification system is used to describe the deepest layer of tissue injury [4].

To prevent pressure ulcers the confounding factors need to be eliminated. In the acute care setting patients usually develop pressure

ulcers within the first 2 weeks of admission and within 72 hours in the ICU setting [6]. Skin assessment, risk assessment, repositioning, nutritional status, and support surfaces are all key pressure ulcer prevention strategies. These concepts need to be considered when implementing an individualized prevention strategy [4].

Skin assessment

In an effort to establish a baseline assessment of the patient's skin, a full skin assessment should be completed upon admission to the unit and daily. A patient's skin should be inspected from head to toe and should focus on the most high-risk areas including over bony prominences, skin-folds (intertriginous areas), between the toes, and all areas of skin in contact with medical devices. All garments and stockings should be removed to visualize the skin [4].

Risk assessment

A patient's risk for pressure ulcer development should be evaluated to allow for implementations of interventions to mitigate their risk of development [7]. A risk assessment should be performed to identify the vulnerability of pressure ulcer development and to provide guidance for the implementation of preventative interventions. A patient's risk should be assessed at regular intervals. In the acute care setting the initial assessment in made on admission to the unit, then subsequently when the patient's condition changes or worsens and every 24–48 hours. The two most widely studied and validated risk assessment scales are the Braden and Norton Scales. The Braden scale consists of six subcategories. Each category is scored 1 for the (most at risk) to 4 (least at risk) with the exception of the friction and shear subcategory which is score 1–3. The numbers are added providing a total score that ranges from 4 to 23. If a score falls below 18 the patient is considered at risk for pressure ulcer development. The Norton score includes five parameters: physical condition, mental condition, activity, mobility, and incontinence. The rating for each category is 1–4 with a score potential of 5–20. For both the Braden and Norton scales the lower the score identifies a greater risk of developing a pressure ulcer [6]. Studies focusing on risk factors for critically-ill patients have identified several demographic and clinical factors. A retrospective, correlational study of 347 patients admitted to a medical-surgical intensive care unit found that age, length of stay, mobility, friction/shear, norepinephrine infusion, and cardiovascular disease explained a major part of the variance in pressure ulcers [8]. Another study focusing on the incidence of pressure ulcer development in intensive care unit (ICU) patients found that increased severity of illness as measured with the Acute Physiology and Chronic Health Evaluation (APACHE II) was associated with higher incidence of pressure ulcer development [9].

Nutrition assessment

Although the underlying relationship is uncertain, low body weight, poor food intake, and poor nutritional status are all risk factors for the development of pressure ulcers. Patients must have sufficient calories, fluid and proteins to reduce the risk of development. Patients must also maintain adequate hydration. All patients at nutritional risk should have an evaluation by a registered dietitian [4].

Repositioning

Repositioning should be scheduled for bed and chair bound patients who are at risk of pressure ulcer development. The patient's overall condition needs to be considered when repositioning. If the patient cannot be turned due to a medical condition then an advanced support surface should be used and attempts made for slight adjustments in position. Patients at risk should not sit for periods of time greater than 1 hour and they should use pressure relief chair cushions. If the patient is independent they should reposition themselves every 15 minutes when in the chair. Heels should be suspended off the surface of the bed to prevent pressure on that area. The use of a pillow or a heel elevation device is recommended [6]. Donut devices are no longer used for pressure relief; they have been found to cause ischaemia over the pressure area [1]. A turning schedule for bed bound patients is one of the most important concepts of pressure ulcer prevention. When turned to the side patients should be rotated to a 30° lateral position to prevent pressure on the trochanter. Pillows or blankets may be used to pad areas that may touch such as between the knees. Alterations to the position should be made regularly and frequently, rotate positioning on the right side, back, left side, back [6].

Support surfaces

Support surfaces should be use for those individuals at risk for pressure ulcer development. They are used as adjunct therapy, and are not to replace turning and repositioning. The support surface functions better with minimal linen and pads, between the patient and the surface. Continence pads that are compatible with the support surface should be used. There are many terms associated with support surfaces technology. Immersion refers to how deep the body penetrates into the surface to allow for the pressure to distribute over a large area and not directly over the bony prominence. Envelopment is the surfaces ability to conform to the body. Microclimate is the temperature of the skin, and the moisture or humidity of the interface between the surface of the skin and the support surface. The components of the support surface vary from solid, fluid, to air. They can be used alone or in combination. The exterior is often made of a material that reduces shear and friction. Alternating pressure or active surfaces have the ability to distribute the load over the area in contact with the patient's body. They require a motor to inflate and deflate the surface, which distributes the load.

A reactive surface is one that may or may not require a motor. This surface changes based on the load of the weight placed on the surface. There are a number of different types of reactive surfaces—continuous lateral rotation, low air loss, and air fluidized beds are examples. Low air loss is a feature that provides flow of air continuously across the surface of the skin to manage moisture. The bed is calibrated for pressure redistribution based on the patient's height and weight. Air fluidized therapy beds are used in cases where the patient has no turning surface, has had a muscle flap or skin graft or has suffered extensive burns. Two-thirds of patient immerses into the surface of the bed and the patient essentially 'floats' on the surface. Mattress overlays are surfaces that are placed on top of the mattress. There are indications and contraindications for the use of the different support surfaces. When selecting a support surface the patient's individual needs must be considered [4].

For the critically-ill patient, several specific measures are advocated for preventing pressure ulcers including frequent repositioning, continuous lateral rotation, progressive mobility, and frequent skin assessments, in addition to managing moisture and maximizing nutritional support [10–13].

Conclusion

Hospitalized patients, especially the critically ill, should be evaluated for the risk of pressure ulcer development upon admission. An individualized care plan should be implemented to focus on the specific factors placing the patient at risk including, but not limited to the use of skin care products and the use of a support surface if it is deemed necessary. Knowledge of pressure prevention strategies and the various products is important for critical care clinicians. A pressure ulcer prevention strategy should also include education for the patient and their caregivers.

Acknowledgements

Text credit for Pressure Ulcer Stages: Reproduced with permission from National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance. Prevention and Treatment of Pressure Ulcers: Clinical Practice Guideline. Emily Haesler (Ed.). Cambridge Media: Osborne Park, Western Australia; 2014.

References

1. European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel (2009). *Prevention and Treatment of Pressure Ulcers: Quick Reference Guide*. Washington DC: National Pressure Ulcer Advisory Panel.
2. Moore Z and Webster J. (2011). Dressings and topical agents for preventing pressure ulcers. *Cochrane Database of Systematic Reviews* **8**, CD009362.
3. Niederhauser A, Lukas CV, Parker V, Ayello EA, Zulkowski K, and Berlowitz D. (2012). Comprehensive programs for preventing pressure ulcers: a review of the literature. *Advances in Skin and Wound Care*, **15**, 167–88.
4. Bryant, N, and Nix D. (2010). *Acute and Chronic Wounds Current Management Concepts*, 4th edn. Kidlington: Mosby.
5. National Pressure Advisory Panel. (2009). *Pressure Ulcer Prevention and Treatment—Clinical Practice Guideline*. Washington: National Pressure Advisory Panel.
6. Wound, Ostomy and Continence Nurses Society. (2010). Guideline for Prevention and Management of Pressure Ulcers. In WOCN Clinical Practice Guideline Series. Mount Laurel, NJ, Wound, Ostomy and Continence Nurses Society
7. European Pressure Ulcer Advisory Panel. (2011). *EPUAP-NPUAP-PPPIA International Pressure Ulcer Guidelines*. Available at: http://www.epuap.org/guidelines/ (accessed September 5, 2013).
8. Cox J. (2011). Predictors of pressure ulcers in adult critical care patients. *American Journal of Critical Care*, **20**, 364–75.
9. Shanin ES, Dassen T, and Halfens RJ. (2009). Incidence, prevention and treatment of pressure ulcers in intensive care patients: a longitudinal study. *International Journal of Nursing Studies*, **46**, 413–21.
10. Jankowski IM. (2010). Tips for protecting critically ill patients from pressure ulcers. *Critical Care Nurse*, **30**, S7–9.
11. Uzum O, Aylaz R, and Karadağ E. Protective Study, Reducing Pressure Ulcers in Intensive Care Units at a Turkish Medical Center. *Journal of Wound Ostomy and Continence Nursing*, **36**(4), 404–11.
12. Institute for Healthcare (IHI). (2008). *How to Guide: Prevent Pressure Sores*. Cambridge, MA: IHI. Available at: http://www.ihi.org/knowledge/Pages/Tools/HowtoGuidePreventPressureUlcers.aspx (accessed 5 September 2013).
13. Agency for Healthcare Research and Quality. Preventing Pressure Ulcers in Hospitals: A Toolkit for Improving Quality of Care. http://www.ahrq.gov/research/ltc/pressureulcertoolkit/putool3a.htm (Accessed September 5, 2013).

CHAPTER 280

Dressing techniques for wounds in the critically ill

Ruth Kleinpell and Laura Crawford

Key points

- The appropriate selection of dressings for wounds and pressure ulcers can facilitate healing, although there is insufficient evidence to indicate which specific dressings are the most effective.
- A number of factors determine the selection of a dressing in the management of pressure ulcers, including the wound size, location, amount of drainage or exudates, condition of periwound, caregiver needs, ease of use, and costs, among other factors.
- The size and extent of tissue invasion can also determine the dressing size and material. As general concepts, larger wounds often need packing and wounds with exposed tendons or ligaments require moisture and occlusive dressings.
- While gauze dressings are absorptive and permeable to water, water vapour and oxygen, practice varies widely in the use of gauze dressings. Often, advanced wound dressings are used over gauze dressings for pressure ulcers.
- For the purposes of pressure ulcer prevention, several types of dressings are used to promote skin protection including semi-permeable film dressings, which are most often a thin polyurethane membrane coated with a layer of an acrylic adhesive; hydrocolloid dressings, which contain a dispersion of gelatin, pectin, and carboxymethylcellulose together with other polymers and adhesives; or foam dressings, such as an open cell, hydrophobic, polyurethane foam sheet. Additionally, topical agents can be used in isolation or in combination with dressings.

Introduction

For the purposes of pressure ulcer prevention, several types of dressings are used to promote skin protection including semi-permeable film dressings which are most often a thin polyurethane membrane coated with a layer of an acrylic adhesive; hydrocolloid dressings, which contain a dispersion of gelatin, pectin, and carboxy methylcellulose together with other polymers and adhesives; or foam dressings such as an open cell, hydrophobic, polyurethane foam sheet [1]. Additionally, topical agents can be used in isolation or in combination with dressings.

The appropriate selection of dressings for pressure ulcers can facilitate healing, although there is insufficient evidence to indicate which specific dressings are the most effective [2]. The primary function of a dressing for e.g. exudates management, may assist the health care clinician to choose one type of dressing over another based on the characteristics of the wound [3]. A number of factors determine the selection of a dressing including the wound size, location, amount of drainage or exudates, condition of periwound, caregiver needs, ease of use, and costs (Box 280.1) [4].

The aetiology or cause of the wound will directly affect the choice of dressing as factors such as whether a pressure ulcer has undermining and requires packing to fill dead space need to be considered. Other considerations related to aetiology include whether exudates management and compression are required as is the case with venous insufficiency, or whether moisture is preferred, as is often the case with arterial ulcers [2]. Factors related to the history of the wound including the duration and course of wound healing, and prior dressings or treatment strategies that have been used need to also be considered [2].

Box 280.1 Factors influencing the choice of dressing for pressure ulcers and wounds

- Location.
- Drainage/exudate.
- Wound factors (e.g. infection, necrosis).
- Size, depth, and presence of undermining or tunnelling.
- Wound history.
- Comorbid conditions.
- Goals for healing.
- Condition of periwound.
- Individual/caregiver needs (e.g. pain reduction, odour control).
- Availability.
- Ease of use.
- Cost/reimbursement of the dressing.

Data from Wound, Ostomy and Continence Nurses Society (WOCN) *Guideline for Prevention and Management of Pressure Ulcers*, WOCN Clinical Practice Guideline Series, (2010).

Comorbid conditions such as diabetes mellitus, which can impair wound healing, the presence of obesity, which can increase the risk of dehiscence, or the presence of arterial and venous disease, in which compression may be contraindicated, may need to also be considered. The size and extent of tissue invasion can also determine the dressing size and material. As general concepts, larger wounds often need packing and wounds with exposed tendons or ligaments require moisture and occlusive dressings. The amount and type of exudates is another factor that will impact the selection of dressings. Containment of exudates is important to managing the increased bioburden, protecting the periwound skin, controlling odour, and avoiding overuse of wound care products [5].

Dressing options

A large number of products and dressing options are available for wound and pressure ulcer management. Occlusive or semi occlusive dressing help to maintain wound bed moisture, which promotes re-epithelialization and wound closure [6]. The main occlusive or semi-occlusive dressings include hydrocolloid dressings, alginates, hydrogels, foam dressings, hydrofibre dressings, and paraffin gauze and non-adherent dressings. Gauze rolls and dressings can be used to additionally secure or anchor the tissue interface dressings. Other products used for wound care include hyaluronic acid cream or dressings, dressings supplemented with cadexomer iodine or silver, and dressings containing medical-grade honey [6]. Maintaining a moist ulcer bed is recommended for wound care, when the ulcer bed is clean and granulating, to promote healing or closure [6].

Often, institutions will outline the choice of products to be used for various types of wounds. Table 280.1 outlines one institutional resource for clinicians that outline different products, options for use, and instructions for application. Often, dressing options are outlined as part of an overall skin assessment and treatment plan of care (Fig. 280.1), or part of reference guides for clinical care (Table 280.2).

Table 280.1 Wound care products. This guide should be used in conjunction with a wound care algorithm (see Fig. 280.1)

Products	Options	Instructions for application	Tips
(1) Wound cleanser	Normal saline	◆ Cleanse wound prior to each dressing change for each of the following products (2–9). ◆ Be sure peri-wound skin is free of any residue before applying any products below.	Normal saline: expires 24 hour after opening.
	SAF-Clens®AF Dermal* Wound Cleanser (Cleanser Wound Saf Clen 12 oz)*		SAF-Clens®: no expiration. If patient complains of burning, stop use.
(2) Transparent dressing	Tegaderm™ (Dressing Tegaderm 4x10)* (Dressing Tegaderm 4x2)*	◆ Smooth dressing from centre out to edges. ◆ **Removal**: pull horizontal to skin in direction of hair growth. ◆ Used as a secondary dressing, not intended to be changed daily.	Not to be used on fragile skin or infected wounds. **Do not** use on blisters/skin tears.
(3) Hydrogel	DuoDERM® Hydroactive® *GEL (Dressing Duoderm gel 30 gm)*	◆ Apply onto or into wound bed or impregnated into gauze. Fill wound 2/3 full. ◆ Fill space with fluffed gauze. ◆ Apply cover dressing (gauze or ABD). ◆ Change Daily or prn. ◆ **Removal**: Rinse off remaining gel before new dressing is applied.	Expires 7 days after opening. Monitor for tissue maceration.
(4) Hydrocolloid	DuoDERM® CGF® Extra Thin Dressings* (Dressing Duoderm CGFx-Thin 6 × 6)*	◆ Apply, mould into place with warm hands (1 minute). ◆ Allow a minimum of 3 cm beyond wound edges to determine dressing size. ◆ May remain up to 3 days-may change sooner if discomfort, leaking, signs of infection is present or edges begin to roll. ◆ May use waterproof tape (Tape Hy-tape) to secure edges. ◆ May be used as a cover dressings with hydrofibre (6). ◆ **Removal**: Pull on opposite corners and stretch out.	Not to be used on fragile skin or if signs of infection present. Adheres better if warmed when placed. DuoDERM® Signal: used for heavier drainage. Change dressing when drainage extends to green line or edges begin to roll. **Do not** cut prior to application.
	DuoDERM® Signal* (Dressing Duoderm Sacral)* (Dressing Duoderm 5.3 × 5.3)*		
(5) Foam dressing	PolyMem® Foam* (Dressing Polymem Quadrofoam 4 ×4 pad)* (Dressing Polymem Quadrofoam 6.5 × 7.5 pad)*	◆ Apply over wound after cleansing wound. ◆ Allow a minimum of 1 cm beyond wound edges. ◆ Assess dressing daily and change if saturated. ◆ Handles more copious drainage than hydrocolloids. ◆ Maximum wear-time is 7 days. ◆ **Removal**: remove dressing and cleanse wound bed or drainage and residue with wound cleanser.	Use for skin tears, blisters. May use around tubes and/or tracheostomy sites.

(*continued*)

Table 280.1 Continued

Products	Options	Instructions for application	Tips
(6) Hydrofibres	Aquacel®* (Dressing Aquacel T-rope) (Dressing Aquacel 2 × 2) (Dressing Aquacel 6 × 6) Aquacel® Ag Hydrofiber® * (Dressing Aquacel Ag rope) (Dressing Ag 4x4) Dressing Aquacel Ag 8 x 12)	◆ Select an appropriate dressing size: • *Shallow*: cover wound bed. • *Deeper wounds*: apply Aquacel® to wound bed and fill extra space with loosely packed fluffed gauze. ◆ Place in wound bed, may extend ½- inch over wound edges. ◆ May use fluffed gauze over of Aquacel® as a wound filler. ◆ Cover with dry gauze or ABD; can cover with hydrocolloid or composite dressing; Change every 3 days or prn. ◆ Assess daily; changing is drainage dependent. ◆ **Removal**: remove cover dressing then lift Aquacel® from wound bed; cleanse wound to flush out any residue. If dressing adheres to wound, moisten with normal saline or sterile water prior to removal. Consider alternative wound therapies for less absorption.	AQUACEL® Ag Hydrofiber®: antimicrobial ◆ Not for minimally drainage wounds. ◆ Use only on recommendation of wound care nurse. **Avoid using AQUACEL® Ag with any enzymatic debridement ointment (collagenase (Santyl® ointment). Silver may deactivate the effects of enzymatic debridement.
(7) Negative pressure wound therapy	Wound VAC® (wound VAC ATS machine)* FOAM (silver, black, white) (Wound VAC silver dressing Lrg L)* (Wound VAC, dressing large)* (Wound VAC, dressing med)* (Wound VAC, dressing small)* (Connector Y Wound VAC)*	◆ May be used on wounds with less than 20% slough or eschar. If greater than 20%, debridement options need to be implemented first. ◆ Dressing changes Monday –Wednesday–Friday or as ordered by MD or NP. ◆ Refer to Policy on KCI vacuum-assisted closure therapy and Wound VAC®. **Therapy Clinical Guidelines** ◆ Obtain MD or NP order for settings. ◆ Obtain machine, dressing/foam, and canister via EPIC. ◆ Insert canister into machine and plug machine in. May turn on to set settings. ◆ Remove soiled dressing, cleanse wound, pat dry. ◆ Cut Wound VAC® foam to fill wound cavity. May use additional pieces for undermining or tunnelling. Do not over pack the wound bed. Place foam into wound cavity. Cover with drape, removing sheets in numerical order. ◆ Cut 2-cm hole in drape over foam. Apply the trac pad (piece with tubing) directly over hole in drape. ◆ Attach the tubing from the trac pad to the canister tubing. Ensure clamps are open. ◆ Turn the machine on, ensure Wound VAC® therapy settings are correct per MD/NP order. ◆ Be sure foam compresses when therapy is turned on. Assess dressing for air leaks. If air leaks noted, patch with extra drape. ◆ Mark the # of pieces of foam used on dressing ◆ Properly chart dressing change and wound condition. *Normal Pressure Settings*: 125 mmHg. May be continuous or intermittent therapy.	Refer to P&P and Wound VAC® **Therapy Clinical Guidelines**. *Contraindications*: • Malignancy in wound. • Untreated osteomyelitis (may use Wound VAC® therapy for a few days until osteomyelitis is confirmed and then may continue therapy if antibiotics are started). • Non-enteric and unexplored fistula. • Necrotic tissue with eschar present (must be debrided first). • **Do not** place over exposed blood vessels, organs, or tendons. *White Foam*: Non-adherent, use for tunnelling and undermining. *Silver Foam*: Silver-impregnated. Anti-microbial. Order set for Wound VAC® orders must include: equipment, dressing change schedule, and pressure.
(8) Debridement options	Autolytic body mediates debridement in the presence of a moist environment	See above notes on hydrogel, hydrocolloid, and composite dressings.	**Autolytic aids**: transparent dressing, hydrogel, and hydrocolloid.
	Enzymatic collagenase Santyl® ointment (requires MD order to pharmacy)	Debrides soft-tissue ulcers and burns, liquefies non-viable tissue, maintenance debridement by selectively targeting collagen. ◆ After cleaning wound, pat the wound dry. ◆ Apply Santyl® ointment to cover the entire wound bed using a Q-tip or wick.	**Do not** change from one product to another without reconsulting the wound care nurse. Contraindicated in patients who have shown local or systemic hypersensitivity to collagenase.

(*continued*)

Table 280.1 Continued

Products	Options	Instructions for application	Tips
	Sharp	◆ Apply slightly moistened gauze with normal saline (just to wound base). ◆ Cover with dry dressing and secure. ◆ Change daily or PRN if moist. ◆ **Removal**: remove dressing and cleanse wound bed or drainage and residue with wound cleanser. ◆ To be performed by physician or NP only.	Need surgical consult; be sure ABIs, laboratory, consent has been done.
(9) Xenaderm™	Xenaderm™ (Requires MD order to Pharmacy)	◆ Cleanse area with appropriate wound cleanser or soap (Aloe Vesta® cleansing foam). ◆ Apply a thin film bid and prn. ◆ May be left open to air or cover with a dry dressing.	When applied to sensitive areas, a temporary stinging sensation may occur. **Not** intended for use as a barrier cream.

*indicates product can be found in EPIC.

Reproduced with permission from Rush University Medical Center, Chicago, Illinois USA.

Transparent film dressings consist of polyurethane or synthetic polymer sheets and their use is often indicated for absent or minimal exudates, for use as a secondary dressing, or to promote autolysis. Film dressings are recommended to protect body areas at risk for friction injury [6].

Cover dressings are indicated when exudates are present, when skin is fragile, or if there is risk of frequent soiling due to incontinence. Cover dressings can range from gauze with tape for pressure ulcers with none to moderate exudates, foam dressings with tape or composite for moderate to heavy exudates, hydrocolloid, film or composite cover dressings when frequent soiling due to incontinence is a factor, to the use of stretch gauze or net when a critically-ill patient has fragile skin [6].

Gauze dressings are used to adhere to wound tissue and are available in rolls, strips, or squares, which may include cotton, rayon, or polyester. While gauze dressings are absorptive and permeable to water, water vapour, and oxygen, practice varies widely in the use of gauze dressings. Often, advanced wound dressings are used over gauze dressings for pressure ulcers [6].

Hydrocolloids consist of carboxymethylcellulose combined with pectin, which is absorbent and maintains a moist wound surface. Hydrocolloid dressings are recommended for clean Stage II pressure ulcers in body areas where they will not roll or melt, or for shallow Stage II pressure ulcers [6]. Due to their occlusive properties, hydrocolloids are not recommended for ischaemic wounds [6].

Hydrofibre consists of highly absorbent carboxymethylcellulose, which acts to bind exudates in the centre. The use of hydrofibre requires a secondary dressing.

Hydrogels consists of a three-dimensional cross-linked structure made up of hydrophilic polymers. They are available as amorphous gel or as sheets and are used to increase moisture content. Hydrogel dressings are indicated for shallow, minimally-exudating pressure ulcers or for pressure ulcers without depth and contours [6].

NaCl impregnated dressings can be used for wounds with moderate to large amount of exudates. The hypertonic medium discourages bacterial proliferation and promotes mechanical and autolytic debridement [6]. Petrolatum impregnated dressings are often used for wounds with minimal exudates. They are non-adherent and are used to protect the wound base and perimeter, while also providing a moist environment to promote epithelialization [6].

There are several forms of silver-impregnated dressings available for wound care. Silver ions are biocidal at very low concentrations due to the ability of microbial cells to absorb and concentrate silver from very dilute solutions [6]. Silver-impregnated dressings should be considered for ulcers at high risk of infection or for pressure ulcers that are infected or heavily colonized [6]. A *Cochrane Database Systematic Review* reported that silver dressings did not lead to pressure ulcer healing, but did results in reduction of the ulcer area [7].

Topical antimicrobials can be used as wound applications for their antibacteriocidal, as well as for their absorbency properties.

Alginate dressings are derived from seaweed and are highly absorbent and biodegradable. They have haemostatic properties and help to maintain a moist environment [6]. Collagen has mild absorptive capacity, and is used to stimulate wound repair and epithelial activity. Alginate dressings should be considered for the treatment of moderately and heavily draining exudating ulcers [6].

Foam dressings are made from hydrophilic polyurethane and are highly absorbent. Foams are beneficial as they decrease maceration of the periwound tissue. Foam dressings should be considered for use on exudative Stage II and shallow Stage III pressure ulcers [6].

Negative pressure wound therapy involves the use of subatmospheric pressure to promote contraction, remove excess exudates, reduce oedema, and increase blood flow. This therapy is often indicated for deep chronic open wounds, dehisced surgical sites, pressure ulcers, mesh grafts, and tissue flaps. Negative pressure wound therapy requires specific training and can be a costly option for wound management. An example of a negative pressure wound therapy is the VAC system [6].

Clean versus sterile dressing techniques

The Wound, Ostomy and Continence Nurses Society (WOCN) Wound Committee and the Association for Professionals in Infection Control and Epidemiology in the United States formulated

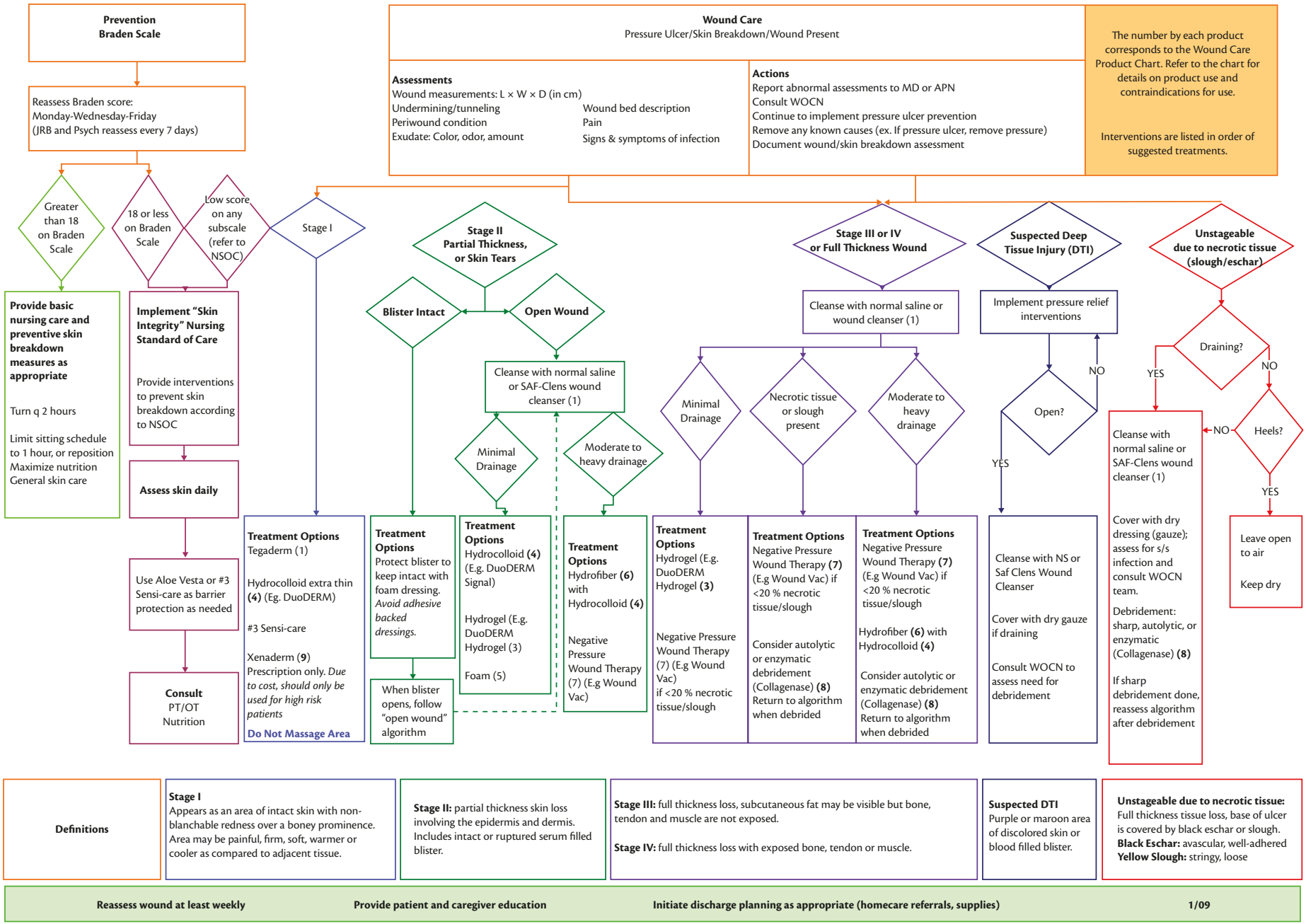
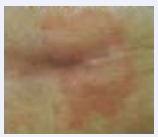
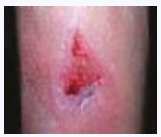
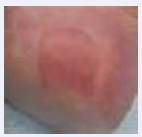
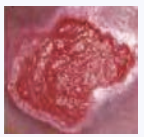
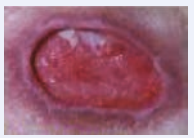
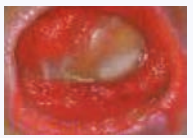
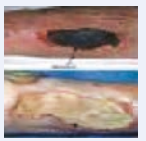
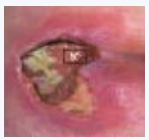


Fig. 280.1 Example of skin assessment and treatment plan of care.

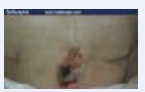
Reprinted with Permission, Rush University Medical Center, Chicago Illinois USA.

Table 280.2 Skin and wound care quick reference guide

For wounds that need a topical dressing	Intact skin Stage I Reddened area	Partial Thickness			Full thickness		Unstageable Slough/Eschar	Infected wounds
		Skin tear *With or without flap*	**Blister**	**Stage II**	**Stage III**	**Stage IV**		
This reference is not inclusive to all wounds								
Always clean wound with SAF-Clean™ AF (no expiration date) or saline (expire 24 hr) prior to each dressing change. Protect the periwound skin by applying **AloeVesta®#3 Protective Ointment** for draining wounds. Protect Periwound skin using No-Sting Barrier Film under tape. Avoid tape on fragile skin. Consider Xspan, Montgomery Straps (Senn Straps) or Kerlix to secure dressing Avoid diapers while in bed.	Do not massage area, turn Q2 hrs to relieve pressure **Preventing/ Friction** Apply **AloeVest #3 Ointment**, maintain layer on skin; Apply multiple time daily Hydrocolloid (DuoDERM® Extra Thin) every 3–5 days **Incontinence** Urinary: Cleanse area using **Aloe Vesta® 3-n-1 Cleansing Foamn.** *For Non-reddened, intact skin: Apply **Aloe Vesta® #3 Portective Ointment** daily and PRN. ***For Fecal**: Apply **Sensi-Care® #3 Protective Barrier** daily and PRN. Do Not Scrub off.	**Non Draining and Draining Wounds,** Aply foam (PolyMem®) over wound and extending about Icm beyound wound edges, and wrap with Kerlix. **Difficult Locations** *(Non-Draining / Minimal Drainage)* Apply **Xenaderm™** BID and PRN over open area.	Intact Blister Apply foam (PolyMem®) over blister to protect and extending about 1cm beyond blister edges, and wrap with Kerlix. Open Blister Apply foam (PolyMem®) over wound and extending about 1 cm beyond wound edges, and wrap with Kerlix	**Dry** **Hydrogel** (DuoDERM® Hydroactive® GEL) daily and PRN. May cover with gauze, ABD pad or DuoDERM® Signal) **Minimal Drainage** **Hydrocolloid** DuoDERM® Signal (every 3-5 days and PRN) **Foam** Polymem secure with tape every 3–5 days or when 75% saturated. **Moderate Drainage** Hydrofiber® (AQUACEL®) May cover with gauze or ABD pad daily *OR* may cover with hydrocolloid (DuoDERM® Signal every 3–5 days and PRN.)	**Minimal Drainage** **Hydrogel** (DuoDERM® Hydroactive® GEL) cover wound bed and edges, Cover with dry gauze, ABD pad daily or DuoDERM® Signal every 3-5 days. **OR** Saline moistened Hydrofiber® (AQUACEL®). May cover with gauze or ABD pad daily *OR* Signal every 3-5 days and PRN. **OR** Hydrogel (Duo DERM® Hydroactive® GEL) impregnate gauze, pack into wound and cover with dry dressing. Change BID. **Moderate to Heavy Drainage** Hydrofiber® (AQUACEL® loosely to pack wound bd and edges, May cover with gauze or ABD pad daily. Or may cover with hydrocolloid (DuoDERM®) every 3–5 days and PRN.	**Minimal Draingae** **Hydrogel** (DuoDERM® Hydroactive® GEL) daily and PRN to cover wound bed and edges. Cover with dry gauze or ABD pad or DuoDERM® Signal. **OR** Use **Negative Pressure Wound Therapy** (Wound V.A.C.®)*** Dressing change every Monday, Wednesday and Friday. **Moderate to Heavy Drainage** Hydrofiber® (AQUACEL®) loosely to pack wound bed and edges and cover with hydrocolloid (**DuoDERM®) every 3–5 days and PRN** **OR** User Negative Pressure Wound Therapy (**Wound V.A.C®)*** Dressing change every Monday. Wednesday. and Friday.	**Surgical debridement** may be necessary. **Fibrin/Slough** **Collaganase** (Santyl® Ointment) daily and PRN to cover wound bed and edges. Cover with slightly moist gauze or petroleum gauze directly over wound then with dry gaze or ABD pad. **Dry Eschar on Heels** Leave open to air and elevate. **Draining** Cover with gauze and wrap with Kerlix Assess for signs of infection Consult Wound Care RN. Suspend heels at all times using pillows or heel lift boots.	Notify MD of signs and symptoms of infection. Recommend wound culture and/or tissue biopsy to guide therapy. **Wound Culture Procedure** Always clean wound with sterile saline before obtaining wound culture. Gently rotate swab over wound in "Z" pattern using enough pressure to elicit exudate. **Surgical Debridement** may be necessary. **Managing Drainage** Apply **Hydrofiber® with silver** (AQUACEL® Ag) daily and PRN. May cover with ABD pad or Pack Heavy Drainage (12x10) **OR**

(*continued*)

Table 280.2 Continued

For wounds that need a topical dressing	Intact skin Stage I Reddened area	Partial Thickness			Full thickness		Unstageable Slough/Eschar	Infected wounds
		Skin tear *With or without flap*	**Blister**	**Stage II**	**Stage III**	**Stage IV**		
Assess wound on admission and with each dressing change. Measure wound weekly *Mondays* Reevaluate Effectiveness of treatment plan weekly. Call wound Care Nurses for further management.	*For mascerated, Severe incontinent-breakdown/ refractory incontinence-breakdown: Apply **ILEX** over area, covered with **Sensi Care® #3 Protective Barrier** daily and PRN.			**Heavy Drainage** **Hydrofiber® (AQUACEL®) May cover with gauze or ABD pad daily, Or may cover with hydrocolloid (DuoDERM® Signal) every 3–5 days and PRN.**	**OR** Use Negative Pressure Wound Therapy (**Wound V.A.C.®**)* Dressing change every Monday. Wednesday, and Friday.			Use **Negative Pressure Therapy** (Wound V.A.C.®) ***Use V.A.C.® GranuFoam™ with silver dressing. Dressing change every Monday, Wednesday, and Friday if antibiotics being used concomitantly. *Wound V.A.C.® is contraindicated for presence of untreated osteomyelitis, slough/ necrotic tissue more than 20%, malignancy in the wound, and placement over exposed blood vessels or organs. Application of Wound V.A.C® may be painful, give pain medication 30 minutes prior to initiation or dressing change.
	Avoid Adhesive Dressing on Fragile Skin (i.e. transparent, hydrocolloid)		If wound has more than 20% slough/necrotic tissue, see treatment plan for unstageable ulcer.				Suspected Deep Tissue Injury Implement measures to relieve pressure If draining- cover with gauze- Avoid adhesive dressings Consult WOCN 	

Reproduced with permission from Rush University Medical Center, Chicago, Illinois, USA.

Compiled by Rush University Medical Center Wound Care Team 12/10.

guidelines for the use of clean versus sterile dressings for the management of chronic wounds.

Sterile technique is generally defined as meaning free from microorganisms [8]. The use of sterile technique is aimed at reducing exposure to micro-organisms and maintaining objects and areas as free from micro-organisms as possible [4]. In comparison, clean technique means free of dirt, marks, or stains [8]. The use of clean technique is focused on reducing the overall number of micro-organisms or to prevent or reduce the risk of transmission of microorganisms from one person to another or from one place to another [4]. The use of clean technique is also referred to as non-sterile. Clean technique is considered most appropriate for routine dressings for chronic wounds, such as venous ulcers, or wounds healing by secondary intention with granulation tissue [4].

The Centers for Disease Control and Prevention recommend the use of sterile technique for post-operative management of wounds for 24–48 hours [4]. Clinical practice guidelines for pressure ulcer treatment, published by the Agency for Health Care Policy and Research, recommend the use of clean technique for pressure ulcers dressings [9]. The National Pressure Ulcer Advisory Panel-European Pressure Ulcer Advisory Panel guidelines for pressure ulcers do not address the use of clean or sterile technique other than to outline that tap water or potable water can be used to clean pressure ulcers and that sterile instruments are needed for sharp debridement [10,11]. An integrative literature review of seven published studies of clean and sterile technique for dressings confirmed a lack of consensus about the benefit of clean versus sterile technique to improve healing or infection rates, but identified that clean technique results in lower costs [12].

Support services

A number of pressure-relieving support surfaces are available for use with dressings to promote healing of pressure ulcers, including mattress overlays, foam mattresses, alternating pressure mattresses, air filled devices, and dry floatation cushions. A recent *Cochrane Collaborative Synthesis Review* identified that there is no conclusive evidence about the superiority of any support surface for the treatment of existing pressure ulcers [13].

Additional considerations

The National Pressure Ulcer Advisory Panel clinical practice guidelines [6] outline a number of general recommendations for the use of dressings for pressure ulcers and wounds. These include following manufacturer recommendations for use of a dressing or dressing product, particularly related to the frequency of dressing changes. A dressing should be selected that remains in contact with the wound bed or skin barrier product to keep the periwound dry and prevent maceration [14–16]. Careful removal of dressings is recommended on fragile skin to reduce tissue trauma. As a part of dressing care, assessment and management of pressure ulcer pain should be conducted as a routine part of patient care and with dressing changes. Additionally, ongoing patient and family education with dressing care is an indicated part of wound care management.

Conclusion

A number of factors affect the choice of dressing for pressure ulcer and wound care management. The type of dressing indicated may change over time as the ulcer heals or changes. Knowledge of the indications for use of currently available wound care products and dressings is important for critical care clinicians and often, consultation with a wound care specialist is recommended for optimal management of pressure ulcers and wounds in the critically-ill patient. This chapter has provided an overview of dressing choices and indications for use and examples have been provided from institutional protocols. As wound care guidelines may vary based on institutional protocols, clinicians are advised to consult their specific wound care policies and guidelines.

References

1. Moore Z, Webster J, and Review Group, Cochrane Wounds Group. (2011). Dressings and topical agents for preventing ulcers. *Cochrane Database of Systematic Reviews*, **8**, CD009362.
2. Wound, Ostomy and Continence Nurses Society (WOCN). (2010). *Guideline for Prevention and Management of Pressure Ulcers*, WOCN Clinical Practice Guideline Series. Mount Laurel, NJ: WOCN.
3. Cutting K, White R, Hoekstra H. (2009). Topical silver-impregnated dressings and the importance of the dressing technology. *International Wound Journal*, **6**(5), 396–402.
4. Wound, Ostomy and Continence Nurses Society (WOCN) (2011). *Wound Committee and the Association for Professionals in Infection Control and Epidemiology Inc. (APIC) Guidelines Committee. Clean vs Sterile Dressing Technique for Management of Chronic Wounds*, Fact sheet. Mount Laurel, NJ: WOCN.
5. Rolstad BS and Ovington LG. (2007). Principles of wound management. In: Bryant RA and Nix DA (eds) *Acute & Chronic Wounds: Current Management Concepts*, 3rd edn, pp. 391–426. St Louis, MO: Mosby.
6. National Pressure Ulcer Advisory Panel (NPUAP). Pressure Ulcer Definition and Stages. Washington DC: NPUAP. Available at: http://www.npuap.org
7. Vermeulen H, van Hattern J, Storm-Versloot M, and Ubbink D. (2007). Topical silver for treating infected wounds. *Cochrane Database of Systematic Reviews*, **1**, CD005586.
8. Rowley S, Clare S, Macqueen S, and Molyneux R. (2010). ANTT v2: An updated practice framework for aseptic technique. *British Journal of Nursing*, **19**, S5S11.
9. Bergstrom N, Bennett MA, Carlson CE, et al. (1994). *Treatment of Pressure Ulcers*, Clinical Practice Guideline No, 14, AHCPR Publication No. 95-0642. Agency for Health Care Policy and Research, Public Health Service. Rockville, MD: US Department of Health and Human Services.
10. NPUAP-EPUAP (National Pressure Ulcer Advisory Panel–European Pressure Ulcer Advisory Panel). (2009). *Prevention and Treatment of Pressure Ulcers: Clinical Practice Guideline*. Washington DC: National Pressure Advisory Panel.
11. European Pressure Ulcer Advisory Panel (2011). *Pressure Ulcer Prevention Guidelines* 2011. Available at: http://www.epuap.org/guidelines/ (accessed 1 May, 2011).
12. Ferreira AM and de Andrade D. (2008). Integrative review of the clean and sterile technique, agreement and disagreement in the execution of dressing. *Acta palulista de Enfermagem*, **21**, 117–21.
13. McInnes E, Dumville JC, Jammali-Blasi A, and Bell-Syer SE. (2011). Review Group: Cochrane Wound Group. Support Surfaces for treating pressure ulcers. *Cochrane Database of Systematic Reviews* **12**, CD009490.
14. Bryant N and Nix D. (2010). *Acute and Chronic Wounds Current Management Concepts*, 4th edn. St Louis, MO: Mosby.
15. John Hopkins Medicine. *Wound and Pressure Ulcer Management.* Available at: http://www.hopkinsmedicine.org/gec/series/wound_care.html (accessed 1 April, 2011).
16. Salcido R. Lorenzo CT. (2012). Pressure ulcers and wound care. Medscape Online. Available at: http://emedicine.medscape.com/article/319284-overview

SECTION 13

Infection

PART 13.1

Diagnosis and surveillance

CHAPTER 281

Microbiological surveillance in the critically ill

A. P. R. Wilson

Key points

- The ICU is a focus for the emergence of bacterial resistance.
- Overuse of antibiotics is the main driver.
- Catheter-associated bacteraemia rates are the most frequently used performance indicator.
- Methicillin-resistant *Staphylococcus aureus* (MRSA) screening and topical suppression is effective in preventing spread.
- Screening for multiresistant Gram-negative bacteria needs to be considered according to local prevalence.

Introduction

Of all hospital wards, the intensive care unit (ICU) is the one with the highest risks of acquisition and transmission of hospital-acquired infection. Most patients are given antibiotics, there are numerous invasive procedures, and a large number of staff frequently come into contact with the patient. Infections acquired in the ICU have significant consequences for the rest of the hospital when the patient is discharged to a general ward. Furthermore, colonization or infections with multiresistant organisms can significantly delay discharge of a patient from ICU at considerable cost to the hospital. Surveillance is important to identify emerging outbreaks of multiresistant infections and the overuse of antibiotics that can give rise to them. Continuous collection of data using widely recognized definitions can allow comparisons between units and be used to reduce rates in outliers. Definitions and methods should be based on recognized international systems such as those of Centers for Disease Control (CDC) or European Centre for Disease Control (ECDC). National networks such as The Intensive Care National Audit & Research Centre (ICNARC) should form the basis for extracting denominator numbers and exchange of information between units.

Surveillance definitions

Identifying rates of infection and feeding back the results to the clinical teams is effective in reducing rates. Local and timely investigation of the causes of an infection is the best method of preventing further cases. Root cause analysis is a formal tool that has been used widely to identify specific failings and strategies to avoid them in future. In the USA nosocomial infection is no longer reimbursed by insurance companies and in other countries there is increasing scrutiny of these infections and in some cases financial penalties are applied. As a result there is now much interest in surveillance as a means of improving patient outcome.

The ECDC has used a range of definitions in multinational ICU surveillance in Europe [1]. ICU-acquired infection is defined as occurring later than 48 hours after admission. Device associated health care-associated infection (HAI) is an infection in a patient with a device used within 48 hours before onset of infection. Devices are intubation, central vascular catheter (CVC), and urinary catheter. Elsewhere CDC definitions are widely used, but not specific to ICU [2].

Antimicrobial resistance

Antibiotic consumption and resistance levels vary widely between units. Defined daily doses per 1000 occupied bed days is a common comparative measure, but the definition of length of stay must be agreed and antibiotics delivered to ICU may not necessarily be used. Dosage increased due to severity of illness or reduced due to renal failure are sources of error. One study found no relationship between prevalence of multiresistant pathogens and consumption of carbapenems, quinolones, or cephalosporins [3]. Poor hand hygiene or lack of antibiotic control may be an explanation. High rates of resistance in pseudomonas are related to high usage of carbapenems and quinolones.

Catheter-related or associated bacteraemia

Central line-associated bloodstream infections increase the length of stay in ICU and increase the risk of mortality. With appropriate catheter management these infections are avoidable and so catheter-associated bacteraemia is likely to emerge as a standard performance measure Box 281.1. Surveillance can cease 48 hours after the patient leaves the unit [1]. Bloodstream infections are central-line associated when a central line or umbilical catheter was in place (or within 48 hours) and not secondary to an infection at another site. If a line was inserted in the Emergency Department and is diagnosed within 24 hours of arrival in ICU it is still considered ICU associated. If it occurs within 48 hours of transfer out of an ICU it is attributed to that ICU. Pacemaker wires, femoral arterial catheters, intra-aortic balloon pump devices, or devices without lumens are not counted as central lines. The catheter-associated bloodstream infection rate is expressed per 1000 central line days. Surveillance at least at a regional level should be continuous.

Box 281.1 Surveillance definition CDC Device Associated Module January 2012

Infections associated with complications of infections already present on admission are not considered healthcare associated.

Primary blood stream infections (BSI)

Laboratory confirmed and not secondary to community-acquired infection or hospital-acquired infection meeting CDC criteria at another body site. The central line or umbilical catheter must be in place at the time or within 48 hours before onset of the event.

Laboratory-confirmed BSI

Must meet one of:

- Recognized pathogen cultured from one or more blood cultures and organism cultured from blood is not related to an infection at another site.
- Patient has at least one of following signs or symptoms: fever (>38ºC), chills or hypotension, and signs and symptoms and positive laboratory results are not related to an infection at another site and common commensal is cultured from two or more blood cultures drawn on separate occasions.
- Patient <=1 year of age and at least one of fever (>38ºC core), hypothermia (<36ºC) apnoea, or bradycardia and signs and symptoms and positive laboratory results are not related to an infection at another site and common skin commensal is cultured from two or more blood cultures drawn on separate occasions

Reproduced from CDC Device Associated Module January 2012: Central Line-Associated Bloodstream Infection Event (CLABSI).

One of the most significant examples of the efficacy of surveillance was the successful Michigan program to reduce CVC infections [4]. This project used peer pressure to encourage ICUs to join the program, created strong networking in the group, portraying catheter-related bacteraemia as a social problem, used a bundle of measures to reduce infections and data generated as a disciplinary measure. Four recommendations were applied related to insertion of the catheter: hand washing, using full barrier precautions, cleaning the skin with chlorhexidine, and avoiding the femoral site when possible. The fifth recommendation was to remove unnecessary catheters. In 90 ICUs, the number of catheter-related bloodstream infections was collected over 3 years. The mean and median rates of catheter related bloodstream infection per 1000 catheter days decreased from 7.7 and 2.7 at baseline to 1.3 and 0 at 16–18 months to 1.1 and 0 at 36 months. The project demonstrated that through a bundle of measures and a quality improvement ethos, improvements could be achieved and sustained.

As a result other countries have considered using catheter-associated or catheter-related blood stream infection as a measure of ICU performance in preventing nosocomial infection. 'Matching Michigan' was run by the National Patient Safety Agency in the UK. Definitions were based on CDC and ECDC and gained wide participation despite being voluntary and time limited. Results were sufficiently encouraging to consider a national voluntary quality improvement scheme [5]. Other studies have demonstrated that audit and feedback of these infections gradually reduces the number of cases.

In many countries, computerized data collection of morbidity and mortality is becoming more extensive, but infection surveillance is not usually the primary focus. While catheter-related bacteraemia requires additional laboratory resources for diagnosis (semiquantitative analysis of blood samples or roll cultures of catheter tips), catheter-associated bacteraemia is less stringent and more easily applicable. Collection of data on catheter-associated bacteraemia may not require significant extra resource as long as duplicate data entry is avoided. Voluntary surveillance may be under-reported if results are used for performance management or reimbursement or if there are major resource implications. On the other hand mandatory surveillance can be costly and less useful in small units. The main parameter for surveillance should be CVC associated infection expressed as a proportion of CVC patient-days using the ECDC definition. CVC patient-days (number of patients with at least one CVC in situ every 24 hours summed over one month) are needed to calculate device-associated rates. In the longer term, it would be desirable for microbiology departments to develop capacity for routine semi-quantitative cultures to allow use of catheter-related bloodstream infection as the eventual ideal marker.

Ventilator-associated pneumonia

Ventilator-associated pneumonia shortens patient survival and can arise from cross infection. However definitions are problematic and the use of bronchoscopy for diagnostic purposes varies widely between countries. Rates identified by the treating surgical intensivist and the infection control service in the same hospital can differ widely [6]. Therefore, it cannot be recommended as a subject for long-term surveillance.

Pathogen surveillance

Pseudomonas

Pseudomonas aeruginosa, including multiresistant strains, contaminating taps and other water sources in ICUs has been associated with the development of bacteraemia in patients, particularly neonates [7]. The hands of staff are the likely means of transmission and bathing infants in tap water a probable source. The hand wash station should only be used for hand washing and not for disposal of body fluids. Outbreaks have been reported with detergent diluted with contaminated tap water. Some neonatal units check rectal swabs every week to establish the prevalence of pseudomonal carriage, which can be helpful in monitoring the effect of interventions.

Studies confirm the effectiveness of point of use water filtration in reducing infection in critical care units. In one study, pseudomonas infections fell by 56% and water isolates fell from 97% to 0% when filters were introduced [8]. However filters have to be replaced monthly and are expensive. Sensor taps have been implicated in some outbreaks of Pseudomonas bacteraemia, probably because of biofilm accumulation in the end of the tap due to poor water flow and the thermoregulatory valve providing a carbon source. Surveillance of water samples in augmented care units for *Pseudomonas aeruginosa* has been advised.

Methicillin-resistant *Staphylococcus aureus*

In hospitals where methicillin-resistant *Staphylococcus aureus* (MRSA) is prevalent, the likelihood of carriage and acquisition is often highest in the ICU. Identification of carriage followed by topical suppression has been successful in reducing the risk of transmission. MRSA screening in many countries is performed on admission to hospital and/or the critical care unit. If a rapid PCR based method is used, the result is available the same day allowing immediate source isolation and more appropriate use of glycopeptides. If not, a patient with unknown carriage status may need to be source isolated or treated with topical suppression pending a result. All carriers are treated with topical chlorhexidine and mupirocin to reduce shedding into the environment and cross infection. Identified carriers should be source isolated in a single room. Units with universal screening report higher rates of MRSA as the result of better ascertainment, but only 20% of cases are likely to have been acquired during ICU stay [9].

Although topical suppression of all patients was cost effective in the short term, it carries a risk of selection of resistance. Rapid PCR based screening of all patients on admission and weekly thereafter is most cost effective [10]. Isolation or cohorting without topical suppression is effective, but increases costs unless prevalence is high (10%). The use of topical chlorhexidine and mupirocin may have been responsible for the dramatic reduction in MRSA prevalence in some countries, but probably is not cost effective when prevalence is already low.

Extended spectrum β-lactamase-producing Gram-negative bacteria

Extended spectrum β-lactamase producing Gram negative bacteria (ESBL) are rapidly increasing as a cause of invasive infection in ICU. Overuse of antibiotics is a major driver. Screening may be justified in units where there have been previous outbreaks or control of antibiotic use is poor. Surveillance over 11 years in Dutch ICUs showed changes in antimicrobial resistance in *Klebsiella pneumoniae*. Resistance to ceftazidime rose from 4.2% to 10.8%, ciprofloxacin from 5.8 to 18.5% and cefuroxime from 2.8 to 7.9% [11]. The prevalence of ESBL increased from 2% to 8%. Resistance was significantly greater in ICU than surgical wards.

Acinetobacter

Outbreaks of multiresistant Acinetobacter are very disruptive to the functioning of critical care units and cause bacteraemia and serious respiratory infection. Control of spread can be very difficult even with full infection control measures. Few ICUs screen routinely for the organism except during an outbreak. However, active surveillance (testing and either isolating or decolonizing) is cost saving when the colonization prevalence is greater than 1%. [12]. Even slight increases in length of stay in ICU can give rise considerable additional costs. Swabbing pharynx, wounds, axilla, and groin has a low sensitivity 13–78% compared with a sponge wiped on the upper arm and thigh (89%).

Future prospects

As health systems become more focussed on preventable infections, mandatory surveillance (or least peer pressure) will become more common. Financial incentives or penalties may be applied on the basis of reported numbers of hospital-acquired infections. While considerable reductions in infection rates can be achieved, use of national surveillance networks, standard definitions and methodologies are essential to ensure valid comparisons between units and appropriate actions for outlying performances.

References

1. European Centre for Disease Prevention and Control (2012). European surveillance of Healthcare-associated Infections in Intensive Care Units. HAIICU Protocol v 1.01: Standard and Light. Available at: http://www.ecdc.europa.eu/en/aboutus/calls/Procurement%20Related%20Documents/5_ECDC_HAIICU_protocol_v1_1.pdf (accessed 28 October 2015).
2. Centers for Disease Control (2012). Bloodstream Infection Event (Central Line-associated Bloodstream Infection and Non-central Line-associated Bloodstream Infection). Available at: http://www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABScurrent.pdf (accessed 28 October 2015).
3. Hanberger H, Arman D, Gill H, et al. (2009). Surveillance of microbial resistance in European Intensive care Units: a first report from the Care-ICU programme for improved infection control. *Intensive Care Medicine*, **35**, 91–100.
4. Pronovost PJ, Goeschel CA, Colantuoni E, et al. (2010). Sustaining reductions in catheter related bloodstream infections in Michigan intensive care units: observational study. *British Medical Journal*, **340**, c309.
5. Julian Bion, Annette Richardson,Peter Hibbert et al. (2012) 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. *British Medical Journal Quality Safety* doi:10.1136/bmjqs-2012-001325.
6. Thomas BW, Maxwell RA, Dart BW, et al. (2011). Errors in administrative-reported ventilator-associated pneumonia rates: are never events really so? *American Surgeon*, **77**, 998–1002.
7. Crivaro V, Di Popolo A, Caprio A, et al. (2009). *Pseudomonas aeruginosa* in a neonatal intensive care unit: molecular epidemiology and infection control measures. *Bio Medical Centre Infectious Diseases*, **9**, 70.
8. Trautmann M, Halder S, Hoegel J, Royer H, and Haller, M. (2008). Point-of-use water filtration reduces endemic *Pseudomonas aeruginosa* infections on a surgical intensive care unit. *American Journal of Infection Control*, **36**, 421–9.
9. Kohlenberg A, Schwab F, Behnke M, Geffers C, and Gastmeier P. (2011). Screening and control of methicillin-resistant *Staphylococcus aureus* in 186 intensive care units: different situations and individual solutions. *Critical Care*, **15**, R285.
10. Edgeworth JD. (2011). Has decolonization played a central role in the decline in UK methicillin-resistant *Staphylococcus aureus* transmission? A focus on evidence from intensive care. *Journal of Antimicrobial Chemotherapy*, **66**, (2), ii41–7.
11. van der Donk CF, Beisser PS, Hoogkamp-Korstanje JA, Bruggeman CA, Stobberingh EE, and the Antibiotic Resistance Surveillance Group. (2011), A 12 year (1998–2009) antibiotic resistance surveillance of *Klebsiella pneumoniae* collected from intensive care and urology patients in 14 Dutch hospitals. *Journal of Antimicrobial Chemotherapy*, **66**, 855–8.
12. Lee BY, McGlone SM, Doi Y, Bailey RR, and Harrison LH. (2011). Economic value of *Acinetobacter baumannii* screening in the intensive care unit. *Clinical Microbiology and Infection*, **17**, 1691–7.

CHAPTER 282

Novel biomarkers of infection in the critically ill

David T. Huang and Ayan Sen

Key points

- There is insufficient evidence for the routine use of novel biomarkers in infection and sepsis.
- A large number of biomarkers have been studied to date, but most studies only demonstrate correlation with outcome, rather than improvement in outcome.
- Several biomarkers are of prognostic value with strong associations with poor outcomes and mortality.
- Procalcitonin guidance to reduce antibiotic usage is promising, but most supporting data come from emergency department studies in a single European country.
- The future may involve development of high sensitivity assays, molecular strategies and a 'panel approach', all of which need to be investigated in well-designed studies.

Background

Over 25% of all annual deaths in the world are due to infection. Sepsis is defined as infection (probable or documented) with systemic manifestations such as systemic inflammatory response syndrome (SIRS) [1]. Severe sepsis is defined as sepsis with sepsis-induced organ dysfunction or tissue hypoperfusion. Severe sepsis is common, consumes considerable health care resources, and is associated with high mortality [2]. Surveillance and early response to infection and sepsis depend on rapid clinical diagnosis. The septic response is a complex chain of events involving inflammatory, humoral, cellular, and circulatory abnormalities. Early diagnosis and risk stratification facilitate timely and specific treatment, but are complicated by the highly variable and non-specific nature of the signs and symptoms of sepsis.

Biomarkers can be of value if they can improve medical decision-making by indicating the presence, absence, or severity of infection and sepsis determining aetiology (e.g. bacterial versus viral infection), and distinguishing systemic sepsis from local infection. Other potential uses include prognostication, guiding antibiotic therapy, and evaluating response to therapy. Large numbers of biomarkers have been studied in infection and sepsis. However, in many cases, reliability, validity, and clinical utility have not been fully evaluated, in part due to limitations of experimental models for human sepsis, and lack of a 'gold standard' for the diagnosis of infection or sepsis, prognosis of severe infections and sepsis [3].

White blood cells

The white blood cell (WBC) count is the most commonly used infectious biomarker. An elevated WBC is suggestive of an infection, but cannot be used in isolation and can indicate inflammation without infection ('false positive') or be absent despite infection in the elderly and immunocompromised ('false negative'). SIRS criteria include a WBC >14,000 or <4000 cells/mm^3, or a bandemia >10% [2].

C-reactive protein

C-reactive protein (CRP) is an acute-phase protein released by the liver after the onset of inflammation or tissue damage. It has been studied and used extensively in clinical practice as a biomarker of infection, inflammation, and sepsis. Its production is controlled by interleukin-6, an inflammatory cytokine. The median concentration of CRP in young adult blood donors is 0.8 mg/L, the 90th percentile is 3.0 mg/L, and the 99th percentile is 10 mg/L. A high-sensitivity CRP (hs-CRP) test measures low levels of CRP using laser nephelometry. The test gives results in 25 minutes with a sensitivity of 0.04 mg/L. Exact sensitivities and specificities of CRP for the diagnosis of bacterial infections vary in different studies and therefore its role should be interpreted based on context [4]. CRP level is also elevated during inflammatory states of non-infectious aetiologies, e.g. autoimmune disorders, myocardial infarction. As a result, its role in diagnosis of infection and sepsis is modest at best. Studies of critically-ill patients showed that elevated plasma concentrations of CRP correlate with an increased risk of organ failure and/or death. However, in studies of post-operative sepsis, procalcitonin and IL-6 levels significantly decreased in survivors from days 1 to 14, whereas CRP levels did not. Therefore, its role in prognostication in patients with sepsis is questionable. Elevated hsCRP at a stable phase of health was associated with increased risk of future sepsis events over 4.6 years of follow-up [5].

Procalcitonin

In normal physiological conditions, pro-calcitonin (PCT) is synthesized by thyroid C cells and serum levels are low (0.1 ng/mL) [4]. In bacterial infection, PCT is ubiquitously synthesized in multiple extrathyroidal tissues. PCT levels increase within 4–12 hours upon stimulation, and circulating PCT levels halve daily when the infection is controlled by the host immune system and antibiotic

therapy. A sample can be collected and sent to the laboratory with an average turnaround time of less than 3 hours. PCT can, however, increase after trauma or surgery, particularly major abdominal surgery, and in pancreatitis. Some authors report that PCT levels only transiently increase for 12–24 hours after surgery and in the absence of infection, fall back to normal levels. This is in contrast to both CRP and WCC, which can stay elevated for a number of days after surgery without underlying infection. PCT has a half-life of less than 24 hours.

Bacteraemic infections cause the highest rises in PCT with lower or negligible rises in localized, viral, and intracellular bacterial (e.g. Mycoplasma pneumonia) infections. In patients with community-acquired pneumonia (CAP) and urinary tract infections, PCT at a cut-off of 0.1 μg/L had a very high sensitivity to exclude bacteraemia [6,7]. PCT may not only differentiate between viral and bacterial infections, but also indicate the presence of bacterial super-infection in patients with viral diseases. Gram-negative bacteraemia may cause higher PCT rises than Gram-positive bacteraemia.

Six meta-analyses have been performed on the diagnostic accuracy of PCT to detect infection in different patient populations. Some of these meta-analyses identified PCT as being helpful for the diagnosis of clinically or microbiologically documented infection [8,9] whereas others have found moderate or moving towards null effect in the detection of bacteraemia [10]. However past studies did not use the high sensitivity PCT (Kryptor); this may have contributed to some to the discrepant conclusions. Recent guidelines issued by the Infectious Diseases Society of America suggest that use of PCT as an adjunctive diagnostic marker to differentiate sepsis from SIRS of a non-infectious origin may be considered [11]. However, the 2012 Surviving Sepsis Campaign Guidelines state 'the utility of procalcitonin levels or other biomarkers (such as C-reactive protein) to discriminate the acute inflammatory pattern of sepsis from other causes of generalized inflammation (e.g., post-operative, other forms of shock) has not been demonstrated. No recommendation can be given for the use of these markers to distinguish between severe infection and other acute inflammatory states' [2].

PCT may have a role in antibiotic stewardship and de-escalation. Thirteen randomized controlled studies, in which 4,395 patients were enrolled, showed a reduction in the prescription of antibiotics of between 74% and 11% and a reduction of days on antibiotics by 13% to 55% [12]. Most of those studies were performed with patients with clinically diagnosed respiratory tract infections in Swiss emergency departments, and less data exist for ICU patients. PCT levels in response to sepsis do not appear to be significantly affected by the use of steroids. PCT can be elevated in renal impairment, severe trauma and surgery or in patients after cardiac shock, acute graft-versus-host disease, immunotherapy, autoimmune diseases, and paraneoplastic syndromes. The role of PCT in systemic fungal infections is unclear. *Candida*-related severe sepsis or septic shock does not necessarily elicit a substantial increase in serum levels.

sTREM-1

Soluble triggering receptor expressed on myeloid cells 1 (TREM-1), a recently discovered member of the immunoglobulin superfamily, is greatly upregulated in infections, but not in non-infectious inflammatory conditions. It has been suggested that plasma sTREM-1 levels as an indicator of sepsis were superior to those of CRP and PCT. A meta-analysis found that the sensitivity of sTREM-1 for the diagnosis of bacterial infection, was 0.82 and that the specificity was 0.86 [13]. Other studies have reported that it is inferior to CRP and PCT.

Coagulation biomarkers

Protein C serum concentrations in neutropenic patients have been described to be significantly decreased, before clinical signs of severe sepsis and septic shock are apparent. Biphasic waveform (BPW) analysis, a new biological test derived from the activated partial thromboplastin time, has been proposed for the diagnosis of sepsis. The major limitation of coagulation parameters is that coagulation pathway abnormalities may be triggered by other disease states, such as trauma, obstetrical disorders, or cancer.

Other biomarkers

The quest for the magic biomarker, the 'troponin of sepsis' continues with several other acute phase reactants having failed to show clinical utility beyond a strong correlation with adverse outcomes. These include resistin, 'long' pentraxin 3, alpha-1 acid glycoprotein, and hepcidin, pro-inflammatory cytokines like IL-6 and IL-8, TNF-alpha, HMB1, proadrenomedullin, Macrophage migrating inhibitory factor (MgIF) and anti-inflammatory, endothelial, and apoptotic aspects of systemic inflammation, such as interleukin-1 receptor antagonist (IL-1ra) and IL-10. These biomarkers are of limited value because they can be induced by numerous non-infectious diseases like major surgery and major trauma, autoimmune disorders, viral infections, and transplant rejection. In a large US cohort study of subjects hospitalized with community acquired pneumonia, the circulating cytokine response to pneumonia was noted to be heterogeneous with considerable overlap between those who do and do not develop severe sepsis [14].

Panels of biomarkers

Combinations of biomarkers reflecting various aspects of the host response have been proposed to overcome limitations of single biomolecules. A panel consisting of sTREM-1, PCT, and CD64 index called the 'bioscore' was higher in patients with sepsis. In the emergency department (ED), the usefulness of a combination of suPAR, sTREM-1, and MgIF with CRP, PCT, and neutrophils was evaluated in patients with SIRS and found to have better sensitivity and specificity than any single marker [15]. Similarly, a biomarker panel of NGAL, IL-1ra, and protein C was predictive of severe sepsis, septic shock, and death in ED patients with suspected sepsis [16].

Molecular diagnostics

Blood culture reflects the current gold standard for the detection of bloodstream infection, since viable micro-organisms isolated from the blood can be analysed to identify species and susceptibility to antimicrobial therapy. However, culture data is impaired by the delay in the time to results and the fact that positive blood cultures can be found for only approximately 30% of severe sepsis patients. A number of molecular approaches to improve conventional culture-based identification, including PCR, have been suggested, such as

matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry, which may decrease the time to result to 4 hours. Another alternative strategy is the extraction and amplification of microbial nucleic acids from a positive blood culture and subsequent hybridization on a microarray platform to detect specific bacterial genes [17], which has recently been evaluated in an observational multi-centre design with conventional blood culture as the comparator. The assay had an overall sensitivity of 94.7% and a specificity of 98.8%, and 100% for meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia, and resulted 18 hours faster than conventional blood culture [18]. However, shortcomings include an incomplete coverage of pathogens, the inability of the test to be applied directly to a biological sample, and restricted information regarding antimicrobial susceptibility.

PCR-based approaches, which amplify microbial nucleic acids directly from the bloodstream, carry the potential to improve the detection of infection with typical sepsis-associated bacteria, such as, streptococci and staphylococci, and also polymicrobial infections, including fastidious, multi-resistant, and fastidious species such as fungi. Comparable data are currently available only from studies which used the SeptiFast multiplex PCR. Concordance of PCR and blood culture results with respect to the recovery of blood culture-positive results by PCR was moderate to good in most, but not all studies. PCR-based approaches have potential as a supplement to blood cultures to reduce the time to results to readjust and narrow the spectrum of antimicrobial therapy, specifically for infections such as those by *Candida* or MRSA.

Conclusion

At present, there is insufficient evidence for the routine use of novel biomarkers in infection and sepsis. A large number of biomarkers have been studied to date, but have been constrained by lack of a 'gold standard', varying sensitivities and specificities, and inability to distinguish between infectious or inflammatory causes of a SIRS response. Most importantly, few have gone beyond correlation with outcome, to what really matters—improvement in outcome. The future is promising with development of high sensitivity assays, molecular strategies, and a 'panel approach', all of which need to be investigated in well-designed future studies, including randomized trials that can determine the true clinical utility of novel biomarkers of infection.

References

1. Dellinger RP, Levy MM, Rhodes A, et al. (2013). Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 *Critical Care Medicine*, **41**, (2),580–637.
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, and Pinsky MR. (2001). Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Critical Care Medicine*, **29**, (7),1303–10.
3. Reinhart K, Bauer M, Riedemann NC, and Hartog CS. (2012). New approaches to sepsis: molecular diagnostics and biomarkers. *Clinical Microbiology Review*, **25**, (4),609–34.
4. Kibe S, Adams K, and Barlow G. (2011). Diagnostic and prognostic biomarkers of sepsis in critical care. *Journal of Antimicrobiological Chemotherapy*, **66**(Suppl. 2), ii33-40.
5. Wang HE, Shapiro NI, Safford MM, et al. (2012). High-sensitivity C-reactive protein and risk of sepsis; abstract. *Critical Care Medicine*, **12**(40).
6. Müller F, Christ-Crain M, Bregenzer T, et al. (2010). Procalcitonin levels predict bacteraemia in patients with community-acquired pneumonia: a prospective cohort trial. *Chest*, **138**, 121–9.
7. van Nieuwkoop C, Bonten TN, van't Wout JW, et al. (2010). Procalcitonin reflects bacteraemia and bacterial load in urosepsis syndrome: a prospective observational study. *Critical Care*, **14**, R206.
8. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. 2006. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. *Critical Care Medicine*, **34**, 1996–2003.
9. Jones AE, Fiechtl JF, Brown MD, Ballew JJ, and Kline JA. (2007). Procalcitonin test in the diagnosis of bacteraemia: a meta-analysis. *Annuals of Emergency Medicine*, **50**, 34–41.
10. Tang BM, Eslick GD, Craig JC, and McLean AS. (2007). Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infectious Diseases*, **7**, 210–17.
11. O'Grady NP, Barie PS, Bartlett JG, et al. (2008). Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. *Critical Care Medicine*, **36**, 1330–49.
12. Schuetz P, Chiappa V, Briel M, and Greenwald JL. (2011). Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. *Archives of Internal Medicine*, **171**, 1322–31.
13. Jiyong J, Tiancha H, Wei C, and Huahao S. (2009). Diagnostic value of the soluble triggering receptor expressed on myeloid cells-1 in bacterial infection: a meta-analysis. *Intensive Care Medicine*, **35**, 587–95.
14. Kellum JA, Kong L, Fink MP, et al. (2007). GenIMS investigators understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Archives of Internal Medicine*, **167**, (15), 1655–63.
15. Kofoed K, Andersen O, Kronborg G, et al. (2007). Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migration inhibitory factor, soluble urokinase-type plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diagnose infections: a prospective study. *Critical Care*, **11**, R38.
16. Shapiro N, Trzeciak S, Hollander JE, et al, (2009). A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis. *Critical Care Medicine*, **37**, (1),96–104.
17. Tissari P, Zumla A, Tarkka E, et al. (2011). Accurate and rapid identification of bacterial species from positive blood cultures with a DNA-based microarray platform: an observational study. *Lancet*, **375**, 224–30.
18. McDonald RR, Antonishyn NA, Hansen T, et al. (2005). Development of a triplex real-time PCR assay for detection of Panton-Valentine leukocidin toxin genes in clinical isolates of methicillin-resistant *Staphylococcus aureus*. *Journal of Clinical Microbiology*, **43**, 6147–49.

PART 13.2

Nosocomial infection

CHAPTER 283

Definition, epidemiology, and general management of nosocomial infection

Caroline Landelle and Didier Pittet

Key points

- A nosocomial infection or health care-associated infection (HAI) is defined by the World Health Organization (WHO) as an infection occurring in a patient during the process of care in a hospital or other health care facility, which was not present or incubating at the time of admission. This includes infections acquired in the health care facility, but appearing after discharge, and also occupational infections among health care workers (HCWs) of the facility.
- The prevalence of nosocomial infections generally exceeds 25% in intensive care units (ICUs) worldwide. Although ICU beds account for only 5% of all hospital beds and care for less than 10% of patients admitted, ICU-acquired HAIs account for more than 20% of all nosocomial infections.
- Nosocomial infection rates tend to be higher in surgical than in medical ICUs, and higher in adult than in paediatric ICUs (except neonatal ICUs).
- In the adult ICU, the most common site of infection is the lower respiratory tract, whereas bloodstream infections are more prominent in the paediatric ICU.
- Despite accumulated evidence and expert opinion for the effectiveness of hand hygiene in preventing pathogen cross-transmission, HCWs compliance with recommendations remains unacceptably low worldwide, usually 30% to 50%. Successful multimodal interventions have been associated with decreasing HAI rates.

Introduction

Nosocomial or 'hospital' infection were formerly so named to mark their hospital origin. The term 'health care-associated infection' (HAI) is now used to take into account more appropriately the patient care process in today's complex health care systems, often involving long-term, rehabilitation, ambulatory, and home care. HAI is one of the most common medical complications affecting patients in intensive care units (ICUs). In general, HAI prevalence exceeds 25% in ICUs worldwide. Although ICU beds account for only 5% of all hospital beds and care for less than 10% of patients admitted, ICU-acquired HAIs account for more than 20% of all HAI overall. Associated costs are equally tremendous. An assessment of mortality attributable to HAI in the ICU setting is difficult as it shares common risk factors with both the underlying disease and acuity of illness. Crude mortality rates are estimated to vary between 10% and 80% and attributable morbidity and mortality due to ICU-acquired HAI may be in excess of corresponding rates for the infections that initially led to the patient's hospitalization.

Definition

HAI is defined by the World Health Organization (WHO) as an infection occurring in a patient during the process of care in a hospital or other health care facility, which was not present or incubating at the time of admission. This includes infections acquired in the health care facility, but appearing after discharge, and also occupational infections among health care workers (HCWs) of the facility. The diagnosis of infection at specific body sites, e.g. urinary tract, surgical site, respiratory tract, and blood, should rely on standardized criteria based on clinical, laboratory, microbiological, and imaging parameters. The most commonly used definitions are those of the United States Centers for Disease Control and Prevention [1], although several European countries use also the definitions of the 'Hospital Infection Link for Infection Control through Surveillance' (HELICS) network for ICUs [2]. In particular, work is being conducted on the definition of ventilator-associated pneumonia (VAP) to decrease the complexity and subjectivity of the definition and to allow a more reliable assessment and comparison of quality of care for ventilated patients [3].

Host colonization is a prerequisite for the development of infection, particularly in critical care. Although factors favouring the progression from colonization to infection are not completely understood, it is estimated that almost 50% of ICU-acquired HAI are preceded by colonization with the same microorganism. Factors associated with colonization are similar to infection (duration of hospitalization, high exposure to invasive devices, prolonged antibiotic therapy). Several studies have shown that severity of illness and ICU admission contributed to rapid colonization with gram-negative bacteria. Often these are endemic in the ICU and imply that the physiological flora of a patient can be substituted by the local endemic flora after some days in this setting.

Epidemiology

In 1992, the European Prevalence of Infection in Intensive Care (EPIC) study [4] included data from 1417 ICUs in 17 West European countries and provided valuable information on the prevalence and epidemiology of infection in critically-ill European patients. Fifteen years later, the Extended Prevalence of Infection in Intensive Care (EPIC II) study was conducted to provide a picture of the extent and patterns of infection in ICUs worldwide [5]. In 2007, 14,414 patients in 1265 ICUs from 75 countries participated in a one-day point prevalence survey. Of 13,796 patients aged >18 years, 7087 (51%) were considered to be infected. Patients who had longer ICU stays prior to the study day had higher infection rates. Infection prevalence varied markedly by geographical region, ranging from 46% to 60%. There was a significant relationship between the percentage of infected patients and the hospital mortality rate. This likely reflects differences in critical care practices between countries and underlines the importance of controlling for case mix when interpreting and comparing HAI rates between hospitals or countries.

The frequency of the occurrence of infection may also differ among different sites in the ICU and within a hospital as well illustrated by the annual United States National Healthcare Safety Network (NHSN) report [6]. Urinary tract infections predominate in general wards, whereas the most common ICU-acquired HAIs are lower respiratory tract infections. The type of ICU also plays a role. Infection rates tend to be higher in surgical than in medical ICUs, and higher in adult ICUs than in paediatric units, with the exception of neonatal ICUs. In adult ICUs, the lower respiratory tract is the most common site of infection, whereas bloodstream infections are more prominent in paediatric and neonatal ICUs. High rates of pulmonary infections are unique to adult ICUs where patients are frequently admitted because of respiratory distress and require mechanical ventilation. Although primary bacteraemia and infections due to vascular devices are less common than lower respiratory tract infections, morbidity, and mortality associated with these infections are particularly high.

When HAI rates have been compared over shorter increments of time, i.e. monthly, wide variations can be noted. Observations in different ICUs suggested that the level of skilled nursing care may be an important determinant of this variation. Several studies show that overcrowding, understaffing, or an imbalance between workload and resources are important determinants of HAI and microorganism cross-transmission in ICUs. The higher the workload, the lower the compliance with preventive measures, and the higher the rate of HAI. Importantly, not only the number of staff, but also the level of training affects outcomes. The causal pathway between understaffing and infection is complex and several factors may contribute, including primarily lack of time to comply with infection control recommendations.

Additional reasons for high rates include selection pressure for resistant organisms induced by high antimicrobial use and extensive exposure to medical devices. The patient's underlying conditions play also an important role. Several studies demonstrate a correlation between the number of active comorbidities, the HAI rate, and other medical complications. In addition, almost all ICU patients are equipped with at least one vascular access or device breaking the normal skin barrier, thus enabling a direct connection to the external environment.

HAI do not only occur individually, they can develop also as outbreaks. Epidemics are associated with specific organisms sometimes introduced from outside and remaining within the ICU because of the continuous selection pressure of antibiotics. These do not necessarily need to be virulent—it is sufficient to be resistant enough in order to persist. Leading pathogens are methicillin-resistant *Staphylococcus aureus* (MRSA), multiresistant non-fermentative Gram-negative rods, such as *Pseudomonas* sp., *Enterobacter* sp., *Serratia* sp., *Stenotrophomonas maltophilia,* and *Acinetobacter* sp., all of which can become long-lasting problems. Pathogens producing extended-spectrum beta-lactamases (ESBL), such as *Klebsiella* sp. or *Escherichia coli,* are equally a major concern in many countries worldwide. In some parts of the world, vancomycin-resistant enterococci (VRE) and carbapenem-resistant *Enterobacteriae* have completed recently this list of worrisome pathogens. Last, but not least, non-bacterial pathogens can become a problem, e.g. the steady increase of HAI caused by non-albicans *Candida* sp.

Surveillance

Although resource-demanding, correctly performed surveillance is a condition *sine qua non* for effective infection control. Surveillance may help to define and detect common or unusual sources of cross-infection or failures in care management. It summarizes rates and reports feedback for corrective actions and is best performed by dedicated, specifically-trained, infection control staff in close collaboration with the ICU team. Controversy exists if surveillance should be continued post-discharge. It is wise to prolong it for a brief period after the patient has left the ICU because ICU-acquired HAIs may become evident only in the following days while the patient is in the general ward. Of note, this approach is labour-intensive and may not always be justified as only few HAIs may be detected after discharge. Target-oriented, post-discharge surveillance could be a rational alternative.

Surveillance has a major impact on the incidence of infections. However, to understand the meaning of infection rates always implies comparison. On a micro-epidemiological level, this implies comparison of endemic rates over time within the same population, before and after an intervention or system change, or outbreak detection. Inter-institutional comparison, termed 'benchmarking', is increasingly common with the aim of improving the effectiveness of health care and promoting patient safety. Similar comparisons might soon be made between different health care settings. Benchmarking among health care structures requires meticulous adjustment for case-mix and failure to adjust adequately for infection-associated factors will erroneously punish commitment to more challenging medical tasks and hinder quality improvement [7]. This is a field of intense research and expanding knowledge. Standardization of the surveillance method is a second challenge that has to be addressed to make comparison possible [8]. This obviously clashes with the will to improve and adapt definitions to medical progress and local specificities. Adjustment should be implemented according to variations in the use of microbiological investigation within the different health care settings and type of diagnostic techniques applied. Diagnostic power and accuracy largely impact on infection rates. Voluntary participation in a surveillance network, confidentiality, and adequate feedback of results are the prerequisites for health care settings' adherence to the method and dedication to data quality.

Indicators

Prevention must be guided by the measurement of indicators that identify gaps and point to the most appropriate solutions. These indicators are composed of HAI rates, structure indicators (e.g. alcohol-based hand rub available at the point of care), process indicators (e.g. hand hygiene compliance), and audits using checklists to assess if correct procedures and equipment are in place. This is known as the 'recognize-explain-intervene' concept, which was validated for the first time on a large scale by the Study on the Efficacy of Nosocomial Infection Control (SENIC) project carried out in United States hospitals in the 1980s [9]. While demonstrating that 35–50% of HAI are preventable by a few fundamental practices (e.g. correct use of urinary catheters and vascular access lines, therapy and support of pulmonary functions, surveillance of surgical procedures, timely hand hygiene, and application of isolation precautions), the SENIC project identified key elements for the success of an infection control programme: one infection control nurse per 200–250 beds; one epidemiologist per hospital (1000 beds); organized surveillance for HAI; and systematic feedback of HAI rates to administrators and HCW. Facing today's challenge in health care in general and in ICUs in particular, the respective needs are one infection control nurse per 100–150 acute care hospital beds and one per ~25–35 ICU beds.

Standard precautions

Standard precautions refer to the comprehensive set of recommendations that must be followed in each care process and across all health care settings, regardless of the presence of an infectious pathogen. These precautions represent the primary strategy to prevent pathogen transmission among patients and HCW. They include the performance of hand hygiene according to pre-specified guidelines, use of personal protective equipment, respiratory hygiene/cough etiquette, safe injection practices, use of masks for catheter insertion, and lumbar puncture procedures, safe handling of contaminated equipment, textiles and laundry, routine cleaning and disinfection of environmental surfaces, and protective measures related to building construction and renovation.

Hand hygiene: a transversal measure

HCWs' hands are the principal instruments in the course of complete nursing and highly invasive care in the ICU. Although hand hygiene is the single most important measure to prevent cross-transmission and to reduce the rate of nosocomial colonization and infection, compliance among HCWs is unacceptably low worldwide. Explanations for such a low compliance include insufficient time due to high workload, inconvenient access to hand cleansing facilities, inferior priority compared with other patient needs, lack of institutional priority for hand hygiene, lack of institutional safety climate, lack of leadership of senior medical and nursing staff, allergy or intolerance to hand hygiene solutions, and lack of awareness of recommendations or scepticism regarding their effect on HAI. Not surprisingly, high workload is correlated with an increasing number of hand hygiene opportunities per hour of patient care. To overcome the time constraint factor, hand hygiene indications have been condensed into five moments when action is required during health care [10,11] (Fig. 283.1).

During the past decade the strength of evidence in favour of alcohol-based hand antisepsis, unless hands are visibly soiled, has

Fig. 283.1 The 'My 5 moments for hand hygiene' concept.

Reprinted from *Journal of Hospital Infection*, **67**(1), Sax H et al., 'My five moments of hand hygiene: a user-centred design approach to understand, train, monitor and report hand hygiene', pp. 9–21, copyright 2007, with permission from Elsevier and Healthcare Infection Society.

become simply overwhelming. If actively promoted, alcohol-based hand rub can improve compliance with hand hygiene recommendations and can reduce HAI and transmission rates [12]. In high-demand settings such as ICUs, an alcohol-based hand rub appears to be the only method that might allow reasonable compliance. In addition, alcohol-based hand rubs with gels, rinses, or foams containing emollients are less harmful to the skin than regular hand washing with soap and water.

Multimodal strategies, including 'bundle' approach

As defined by the US Institute for Healthcare Improvement (www.ihi.org), 'care bundles, in general, are groupings of best practices with respect to a disease process that individually improve care, but when applied together result in substantially greater improvement. The science supporting the bundle components is sufficiently established to be considered standard of care'.

The proportion of HAI potentially preventable under routine working conditions remains unclear. Several reports suggest a great potential, ranging from a decrease of 10% to a maximum of 70%, depending on the setting, study design, baseline infection rates, and type of infection. The most important potential was identified for catheter-related bacteraemia. Although the optimal approach to reducing ICU-acquired HAI is unclear, studies and large quality improvement initiatives have shown that multimodal strategies can decrease HAI rates [13,14]. Problems of multiresistant organisms and isolation strategies, antibiotic control, selective oral or digestive decontamination, and prevention of some key ICU-specific infections are addressed in other chapters.

References

1. Horan TC, Andrus M, and Dudeck MA. (2008). CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *American Journal of Infection Control*, **36**, 309–32.
2. Hospitals in Europe Link for Infection Control through Surveillance (HELICS) Surveillance of Nosocomial Infections in Intensive Care Units: Master Protocol (2004). Available at: http://ecdc.europa.eu/en/activities/surveillance/HAI/Documents/0409_IPSE_ICU_protocol.pdf (accessed 10 June 2012).
3. Klompas M, Kleinman K, Khan Y, et al. (2012). Rapid and reproducible surveillance for ventilator-associated pneumonia. *Clinical Infectious Diseases*, **54**, 370–7.
4. Vincent JL, Bihari D, Suter PM, et al. (1995). The prevalence of nosocomial infection in intensive care units in Europe: results of the European Prevalence of Infection in Intensive Care (EPIC) study. *Journal of the American Medical Association*, **274**, 639–44.
5. Vincent JL, Rello J, Marshall J, et al. (2009). International study of the prevalence and outcomes of infection in intensive care units. *Journal of the American Medical Association*, **302**, 2323–9.
6. Dudeck MA, Horan TC, Peterson KD, et al. (2011). National Healthcare Safety Network (NHSN) Report, data summary for 2010, device-associated module. *American Journal of Infection Control*, **39**, 798–816.
7. Sax, H. and Pittet, D. (2002). Interhospital differences in nosocomial infection rates: importance of case-mix adjustment. *Archives of Internal Medicine*, **162**, 2437–42.
8. Gastmeier P, Kampf G, Wischnewski N, et al. (1998). Importance of the surveillance method: national prevalence studies on nosocomial infections and the limits of comparison. *Infection Control and Hospital Epidemiology*, **19**, 661–7.
9. Haley RW, Morgan WM, Culver DH, et al. (1985). Update from the SENIC project. Hospital infection control: recent progress and opportunities under prospective payment. *American Journal of Infection Control*, **13**, 97–108.
10. Sax H, Allegranzi B, Uçkay I, Larson E, Boyce J, Pittet D. (2007). "My five moments for hand hygiene": a user-centred design approach to understand, train, monitor and report hand hygiene. *Journal of Hospital Infection*, **67**, 9–21.
11. World Health Organization (2009). *The World Health Organization Guidelines on Hand Hygiene in Health Care*. (Geneva: World Health Organization).
12. Pittet D, Hugonnet S, Harbarth S, et al. (2000). Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. *Lancet*, **356**, 1307–12.
13. Eggimann P, Harbarth S, Constantin MN, Touveneau S, Chevrolet JC, and Pittet D. (2000). Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. *Lancet*, **355**, 1864–8.
14. Pronovost P, Needham D, Berenholtz S, et al. (2006). An intervention to decrease catheter-related bloodstream infections in the ICU. *New England Journal of Medicine*, **355**, 2725–32.

CHAPTER 284

Healthcare worker screening for nosocomial pathogens

Paul Van Buynder and Elizabeth Brodkin

Key points

- Healthcare workers (HCW) are both at risk of becoming infected in the health care setting as well as being a known source of nosocomial infection.
- Employers and HCW have an ethical responsibility to prevent occupationally acquired infections and avoid causing harm to patients by transmitting disease.
- After any recognized blood borne pathogen (BBP) exposure incident, timely post-exposure risk assessment, along with a schedule of follow-up BBP screening should be undertaken.
- Screening for and management of potential transmission sources can reduce risks.
- HCW vaccination strategies can further reduce risks.

Screening and management of specific pathogens

Blood-borne pathogens

Health care worker (HCW) screening for blood-borne pathogens (BBP) focuses on the three viruses which are responsible for most health care-associated blood-borne infections, Human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Infection control guidelines for BBP screening of HCWs reflect an increasing focus on the potential risk of nosocomial BBP transmission from an infected HCW-to-patient, in addition to early identification of patient-to-HCW BBP transmission [1,2].

Guidelines for HCW screening and subsequent management of infected HCW vary across jurisdictions internationally, with differing thresholds for the scope of practice of infected HCW. Some jurisdictions, such as United States of America (USA), Canada, and Australia allow for case-by-case review of infected HCWs by an expert review committee to assess the scope of practice restriction [3,4].

Voluntary screening for HBV, HCV and HIV infection is a professional and ethical responsibility of each HCW who has potential exposure to BBPs. HCW regulatory authorities in many jurisdictions, such as the USA, Canada, Australia, and a number of European countries promote, but do not mandate BBP screening by HCW. In the United Kingdom (UK), such screening is explicitly mandated for new (but not currently practising) HCW who will perform 'exposure prone procedures' (EPP), which are procedures that are assessed to pose a higher risk of HCW-to-patient BBP transmission [5]. Most guidelines either make no recommendation for repeat BBP screening (e.g. U.K.) or do not recommend a specific frequency of BBP screening in HCWs not previously known to be infected (e.g. U.S.A, Canada, Germany). Recent Australian guidelines propose a minimum one-year periodicity for HCW performing EPP. Some regulatory agencies advise a re-screening frequency based on personal assessment of risk of acquisition of BBP infection.

In general, where guidelines recommend practice restrictions for infected HCW, exclusions are limited to performance of EPP only. Notably, UK guidelines indicate that the intensive care setting does not 'generally' involve EPPs by medical or nursing staff; however, these guidelines indicate certain procedures involving accident or emergency care as EPP, which could possibly be performed in critical care settings. Further complicating the assessed potential for performing EPP in critical care settings is a lack of international consensus in defining or categorizing specific procedures as EPP.

After any recognized BBP exposure incident, timely post-exposure risk assessment, along with a schedule of follow-up BBP screening should be undertaken. Where indicated, HIV post-exposure prophylaxis should ideally be initiated within two hours of exposure, while HBV prophylaxis, including hepatitis B immune globulin, and/or hepatitis B vaccine, is preferably begun within 48–72 hours of exposure.

Hepatitis B pre-exposure immunization and screening of post-vaccination anti-HBs level one to three months after the final vaccine dose are highly recommended for all HCW. Hepatitis B vaccine non-responders, in addition to HCW performing EPP, should have further Hepatitis B surface Antigen (HBsAg) testing and HBV-infected HCW should undergo HBeAg and/or HBV-DNA screening to assess their degree of infectivity. Although HBeAg-positive status generally requires exclusion from performing EPPs, guidelines for similarly restricting HBV-infected, HBeAg-negative HCWs differ according to varying HBV-DNA levels, ranging from: any level of detectable HBV-DNA (Australia); 103 GE/mL (UK); 104 GE/mL (U.S.A. and European Consensus Group); or 105 GE/mL (Netherlands). Jurisdictions that permit HCWs with detectable HBV-DNA to continue performing EPPs, require varying frequency of ongoing nucleic acid testing to monitor viral levels, ranging from every 3 months in Australia, to twice per year in the USA, and annually in the UK [6].

Variance across jurisdictions also exists for managing HCV-infected HCW. In general anti-HCV-positive,

HCV-RNA-positive HCW are restricted from performing EPP. Some guidelines (USA) permit HCV-infected HCW with HCV-RNA levels up to 104 GE/mL who have not been implicated in cases of HCW-to-patient HCV transmission, to continue performing EPP although affected HCW are required to 'double-glove' and undertake semi-annual HCV nucleic acid testing. Australian guidelines make provision for HCW who achieve a sustained viral response following HCV treatment (i.e. undetectable HCV-RNA 6 months after completion of treatment) to resume performing EPP, with annual HCV-RNA rescreening.

Most jurisdictions exclude HIV-infected HCW from performing EPPs, regardless of HIV-RNA level (even if 'undetectable' by sensitive nucleic acid testing). Some USA guidelines are more permissive (i.e. Society for Healthcare Epidemiology of America, or SHEA), allowing HIV-infected HCW with HIV-RNA levels less than 500 GE/mL to continue performing EPP, with similar ongoing practice and follow-up test requirements as for HCV [3].

As available data increases, HCW screening and management guidelines will require ongoing review to optimally manage BBP-infected HCWs who achieve long term sustained, viral response using increasingly effective therapies.

Tuberculosis

All health care settings require a tuberculosis (TB) infection control program, a key component of which is screening HCW who are at risk for disease or who might be exposed to infected persons or clinical specimens [7].

Baseline screening of HCW allows for detection and treatment of latent and active TB disease before employment begins, and provides a basis for comparison should the worker be exposed to *Mycobacterium* TB. New HCW (or staff with no evidence of prior screening) who will be exposed to patients or clinical specimens, should only begin work after they have undergone a health check and TB screen, or can produce evidence of having been screened in the previous 12 months. The health check should include:

- Personal or family history of TB.
- Any signs and symptoms of TB disease.
- Evidence of Tuberculin skin testing (TST) or Interferon Gamma release Assay (IGRA) testing and Bacille Calmette–Guérin, (BCG) scar check by an occupational health professional.
- Previous TST results in the last five years if available.

HCWs should not begin work if they have signs and symptoms of active TB disease.

New HCWs who are not entrants from high incidence countries and have not previously had BCG vaccination should be offered TST testing. If the TST is positive IGRA testing should be performed. If both the TST and IGRA are positive the worker should have a chest X-ray and a medical assessment for latent or active disease.

IGRA testing should be offered to new HCW who have recently arrived from high incidence countries or who have worked in settings where TB is prevalent. If the IGRA is positive the HCW should be referred for medical assessment [8].

The frequency of ongoing screening for established HCW should be determined by the risk of exposure in their particular setting. Risk varies by patient population, prevalence of TB in the community, occupational group, and effectiveness of TB infection control measures. Settings in which infected persons or clinical specimens are unlikely to be present are considered low risk. Medium risk refers to settings in which HCW will or are likely to be exposed to infected persons or specimens. Potential ongoing transmission should be applied to any setting where there is evidence of person-to-person transmission during the previous year.

After baseline screening for TB, additional screening of HCW in low risk settings is not needed unless an exposure to M. TB occurs. HCW in medium risk settings should be screened annually by health check, and by TST/IGRA testing for those with negative baseline testing. In settings with potential ongoing transmission workers may need to be screened every eight to 10 weeks until the problem has been corrected and transmission has ceased. HCW who transfer from one setting to another may be at higher risk in the new setting and the frequency of screening should be adjusted accordingly.

Methicillin-resistant *Staphylococcus aureus*

HCW can become colonized with MRSA. One retrospective review of published data found HCW to have an average colonization rate of 5% and transmission to be documented from both transiently and persistently colonized HCW. No trials have been published on the benefit of routine HCW screening for MRSA colonization although this practice occurs in the Netherlands, Scandinavia, and Western Australia. This practice is not routinely recommended unless staff were epidemiologically linked to new MRSA cases or a cluster of infections, or if an outbreak persists despite appropriate control measures. Molecular testing has been helpful in these situations. Surveillance for skin and soft tissue infections in staff is also warranted in an outbreak. Eradication therapy should be provided for positive staff in these settings.

Screening of patients in critical care areas has been deemed cost effective by a Health Protection Authority modelling study and screening of all hospital admissions is required in the United Kingdom, but remains contentious with studies examining the link between colonization and infective complications showing conflicting results [9,10].

Other antibiotic resistant organisms

Routine screening of healthcare workers for vancomycin resistant enterococci (VRE), carbapenem-resistant Enterobacteriaceae (CRE) and Extended Spectrum Beta Lactamase (ESBL) producing organisms is not recommended as there is no evidence that rectal colonization of staff contributes to transmission.

Vaccination of health care workers

Recommendations for vaccination of HCW are largely based on either risk to the HCW for acquiring disease or the risk of HCWs transmitting disease to patients. A review of HCW vaccination status should occur at the time of hire and then annually with influenza vaccination. Robust HCW vaccination policies should be accompanied by secure record systems so that susceptible individuals can be identified during times of outbreaks [11].

Hepatitis B vaccine should be made available at no cost to all HCW who are exposed occupationally to infectious materials, preferentially during training prior to exposure. The three dose regime at zero, one, and six months produces a protective antibody response in over 90% of healthy young adults and lasts for over 20 years in vaccine responders. Post vaccination serologic testing should be undertaken after the third dose to confirm the presence

of hepatitis B surface antibody (anti-HBs >10mIU/mL). For those with an inadequate immune response after a complete vaccine series, (i.e. less than 10 IU/L), a second complete series of hepatitis B vaccine is recommended in many jurisdictions. UK guidelines also recommend offering an additional single vaccine dose to those with an intermediate response (i.e. 10-100 IU/L).

Non-responders who are not infected with Hepatitis B are susceptible and should be educated about preventing infection and post-exposure prophylaxis. Non-responders who are HBsAg positive should be counselled about preventing transmission to others and have their practice reviewed. Post exposure prophylaxis after significant exposure to blood or body fluids should be based on the HBsAg status of the source and the immune status of the exposed HCW. HCW engaging in high- risk personal practices associated with an increased risk of non-occupational acquisition of blood borne viruses have a responsibility to regularly check their status.

Many HCW are infected with influenza each year. Vaccinating HCW decreases morbidity in health care settings particularly in long term care and vaccination helps maintain a workforce in winter by reducing absenteeism. Professional bodies have recommended HCW vaccination as an ethical imperative for many years, but uptake has been almost universally disappointing and often less than 50%. In view of the failure of education, many organizations and some United States jurisdictions have now mandated HCW influenza vaccination [12].

Measles remains common in some parts of the world leading to travel related importations and risks of transmission even in areas where measles has been declared eliminated. Persons infected with measles are likely to seek medical care and measles transmission has been shown to occur in medical settings during outbreaks. HCW are at higher risk of acquiring measles. Exposure response in medical settings is expensive and entails reviewing measles immunity, and excluding and vaccinating the non-immune. All HCW born after 1956 should be vaccinated with two doses of Measles Mumps Rubella (MMR) vaccine and a record should exist in all facilities documenting these doses or documenting laboratory evidence of immunity or disease. Serological confirmation after vaccination is not required.

Mumps transmission in medical settings is also well recognized and the management of cases associated with similar economic costs as measles. Immunity to mumps vaccine wanes over time and correlates of protection are not known. All HCW should provide presumptive evidence of immunity to mumps. Despite waning immunity, two doses of MMR vaccine is considered sufficient protection.

Evidence of transmission of rubella in medical settings is scant in areas where rubella elimination has been achieved although it was common prior to that. All HCW should have documented evidence of immunity. History of disease is not considered adequate.

Pertussis is a highly contagious disease with a high risk of hospitalization and significant mortality in the very young. Since the widespread use of acellular pertussis vaccines in the last decade, with a duration of protection of only between 5 and 10 years, outbreaks are occurring on a regular basis. Documented transmission within medical settings has occurred and outbreak management is costly. All HCW in contact with young children should receive decennial booster vaccines and consideration should be given to boosting after 5 years in an outbreak setting. Modelling post outbreak has shown that HCW vaccination for pertussis is cost saving.

Vaccination against other preventable diseases such as varicella may be indicated depending on local epidemiology and local vaccination coverage data.

References

1. Carlson AL, and Perl TM. (2010). Health care workers as source of hepatitis B and C virus transmission. *Clinical Liver Disease*, **14**, 153–68.
2. Deuffic-Burban S, Delarocque-Astagneau E, Abiteboul D, Bouvet E, and Yazdanpanah Y. (2011). Blood-borne viruses in health care workers: prevention and management. *Journal of Clinical Virology*, **52**, 4–10.
3. Society for Healthcare Epidemiology of America. (2010). Guideline for management of health care workers who are infected with hepatitis B virus, hepatitis C virus, and/or human immunodeficiency virus. *Infection Control in Hospital Epidemiology*, **31**, (3), 203–32.
4. Communicable Diseases Network Australia. Australian National Guidelines for the Management of Health Care Workers Known to be Infected with Blood-borne Viruses. 28 Feb 2012. Available at: http://www.health.gov.au/ (accessed 28 February 2012).
5. UK Department of Health. (2007). Healthy Clearance for tuberculosis, hepatitis B, hepatitis C and HIV: New health care workers, 1–58. Available at: http://www.dh.gov.uk/
6. CDC. (2012). Updated CDC recommendations for the management of hepatitis b virus-infected health-care providers and students. *Morbidity and Mortality Weekly Report*, **61**, (RR03), 1–12.
7. CDC. (2005). Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, *Morbidity and Mortality Weekly Report*, **54**(RR17), 1–141.
8. CDC. (2010). Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. *Morbidity and Mortality Weekly Report*, **59**(RR05), 1–25.
9. Hawkins G, Stewart S, Blatchford O, and Reilly J. (2011). Should healthcare workers be screened routinely for methicillin-resistant *Staphylococcus aureus*? A review of the evidence. *Journal of Hospital Infections*, **77**(4), 285–9.
10. Rowbotham JV, Graves N, Cookson BD, et al. (2011). Screening, isolation, and decolonisation strategies in the control of methicillin resistant *Staphylococcus aureus* in intensive care units: cost effectiveness evaluation. *British Medical Journal*, **343**, 5694.
11. CDC. (2011). Immunization of Healthcare worker personnel. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report*, **60**(RR07), 1–45.
12. Talbot TR, Babcock H, Caplan AL, et al. (2010). Revised SHEA Position Paper: *Influenza Vaccination of Healthcare Personnel Infection Control Hospital Epidemiology*, **31**(10), 987–95.

CHAPTER 285

Environmental decontamination and isolation strategies in the ICU

Leigh Ann Slater and Pamela A. Lipsett

Key points

- The care environment is an important factor in the transmission of health care-associated infections, but its role is incompletely understood.
- Potential avenues for infection transmission include hospital construction, unit and room layout, design materials, disinfection materials and methods, isolation equipment, and staff ratios and training.
- Limited evidence supports many currently employed cleaning and isolation techniques. Many are simply intuitive or based on non-controlled observations.
- Compliance is currently poor with both cleaning and isolation policies.
- Reduced colonization does not always translate to reduced infection rates.

Introduction

There are over 1.7 million health care associated infections annually in the US and 99,000 deaths [1]. With the clinical and financial burden of antibiotic resistance increasing exponentially, agencies such as the Joint Commission have clearly articulated regulations. The environment of care is a potentially important contributor to preventable health care associated infections. Potential avenues for infection transmission range from the initial hospital construction itself to unit and room layout, design materials, disinfection materials and methods, isolation equipment, and staff ratios and training. Better understanding of these avenues for transmission will suggest potential means to decrease the burden of environmental contamination. Several studies have demonstrated a two to three-fold increased risk of acquiring VRE (vancomycin resistant *Enterococcus*), MRSA (meticillin resistant *Staphylococcus aureus*), *Clostridium difficile* or ACB (*Acinetobacter baumanii*) when occupying a room previously used by a patient with one of these organisms [2]. Meanwhile, enhanced surveillance strategies demonstrate suboptimal routine disinfection with the potential to decrease transmission of VRE, MRSA, and ACB by 40% simply by improving compliance with existing cleaning protocols [3]. However, whether improvements in cleaning can lead to a clear decrease in acquired infections remains controversial. This chapter will provide a brief overview of the current understanding of the environment of care and its impact on infection control practices.

Construction

Construction-related risks include the release of airborne fungal diseases, most notably *Aspergillus* spp. The number of health care associated *Aspergillus* infections directly attributable to construction is unknown, but *Aspergillus* has a large cost burden, estimated at over $600 million in 1996 alone [4]. Treatment of *Aspergillus* infection adds 17 days to length of stay, or over $62,000 in costs per patient. Case fatality rate is over 50% overall and over 80% for bone marrow transplant recipients despite treatment, thus the urgency to prevent transmission. Thus during construction periods, high risk individuals such as transplant patients should avoid exposure to these areas.

Waterborne diseases are also a significant risk to the immunocompromised via the potable water supply. These include *Aspergillus* spp. and *Fusarium* spp., which can be transmitted via disruption of the biofilm after a water service interruption. *Pseudomonas* spp. and *Stenotrophomonas* spp. are opportunistic free-floating bacteria and can contaminate surfaces that come in contact with the water. Risk of transmission is heightened if contaminated water is used to wash equipment in direct contact with patients, or if water is allowed to stagnate and microbial count increases above 10,000 cfu/mL. *Legionella* spp. are found widely in soil and water and is easily introduced to the potable water supply, where it can spread through hospital water heaters and distribution systems to individual room faucets. *Legionella* spp. are commonly transmitted via inhalation of the aerosol at waterheads and there is no commonly utilized monitoring or eradication method. It is addressed by surveillance of patients for symptoms, prompt identification and treatment.

Unit design

Historically intensive care unit design emphasized arrangement of patient beds around a centralized nursing station to maximize visibility and communication and to more readily enable rapid response in the event of patient clinical decompensation. With more concern over the potential for cross contamination as well as more attention to the need for privacy and increased family presence, the emphasis has shifted to single occupancy rooms. Single rooms have demonstrated reduction in transmission of MRSA, *Pseudomonas* spp., and *Candida* spp. when compared with multi-bed wards [4].

Important aspects of unit design include optimizing availability of hand hygiene equipment near point of care. Water and alcohol based modalities are equally efficacious for most hand

hygiene. However, soap and water should be used for *Clostridium difficile*, since alcohol based cleansers have no effect against the spores. Alcohol based hand rub stations should therefore not be used in place of appropriate water based hand hygiene for this pathogen. Attention should be paid to sink size and depth to prevent splashing, avoidance of contamination of the faucet aerators, hands-free activation of the stream, direction of stream away from the drain, water pressure and temperature, proper drainage, and separate sinks for the toilet area versus for the remainder of the patient room. No storage should be allowed underneath the sinks. Travel distance for waste disposal should be minimized.

Water access for acute dialysis is another important consideration and care should be taken to avoid plugged lines and hoses with resultant mould growth. Waterproofing can be accomplished by gypsum board installed 10 mm (3/8″) above the floor board to prevent fluid wicking from floods [4].

Room design

The current trend is toward single occupancy rooms. Attention should be paid to ergonomic locations and heights of hand hygiene stations as well as to minimizing travel distance for waste disposal and separating it from the remainder of the room. The ideal arrangement may be a toilet room between every two patient rooms, to avoid transporting waste to a distant central area. In addition, patient rooms should have flexibility to increase acuity so that patient room transfers can be minimized, as increased transfers are linked to increased infection transmission. Specific isolation room design concepts will be discussed in a later section.

Surfaces and materials

Contaminated surfaces play an important role in the spread of MRSA, VRE, norovirus, *Clostridium difficile*, hepatitis B virus, and *Candida* spp., as well as *Acinetobacter* spp., *Pseudomonas* spp. and other multi-drug resistant Gram-negative bacilli. All of these organisms are able to colonize patients' and health care workers' (HCW) hands and can survive and remain virulent for prolonged periods on environmental surfaces. Surfaces in general need to be easy to clean with topical disinfectants at the appropriate concentration, duration, and frequency. There is little evidence identifying clearly superior surface materials that contribute to the reduction of health care associated infection. Desirable surfaces will be nonporous, non-cloth, smooth, water resistant, sealed, flat or with rounded corners, free of crevices, and durable against corrosion with the required frequent cleaning. Furniture should have 150–300 mm (6–12″) clearance above the floor to permit thorough cleaning. Soft or upholstered furniture or carpet must be discarded if soiled, as must be any furniture with soiled exposed particleboard. Intact hardwood laminate can be cleaned with dilute bleach. Some manufacturers use fungicides, antimicrobials, or insecticides in their floor treatments or upholstery. Copper has intrinsic antimicrobial properties and is gaining acceptance over the more common stainless steel, but has not been shown to decrease cross-contamination [4]. Drapes, curtains, and other porous materials must be discarded after each patient if they cannot be sterilized for reuse. Particular care must be taken with the sterilization of ventilator equipment between patients.

Disinfection materials and methods

Commonly used surface disinfectants include sodium hypochlorite, sodium hydroxide, alcohols at 70 or 90% (ethanol, 1-propanol, 2-propanol), phenols, and quaternary ammonium compounds. Care must be taken to use these per the package instructions to ensure they are applied at adequate concentration, duration, and frequency. In addition, knowledge of specific pathogens is necessary as they may be selectively resistant to certain agents.

Norovirus, *Clostridium difficile*, and *Acinetobacter* spp. can all survive on environmental surfaces for weeks and are resistant to commonly used disinfectants. Norovirus can be transmitted by faecal-oral route either directly person-to-person, via surfaces or contaminated food or even by inhalation of aerosolized vomitus. It has high infectivity with a low inoculating dose and a long shedding time. As it cannot be cultured, surrogate data from caliciviruses suggests that alcohol, phenols, and quaternary ammonium compounds are less likely to be effective cleaning agents, with the effect highly dependent on the precise formulation. Sodium hypochlorite solution is effective when used at 1000–3000 ppm. Hand hygiene with soap and water for at least one minute completely removes norovirus as demonstrated by reverse transcription polymerase chain reaction (RT-PCR) [1].

Clostridium difficile can be transmitted by faecal-oral route directly, via fomites or the hands of HCW. The vegetative form survives 15 minutes on a dry surface, but up to 6 hours on a moist surface, and spores can persist up to 5 months. 70% isopropanol, phenols, and quaternary ammonium compounds are not sporicidal [1]. Use of 1:10 diluted (5000 ppm) sodium hypochlorite is effective at reducing *Clostridium difficile* infections in the setting of an epidemic or high endemic caseload; this is advocated as effective against spores, but still leaves 10% *Clostridium difficile* positive toilets in rooms with *Clostridium difficile* positive patients [5]. Spores are thus a frustrating problem and the key to reducing transmission with this pathogen. Accelerated 0.5% H_2O_2 was found to be effective at spore removal in non-epidemic conditions [5]. Proper hand hygiene with soap and water is most effective at removing spores.

Acinetobacter spp. can survive for weeks on many different dry surfaces as well as in water; humidity prolongs its survival. It is often present in reservoirs such as respiratory equipment. It is susceptible to phenols, quaternary ammonium compounds, accelerated 0.5% H_2O_2, and UV light. 70% ethanol and 10% povidone-iodine are most effective at cleaning heavily contaminated hands [1].

For terminal cleaning of rooms or eradication of units such as during an epidemic, various no touch disinfection methods may be utilized after the initial room cleaning. An automated ultraviolet-C device for hospital room disinfection has been demonstrated to reduce frequency of positive MRSA and VRE cultures by 93% and *Clostridium difficile* cultures by 80%, with 45 minutes of treatment required to reduce spores > 2–3 $\log_{10}$ cfu/cm^2; MRSA and VRE killing were equivalent with 20 minutes versus 45 minutes of treatment [6]. However, such devices only function optimally after proper surface decontamination and only when used with the proper duration and treatment radius and intensity. Inferior cleaning rates (< 30%) have been demonstrated with commonly contaminated fixtures including doorknobs and light switches.

Alternative no touch disinfection methods include the use of gaseous agents such as H_2O_2, chlorine dioxide, and ozone, which are all powerful oxidizing agents [7]. All require the room to be

precleaned and pose some small hazard to staff. The vapourized H_2O_2 system manufactured by Bioquell reduced *Clostridium difficile* infection 53% during an epidemic, but no controls were utilized in the study [8]. The system requires removal of the patient from the room so it can be sealed completely with tape, including heating, ventilation, and air conditioning ducts. Treatment with vaporized H_2O_2 requires up to 5 hours compared with 1 hour for bleach cleaning, an important factor in patient throughut and bed availability. The newer system manufactured by Bioquell has considerably reduced the required disinfection time, minimizing this concern. Chlorine dioxide is sporicidal, but can penetrate plastics commonly found in the clinical setting, as well as being explosive at concentrations above 10% and yielding toxic chlorine gas. Ozone's corrosiveness and toxicity likewise limits its application in the clinical setting, as 15 minutes at 0.2 ppm is enough to induce respiratory symptoms while providing insufficient antimicrobial effect [7].

Isolation

Basic isolation concepts begin with the use of standard precautions for all patients, including hand hygiene before and after each contact and use of gloves for contact with any body fluid other than sweat. Transmission of blood-borne pathogens such as HIV, and hepatitis B and C can be minimized by adherence to standard precautions. For patients with certain specific infections, more stringent isolation protocols are required. The presence of such pathogens should be identified early and communicated broadly with appropriate signage and order sets to alert all HCW to the need to observe heightened precautions and cleaning protocols. The universal use of mandatory isolation remains controversial [9].

Certain infections require designated isolation rooms within an ICU. With the airborne infection isolation room (AIIR), air flow is directed into the room, i.e. these are negative pressure rooms suitable for airborne precautions. A minimum of 12 air changes per hour are required, as are gloves, gown, and N95 type particle respirator masks [4]. AIIR protect against airborne droplets, which are 5 μm or smaller and can remain suspended in the air for a long time and disperse widely. Such infections include tuberculosis, measles, varicella, herpes zoster, and the viral haemorrhagic fevers such as Lassa, Ebola, and Marburg viruses [10].

Standard droplets do not require a negative pressure room, but simply a single room along with gloves, gown, and mask. These droplets are larger than 5 μm and do not remain suspended in air as long or disperse as widely as the airborne droplets. Dispersal is typically limited to one meter. These infections include influenza, rubella, mumps, and meningitis (*Haemophilus influenzae* and *Neisseria meningitidis*) [10].

Contact precautions include single room and use of gown and gloves for each contact. In some settings and countries they are required for MRSA/glycopeptide intermediate *Staph. aureus*, VRE, *Clostridium difficile*, varicella, herpes zoster, and the viral haemorrhagic fevers (Lassa, Ebola, Marburg) [10]. Local epidemiology authorities may identify other pathogens, such as *Acinetobacter* spp., *Pseudomonas* spp., or other multi-drug resistant or Gram-negative bacilli that should have strict isolation precautions. These measures are reinforced by appropriate universal surveillance for pathogens, such as MRSA nasal swab, and VRE rectal swab, as well as by prompt recognition of diarrhoea or ileus prompting *Clostridium difficile* stool antigen and culture [11]. The routine use of isolation procedures (gown, gloves +/- masks) for all ICU patients has been favoured by some authors as a means to improve hand hygiene and more generally to decrease transmission of infections. While in some cases these more global isolation measures have been effective, the widespread use of mandatory isolation for all patients cannot be endorsed.

For immunosuppressed patients, a protective environment room is required, with the airflow directed out of the room and use of gloves, gown, and mask. Key opportunistic pathogens targeted include *Aspergillus* spp. and other airborne fungi, *Pneumocystis* spp., *Toxoplasma* spp., CMV, John Cunningham virus, tuberculosis, and *Mycobacterium avium* complex.

Staffing issues

Caregiver:patient ratio is a major contributor to staff stress level and understaffing clearly can lead to staff being overwhelmed and overburdened with increased chance of cross-contamination while moving between patient rooms. There may be more frequent trips required and less time to perform adequate hand hygiene. Hand hygiene campaigns and other educational interventions are useful reminders, but of limited impact in the face of inadequate staffing for the level of acuity and nursing activities. Other staffing approaches can include cohorting infected or colonized patients or cohorting staff caring for such patients to limit cross-contamination opportunities.

Patient specific interventions

Patient specific interventions for the prevention of transmission of pathogens include global measures such as providing daily chlorhexidine baths and frequent changes and skin care, use of linens made of cotton or other material designed to wick away moisture, maintenance of normothermia and glycaemic control, and proper antibiotic husbandry to cover likely pathogens while avoiding selection of resistant microbes.

Surveillance/quality control

Feedback about the efficacy of environmental cleaning and isolation strategies is paramount to achieving significant reduction in health care associated infection. Of particular importance, many currently employed cleaning and isolation strategies have a very limited evidence base. Many are simply intuitive or based on non-controlled observations. The cost of performing rigorous studies may be prohibitive. In addition, reduced colonization does not always translate to reduced infection rates. As one example, a crossover study of enhanced cleaning accomplished a significant reduction in MRSA hand carriage rate of HCW, but no change in the infection rate of patients. The authors calculated that data from at least 40,000 patients would be required to demonstrate a difference in MRSA infection rate with 80% power [12,13].

Quality control can be understood in terms of both process measures and outcome measures. Process measures could include education, checklists, or covert practice observation to assure that disinfectants are being diluted and applied properly, according to manufacturer recommendations for concentration, duration, and frequency [2,14]. Outcome measures include various forms of surveillance for post-clean contamination, such as swab or agar slide cultures, fluorescent gel, and adenosine

triphosphate (ATP) bioluminescence technologies [2,15,16]. They may also involve some assessment of the cost-effectiveness of different disinfection products and strategies. A key concept is that of measuring cleaning process (observation and fluorescent gel) versus cleanliness (swab and slide cultures, ATP bioluminescence) [2,16]. It is estimated that only 34% of surfaces currently are cleaned in accordance with institutional policy, providing a significant opportunity for improvement [2]. Data gleaned from such investigations should be utilized in recurrent educational programs to improve compliance with the best evidence based guidelines, promulgated by national authorities. Feedback rendered in a blame-free context with clear specific recommendations for improvement will yield the best result.

Conclusion

The care environment is an important factor in the transmission of health care-associated infections, but its role is incompletely understood. In particular, there is a limited evidence base for many currently employed cleaning and isolation techniques. There is, however, ample evidence of poor compliance with established cleaning and isolation protocols. Given the severe health and cost burden of health care-associated infections, increasing attention is being devoted to the impact of the environment of care. Work is ongoing to establish optimal regimens from an efficacy and cost perspective.

References

1. Weber D, Rutala WA, Miller MB, Huslage K, and Sickbert-Bennett E. (2010). Role of hospital surfaces in the transmission of emerging health care-associated pathogens: norovirus, *Clostridium difficile*, and *Acinetobacter* species. *American Journal of Infection Control*, **38**, S25.
2. Carling P and Bartley J. (2010). Evaluating hygienic cleaning in health care settings: what you do not know can harm your patients. *American Journal of Infection Control*, **38**, S41.
3. Hota B, Blom DW, Lyle EA, Weinstein RA, and Hayden MK. (2009). Interventional evaluation of environmental contamination by vancomycin-resistant enterococci: failure of personnel, product or procedure? *Journal of Hospital Infection*, **71**, 123.
4. Bartley J and Streifel A. (2010). Design of the environment of care for safety of patients and personnel: does form follow function or vice versa in the intensive care unit? *Critical Care Medicine*, **38**, (8),S388.
5. Alfa M, Lo E, Wald A, Dueck C, DeGagne P, and Harding GKM. (2010). Improved eradication of Clostridium difficile spores from toilets of hospitalized patients using an accelerated hydrogen peroxide as the cleaning agent. *British Medical College of Infectious Diseases*, **10**, 268.
6. Nerandzic M, Cadnum JL, Pultz MJ, and Donskey CJ. (2010). Evaluation of an automated ultraviolet radiation device for decontamination of *Clostridium difficile* and other healthcare-associated pathogens in hospital rooms. *British Medical College of Infectious Diseases*, **10**, 197.
7. Davies A, Pottage T, Bennett A, and Walker J. (2010). Gaseous and air decontamination technologies for *Clostridium difficile* in the healthcare environment. *Journal of Hospital Infection*, doi:10.1016/j.jhin.2010.08.012.
8. Otter JA, Yezli S, Schouten MA, van Zanten ARH, Houmes-Zielman G, and Nohlmans-Paulssen MKE. (2010). Hydrogen peroxide vapor decontamination of an intensive care unit to remove environmental reservoirs of multidrug-resistant Gram-negative rods during an outbreak. *American Journal of Infection Control*, **38**, 754.
9. Prowle J, Heenen S and Singer M. (2011). Infection in the critically ill—questions we should be asking. *Journal of Antimicrobial Chemotherapy*, **66**, S2:ii3.
10. Loo V. (2008). Infection control in surgical practice. In Valentine RJ, editor. ACS Surgery: Principles and Practice. 7th ed. BC Decker.
11. Bobo L and Dubberke E. (2010). Recognition and prevention of hospital-associated enteric infections in the intensive care unit. *Critical Care Medicine*, **38**, (8),S324.
12. Morter S, Bennet G, Fish J, et al. (2011). Norovirus in the hospital setting: virus introduction and spread within the hospital environment. *Journal of Hospital Infection*, **77**, 106.
13. Wilson APR, Smyth D, Moore G, et al. (2011). The impact of enhanced cleaning within the intensive care unit on contamination of the near-patient environment with hospital pathogens: a randomized crossover study in critical care units in two hospitals. *Critical Care Medicine*, **39**, (4),1.
14. Dumigan DG, Boyce JM, Havill NL, Golebiewski M, Balogun O, and Rizvani R. (2010). Who is really caring for your environment of care? Developing standardized cleaning procedures and effective monitoring techniques. *American Journal of Infection Control*, **38**, 387.
15. Carling PC, Von Beheren S, Kim P, and Woods C. (2008). Intensive care unit environmental cleaning: an evaluation in sixteen hospitals using a novel assessment tool. *Journal of Hospital Infection*, **68**, 39.
16. Moore G, Smyth D, Singleton J, Wilson P. (2010). The use of adenosine triphosphate bioluminescence to assess the efficacy of a modified cleaning program implemented within an intensive care setting. *American Journal of Infection Control*, **38**, 617.

CHAPTER 286

Antimicrobial selection policies in the ICU

David L. Paterson and Yoshiro Hayashi

Key points

- Consider the potential source of infection when making empiric antibiotic choices.
- Local epidemiology in your intensive care unit (ICU) may differ from that published elsewhere.
- De-escalate antibiotics to the narrowest possible spectrum, when susceptibilities allow.
- Super bugs are now widespread in many ICUs—colistin is the last-line antibiotic and should be used prudently.
- Antibiotic stewardship is important in ICUs and pertains not just to initiation of antibiotics, but also to limiting duration of antibiotic courses.

Introduction

The selection of an antibiotic for an individual critically-ill patient depends on a number of factors. These include the patient's allergies and renal function, the likely bacterial and fungal pathogens typically found at the potential site of infection, prior isolation of antibiotic resistant pathogens, prior antibiotic use, the local epidemiology of antibiotic resistance, costs of comparator drugs, and the potential ecological effect of prescribed antibiotics. Five key policy issues determine antibiotic selection:

- The microbiological differential diagnosis.
- Use of epidemiology data.
- Adjusting antibiotic therapy with the aid of microbiology results.
- Special considerations for resistant organisms.
- Antimicrobial stewardship.

Microbiological differential diagnosis based on suspected source of infection and empiric regimens

Initial empiric antimicrobial therapy can be defined as the use of an antimicrobial for a patient with symptoms and signs of a serious infection prior to identification of the bacteria and the availability of susceptibilities. When making an initial antibiotic choice, definition of the likely location of infection based on clinical symptoms and signs and basic diagnostic testing is important because the microbiological differential diagnosis differs depending on the infection site (Table 286.1). For example, all of *Staphylococcus aureus, Enterococcus faecalis* and *Candida* spp. are frequent pathogens in intensive care units (ICU), but *S. aureus* is an extremely infrequent pathogen for urinary tract infection and neither *E. faecalis* nor *Candida* spp. typically cause pneumonia.

It is important to decide whether *Pseudomonas aeruginosa,* carbapenem resistant *Enterobacteriaceae/Acinetobacter* spp., MRSA, and/or *Candida* spp. need to be covered. As a general rule, most ICU-acquired infections such as late-onset ventilator-associated pneumonia (VAP) require both anti-pseudomonal and anti-MRSA cover, while most community-acquired infections do not except for special situations (e.g. MRSA cover for severe community acquired pneumonia where community-associated MRSA is endemic, especially following influenza infection). Fever in neutropenic patients requires anti-pseudomonal cover and most cases of undifferentiated ICU-acquired infections need both anti-pseudomonal and anti-MRSA cover in the initial therapy. The addition of antibiotics active against carbapenem-resistant Enterobacteriaceae or *Acinetobacter* spp. will depend on local epidemiology.

Before the initiation of any antibiotic treatment, obtaining appropriate specimens for culture, especially blood cultures, is crucial to facilitate subsequent important decisions such as antibiotic discontinuation, antibiotic rationalization, and duration of antibiotics (e.g. *Staphylococcus aureus* blood stream infection may require longer duration of antibiotic therapy).

Clinicians should be aware that some patients with symptoms and signs of a serious infection do not, in fact, have an infection at all. Systemic inflammatory response syndrome (SIRS) may have non-infectious aetiologies (e.g. burns, trauma, post-surgery, acute pancreatitis). Many non-infective pulmonary complications in mechanically ventilated patients (e.g. fluid overload, acute respiratory distress syndrome (ARDS)) mimic ventilator-associated pneumonia [1]. In these situations, antibiotic therapy is not only unnecessary, but creates an increased risk of disturbance of endogenous flora, potentially leading to *Clostridium difficile* infection or colonization with antibiotic-resistant bacteria [2,3]. Unfortunately even in the state-of-the-art practice, differentiation of these conditions is often difficult. Thus, daily review of antibiotic therapy by an experienced clinician is important.

Use of epidemiological data to guide antibiotic choice

Epidemiological data on antibiotic susceptibilities is a useful tool in the selection of empiric antibiotic therapy, because the expected reliability of each agent is significantly variable depending on the

Table 286.1 Microbiological differential diagnosis based on source of infection and suggested empiric antimicrobial regimen

Source of infection	Microbiological differential diagnosis	Possible empiric antimicrobial regimen
Community-acquired pneumonia	**No risk of multidrug resistant organisms:** *S. pneumoniae, H. influenzae, Legionella* spp., *Mycoplasma pneumoniae* **Risk of multidrug resistant organisms:** nosocomial GNB, such as *P. aeruginosa* in addition to the above **If CA-MRSA is of concern**	◆ Ceftriaxone + azithromycin ◆ Penicillin + doxycycline ◆ Piperacillin/tazobactam + azithromycin ◆ Cefepime + azithromycin ◆ Add vancomycin, clindamycin or linezolid to the above
Ventilator-associated pneumonia, hospital-acquired pneumonia, health care-associated pneumonia	**No risk of multidrug resistant organisms:** *S. pneumoniae, H. Influenzae, MSSA, sensitive E. coli and K. pneumoniae* **Risk of multidrug resistant organisms:** nosocomial organisms such as *P. aeruginosa*, ESBL-producing *E. coli* and *K. pneumoniae, Enterobacter* spp., *Serratia* spp., and MRSA in addition to the above	◆ Ceftriaxone (applicable to some northern European countries only) ◆ Piperacillin/tazobactam ± vancomycin ± amikacin ◆ Cefepime ± vancomycin ± amikacin ◆ Meropenem ± vancomycin ± amikacin
Community-acquired urinary tract infection	Mostly *E. coli*	◆ Ampicillin + gentamicin ◆ Ceftriaxone ◆ Ertapenem
Complicated urinary tract infection	*E. coli* including ESBL producer *P. aeruginosa*	◆ Piperacillin/tazobactam ±gentamicin ◆ Ertapenem ◆ Meropenem
Catheter-associated blood stream infection	*S. epidermidis* *S. aureus*, including MRSA *Enterococcus* spp. Nosocomial GNB including: *P. aeruginosa, Candida* spp.	Vancomycin + piperacillin/tazobactam ± fluconazole or echinocandin
Community-acquired intra-abdominal infection	Anaerobes, such as *Bacteroides* spp. GNB such as *E. coli*	◆ Ceftriaxone + metronidazole ◆ Ertapenem
Hospital-acquired intra-abdominal infection	Nosocomial organisms such as *P. aeruginosa*, ESBL-producing *E. coli* and *K. pneumoniae, Enterobacter* spp., *Serratia* spp., MRSA, *Enterococcus* spp., including VRE and *Candida* spp. in addition to the above	◆ Cefepime + metronidazole ± vancomycin ± fluconazole or echinocandin ◆ Piperacillin/tazobactam ± vancomycin ± fluconazole or echinocandin ◆ Meropenem ± vancomycin ± fluconazole or echinocandin
Complicated skin and soft tissue infection	**Community-acquired:** *S. pyogenes, S. aureus* (CA-MRSA where endemic), *Clostridium perfringens* **History of exposure to seawater/freshwater:** *Aeromonas hydrophila, Vibrio vulnificus* **Diabetic foot infection:** nosocomial organisms including MRSA and *P. aeruginosa*	◆ Penicillin G + clindamycin ◆ Meropenem + ciprofloxacin ◆ Piperacillin/tazobactam ± linezolid ◆ Meropenem ± linezolid
Community-acquired meningitis	*S. pneumoniae, Neisseria meningitidis* **If immunocompromised or age > 50:** *Listeria monocytogenes*	◆ High dose ceftriaxone + high dose vancomycin + aciclovir (until HSV negative) ◆ Add high dose ampicillin
Post-neurosurgical meningitis	*S. aureus* including MRSA, *S. epidermidis*, nosocomial GNB, including *P. aeruginosa*	◆ High dose vancomycin + high dose meropenem ◆ High dose vancomycin + high dose cefepime
Neutropenic fever	Nosocomial GNB including *P. aeruginosa, S. aureus*, including MRSA	◆ Cefepime + vancomycin ◆ Piperacillin/tazobactam + vancomycin ◆ Meropenem + vancomycin
Community-acquired undifferentiated sepsis	*S. pneumoniae, N. meningitidis*, sensitive GNB such as *E. coli*	**If meningitis is possible:** high dose ceftriaxone + high dose vancomycin + aciclovir ± gentamicin **If meningitis is unlikely:** piperacillin/tazobactam
Hospital-acquired undifferentiated sepsis	Nosocomial GNB, including *P. aeruginosa, S. aureus*, including MRSA, *Candida* spp. if risk factors present	◆ Piperacillin/tazobactam + vancomycin ± amikacin ± fluconazole or echinocandin ◆ Cefepime + vancomycin ± amikacin ± fluconazole or echinocandin ◆ Meropenem + vancomycin ± amikacin ± fluconazole or echinocandin

location (e.g. country, city, specific ICU). The following three methods can be used to increase the chance of adequate therapy.

Use of data from surveillance studies

Antibiotic resistance surveillance programs assist clinicians to ensure a substantial probability of effectiveness of empiric therapy [4]. For example, a Spanish nationwide surveillance of Enterobacteriaceae causing community-acquired urinary tract infection showed 56.7%, 30.3%, and 22.9% of *E. coli* isolates were non-susceptible to ampicillin, sulfamethoxazole-trimethoprim and ciprofloxacin, respectively [5]. Therefore, those agents would be a poor empiric choice for patients with suspected urosepsis in that country. National and international trends in antibiotic resistance, derived from sequential examination of surveillance data can also alert clinicians to a need to re-examine their empiric antibiotic choices. For example, the emergence of substantial degrees of fluoroquinolone resistance in *P. aeruginosa* described in national surveillance studies in the United States [6] necessitated discontinuation of use of fluoroquinolones as sole agents to cover Gram-negative bacilli (GNB) in empiric therapy for most of ICU-acquired infections.

Use of 'unit-based antibiograms' and 'combination antibiograms'

Unit-based antibiograms are cumulative antibiotic susceptibility reports from patients in a particular ward of the hospital (e.g. a specific ICU) in a specified time period. They are potentially more useful than international, national, or hospital-specific antibiograms for a prescriber making decisions about antibiotic therapy in a specific ICU. Unit-based antibiograms have been shown to have substantially different antibiotic susceptibility results compared to hospital-wide antibiograms [7,8].

Traditional antibiograms provide susceptibility data for organisms to a range of antibiotics, but do not answer the question of what antibiotic combinations may be optimal for providing coverage for any given organism. Combination antibiotic therapy is necessary as initial empiric antibiotic therapy for infections where *P. aeruginosa* is prominent, for example, because in most ICUs <90% *P. aeruginosa* strains are susceptible to any particular antipseudomonal beta-lactam [9]. Thus, for example, a traditional antibiogram does not give data as to what aminoglycoside or fluoroquinolone should be used in combination with a core antipseudomonal beta-lactam to ensure that initial empiric cover is optimized. A combination antibiogram provides information on the percentage of isolates susceptible to a particular antibiotic if the isolate is resistant to a core antipseudomonal antibiotic. For example, Bhat et al. [10] showed that, of the *P. aeruginosa* isolates resistant to cefepime in their institution, 19.5% were resistant to amikacin, 82.9% to ciprofloxacin, 43.9% to gentamicin, 87.8% to levofloxacin, and 39.0% to tobramycin. Therefore, in this case, combinations of cefepime plus amikacin would be much more likely to improve adequacy of initial empiric therapy than a combination of cefepime plus a fluoroquinolone. Unit-based, combination antibiograms can be constructed to complement individualized antibiotic choices.

Review of prior antibiotic use and previously isolated organisms with resistance profiles

Attention needs to be given to prior antibiotic use and previously isolated organisms with their resistance profiles because such knowledge could be useful to improve the adequacy of initial empiric therapy. For example, in one study [10], 37% of patients who received piperacillin/tazobactam in the month prior to the current infection were newly infected with a piperacillin/tazobactam-resistant strain and 64% of patients who had isolation of piperacillin/tazobactam-resistant GNB in the month prior to the current infection were now infected with piperacillin/tazobactam-resistant *P. aeruginosa*. Therefore, piperacillin/tazobactam was only considered appropriate initial empiric therapy if the patient had neither received the antibiotic nor had isolation of a piperacillin/tazobactam-resistant organism in the past month. Comparable findings were made with respect to cefepime. The policy to avoid antibiotics which were used in the last one month and antibiotics which have not demonstrated *in vitro* activity against bacteria from the patient in the last month may be useful not only to increase the chance of appropriate empiric treatment, but also to maintain antibiotic heterogeneity in the ICU.

Adjusting antibiotic therapy with the aid of microbiology results

Antibiotic rationalization should be considered at the following three stages: when formal identification is not completed, but the provisional identification is available, when the identification of organism is complete, but susceptibilities are awaited (which is now frequent with the advent of matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry identification systems in many clinical laboratories), and when both identification and susceptibilities are complete. Even in empiric therapy with the best prediction strategy, antibiotic rationalization is often required in order to provide more reliable treatment than the initial therapy, to reduce the risk of antibiotic collateral damage, and to secure treatment for organisms which were initially not considered for the treatment, but revealed to have been the potential causative organism.

Optimizing choice for therapy when the organism is known, but susceptibilities are awaited

The new MALDI-TOF technology provides far more rapid organism identification than semi-automated technology used in laboratories over the last two decades. Close liaison with clinical microbiologists may allow clinical use of identification data to amend the initial regimen, even when susceptibility results are not available. For example, anti-pseudomonal therapy must be ensured if *P. aeruginosa* is identified. An important role of the microbiology laboratory is in alerting prescribers to the possibility of an organism not routinely covered by standard anti-pseudomonal therapy. For example, the identification of *Stenotrophomonas maltophilia* from respiratory specimens should allow treatment for this organism with co-trimoxazole, if there is a high clinical likelihood of VAP.

While MALDI-TOF systems in their current state do not provide rapid susceptibility results, they can be used to identify epidemic clones of multiply resistant organisms.

Earlier appropriate antibiotic therapy may be initiated for multi-resistant epidemic organisms, such as vancomycin-resistant enterococci (VRE), carbapenem-resistant *A. baumannii* or KPC- or extended-spectrum beta-lactamase (ESBL)-producing *K. pneumoniae* or *E. coli*, if the characteristic phenotype of these organisms is observed on incubation of specimens on solid media [11].

Direct susceptibility tests, although clearly not standardized, may also provide similar benefit. Bouza et al. demonstrated in

Table 286.2 Suggested antibiotics for definitive therapy

Causative organism	Antibiotics for definitive therapy	Alternative choice
Gram-positive cocci		
Enterococcus spp.	Ampicillin	Vancomycin (if ampicillin-resistant)
Staphylococcus aureus (MSSA)	Flucloxacillin, nafcillin, oxacillin	Cefazolin
Staphylococcus epidermidis	Vancomycin	
Streptococcus pneumoniae (penicillin sensitive)	Penicillin	Ampicillin, ceftriaxone
Group A, B, C, F, G streptococci	Penicillin	Ampicillin, ceftriaxone
Viridans streptococci	Penicillin	Ampicillin, ceftriaxone, vancomycin
Gram-positive bacilli		
Bacillus anthracis	Penicillin	Ampicillin, ciprofloxacin
Corynebacterium jeikeium	Vancomycin	Linezolid
Listeria monocytogenes	Ampicillin	
Nocardia spp.	Co-trimoxazole	
Gram-negative cocci		
Neisseria meningitidis	Penicillin G	Ampicillin, ceftriaxone
Gram-negative bacilli		
Aeromonas hydrophila	Ciprofloxacin	Co-trimoxazole
Achromobacter xylosoxidans	Meropenem	Co-trimoxazole
Acinetobacter baumannii	Colistin	Meropenem if susceptible
Burkholderia cepacia	Co-trimoxazole	
Campylobacter jejuni	Ciprofloxacin	
Citrobacter spp.	Cefepime	Ciprofloxacin, meropenem
Escherichia coli	Ceftriaxone	Meropenem (if ESBL producer)
Enterobacter spp.	Cefepime	Ciprofloxacin, meropenem
Haemophilus influenzae	Ampicillin	Ceftriaxone (if ampicillin-resistant)
Klebsiella spp.	Ceftriaxone	Meropenem (if ESBL producer); colistin (if carbapenem resistant)
Legionella pneumophila	Azithromycin	Ciprofloxacin
Proteus mirabilis	Ceftriaxone	Ciprofloxacin
Proteus vulgaris	Ceftriaxone	Ciprofloxacin
Pseudomonas aeruginosa	Piperacillin/tazobactam, ceftazidime, cefepime, meropenem, ciprofloxacin	Colistin
Salmonella spp.	Ceftriaxone	Ciprofloxacin
Serratia marcescens	Cefepime	Ciprofloxacin, meropenem
Shigella spp.	Ciprofloxacin	Co-trimoxazole, azithromycin
Stenotrophomonas maltophilia	Co-trimoxazole	Ciprofloxacin
Vibrio cholera	Ciprofloxacin	Co-trimoxazole
Vibrio vulnificus	Doxycycline + ·ceftazidime	
Clostridium difficile	Oral or intravenous metronidazole	Oral vancomycin
Non-difficile *Clostridium* spp.	Penicillin	Clindamycin
Mycoplasma		
Mycoplasma pneumoniae	Azithromycin	Levofloxacin, doxycycline

(*continued*)

Table 286.2 Continued

***Candida* spp.**		
Candida albicans	Fluconazole	Echinocandin
Candida tropicalis	Fluconazole	Echinocandin
Candida parapsilosis	Fluconazole	Echinocandin
Candida glabrata	Echinocandin	
Candida krusei	Echinocandin	
Candida lusitaniae	Echinocandin	

randomized controlled trials (RCT) with VAP patients that the rapid reporting of susceptibility testing of respiratory specimens led to decreased antibiotic consumption, decreased rates of *C. difficile* infection, and fewer days of receiving mechanical ventilation than the standard procedure group [12].

Despite not being final susceptibilities, early amendment of the initial empiric antibiotics with the these interventions may provide some clinical benefit.

'Fine-tuning' therapy when identification and susceptibilities are complete

When identification and susceptibility testing results are available for the clinician, antibiotic regimens can be 'fine-tuned.' Although it is sometimes not feasible in the treatment of serious infections, de-escalation is a reasonable and favourable strategy if the causative organism is found to be treatable with narrower spectrum antibiotics than used empirically. This may not only minimize antibiotic collateral damage, but also provide more reliable therapy. For example, anti-staphylococcal penicillins such as flucloxacillin or nafcillin have a superior track record in the treatment of serious infections due to meticillin sensitive *S. aureus* (MSSA) than vancomycin or carbapenems, although these agents may be active against MSSA. Continuous use of broad spectrum antibiotics is more likely to lead to risks of antibiotic collateral damage such as *C. difficile* associated disease and emergence of carbapenem-resistant GNB than use of an antibiotic only active against MSSA. Antibiotics for the definitive therapy of common organisms in ICU are shown in Table 286.2.

Table 286.3 Antibiotic therapy for drug-resistant organisms

Causative organism	Antibiotics for definitive therapy	Alternative choice
Hospital-associated MRSA	Vancomycin	Linezolid for pneumonia, and skin and soft tissue infection daptomycin for blood stream infection, but not for pneumonia
Community-associated MRSA	Linezolid	Vancomycin + clindamycin
Vancomycin non-susceptible *S. aureus*	Linezolid for pneumonia and skin and soft tissue infection daptomycin for blood stream infection, but not for pneumonia	
Vancomycin -resistant *E. faecalis*	High dose ampicillin (if sensitive) linezolid	Daptomycin
Vancomycin-resistant *E. faecium*	Linezolid	Daptomycin
Penicillin-resistant *S. pneumoniae* (non-meningitis)	High dose ampicillin	High dose ceftriaxone vancomycin
Penicillin-intermediate *S. pneumoniae* (meningitis)	High dose ceftriaxone	Vancomycin
Penicillin-resistant *S. pneumoniae* (meningitis)	High dose vancomycin + high dose ceftriaxone + rifampicin	
ESBL-producing Enterobacteriaceae	Meropenem	Ciprofloxacin (if sensitive) Amikacin (if sensitive)
Carbapenem-resistant Enterobacteriaceae	High dose meropenem extended infusion + colistin + tigecycline	Amikacin (if sensitive)
Pan-beta-lactam and quinolone resistant *P. aeruginosa*	Colistin	Amikacin (if sensitive)
Carbapenem-resistant *A. baumannii*	Colistin	High dose ampicillin/sulbactam (if sensitive)

Special considerations for drug-resistant organisms

Issues of antibiotic resistance in ICU have become increasingly serious across the globe. This pertains not only to relatively resistant bacteria in nature such as *P. aeruginosa* and *A. baumannii*, but also those which used to be susceptible to a wide variety of antibiotics, such as *S. aureus, E. coli*, and *K. pneumonia.* MRSA and multiply resistant *K. pneumoniae* and *E. coli* have already become common issues in many ICUs. At an extreme end of the spectrum are ICUs in some parts of the world where 90% of *A. baumannii* isolates, > 50% of *P. aeruginosa* isolates and >75% of *K. pneumoniae* isolates are resistant to carbapenems. Treatment for resistant organisms may require specialist input from Infectious Diseases Physicians or Clinical Microbiologists. Table 286.3 summarizes antibiotic choice for representative resistant organisms in ICU.

Working in an institutional framework: antimicrobial stewardship programs

Antimicrobial stewardship programs have become an integral component of most large hospitals. As stated in the Infectious Diseases Society of America and Society of Health Care Epidemiologists of America guidelines on antimicrobial stewardship programs, the primary goal of such programs is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use such as toxicity, the selection of pathogenic organisms (for example, *Clostridium difficile*) and the emergence of resistance. This goal should be compatible with care of patients with suspected infections in the ICU.

However, the execution of antimicrobial stewardship programs in the ICU environment may be quite different from that of a ward environment. 'Front-end' approvals, whereby a prescriber seeks approval from a physician or pharmacist from the Antimicrobial Stewardship Program, are rarely employed in ICUs. The major reason for this is the need for no delays in administration of antibiotics to septic patients. However, there is a role for discussion of choice of antibiotic with an Infectious Diseases Physician or Clinical Microbiologist, particularly when the patient is likely to be infected with a multidrug resistant pathogen. Other major contributions of antimicrobial stewardship programs in the ICU are: (1) to help create antibiotic guidelines for empiric choice of antibiotics, and (2) to help limit duration of antibiotic choices.

Conclusion

In summary, clinicians should apply logic in their selection and use of antimicrobials in the severely ill patient, rather than to use a 'tradition-based' method of selecting treatment. Tradition is hard to break, but results in patients receiving inappropriate antibiotics as well as contributing to the development of resistance in bacteria through increased selection pressure. Information is available with which to make a more logical choice of antibiotic, and closer liaison with microbiologists, antimicrobial pharmacists and infectious diseases physicians will greatly facilitate the decision-making process.

References

1. Chastre J, Luyt CE, Combes A, and Trouillet JL. (2006). Use of quantitative cultures and reduced duration of antibiotic regimens for patients with ventilator-associated pneumonia to decrease resistance in the intensive care unit. *Clinical Infectious Disease*, **43**(2), S75–81.
2. Muto CA, Pokrywka M, Shutt K, et al. (2005). A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infection Control in Hospital Epidemiology*, **26**(3), 273–80.
3. Donskey CJ. (2006). Antibiotic regimens and intestinal colonization with antibiotic-resistant Gram-negative bacilli. *Clinical Infectious Diseases*, **43**(2), S62–9.
4. Masterton RG. (2000). Surveillance studies: how can they help the management of infection? *Journal of Antimicrobial Chemotherapy*, **46**(2), 53–8.
5. Cuevas O, Cercenado E, Gimeno M, MarÃn M, Coronel P, and Bouza E. (2010). Comparative in vitro activity of cefditoren and other antimicrobials against Enterobacteriaceae causing community-acquired uncomplicated urinary tract infections in women: a Spanish nationwide multicenter study. *Diagnostic Microbiology and Infectious Disease*, **67**(3), 251–60.
6. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, and Quinn JP. (2003). Antibiotic resistance among Gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. *Journal of the American Medical Association*, **289**(7), 885–8.
7. Binkley S, Fishman NO, LaRosa LA, et al. (2006). Comparison of unit-specific and hospital-wide antibiograms: potential implications for selection of empirical antimicrobial therapy. *Infection Control in Hospital Epidemiology*, **27**(7), 682–7.
8. Lamoth F, Wenger A, Prodhom G, et al. (2010). Comparison of hospital-wide and unit-specific cumulative antibiograms in hospital- and community-acquired infection. *Infection*, **38**(4), 249–53.
9. American Thoracic Society; Infectious Diseases Society of America. (2005). Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine*, **171**(4), 388–416.
10. Bhat S, Fujitani S, Potoski BA, et al. (2007). Pseudomonas aeruginosa infections in the Intensive Care Unit: can the adequacy of empirical beta-lactam antibiotic therapy be improved? *International Journal of Antimicrobial Agents*, **30**(5), 458–62.
11. Paterson DL and Bonomo RA. (2005). Extended-spectrum beta-lactamases: a clinical update. *Clinical Microbiology Reviews*, **18**(4), 657–86.
12. Bouza E, Torres MV, Radice C, et al. (2007). Direct E-test (AB Biodisk) of respiratory samples improves antimicrobial use in ventilator-associated pneumonia. *Clinical Infectious Diseases*, **44**(3), 382–7.

CHAPTER 287

Oral, nasopharyngeal, and gut decontamination in the ICU

Evelien Oostdijk and Marc Bonten

Key points

- Selective decontamination of digestive tract (SDD) aims to eradicate micro-organisms from the intestine, the stomach, and the oropharynx by non-absorbable antibiotics, which are combined with systemic antibiotic prophylaxis during the first days of ICU admission.
- An alternative to SDD is selective oropharyngeal decontamination (SOpD) alone.
- Both SDD and SOpD pursue decontamination of the oropharynx to prevent ventilator associated pneumonia.
- Dutch studies show SDD and SOpD are associated with reduced ICU-mortality, ICU-acquired bacteraemia with Gram-negative bacteria, and systemic antibiotic use.
- It is currently unknown to what extent these effects can be achieved in settings with different bacterial ecology.

The concept

In 1971 the concept of colonization resistance was proposed by van der Waaij et al. [1], who suggested a beneficial effect of the anaerobic flora in resisting colonization by aerobic Gram-negative bacilli in the digestive tract in ICU patients. Many infections are caused by enteric bacilli, presumably from endogenous origin. Selective decontamination of the digestive tract (SDD) was developed to selectively eliminate the aerobic Gram-negative bacilli from the digestive tract, leaving the anaerobic flora unaffected. The first clinical studies with SDD were performed in granulocytopenic patients yielding favourable results [2]. In the early 1980s, Stoutenbeek and co-workers [3] adapted the principle for ICU patients. The full concept of SDD aims to eradicate micro-organisms from the intestine, the stomach, and the oropharynx by non-absorbable antibiotics, which are combined with systemic antibiotic prophylaxis during the first days of ICU admission. In the SDD regimen the combination of colistin and an aminoglycoside are generally used, both are effective against Gram-negative bacilli and *Staphylococcus aureus*, non-absorbable and do not affect the anaerobic intestinal flora. Amphotericin was added to prevent overgrowth with yeasts and systemic prophylaxis to prevent early infections. Since the introduction of this preventive strategy, more than 45 randomized studies and multiple observational studies in a variety of ICU populations have been performed [4]. However, there are large differences in the regimens of SDD that were studied, the endpoints used, and the designs applied.

Several meta-analyses of SDD studies have been published, with more or less comparable results. They generally conclude that SDD decreases the incidence of ventilator-associated pneumonia (VAP) caused by aerobic Gram-negative bacteria with relative risk reduction (RRRs) ranging from 0.40 to 0.78, although reported outcomes regarding prevention of VAP were related to the methodological quality of the individual studies [5].

As an alternative to SDD, investigators have evaluated the effects of oropharyngeal decontamination alone [6,7]. In a prospective randomized placebo-controlled double-blind study, 87 patients received topical antimicrobial prophylaxis in the oropharynx and 139 patients received placebo. The aim of the study was to prevent VAP by modulation of oropharyngeal colonization, without influencing gastric and intestinal colonization and without systemic prophylaxis. Oropharyngeal colonization present on admission was eradicated in 75% of the patients (4% among control patients) and only 10% of study patients acquired oropharyngeal colonization, as compared to 61% of control patients. There were no significant differences in gastric and intestinal colonization. This regimen resulted in a RRR for VAP of 0.62 (95% CI 0.26–0.98) [6].

Experience with SDD/SOpD in the Netherlands

Most detailed data on the effects of SDD and SOpD in ICU-patients come from two studies performed in Dutch ICUs [7,8] The ecological setting of these ICUs is characterized by low levels of antibiotic resistance: For instance, prevalence of meticillin-resistance among *Staphylococcus aureus* isolates was <1%, of vancomycin-resistance among enterococci was <1%, and of extended-spectrum betalactame production among Enterobacteriaceae was <5%.

In the first study two ICU-wards, within a single university hospital, were compared. In one unit all eligible patients (n = 466) received during a two-year period SDD and in the other unit none of the 468 admitted patients received SDD [8]. Eligibility was defined as an expected duration of intubation of at least 48 hours or an expected stay in ICU of at least 72 hours if not intubated. The second study was a multicentre cluster-randomized cross-over study in 13 ICUs in the Netherlands [7]. During study-periods of six months all eligible patients (same criteria as in [8]) in a single unit received SDD, SOpD or standard care (no SDD and no SOpD), and all three regimens were applied in random order in all participating ICUs. The SDD-regimen was identical in both studies and in both studies interventions were applied for all patients eligible. As

SDD and SOpD pursue a change in the bacterial ecology within the unit, a study design in which all patients are exposed to the same procedures in time is the best to quantify effectiveness. If patients are individually randomized decontaminated patients may offer some protection against acquired colonization and subsequent infection in those receiving standard care, and vice versa, and this will underestimate true effectiveness.

Effects on patient outcome

In both studies the 'classical' SDD regimen (tobramycine, colistine and amphotericin B) was, compared to a control population (no SDD/SOpD), and SDD and SOpD were associated with reduced mortality. In the cluster-randomized study both SOpD and SDD were associated with a lower day-28 mortality. Compared to the control population, the RRR for day-28 mortality was 11% and 13% for SDD and SOpD, corresponding to an absolute mortality reduction on day-28 of 2.9% and 3.5% for SDD and SOpD [7]. In the single-centre study the RRR for ICU- and hospital-mortality was 35% and 22%, respectively [9].

The design of both studies had, undoubtedly, many advantages as compared to a study with randomization of individual patients, but had, inevitably, also some disadvantages. In a cluster-randomized design individual patients are not randomized, which may facilitate inclusion bias. In the cluster-randomized study patients included in the control population had—at the time of ICU-admission—on average a lower APACHE-II score, were less frequently mechanically ventilated and were more frequently admitted for surgical reasons. All these determinants are associated with a better prognosis. A random-effects logistic-regression model was used to adjust for these baseline differences, which may not adjust for all confounders. In the single-centre study SDD was applied in one ICU-ward only and the availability of beds determined in which ICU a new patient was admitted. Although baseline characteristics were comparable for both groups, residual confounding cannot be ruled out. Nevertheless, both studies provide convincing evidence that SDD and SOpD reduce ICU-mortality under the circumstances tested.

Effects on ventilator-associated pneumonia

Both SDD and SOpD pursue decontamination of the oropharynx to prevent VAP. In many studies the incidence of VAP, therefore, was the primary study endpoint, though this comes with major methodological problems. The most widely used combination of clinical, radiographic, and microbiological criteria are partly subjective and have suboptimal specificity, as other conditions, such as acute respiratory distress syndrome (ARDS), may have a similar clinical presentation. Bronchoalveolar lavage with quantitative microbiological cultures of obtained samples has a higher specificity, but this invasive approach is used infrequently for routine diagnostic purposes. The use of subjective criteria for endpoint determination in the absence of blinding may introduce considerable bias. Only few studies quantified the effects of decontamination on VAP incidence using both a double-blind placebo-controlled design and invasive diagnostics with quantitative culturing in all patients with a clinical suspicion of VAP. In one such study, in the Netherlands, the RRR of VAP was 55% when applying SOpD ($p < 0.05$) [6]. There are several meta-analyses in which SDD and SOpD are associated with statistically significant reductions in the incidence of VAP, but the before-mentioned methodological drawbacks apply to almost all individual studies included in these analyses.

Effects on ICU-acquired bacteraemia, antibiotic use and costs

In the Dutch multicentre study the RRR of ICU-acquired bacteraemia caused by enteric Gram-negative bacteria was, compared to standard care, 81% and 30% for SDD and SOpD, respectively [7]. The incidence difference between SDD and SOpD also reached statistical significance, and results from a post-hoc analysis suggest that this difference in effectiveness resulted from successful intestinal decontamination, that is pursued during SDD, but not during SOpD.

In the Dutch multicentre study SDD and SOpD were associated with a 10% reduction in systemic antibiotic use, which included the routine use of cefotaxim during the first four days as part of SDD. As part of SDD it is recommended not to prescribe antibiotics with anti-anaerobic activity, which resulted in a decline in the intravenous use of clindamycin, piperacillin-tazobactam, and carbapenem antibiotics and in a relative increase of 85% in the use of cephalosporins [7].

The results of this multicentre study were used to determine the cost-effectiveness of SDD and SOpD, in which costs for microbiology, antibiotics, and length of stay were compared to the benefits of life years gained, based on hospital mortality data. Both SOpD and SDD were associated with lower cost and were more effective than standard care. Even if the daily costs of the topical medication would increase tenfold (from €4 to €40 for SOpD and from €40 to €400 for SDD) SOpD would remain cost-saving. In such a scenario the costs of SDD would be €21,590 per life year gained.

Effects on antibiotic resistance

The benefits of SDD and SOpD should be carefully balanced against the potential disadvantages in the short-term, but also in the long-term. These include resistance against any of the antibiotics used and increased transmission of antibiotic-resistant bacteria in general because of the higher antibiotic pressure induced. In a systematic review and meta-analysis of 64 studies there was no evidence of a higher incidence of acquisition of resistance during SDD, as compared to control populations [4]. In the two Dutch studies SDD and SOpD were strongly associated with reduced incidences of infection and carriage with antibiotic-resistant bacteria (Table 287.1) [7,9]. As compared to SOpD, SDD offered better protection against ICU-acquired bacteraemia with antibiotic-resistant bacteria and against acquired carriage of the respiratory tract with Gram-negative bacteria intrinsically resistant to colistin and with acquired resistance for third-generation cephalosporins. The latter is quite remarkable, as the use of these antibiotics had increased with 85% during SDD.

The ecological effects of SDD and SOpD were determined through monthly one-day point prevalence surveillance of all patients present in any of the 16 participating ICUs [8]. The implementation of SDD/SOpD was immediately followed by a decline in the prevalence of antibiotic-resistant Gram-negative bacteria in the respiratory tract, but during the months that the interventions were used the prevalence of ceftazidim resistance increased (β 0.09 ($p < 0.05$). After discontinuation of SDD/SOpD the prevalence returned to pre-intervention levels. Similar observations were made for intestinal carriage: a rapid decline in prevalence after implementation of SDD, and a rapid return to pre-intervention prevalence levels after discontinuation. Only for ceftazidim resistance prevalence levels

Table 287.1 Overview of various endpoints obtained from Dutch randomized studies comparing SDD and/or SOpD to control

Endpoint		SDD versus control	SOpD versus control	SDD versus SOpD
Mortality	Day 28	RRR 13% [7]* ($p < 0.05$)	RRR 11% [7]* ($p < 0.05$)	
	Intensive Care mortality	RRR 15% [7]* ($p < 0.05$) RRR 35% (95% CI 15%–51%) [9]	RRR 10% [7]* ($p < 0.05$) RRR 33% (95% CI –5%–57%) [6]	
	Hospital mortality	RRR 9% [7]* ($p < 0.05$) RRR 22% (95% CI 4%–37%) [9]	RRR 11% [7]* ($p < 0.05$) RRR 22% (NS) [6]	
	One year survival	RRR 4% (NS) [4]	RRR 7% (NS) [4] RRR –1% (NS) [6]	
Infections	ICU-acquired bacteraemia	RRR 56% (95% CI 0.43–64%) [7]	RRR 32% (95% CI 14–47%) [7]	RRR 35% (95% CI 15–51%) [7]
	Enterobacteriaceae	RRR 81% (95% CI 68–88%) [7]	RRR 30% (95% CI 2–50%) [7]	RRR 72% (95% CI 53–84%) [7]
	GNF-GNR	RRR 57% (95% CI 33–74%) [7]	RRR 51% (95% CI 13–73%) [7]	RRR 12% (NS) [7]
	Candida species	RRR 51% (NS) [7]	RRR 9% (NS) [7]	RRR 47% (NS) [7]
	Enterococci	RRR 15% (NS) [7]	RRR 7% (NS) [7]	RRR 9% (NS) [7]
	VAP		RRR 55% (95% CI 3–79%) [6]	
Resistance	ICU-acquired bacteraemia with HRMO	RRR 59% (95% CI 6–82%) [17]	RRR –10% (95% CI–105–41%) [17]	RRR 62% (95% CI 15–83%) [17]
	Acquired respiratory tract colonization HRMO	RRR 42% (95% CI 22–57%) [17]	RRR 35% (95% CI 13–51%) [17]	RRR 11% (NS) [17]
	Tobramycin resistant GNB	RRR –21% (NS) [17]	RRR –8% (NS) [17]	RRR –11 (NS) [17]
	Cefotaxim resistant Enterobacteriaceae	RRR 74% (95% CI 39–88%) [17]	RRR 1% (NS) [17]	RRR 63% (95% CI 38–88%) [17]
	Intrinsically colistin resistant GNB	RRR 59% (95% CI 43–71%) [17]	RRR 16% (NS) [17]	RRR 51% (95% CI 31–65%) [17]
	Non-intrinsically colistin resistant GNB	RRR 31% (NS)	RRR –6% (NS)	RRR 35% (NS)
	Acquired colonization with *P. aeruginosa*^			
	Ceftazidime resistant	RRR 83% (95% CI 23–96%) [9]		
	Ciprofloxacin resistant	RRR 92% (95% CI 39–99%) [9]		
	Imipenem resistant	RRR 94% (95% CI 51–99%) [9]		
	Tobramycin resistant	RRR -5% (NS) [9]		
	Acquired colonization with other GNB^			
	Ceftazidime resistant	RRR 19% (NS) [9]		
	Ciprofloxacin resistant	RRR 70% (95% CI 37–85%) [9]		
	Imipenem resistant	RRR 90% (95% CI 19–99%) [9]		
	Tobramycin resistant	RRR 56% (95% CI 26–73%) [9]		
	Polymyxin	RRR –57% (NS) [9]		

*Corrected for present baseline differences using a random-effects logistic regression model.

^Acquired colonization in sputum, throat, rectum, axilla, and wounds.

SDD, selective digestive tract decontamination; SOpD, selective oropharyngeal decontamination; RRR, relative risk reduction; 95% CI, 95% confidence interval; ICU, intensive care; VAP, ventilator-associated pneumonia; HRMO, highly resistant micro-organism; GNB, Gram-negative bacteria.

PC, personal communication; Effects of Decontamination of the Digestive and Oropharynx in ICU Patients on one-year survival, Oostdijk E.A.N. De S with A.M.G.A., Bonten M.J.M., On behalf of the Dutch SOD-SDD trialists group, accepted for publication.

Data from: Oostdijk EA et al., 'Effects of Decontamination of the Digestive and Oropharynx in ICU Patients on one-year survival', *Journal of the American Medical Association*, 2014, **312**(14), pp. 1429–37; and various sources, see references.

remained elevated after SDD, as compared with pre-intervention. Stable and low prevalence levels of resistance during SDD were observed in longitudinal studies from Germany and Spain [10,11]. However, there are also reports of higher prevalence of carriage with Gram-positive bacteria during SDD, including MRSA, and of outbreaks with ESBL-producing Gram-negative bacteria.

Colistin is an old antibiotic, increasingly used worldwide as a last resort agent to treat infections with multiple antibiotic-resistant Gram-negative bacteria. Little is known about the mechanisms of resistance to colistin, but long-term intravenous treatment is considered an important risk factor. In Dutch ICUs daily use of topical colistin, as in SDD and SOpD, was not associated with acquired

carriage of colistin-resistant Enterobacteriaceae in the respiratory tract [12]. Observed rates of acquired carriage were 1.1, 0.7 and 0.8 per 1000 patient days at risk during SOpD, SDD and control, respectively. For rectal carriage (only measured during SDD) comparable rates were observed, but the risk increased (to 15.5 per 1000 patient days at risk) in patients colonized with tobramycin-resistant Enterobacteriaceae.

Eradication or suppression of carriage reduces colonization pressure, and as such SDD has been applied successfully as a control measure (together with other interventions) during outbreaks, for instance in France and the UK [13,14]. In the Dutch setting, eradication of intestinal carriage with Enterobacteriaceae during SDD was equally successful for strains that were susceptible or resistant to third-generation cephalosporins. Eradication, was less effective, if these bacteria were also resistant to tobramycin [15]. In Israel SDD (with gentamycin and polymyxin E) was tested in a double-blind placebo-controlled trial for its effectiveness in eradicating carriage with carbapenem-resistant Gram-negatives [16]. Among those that received SDD 61% had a negative rectal culture after 2 weeks, as compared to 16% in the placebo group (OR 0.13 (0.02-0.74)). All throat cultures were negative after one week in SDD patients, as compared to 14.2% in the placebo group. Nevertheless, after discontinuation of SDD, carriage rates rapidly increased again.

Adverse events

The oral paste used in SDD and SOpD may cause oesophageal obstruction if not dispelled carefully before application of the next dosage. Furthermore, sustained use of SDD may lead to some absorption of tobramycin from the intestinal tract. For instance, 83 of 100 patients had detectable tobramycin levels in blood (>0.050mg/L) [17], and 12 out of 19 patients that received both continuous venovenous haemofiltration and SDD had detectable tobramycin levels, in one patient being toxic (>3.0mg/L) [18].

The recent large studies performed in Dutch ICUs have provided strong evidence that, in that particular ecological setting, SDD and SOpD reduce ICU-mortality, ICU-acquired bacteraemia with Gram-negative bacteria, and systemic antibiotic use in a cost-effective manner. During a period of ten years there was no evidence that SDD or SOpD were associated with increased resistance in these ICUs. If any, both measures were associated with reductions in systemic antibiotic resistance. These counterintuitive observations might result from the overall lower usage of systemic antibiotics or from the fact that the topical antibiotics are still active against many resistant bacteria. Yet, all studies have used conventional culture techniques that may suffer from antibiotic carryover effects, and it is currently unknown to what the non-culturable flora is affected by SDD and SOpD. In Dutch ICUs SDD and SOpD appear equally effective on relevant clinical outcomes, such as survival and length of stay. SDD seems more protective against ICU-acquired bacteraemia and respiratory tract carriage with resistant Gram-negative bacteria, and SOpD seems to have a more attractive cost-effectiveness profile.

It is currently unknown to what extent these effects can be achieved in settings with different bacterial ecology. Although successful application has been reported from several, solitary, ICUs across Europe, more studies are needed. The potential threat of enhanced selection of pre-existing multiresistant pathogens is becoming more important, with the current emergence of carbapenem-resistant pathogens. Nevertheless, if similar effects would be achieved as in Dutch ICUs, these interventions could save 7,000 deaths per year in British ICUs, only. The use of SDD (or SOpD) as a measure to control outbreaks with multidrug resistant bacteria, that could not be controlled with classical infection control measures, should strongly be discouraged, until more data on its ecological safety and effectiveness have been obtained.

References

1. van der Waaij D, Berghuis-de Vries JM, and Lekkerkerk L-v. (1971). Colonization resistance of the digestive tract in conventional and antibiotic-treated mice. *Journal of Hygiene*, **69**(3), 405–11.
2. Sleijfer DT, Mulder NH, de Vries-Hospers HG, et al. (1980). Infection prevention in granulocytopenic patients by selective decontamination of the digestive tract. *European Journal of Cancer*, **16**(6), 859–69.
3. Stoutenbeek CP, van Saene HK, Miranda DR, and Zandstra DF. (1984). The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. *Intensive Care Medicine*, **10**(4), 185–92.
4. Daneman N, Sarwar S, Fowler RA, and Cuthbertson BH. (2013). Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. *Lancet: Infectious Diseases*, **13**(4), 328–41.
5. van Nieuwenhoven CA, Buskens E, van Tiel FH, and Bonten MJ. (2001). Relationship between methodological trial quality and the effects of selective digestive decontamination on pneumonia and mortality in critically ill patients. *Journal of the American Medical Association*, **286**(3), 335–40.
6. Bergmans DC, Bonten MJ, Gaillard CA, et al. (2001). Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study. *American Journal of Respiratory and Critical Care Medicine*, **164**(3), 382–8.
7. de Smet AM, Kluytmans JA, Cooper BS, et al. (2009). Decontamination of the digestive tract and oropharynx in ICU patients. *New England Journal of Medicine*, **360**(1), 20–31.
8. Oostdijk EA, de Smet AM, Blok HE, et al. (2010). Ecological effects of selective decontamination on resistant Gram-negative bacterial colonization. *American Journal of Respiratory and Critical Care Medicine*, **181**(5), 452–7.
9. de Jonge E, Schultz MJ, Spanjaard L, et al. (2003). Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet*, **362**(9389), 1011–16.
10. Ochoa-Ardila ME, Garcia-Canas A, Gomez-Mediavilla K, et al. (2011). Long-term use of selective decontamination of the digestive tract does not increase antibiotic resistance: a 5-year prospective cohort study. *Intensive Care Medicine*, **37**(9), 1458–65.
11. Krueger WA, Lenhart FP, Neeser G, et al. (2002). Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically ill surgical patients: a prospective, stratified, randomized, double-blind, placebo-controlled clinical trial. *American Journal of Respiratory and Critical Care Medicine*, **166**(8), 1029–37.
12. Oostdijk EA, Smits L, de Smet AM, Leverstein-van Hall MA, Kesecioglu J, and Bonten MJ. (2013). Colistin resistance in Gram-negative bacteria during prophylactic topical colistin use in intensive care units. *Intensive Care Medicine*, **39**(4), 653–60.
13. Brun-Buisson C, Legrand P, Rauss A, et al. (1989). Intestinal decontamination for control of nosocomial multiresistant Gram-negative bacilli. Study of an outbreak in an intensive care unit. *Annals of Internal Medicine*, **110**(11), 873–81.

14. Taylor ME and Oppenheim BA. (1991). Selective decontamination of the gastrointestinal tract as an infection control measure. *Journal of Hospital Infection*, **17**(4), 271–8.
15. Oostdijk EA, de Smet AM, Kesecioglu J, and Bonten MJ. (2012). Decontamination of cephalosporin-resistant Enterobacteriaceae during selective digestive tract decontamination in intensive care units. *Journal of Antimicrobiology and Chemotherapy*, **67**(9), 2250–3.
16. Saidel-Odes L, Polachek H, Peled N, et al. (2012). A randomized, double-blind, placebo-controlled trial of selective digestive decontamination using oral gentamicin and oral polymyxin E for eradication of carbapenem-resistant *Klebsiella pneumoniae* carriage. *Infection Control and Hospital Epidemiology*, **33**(1), 14–19.
17. Oudemans-van Straaten HM, Endeman H, Bosman RJ, et al. (2011). Presence of tobramycin in blood and urine during selective decontamination of the digestive tract in critically ill patients, a prospective cohort study. *Critical Care*, **15**(5), R240.
18. Mol M, van Kan HJ, Schultz MJ, and de Jonge E. (2008). Systemic tobramycin concentrations during selective decontamination of the digestive tract in intensive care unit patients on continuous venovenous hemofiltration. *Intensive Care Medicine*, **34**(5), 903–6.

CHAPTER 288

Diagnosis, prevention, and treatment of device-related infection in the ICU

Walter Zingg and Stephan Harbarth

Key points

- Many patients in the intensive care unit (ICU) suffer from one or several device-related health care-associated infections (HAI).
- Intrinsic factors such as age, immunosuppression, neutropenia, or multi-organ failure are preconditions for HAI, but the main risk comes from breaches in aseptic technique of using medical devices.
- Emerging resistance due to the use of broad-spectrum antibiotics and poor infection control is a major challenge in the treatment of device-related HAI.
- Device-related HAI are preventable, but implementation of best practice in infection control is not easy.
- Successful prevention programmes offer a comprehensive protocol; follow a multidisciplinary approach in preparation, and a multimodal training and education programme in implementation.

Introduction

Many patients in the intensive care unit (ICU) suffer from one or several device-related health care associated infections (HAI) during their stay, including central line-associated bloodstream infections (CLABSI), ventilator-associated pneumonia (VAP), and catheter-associated urinary tract infection (CAUTI). Such infections are related to the use of medical devices, such as central lines, intratracheal tubes, and urinary catheters. Utilization ratios expressed as device-days per hospital-days can be up to 70, 50, and 80% for central lines, ventilators, and urinary catheters, respectively. Although factors on the patient side, such as immunosuppression, neutropenia, age, or multi-organ failure are important preconditions, device-related factors such as dwell-time or breaches in aseptic technique are the predominant risk factors for HAIs in the ICU. Shortcomings in structure and organization, such as low nurse-to-patient ratio, high bed-occupancy, or high ratios of float and pool nurses interfere with the use of medical devices and, thus, are equally important [1–3].

Catheter-associated bloodstream infections

Epidemiology

Almost half of all positive blood cultures obtained in a hospital are due to nosocomial BSI. Of these, most are primary and associated with central catheters. CLABSI represent 10–15% of all HAIs in intensive care [4] and the incidence density is two to seven episodes per 1000 catheter-days, depending on ward type, institution, and geographical region. CLABSIs are associated with increased length of stay (7–20 days), additional costs (US$ 3,000–40,000), and an attributable mortality of 2–12% [5].

Microbiology

In most institutions, a shift in predominant organisms from Gram-negative bacilli to Gram-positive cocci has been observed over the past two decades. However, in countries with limited resources, Gram-negative pathogens and, among these, non-fermentative organisms such as *Pseudomonas* species and *Acinetobacter* species are predominant. The shift towards Gram-positive cocci observed in high-resource countries is largely due to the use of intravascular devices and the fact that the proportion of patients with risk factors, such as neutropenia, solid organ and bone marrow transplantation, or the use of immunosuppressive agents has increased. Coagulase-negative Staphylococci (CoNS) are the most common pathogens isolated from blood cultures. Often considered as contaminants, their detection may not always be harmless and an associated mortality up to 18% has been reported. However, mortality from CoNS is usually much lower, while mortality from *Staphylococcus aureus* can be as high as 25%. Detection of *S. aureus* on a catheter tip is a predictor for subsequent bacteraemia, even in the absence of clinical signs and negative blood cultures at the time of catheter removal. The proportion of *Candida* species has considerably increased in many institutions, mainly due to prolonged treatments with multiple and broad-spectrum antibiotics and the use of total parenteral nutrition. CLABSI due to *Candida* species has a poor prognosis with an attributable mortality between 15 and 55%, especially when antifungal treatment is delayed by 3 or more days. An important shift in the epidemiology has occurred over the past decades with decreasing infections due to *C. albicans,* but increasing

infections due to non-albicans isolates, particularly *C. glabrata*. The latter represents an important problem as this species is often resistant to azoles.

Diagnosis

CLABSI is diagnosed by combining clinical signs, such as fever or systemic inflammatory response syndrome (SIRS), with microbiological cultures. If the central line is the most probable source of infection, it should be removed and the tip cultured. Detection of identical species with the same susceptibility testing confirms the catheter as a source. Alternatively, blood can be obtained from the catheter and from a peripheral vein. If the growth time of the blood sampling from the catheter is shorter than the growth time of the blood sampling from the peripheral vein by two hours or more, the central line is the most likely source for the bloodstream infection [6]. This test is called differential time to positivity and has the advantage that the catheter can be left in place.

Treatment

The management of suspected CLABSI in the ICU combines early antimicrobial treatment and the active search for sources other than the catheter. The choice of antibiotics must include at least a substance active against Gram-positive and non-fermentative micro-organisms, taking into account the local susceptibility pattern of bacteria and whether the patient was transferred from a country with a high prevalence of resistance. Immunocompromised or neutropenic patients should receive also an antifungal agent active against *Candida* species. Immediate effective treatment is important as either delayed or inappropriate antibiotic treatment is associated with increased morbidity and mortality. A multidisciplinary approach with close collaboration between the physician in charge of the patient, the infectious disease specialist, and the microbiology laboratory, improves the accuracy of the empiric therapy. Once susceptibility testing from micro-organisms identified from blood cultures is available, antibiotic treatment should be adjusted accordingly. Procalcitonin-based de-escalation of antibiotic therapy can be helpful to reduce antibiotic use. If CLABSI is confirmed, the central line should be removed and a new catheter inserted at a different site. Guide-wire exchange is a risk for recurrent BSI and should be avoided. Recent data suggest that an antibiotic lock in addition to a systemic antibiotic therapy can be used as a salvage strategy in long-term catheters if signs of exit site or tunnel infection are absent and blood cultures reveal the presence of CoNS or enterococci. Removal is mandatory in severe or complicated infections, in the presence of shock, recurrent BSI, and when *S. aureus*, Gram-negative bacilli, or *Candida* species are isolated. Relapse, continuous fever, or bacteraemia despite catheter removal requires active search for complications, such as endocarditis, metastatic abscess, or septic thrombophlebitis.

Prevention

CLABSI prevention programmes must focus on best practice with evidence-based guidelines on catheter insertion and catheter care. The strategy should be multidisciplinary and multimodal to encourage adoption and implementation [7-9]. Further, reduction can be achieved by using chlorhexidine-impregnated dressings, catheters coated with chlorhexidine/silver sulfadiazine or antibiotics, or by daily bathing the patients with chlorhexidine [10]. Lock-solutions with taurolidine, citrate, ethylenediaminetetraacetic acid (EDTA), or ethanol reduce catheter colonization, but still have to prove their efficacy in CLABSI reduction under routine working conditions.

Ventilator-associated pneumonia

Epidemiology

VAP is the most frequent nosocomial infection in critical care, contributing between 30 and 50% to the total number of HAIs. Published VAP rates range widely from 2.5 to 35.7 episodes per 1000 ventilator-days due to case-mix variations, inconsistent use of diagnostic tools, varying definitions, and different reporting modalities. VAP is associated with attributable costs of US$10,000–25,000, which is mainly due to an excess length of stay by 5 to 7 days. Attributable mortality is estimated at about 10–30% [11]. It is particularly high in VAP due to *S. aureus* and is associated with severe sepsis.

Microbiology

The most common pathogen is *S. aureus*, followed by *P. aeruginosa, Haemophilus influenzae, Klebsiella* species, *Streptococcus pneumoniae*, and *Escherichia coli*. Early onset VAP is due more often to *S. pneumoniae* and *H. influenzae*, while late onset VAP is due mainly to *S. aureus* (including meticillin-resistant *S. aureus* (MRSA)) and non-fermentative bacteria, such as *P. aeruginosa*.

Diagnosis

The diagnosis of VAP relies on clinical signs, such as fever, onset of purulent secretions, or worsening gas exchange in combination with radiological findings, such as infiltrates, consolidates, or cavitations. Positive blood cultures, if not related to another infection, contribute to the diagnosis. The addition of quantitative culture samples obtained by bronchoscopic techniques improves diagnostic accuracy by reducing the number of VAP diagnoses by 30% to 50%.

Treatment

Given the high risk of mortality, early and appropriate, broad-spectrum antibiotic therapy should be prescribed with adequate doses to optimize antimicrobial efficacy. An empiric therapy regimen should be installed, including agents from different antibiotic classes than the patient has recently received. VAP due to *P. aeruginosa* should be treated with a beta-lactam antibiotic in combination with an aminoglycoside. Linezolid is an alternative to vancomycin in the treatment of VAP due to MRSA. Infections due to carbapenem-resistant Gram-negative micro-organisms should be treated with a regimen including colistin. De-escalation of antibiotics should be considered once susceptibility data are available. If lower respiratory tract cultures are negative and the patient has improved clinically after 72 hours, antibiotics may be stopped at that time. A treatment duration of 8 days is recommended for patients with uncomplicated VAP who have received an appropriate therapy initially with a good clinical response and with no evidence of infection due to non-fermenting Gram-negative bacilli [12].

Prevention

Similar to CLABSI prevention, a multimodal strategy with strong emphasis on process control should be established. The

components of such a comprehensive intervention programme include:

- Hand hygiene, preferably using alcohol-based hand rub.
- Glove and gown use for endotracheal tube manipulation.
- Backrest elevation to 30–45°.
- Maintenance of tracheal cuff pressure of 20 cmH_2O.
- Use of orogastric tubes.
- Gastric overdistension avoidance.
- Good oral care with chlorhexidine.
- Elimination of non-essential tracheal suctioning.

Good compliance with such techniques has been shown to reduce VAP-rates by 50% [13]. There is evidence that subglottic secretion drainage is effective in VAP prevention.

Catheter-associated urinary tract infection

Epidemiology

The prevalence of CAUTI in the ICU is 12–20% [4] with an incidence density of 1 to 5 episodes per 1000 catheter-days [14].

Microbiology

Similar to non-ICU settings, Enterobacteriaceae (*E. coli, Klebsiella* species, *Proteus* species, *Enterobacter* species, *Citrobacter* species, *Providencia* species, *Serratia* species, *Morganella* species) are the predominant pathogens in CAUTI. However, non-fermentative micro-organisms, such as *Pseudomonas* species, *Acinetobacter baumannii*, and *Stenotrophomonas* species are also isolated. Gram-positive bacteria, such as *Enterococcus* species and *S. aureus* are less frequently identified.

Diagnosis

The definition of CAUTI in the ICU is controversial and challenging as clinical signs such as urgency, frequency, dysuria, or suprapubic tenderness cannot be assessed in sedated patients. The only clinically useful sign is fever. In practice, CAUTI diagnosis is likely if the patient has a fever without apparent source and confirmed by a positive urine culture ($\geq 10^5$ micro-organisms per cm^3 of urine with no more than two species of micro-organisms).

Treatment

CAUTI treatment must take into account antibiotic susceptibility testing from identified micro-organisms. Pre-emptive therapy of ICU-acquired CAUTI must include an antibiotic with activity against Enterobacteriaceae and non-fermentative micro-organisms. Emerging resistance in Gram-negative bacteria is a real concern. Enterobacteriaceae, in most countries harbour extended-spectrum beta-lactamases, in particular *Klebsiella* species and *E. coli*, and carbapenem resistance is emerging worldwide.

Prevention

Most guidelines recommend limiting catheter use by evaluating the necessity of catheterization and reviewing the ongoing need for urinary catheters. Catheter insertion should use an aseptic technique with sterile equipment. Whether silver alloy or antibiotic-impregnated catheters reduce the risk of infection remains a controversial issue. However, there is consensus to use the smallest bore catheter. For catheter maintenance, a closed drainage system should be used, routine irrigation should be avoided, and the drainage bag must be placed below the level of the bladder. Routine urine cultures must be avoided as asymptomatic bacteriuria should not be treated. Systemic antibiotic prophylaxis is not recommended outside urinary tract malformations in small children [15].

Implementation of best practice

The successful implementation of best infection control practices is not an easy task. It depends on individuals, the hospital setting, the local and national context, the design of the prevention programme and how it is structured and conducted [16]. Successful prevention programmes offer a comprehensive protocol; follow a multidisciplinary approach in the preparation phase, and a multimodal training and education strategy in the implementation phase [17]. Education and training sessions should be as practical as possible and actively involve frontline workers, e.g. in workshops, simulator training, and focus groups [17]. Distributing guidelines or merely promoting bundles is insufficient to motivate health care workers to change practice [17]. Messages must be embedded in a multimodal training strategy and actively supported by the top leaders [18]. Champions who actively lead efforts to implement best practices in their teams and a positive organisational culture by fostering working relationships and communication across units and staff groups help in the implementation process. Surveillance of process indicators or outcomes, such as CLABSI, VAP, or CAUTI, preferably in a surveillance network similar to US National Healthcare Safety Network, the German nosocomial infection surveillance system (KISS), or the International Nosocomial Infection Control Consortium (INICC), and in combination with timely performance feedback to health care workers at the frontline help to maintain best practice.

References

1. Hugonnet S, Chevrolet JC, and Pittet D. (2007). The effect of workload on infection risk in critically ill patients. *Critical Care Medicine*, **35**, 76–81.
2. Borg MA, Suda D, and Scicluna E. (2008). Time-series analysis of the impact of bed occupancy rates on the incidence of methicillin-resistant *Staphylococcus aureus* infection in overcrowded general wards. *Infection Control in Hospital Epidemiology*, **29**, 496–502.
3. Howie AJ and Ridley SA. (2008). Bed occupancy and incidence of methicillin-resistant *Staphylococcus aureus* infection in an intensive care unit. *Anaesthesia*, **63**, 1070–3.
4. Vincent JL, Rello J, Marshall J, et al. (2009). International study of the prevalence and outcomes of infection in intensive care units. *Journal of the American Medical Association*, **302**, 2323–9.
5. Zingg W, Walder B, and Pittet D. (2011). Prevention of catheter-related infection: toward zero risk? *Current Opinion in Infectious Disease*, **24**, 377–84.
6. Bouza E, Alvarado N, Alcala L, Perez MJ, Rincon C, and Munoz P. (2007). A randomized and prospective study of 3 procedures for the diagnosis of catheter-related bloodstream infection without catheter withdrawal. *Clinical Infectious Diseases*, **44**, 820–6.
7. Eggimann P, Harbarth S, Constantin MN, Touveneau S, Chevrolet JC, and Pittet D. (2000). Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. *Lancet*, **355**, 1864–8.
8. Zingg W, Imhof A, Maggiorini M, Stocker R, Keller E, and Ruef C. (2009). Impact of a prevention strategy targeting hand hygiene and catheter care on the incidence of catheter-related bloodstream infections. *Critical Care Medicine*, **37**, 2167–73.

9. Zingg W, Cartier V, Inan C, et al. (2014). Hospital-wide multidisciplinary, multimodal intervention programme to reduce central venous catheter-associated bloodstream infection. *PloS One*, **9**, e93898.
10. Climo MW, Yokoe DS, Warren DK, et al. (2013). Effect of daily chlorhexidine bathing on hospital-acquired infection. *New England Journal of Medicine*, **368**, 533–42.
11. Chastre J and Fagon JY. (2002). Ventilator-associated pneumonia. *American Journal of Respiratory Critical Care Medicine*, **165**, 867–903.
12. American Thoracic Society; Infectious Diseases Society of America. (2005). Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *American Journal of Respiratory Critical Care Medicine*, **171**, 388–416.
13. Bouadma L, Deslandes E, Lolom I, et al. (2010). Long-term impact of a multifaceted prevention program on ventilator-associated pneumonia in a medical intensive care unit. *Clinical Infectious Diseases*, **51**, 1115–22.
14. Dudeck MA, Horan TC, Peterson KD, et al. (2011). National Healthcare Safety Network (NHSN) Report, data summary for 2010, device-associated module. *American Journal of Infection Control*, **39**, 798–816.
15. Hooton TM, Bradley SF, Cardenas DD, et al. (2010). Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clinical Infectious Diseases*, **50**, 625–63.
16. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, and Lowery JC. (2009). Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implemental Science*, **4**, 50.
17. Zingg W, Holmes A, Dettenkofer M, et al. (2015). Hospital organisation, management, and structure for prevention of health-care-associated infection: a systematic review and expert consensus. *Lancet Infect Dis*, **15**, 212–24.
18. Saint S, Kowalski CP, Banaszak-Holl J, Forman J, Damschroder L, and Krein SL. (2010). The importance of leadership in preventing healthcare-associated infection: results of a multisite qualitative study. *Infection Control in Hospital Epidemiology*, **31**, 901–7.

CHAPTER 289

Antibiotic resistance in the ICU

Jonathan Edgeworth

Key points

- Most countries are documenting a steady increase in antimicrobial resistance amongst common bacterial pathogens found on the ICU.
- The increase in antimicrobial resistance, particularly amongst Gram-negative bacteria compromises empiric therapy choices and can lead to selection of strains that are resistant to essentially all available antibiotics.
- Infection prevention, control, and antimicrobial stewardship programmes aim to limit the selection and transmission of resistance on the ICU.
- The ability of successful antibiotic-resistant clones to become pandemic necessitates a co-ordinated global response beyond local measures introduced on individual ICUs and health care institutions.
- Advances in rapid diagnostics holds promise of providing identification and information on antimicrobial resistance of bacterial pathogens at the time of initial decision making in the treatment of septic patients on ICU.

Principles of pathogenesis and treatment of ICU-acquired infections

Infections dealt with on a general intensive care unit (ICU) can be defined as either community-associated or health care associated. Community-associated infections usually involve organisms with defined virulence factors conferring the ability to colonize surface epithelia, invade the host and then evade the immune system. In the pre-antibiotic era many were known to have a high mortality. Health care and more specifically ICU-associated infections usually involve organisms capable of colonization, but they require assistance with invasion through epithelial surfaces from a catheter, drain or knife, or the bypassing of other innate defences through insertion of endotracheal and urinary catheters. It is uncertain whether they use mechanisms to evade the immune system and the attributable mortality of ICU-acquired infections is hard to define because of the high background mortality associated with an ICU stay. Nevertheless ICU-patients frequently develop systemic inflammation that in the setting of a community-associated infection would indicate involvement of a virulent pathogen. Microbiological data does not become available for 2–3 days, and although biomarkers of systemic inflammation such as the white-blood cell count, C-reactive protein and procalcitonin are available within a few hours they have high sensitivity, but low specificity for predicting microbiologically confirmed infection. A decision to start antimicrobial therapy is therefore made empirically. Unfortunately, although bacteria commonly associated with ICU-acquired infections are remarkably similar worldwide (Table 289.1), they have higher intrinsic antimicrobial resistance than community bacteria and a frightening ability to acquire further resistance. Consequently, the selection of appropriate antibiotics for acutely unwell patient is challenging. There is usually a need to cover Gram-positive and Gram-negative bacteria (GNB) and sometimes fungi, particularly *Candida* spp. All three groups present problems, but it is particularly acute with GNB because there are such a large number of species and resistance elements. For this reason the main focus of this chapter will be on GNB. Many guidelines recommend two antibiotics active against GNB for treatment of ICU-acquired infections with de-escalation to a single antibiotic around day 3 when culture results become available. There is little evidence to guide length of therapy with practice ranging from 5 to 14 days [1]. Overall about half of ICU patients are judged to be infected at any one time and about 70% are receiving systemic antibiotics [2].

Main resistant organisms and resistance mechanisms

A comprehensive description of antimicrobial resistance genes and mechanisms has been recently reviewed elsewhere [3]. Many common ICU bacteria such as *P. aeruginosa, Enterobacter* spp., MRSA and *Enterococcus faecium* have intrinsic, but predictable resistance to antibiotics commonly used for community infections. Thus empiric therapy for ICU-acquired infections usually comprises one or more antibiotics from 6 main classes, comprising aminoglocosides, fluoroquinolones, third generation cephalosporins, aminopenicillins, carbapenems, and polymixins that have activity against Gram-negative bacteria, with the addition of a glycopeptide or oxazolidinone if MRSA is considered a likely cause. The choice of antibiotic(s) with activity against GNB is usually based on local levels of resistance to each agent and is made challenging by a number of emerging trends including:

- Intercontinental spread of plasmids with extended spectrum β-lactamases (ESBL) particularly CTX-M, active against cephalosporins and aminopenicillins, and often linked fluoroquinolone and aminoglycoside resistance elements that are found in *Klebsiella* spp., *E. coli,* and other Enterobacteriaciae.
- Development of resistance in *P. aeruginosa* to many antibiotic classes under selective pressure of antibiotic use on ICU.
- Endemic colonization of ICUs with organisms such as *A. baumanii* that can be resistant to all commonly used antibiotics.

Table 289.1 A comparison between predominant bacteria causing community and hospital associated intensive care unit infections

Community-associated bacteria	Hospital/ICU associated bacteria
Gram positive	
Staphylococcus aureus (MRSA*) **(IR)**	*Staphylococcus aureus* (MRSA) **(IR, O)**
Streptococcus pneumoniae	Coagulase negative Staphylococci
Group A Haemolytic Streptococcus	*Enterococcus* species (VRE) (**O, IR**)
Group B Haemolytic Streptococcus	
Group C/G Haemolytic Streptococcus	
Gram negative	
Escherichia coli	*Pseudomonas aeruginosa* **(O, AR)**
Klebsiella spp.	*Enterobacter* spp. **(O, AR)**
N. meningitidis	*Escherichia coli* **(AR)**
Haemophilus spp.	*Klebsiella* spp. **(O, AR)**
Moraxella spp.	*Morganella* spp.
Legionella spp.	*Serratia* spp.
	Proteus spp.
	Acinetobacter baumanii **(O, IR)**
	Citrobacter spp.
	Stenotrophomonas spp. **(IR)**
	Hafnia spp.
	Other GNB†

*Community MRSA has become more frequent in some parts of the world.

†There is a large number of different usually environmental GNB found sporadically and occasionally as small outbreaks in ICU that separately can be considered rare but collectively can be identified on about 5–10% of ICU patients (e.g. Chryseomonas, Commomonas. Ochrobacter, Elizabethkingae).

O, frequently reported to cause outbreaks; IR, high level of intrinsic antibiotic resistance; AR, frequent additional clinically relevant acquired resistance.

- Increasing carbapenem resistance due to a variety of mechanisms commonly manifesting as either:
  - *P. aeruginosa* outbreaks.
  - Emergence of intrinsically resistant bacteria, such as *S. maltophilia.*
  - Most importantly, selection of numerous transferable plasmids encoding carbapenemases (eg KPC, IMP, OXA 48 and NDM) within enterobacteriaceae particularly *E. coli* and *Klebsiella* that have the potential for pandemic spread [4].

Together this creates a high degree of uncertainty selecting empiric GNB therapy in ICU patients. There has been an increasing reliance on carbapenems in many ICUs over the past 5–10 years even as first line, but the emergence of resistance compromises this choice and is leading to use of older agents such as colistin that have more side-effects [5].

Main factors increasing the burden of antimicrobial resistance on ICU

Antimicrobial resistance increases on ICU through importation, patient-to-patient transmission, selection in an individual, horizontal gene transfer within and between bacterial species and induction of new resistance (Fig. 289.1) [6]. The relative importance of each pathway varies between species and antibiotic resistance mechanism. Two main factors influence these pathways: antimicrobial use and health care practices.

Importation of resistance on patients (and to a lesser extent staff) reflects antimicrobial use in the community and the result of previous health care contacts. In addition, patients transferred out of ICU often have a prolonged stay on general wards where they may transmit resistance to other patients who then get admitted to ICU. Some patients have multiple admissions to hospital or the ICU providing many opportunities for increasing imported resistance.

Transfer of resistant organisms from patient to patient predominantly occurs via contaminated health care workers hands either directly from patient-to-patient or via inanimate objects. Antibiotic use may also influence transmission although this is likely to be complex given the potentially opposing effects of the many prescribed antibiotics [7].

Induction of resistance due to selection of new mutations during antimicrobial therapy may be a particular problem in units with high antimicrobial consumption. Fluoroquinolones are reported to be associated with induction of resistance in enterobacteriaciae and *P. aeruginosa* during therapy. There is emerging evidence for outbreaks of resistance with transfer of mobile resistance elements both within and between species [8], although the frequency, risk factors, and mechanisms of limiting such resistance are unclear.

Outbreaks of resistance

An outbreak can be defined as a period of increased incidence above an expected background The literature is dominated by reports of species outbreaks with resistant organisms such MRSA, *Acinetobacter* and MDR-*Klebsiella* that presumably drew significant clinical attention at that time. It is not clear what the total burden of outbreaks is on ICU and thereby derive general conclusions about risk factors and dissemination routes [9]. Outbreaks are often identified by a member of the health care team, although there are resistance outbreak detection tools that provide a more objective surveillance method [10,11]. It will be interesting to explore what might underlie the difference between large 'outbreaks' that reach clinical attention, and small clusters of largely sub-clinical and presumably self-terminating transmission clusters. Large outbreaks are often attributed to lapses in infection control practice, a patient or staff 'superspreader' or an environmental reservoir although some bacteria may be more adapted to spread better on the ICU [12].

Preventing the emergence and transmission of resistance on the intensive care unit

There are two main intervention programmes targeting a reduction in antimicrobial resistance: infection prevention and control (IPc), and antimicrobial stewardship.

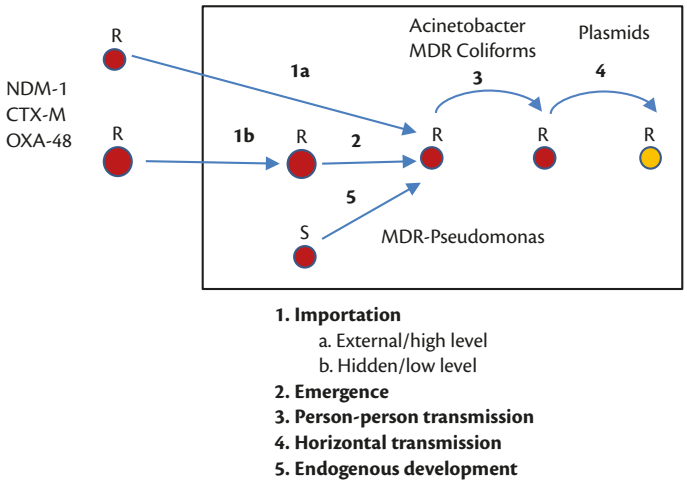


Fig. 289.1 Control of Gram-negative resistance is much more complicated: multiple species, resistance mechanisms and potential routes of transmission. R, resistant; S, sensitive.

An ICU infection prevention and control programme

An effective ICU IPc programme includes universal and targeted measures [13]. Universal measures that can be implemented in all ICUs include universal hand hygiene, environmental cleaning, and a training programme for staff that includes aseptic techniques required for good nursing and medical care. Success of these behavioural and operational practices benefits from a combination of education, training, and audit with clear accountability from 'board to ward' with consequences for poor performance. IPC has been transformed in many countries over the past few years by political, media, and public campaigns, demanding reductions in health care-associated infections to improve patient safety in hospitals.

Targeted components of an IPc programme comprise isolation and decolonization of patients carrying specific resistant organisms. Isolation can be used broadly to define any physical or distance barrier placed around a colonized patient and ranges from gloves and aprons for staff (contact precautions), patient cohorting or side-room isolation with or without staff cohorting, and use of an isolation ward. An additional component of a targeted IPc programme is collection of active surveillance cultures (ASC) to rapidly identify colonized patients and implement infection control interventions. Organisms most frequently screened are MRSA, VRE, and certain MDR-GNBs. A key attribute of a screening programme is the speed of returning results for action. Conventional culture often takes 3–4 days, which could be close to the median length of stay, such that results are delivered as the patient leaves. More rapid laboratory culture and molecular techniques can bring the turnaround time to same day or next day, and some point of care tests are being evaluated for organisms such as MRSA and *C. difficile* that provide results within a few hours. The effectiveness and cost-effectiveness of ASC programmes remains unclear.

Decolonization of patients with known resistant species is the other common targeted intervention, introduced to reduce both infections in the individual patient and transmission to others. With MRSA, decolonization involves use of surface antiseptics such as chlorhexidine and nasal mupirocin. In healthy patients, this has a reasonable chance of effecting MRSA eradication; however, in the ICU setting where patients have multiple skin breaches eradication is not considered achievable and the IPc goal is suppression at surfaces to reduce the bacterial load available to contaminate health care worker hands. The use of systemic antibiotics to further suppress the bacterial load of MRSA is not generally recommended on ICU. There is evidence that surface agents such as chlorhexidine may also suppress VRE at skin sites leading to a reduction in transmission. Skin antiseptics probably have little effect on MDR-GNB transmission, given that they predominantly colonize the gut and respiratory tract. There is evidence that enteral components of the selective digestive decontamination protocol, which includes neomycin and polymixin, suppress GNBs including MDR-GNB carriage in the gut, colonization of the respiratory tract and potentially transmission [14], although it's use has not become widespread in part due to concerns about emergence of resistance.

Although targeted decolonization is an accepted intervention for known MRSA carriers, there is a growing practice of using surface antiseptics such as chlorhexidine for all patients on ICU from admission [15]. Thus, although a distinction is generally made between universal and targeted components of an infection control programme, given that all ICU patients are at high risk of acquiring or carrying resistant organisms universal contact precautions and surface antiseptic decolonization is currently implemented in some ICUs. Although, this may be feasible in some settings, the lack of evidence to support effectiveness and cost-effectiveness of universal measures leads to a wide variation in practice [16].

Antimicrobial stewardship programme

A second approach to controlling antimicrobial resistance on ICU is the reduction of inappropriate antimicrobial prescribing through implementation of a stewardship programme [17]. The principle is that although international and local guidelines are usually in place recommending choice and duration of antibiotic therapy for ICU-acquired sepsis, there is huge scope for variation in practice within and between units. This variation is perhaps compounded by recognition that the grade of evidence supporting treatment guidelines is mostly poor. Stewardship therefore aims to support decision-making and adherence to generally acceptable guidelines endorsed by local stakeholders. Measures include introducing restriction or pre-approval for certain antimicrobials; regular advice provided by a visiting infection specialist to the attending team, on the need, choice, and duration of antibiotics in individual patients; formal review of therapy around day three to implement de-escalation, particularly if combination empiric GNB-therapy is used; and introduction of computer assisted decision making or automatic stop dates. Finally, studies have investigated whether some guidelines are more associated with resistance than others, comparing heavy reliance on a limited range of antibiotics, regular cycling from one class to another or continuous mixing [18,19].

New interventions to help control antimicrobial resistance

A number of new technologies are on the horizon with the potential to provide more and faster clinically-useful microbiological and epidemiological information, which should improve both treatment of sepsis and infection control practice leading to a control of antimicrobial resistance on ICU [20]. Multiplex PCR technologies are in development that can identify organisms in clinical samples within a few hours. Such information could be

used to deliver more appropriate empiric therapy for those with positive samples and in theory the withholding of antibiotics in those with negative samples. High throughput and rapid (same day) whole pathogen genome sequencing (WPGS) technologies are also being developed that may provide genotypic prediction of antimicrobial resistance phenotype and help with early detection of outbreaks. It is still unclear how long these disruptive technologies will take to enter routine practice, whether they will be used to guide both infection control and early therapy decisions, and whether they will save lives and resources and reduce resistance. There also remains an underlying need for better evidence on when to start antibiotics in ICU patients and how long to treat for. It is generally accepted that antibiotics are overused in ICU, but hard to strike a balance at the bedside between the needs of the individual patient for appropriate empiric therapy and the needs of society to prevent emergence of resistance. Hopefully a combination of new evidence from multi-centre randomized studies, including those that evaluating rapid diagnostics will meet this important challenge.

References

1. Corona A, Bertolini G, Ricotta AM, Wilson AP, and Singer M. (2003). Variability of treatment duration for bacteraemia in the critically ill: a multinational survey. *Journal of Antimicrobiology and Chemotherapy*, **5**(5), 849–52.
2. Vincent JL, Rello J, Marshall J, et al. (2009). International study of the prevalence and outcomes of infection in intensive care units. *Journal of the American Medical Association*, **302**(21), 2323–9.
3. Fraimow HS and Tsigrelis C. (2011). Antimicrobial resistance in the intensive care unit: mechanisms, epidemiology, and management of specific resistant pathogens. *Critical Care Clinic*, **27**(1), 163–205.
4. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, and Daikos GL. (2012). Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clinical Microbiology Reviews*, **25**(4), 682–707.
5. Livermore DM, Warner M, Mushtaq S, Doumith M, Zhang J, and Woodford N. (2011). What remains against carbapenem-resistant Enterobacteriaceae? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline. *International Journal of Antimicrobiology Agents*, **37**(5), 415–19.
6. Bonten MJ and Mascini EM. (2003). The hidden faces of the epidemiology of antibiotic resistance. *Intensive Care Medicine*, **29**(1), 1–2.
7. Tacconelli E, De Angelis G, Cataldo MA, Pozzi E, and Cauda R. (2008). Does antibiotic exposure increase the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) isolation? A systematic review and meta-analysis. *Journal of Antimicrobiology and Chemotherapy*, **61**(1), 26–38.
8. MacLean RC, Hall AR, Perron GG, and Buckling A. (2010). The population genetics of antibiotic resistance: integrating molecular mechanisms and treatment contexts. *National Review of Genetics*, **11**(6), 405–14.
9. Gastmeier P, Stamm-Balderjahn S, Hansen S, et al. (2006). Where should one search when confronted with outbreaks of nosocomial infection? *American Journal of Infection Control*, **34**(9), 603–5.
10. Kulldorff M, Heffernan R, Hartman J, Assuncao R, and Mostashari F. (2005). A space-time permutation scan statistic for disease outbreak detection. *PLoS Medicine*, **2**(3), e59.
11. Vlek AL, Cooper BS, Kypraios T, Cox A, Edgeworth JD, and Auguet OT. (2013). Clustering of antimicrobial resistance outbreaks across bacterial species in the intensive care unit. *Clinical Infectious Diseases*, **57**(1), 65–75.
12. Cooper BS, Kypraios T, Batra R, Wyncoll D, Tosas O, and Edgeworth JD. (2012). Quantifying type-specific reproduction numbers for nosocomial pathogens: evidence for heightened transmission of an Asian sequence type 239 MRSA clone. *PLoS Computer Biology*, **8**(4), e1002454.
13. Yokoe DS, Mermel LA, Anderson DJ, et al. (2008). A compendium of strategies to prevent healthcare-associated infections in acute care hospitals. *Infection Control in Hospital Epidemiology*, **29**(1), S12–21.
14. de Smet AM, Kluytmans JA, Blok HE, et al. (2011). Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. *Lancet Infectious Diseases*, **11**(5), 372–80.
15. Huang SS, Septimus E, Kleinman K, et al. (2013). Targeted versus universal decolonization to prevent ICU infection. *New England Journal of Medicine*, **368**(24), 2255–65.
16. Hanberger H, Arman D, Gill H, et al. (2009). Surveillance of microbial resistance in European Intensive Care Units: a first report from the Care-ICU programme for improved infection control. *Intensive Care Medicine*, **35**(1), 91–100.
17. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, and Daneman N. (2011). Impact of antimicrobial stewardship in critical care: a systematic review. *Journal of Antimicrobiology and Chemotherapy*, **66**(6), 1223–30.
18. Raymond DP, Pelletier SJ, and Sawyer RG. (2002). Antibiotic utilization strategies to limit antimicrobial resistance. *Seminar in Respiratory Critical Care Medicine*, **23**(5), 497–501.
19. Sandiumenge A, Diaz E, Rodriguez A, et al. (2006). Impact of diversity of antibiotic use on the development of antimicrobial resistance. *Journal of Antimicrobiology and Chemotherapy*, **57**(6), 1197–204.
20. Koser CU, Holden MT, Ellington MJ, et al. (2012). Rapid whole-genome sequencing for investigation of a neonatal MRSA outbreak. *New England Journal of Medicine*, **366**(24), 2267–75.

PART 13.3

Infection in the immunocompromised

CHAPTER 290

Drug-induced depression of immunity in the critically ill

Russell J. McCulloh and Steven M. Opal

Key points

- Glucocorticoids are the most commonly-used immunosuppressive drugs today and affect gene transcription, leukocyte distribution, and clearance of microbial pathogens.
- Calcineurin and MTOR inhibitors are commonly used in autoimmune diseases and organ transplantation, but require close monitoring for drug-related toxicities and interaction with other medications metabolized by the liver.
- Cytotoxic and antimetabolite medications used in the treatment of various cancers can be associated with bone marrow suppression and pancytopenia.
- Newer biological agents such as monoclonal antibodies target specific immunomodulatory chemokines or chemokine receptors which can result in profound immunosuppression, particularly of cell-mediated immunity.
- Clinicians should use data on infectious complications commonly associated with specific immunosuppressive drugs to help guide their evaluation of immunosuppressed patients suspected to have an opportunistic infection.

Introduction

The use of immunosuppressive drugs is now commonplace in multiple disciplines of medicine and surgery from organ transplantation, neurosurgery, neoplastic diseases, autoimmune diseases and an array of inflammatory diseases affecting many organ systems. These agents have greatly benefitted patients, but come at the price of induction of specific and at times generalized immunosuppression with all the associated risk of infections and even some neoplasms with long-term use of these agents [1]. This chapter will summarize the major categories of immunosuppressive agents now in common use to which critical care specialists need to maintain a working familiarity with their indications, major risks, and side effects. The list of biological agents and monoclonal antibody therapies entering clinical usage is rapidly expanding to fulfil the need for new therapeutic indications and safer immunomodulation than existing agents. We will discuss corticosteroids, transplant regimens and common agents used for neoplastic diseases and inflammatory disorders, and provide a summary of the newer biological agents entering clinical practice.

Glucocorticoids remain the mainstay for anti-inflammatory therapy needs and have proven their worth over the past 75 years of clinical use. The mechanisms of action that account for their anti-inflammatory effects are complex, but increasingly well understood as summarized in Fig. 290.1 [2]. Glucocorticoids are lipid soluble and freely diffuse across cell membranes where they bind to their specific receptors. Glucocorticoid receptors disassociate from Heat Shock Protein 90 when glucocorticoids enter the cell; they dimerize and translocate to the nucleus and markedly alter cellular and transcriptional activity of the cell. Anti-inflammatory genes are upregulated as they have GRE (Glucocorticoid response element) sequences near promoter sites. A prominent effect of steroids is upregulation of IκB-α, a potent inhibitor of the capacity of NFκB to translocate across the nuclear membrane and activate pro-inflammatory genes. Another major impact of glucocorticoids is their capacity to block transcription of inflammatory gene programs at the level of the essential co-activator complex of the transcriptional machinery of the cell. Steroids also block the actions of other transcriptional activators including a number of mitogen activated protein kinases and activator protein 1. Stability of mRNA is impaired by glucocorticoids limiting the translation of mRNA into protein products such as pro-inflammatory cytokines, chemokines, and enzymes that generate prostaglandins and other inflammatory mediators.

Clinical experience has clearly delineated the importance of escalating doses of glucocorticoids and most importantly the duration of steroid use as major determinants of the risk of infectious and metabolic complications of glucocorticoids. High doses of these immunosuppressive agents are remarkably well tolerated for the first 14–21 days of therapy before major complications associated with their use become clinically manifest [3]. Similarly, the administration of low doses of glucocorticoids (<10 mg prednisone or equivalent agents) are tolerated with minimal to no excess infection risk for years of therapy. Numerous functional consequences affecting the cellular constituents of both the innate and adaptive immune systems occur and account for the increase risk of infection from steroids. Neutrophilia with initial use is commonplace as a consequence of decreased egress out of the circulation and increased release from bone marrow stores. Conversely T lymphocytes, NK cells, and eosinophils redistribute to extravascular sites with glucocorticoid use. Of greater functional consequence is steroid-induced reduction in surface expression of Fc receptors, complement receptors (CR3 receptor) and reduced expression of class II molecules and co-stimulatory signals by macrophages, eosinophils, and monocytes. Chemotaxis of monocytes and intracellular killing and cytokine and chemokine signalling are all reduced by

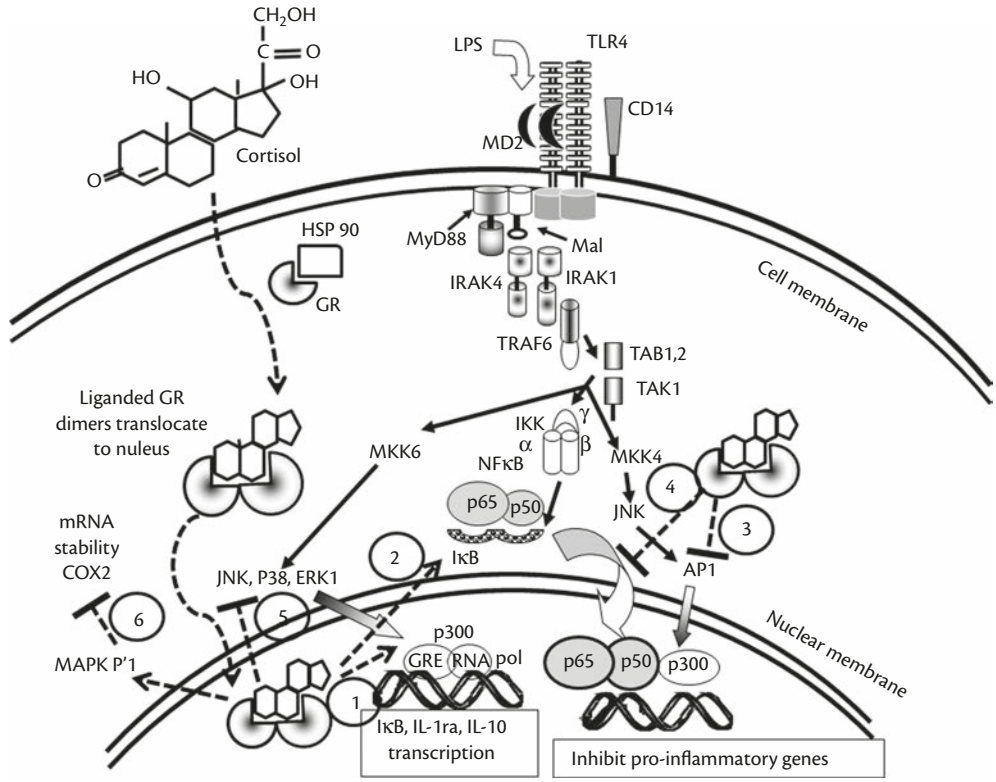


Fig. 290.1 Molecular mechanisms of glucocorticoid anti-inflammatory actions. Glucocorticoids have multiple ant-inflammatory actions including: (1) binding to glucocorticoid response elements at promoter sites for upregulation of anti-inflammatory gene transcription; (2) upregulation of I kappa B levels that block NFκB (nuclear factor from kappa B cell) nuclear translocation; (3) inhibition of AP-1 (activator protein 1) and 4) inhibition of NFκB activation of pro-inflammatory gene transcription by blocking coactivators of transcription; (5) inhibition of MAPK (mitogen activated protein kinase) activated transcriptional factors; (6) activation of MAPK phosphatase-1 that degrades MAPKs and induces mRNA instability with reduced translation of pro-inflammatory mediators and enzymes.

HSP, heat shock protein; GR, glucocorticoid receptor; COX2, cyclooxygenase 2; JNK, janus N terminal kinase; ERK, extracellular receptor activated kinase; GRE, glucocorticoid response element; RNA pol, RNA polymerase; MKK, MAPK kinases; IκK, inhibitor kappa B kinase; TAK, transforming factor beta associated kinase; TAB, TAK binding protein; TRAF6, TNF receptor associated factor 6; IRAK, interleukin-1 receptor associated kinase; MyD88, myeloid differentiation 88; Mal, Myd88 adaptor like; LPS, lipopolysaccharide; TLR4, Toll-like receptor.

corticosteroids resulting in poor microbial clearance and excess infection risk.

Lymphocyte populations, particularly T-cells (both CD4 and CD8 cells) are also affected with reduced proliferative capacity and cytokine generation after exposure to steroids with 2 weeks of starting these drugs. Reduced IL-2 generation associated with steroid use primarily accounts for impaired proliferative capacity of T-cells to respond to intracellular pathogens. B cell and plasma cell populations are only mildly affected by high dose steroids and antibody synthesis is well preserved to recall antigens. NK cell function is well preserved even after long term exposure to glucocorticoids. It should be remembered that therapeutic doses of steroids impair fever generation by the upregulation of lipocortins that block phospholipase A_2. Blockade of fever occurs from reduced arachidonic acid synthesis and thereby loss of prostaglandin E2 alpha levels in the hypothalamic thermoregulatory centre of the brain. Steroid-induced blockade of fever generation not only removes this cardinal sign of inflammation from the clinician's attention, it also likely impairs the capacity to clear pathogens.

An array of well-known opportunistic pathogens and a host of routine pathogens remain a constant concern with the long-term use of glucocorticoids [3–5]. Isoniazid preventive therapy is indicated in steroid-treated patients with evidence of latent tuberculosis. Special concern should be paid to opportunistic fungi and endemic mycoses in specific geographic regions where coccidioidomyocosis and histoplasmosis are prevalent in the environment. The hyperinfection syndrome with strongyloidasis is a real risk in steroid treated patients and should be screened for in endemic regions of the world.

Immunosuppressive agents used in oncology and transplant medication

Calcineurin inhibitors and MTOR inhibitors

Cyclosporin

Cyclosporine (cyclosporin A, CSA) is used for immunosuppression in a variety of circumstances, including human organ transplantation, treating graft-versus-host disease (GVHD) after haematopoietic stem cell transplantation (HSCT) [13], and in the treatment of autoimmune disorders including rheumatoid arthritis, psoriasis, and uveitis [16]. It is a peptide antibiotic that blocks activation of T-cells during antigen receptor-mediated induction of differentiation by binding to cyclophilin, an intracellular protein belonging

to the immunophilin protein class. Together with cyclophilin, cyclosporin forms a complex that inhibits calcineurin, a cytoplasmic phosphatase crucial to activating NF-AT. This transcription factor is necessary for synthesis of several interleukins, including IL-2, IL-3, and IFN-gamma, by activated T-cells. Of note, cyclosporin does not block the effects of these cytokines on primed T-cells or interaction with antigen. Cyclosporin is metabolized by the CYP450 3A enzyme, which means it has multiple drug-drug interactions and requires monitoring of drug levels. Toxicities can include nephrotoxicity, hypertension, hyperglycaemia, liver dysfunction, hyperkalaemia, mental status chances, and seizures.

Tacrolimus

Tacrolimus (FK 506) is a macrolide antibiotic produced by *Streptomyces tsukubaensis*. It suppresses T-cell transcription of NF-AT by binding to the immunophilin FK-binding protein (FKBP). Its immunosuppressive activity is similar to cyclosporin but 10-100 times greater on a per-weight basis. It has been used in a similar array of conditions, including solid-organ transplant, HSCT, and treatment or prevention of GVHD. It is used topically to treat various dermatological conditions including atopic dermatitis and psoriasis. Tacrolimus is metabolized via the CYP450 pathway with similar drug interaction concerns as cyclosporin. Trough levels should be monitored in patients. Toxicities are also similar to cyclosporin, including nephrotoxicity, neurotoxicity, hyperglycaemia, hypertension, and hyperkalaemia, although gastrointestinal effects may be more common [16].

Sirolimus

Sirolimus (rapamycin) is the prototype immunosuppressive macrolide antibiotic that inhibits the kinase activity of mammalian target of rapamycin (mTOR). Other 'rapalogs' in this group include everolimus and temsirolimus. Inhibition of the mTOR pathway has pleiotropic effects on various cellular processes including angiogenesis, metabolism, and cellular proliferation such as interleukin-mediated T-cell activation and proliferation. Sirolimus and the other rapalogs have potential applications in both targeted oncologic therapies as well as immunosuppression. Currently sirolimus is used in preventing solid organ allograft rejection, prevention, and treatment of GVHD, as well as in topical preparations for dermatological disorders. Sirolimus is metabolized by CYP450 3A and P-glycoprotein, with similar concerns for drug-drug interactions as the calcineurin inhibitors. Its half-life is 60 hours, resulting in prolonged toxicity even after drug cessation. Unlike cyclosporin and tacrolimus, sirolimus has no significant nephrotoxicity. However, use of the mTOR inhibitors has been associated with myelosuppression, thrombocytopenia, hepatic dysfunction, diarrhoea, headache, elevated serum triglycerides, and pneumonitis. Additionally, when combined with tacolimus for treatment of HSCT-related GVHD, sirolimus has been associated with increased incidence of haemolytic-uremic syndrome.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) inhibits several T- and B-lymphocyte actions, including mitogen and mixed lymphocyte responses, most likely via inhibition of purine synthesis. A semisynthetic derivative of mycophenolic acid, MMF can be given orally or intravenously. Unlike sirolimus and the calcineurin inhibitors, MMF is not metabolized via the CYP450 3A system. Mycophenolate mofetil is used in combination with prednisone as an alternative to cyclosporin or tacrolimus in patients intolerant to these medications. It also is used in refractory solid organ transplant rejection and GVHD [4]. Outside of transplant medicine, MMF is used to treat lupus nephritis, rheumatoid arthritis, inflammatory bowel disease, and severe atopic dermatitis. Common side effects include headache, hypertension, gastrointestinal disturbances, and reversible myelosuppression.

Thalidomide and derivatives

Thalidomide

Historically known as a sedative drug withdrawn from the market due to its severe teratogenic effects when used in pregnant women, thalidomide is being tested and/or used in a wide array of clinical applications due to its anti-inflammatory, immunomodulatory, and anti-angiogenic effects. It inhibits tumour necrosis factor alpha (TNF-α), decreases neutrophil phagocytic activity, increases IL-10 production, alters adhesion molecule function, and enhances cell-mediated immunity through interaction with T-cells. Current approved applications include treatment of multiple myeloma, erythema nodosum leprosum, and dermatological disease due to systemic lupus erythematosis (SLE). It is under study for use in various oncologic conditions, myelodysplastic syndrome, and GVHD. Besides its teratogenic effects, thalidomide can cause peripheral neuropathy, constipation, rash, fatigue, hypothyroidism, and increased risk for deep venous thrombosis. Currently thalidomide may only be prescribed under close supervision from the manufacturer. The severe side effect profile has prompted the development and study of alternative agents known as immunomodulatory derivatives of thalidomide or IMiDs.

Lenalidomide

The first IMiD approved for treating patients with myelodysplastic syndrome and multiple myeloma, lenalidomide has fewer side effects than thalidomide, although concomitant use of anticoagulant therapy, close monitoring of renal function, and monitoring for neutropenia and thrombocytopenia remain important [17].

Cytotoxic agents and antimetabolites

Azathioprine

Azathioprine is a prototypic immunosuppressive antimetabolite. It is a prodrug of mercaptopurine that is well-absorbed from the GI tract. Azathioprine is cleaved by xanthine oxidase to 6-thiouric acid, and care must be taken to reduce the dose to one-quarter to one-third the usual amount to avoid toxicity. Its mechanism of action is through interference with purine nucleic acid metabolism resulting in destruction of stimulated lymphoid cells, causing cell-mediated and humoral immune suppression. Azathioprine and mercaptopurine are used in renal allograft maintenance, lupus nephritis, Crohn's disease, rheumatoid arthritis, multiple sclerosis, and steroid-resistant idiopathic thrombocytopenic purpura and autoimmune haemolytic anaemias. Azathioprine's primary toxicity is bone marrow suppression, but can also include rash, nausea, vomiting, diarrhoea, and hepatic dysfunction, particularly at higher doses.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that is highly toxic to proliferating lymphoid cells and has some effect against resting cells. High doses may induce tolerance to a new antigen if the drug is

Table 290.1 Other immunosuppresive drugs

	Primary mechanism of action	Major toxicities
Antimetabolites		
Fluorouracil (5-FU)	Blocks DNA methylation during DNA synthesis	Myelosuppression, CNS, heart failure
Cytarabine	Pyrimidine synthesis inhibitor	Myelosuppression, bleeding
Cytotoxic agents		
Dapsone	Inhibits neutrophil migration, adherence	Haemolysis, agranulocytosis
Vincristine	Inhibits mast cell degranulation	Marrow suppression
Bleomycin	Causes DNA strand breaks	Myelosuppression, fevers, skin changes
Pentostatin	Adenosine deaminase inhibitor	Leukopenia, thrombocytopenia
Fingolimod	Decreases lymphocyte recirculation	Lymphopenia, Flu-like syndrome

Table 290.2 Common biological agents and their principal immunological effects and infection risks

Biological agent or antibody	Molecular target	Indications	Infection risk
Polyclonal anti-thymocyte or anti-lymphocyte antibodies	T lymphocytes	Organ transplant rejection	Impaired cell-mediated immunity increases risk of numerous OI
Infliximab (Remicade)	Chimeric murine-human mAb blocks TNF and tmTNF	RA, psoriasis, AS, ulcerative colitis, Crohn's disease	TB, Herpes virus, histo, cocci, other opportunistic bacterial, viral infections
Entanercept (Enbrel)	Type 2 TNFr:Fc IgG blocks sTNF and lymphotoxin	RA, psoriasis, AS, JRA	Lower risk than Infliximab-TB, histo, cocci, other fungi, bacterial, viral infection, OIs
Adalimumab (Humira)	Humanized anti-TNF mAb targets sTNF, tmTNF	RA, psoriasis, AS Crohn's disease	TB, other fungal, viral and bacterial OIs
Golmumab (Simpori)	Human anti-TNF mAb targets sTNF and tmTNF	RA, psoriasis, AS	TB, other bacterial, viral OIs
Certolizumab pegol	Pegylated humanized anti-TNF Fab fragment	Crohn's disease, RA	Limited data, likely similar to other TNF inhibitors
Anakinra (Kineret)	IL-1 receptor antagonist targets IL-1 beta	RA	OI risk less than with TNF inhibitors; URI, pneumonia
Daclizumab (zenapax)	Humanized mAb blocks IL-2R (CD25) on T-cells	Transplant rejection	Low risk of CMV, other OIs
Basiliximab (Simulect)	mAb blocks IL-2R (CD25) on T-cells	Transplant rejection	Low risk of OI, CMV reactivation
Rituximab (Rituxan)	Blocks CD20 on B cells	RA, SLE, B cell neoplastic disease	Some Bacterial infections, CMV, VZV, HBV, PML
Alemtuzumab (Campath)	mAb blocks CD52 on T and B cells, NK cells, myeloid cells	Transplant rejection, CLL, neoplastic disease	Neutropenia; multiple OI with bacterial, viral, fungal pathogens, PJP, PTLD
Tocilizumab (Actemra)	mAb blocks IL-6R on T and B cells	Autoimmune disease, neoplastic disease	URI, might increase risk of other infections
Natalizumab (Tysabri)	Humanized mAb, blocks alpha-4 integrin and lymphocyte trafficking	MS, Crohn's disease	PML, especially if anti-JC virus + and prolonged immune suppression
Belatacept	mAb blocks co-receptor CD28 on T-cells	Kidney transplantation	EBV-associated PTLD, ?PML, UTI, CMV infection
Brodalumab (AMG 827)	mAb blocks IL-17AR	Psoriasis	Limited experience, increased pharyngitis, URI

OI, opportunistic infections; mAb, monoclonal; TNF, tumour necrosis factor; RA, rheumatoid arthritis; histo, histoplasmosis; cocci, coccidioidomycosis; AS, ankylosing spondylitis; JRA, juvenile rheumatoid arthritis; MS, multiple sclerosis; R, receptor; Fc, crystallizable component of immunoglobulin; IL, interleukin; CMV, cytomegalovirus; VZV, varicella zoster virus; HBV, hepatitis B virus; SLE, systemic lupus erythematosis; PML, progressive multifocal leukocencephalopathy; PJP, *Pneumocystis jirovecii* pneumonia; CLL, chronic lymphocytic leukaemia; EBV, Epstein–Barr virus; PTLD, post-transplant lymphoproliferative disorder; UTI, urinary tract infection, URI, upper respiratory infection.

administered with or immediately after the antigen, which can help improve rates of successful engraftment after HSCT. It is also used to prevent or treat GVHD. In addition to its use in oncology, it is used in modest doses for systemic lupus erythematosis, antibody-mediated factor XIII deficiency, pure red cell aplasia, and Wegener's granulomatosis. Side effects include haemorrhagic cystitis, pancytopenia, nausea, vomiting, cardiac toxicity, and electrolyte abnormalities.

Leflunomide

Leflunomide is an orally-active prodrug of a pyrimidine synthesis inhibitor. It has a half-life of several weeks, and is currently used for treatment of rheumatoid arthritis. Owing to its relative lack of cytochrome interactions and antiviral activity against cytomegalovirus, leflunomide is being studied in a wide array of transplant-associated and rheumatologic conditions [19]. Associated toxicities include hepatic dysfunction or damage, nephrotoxicity, and teratogenicity. Patients have also experienced angina and tachycardia while taking leflunomide.

Hydroxychloroquine

An antimalarial agent that also possesses immunosuppressive activity, hydroxychloroquine suppresses antigen processing and loading onto MHC class II molecules, leading to decreased T-cell activation. This is thought to occur through increasing the pH in lysosomes and endosomes. Hydroxychloroquine is used in rheumatoid arthritis and SLE as well as the management and prevention of GVHD. Longitudinal monitoring for retinopathy and permanent visual impairment is necessary in patients on long-term therapy.

Methotrexate

An inhibitor of dihydrofolate reductase, methotrexate is used both in chemotherapy and in the treatment of various malignancies as well as in rheumatoid arthritis and psoriasis [20]. It is a substrate of P-glycoprotein and has multiple drug-drug interactions. Additionally, methotrexate has multiple potential toxicities, including stomatitis, myelosuppression, skin rash, and short-term or long-term central nervous system effects (headache, vomiting, encephalopathy, among others).

Alkylating agents and platinum coordination complexes

These agents, which include nitrogen mustards, ethyleneimines, alkyl sulfonates, nitrosureas, triazenes, and DNA-methylating drugs, are primarily used in the treatment of neoplastic diseases. Their mechanisms of action all involve the alkylation of reactive amines, oxygens, or phosphates on DNA, resulting in cytotoxic effects. They are most effective in rapidly-proliferating tissues, which accounts in part for their immunosuppressive effects. This can result in suppression of all bone marrow-derived cell lines. For some agents, their effects can also be seen on resting-phase immune cells such as mature lymphocytes.

Other immunosuppressive drugs

Additional selected agents with immunosuppressive properties are listed in Table 290.1.

Immunosuppressive antibodies and other biological agents

First utilized as antisera derived from animals for treatment of infections in the pre-antibiotic era, antibody-mediated therapies for rheumatologic and oncologic disorders have experienced a rapid expansion in development and utilization in the past two decades [18]. Current therapies use hybrid antibodies composed of murine- or human-derived constant regions paired with specific active regions that target cell receptors and cytokines. Humanized murine monoclonal antibodies and now even fully human monoclonal antibodies are in clinical use. Table 290.2 lists the common biological agents currently in use for a variety of indications with immunosuppressive or immunomodulatory effects and major infection risks. Some of the agents are markedly immunosuppressive (e.g. rituximab, TNF inhibitors, alemtuzumab) and place the patient at major risk for opportunistic infections, while others are well tolerated or increase infection risk for a specific set of pathogens [6–15].

Worth noting is the remarkable association with the opportunistic JC virus-induced PML associated with natalizumab. This integrin inhibitor is highly effective for some forms of multiple sclerosis and is widely used despite the risk of PML. Patients should be screened for antibodies against JC virus and treated for as short a period as possible to avoid this complication. PML has also occurred during rituximab therapy and is a potential risk with the use of other broadly immunosuppressive agents in this class. As a testament to the degree of immune suppression induced by these biological agents, IRIS (immune reconstitution inflammatory syndrome) has occurred with withdrawal from natalizumab therapy and often necessitates the use of corticosteroids to control this reaction.

References

1. Gea-Banacloche JC, Opal SM, Jorgensen J, Carcillo JA, Sepkowitz KA, and Cordonnier C. (2004). Sepsis associated with immunosuppressive medications: An evidence-based review. *Critical Care Medicine*, **32**(11), S578—90.
2. Moynagh PN. (2003). Toll-like signaling pathways as key targets for mediating the anti-inflammatory and immunosuppressive effects of glucocorticoids. *Journal of Endocrinology*, **179**, 139–44.
3. Giamarellos-Bourboulis EJ, Dimopoulou I, et al. (2010). Ex-vivo effect of dexamethasone on cytokine production from whole blood of septic patients: correlation with disease severity. *Cytokine*, **49**(1), 89–94.
4. Luan FL, Steffick DE, and Ojo AO. (2009). Steroid-free maintenance immunosuppression in kidney transplantation: is it time to consider it as a standard therapy? *Kidney International*, **76**(8), 825–30.
5. Morgensen TH, Berg RS, Paludan SR, and Ostergaard L. (2008). Mechanisms of dexamethasone-mediated inhibition of toll-like receptor signaling induced by *Neisseria meningitidis* and *Streptococcus pneumoniae*. *Infectious Immunology*, **76**(1), 189–97.
6. Hanaway MJ, Woodle ES, Mulgaonkar S, et al. (2011). Alemtuzumab induction in renal transplantation. *New England Journal of Medicine*, **364**, 1909–19.
7. Grinyo J, Charpentier B, Pestana JM, et al. (2010). An integrated safety profile analysis of Belatacept in kidney transplant recipients. *Transplantation*, **90**(12), 1521–7.
8. Papp KA, Leonardi C, Menter A, et al. (2012). Brodalumab, and anti-interleukin-17-receptor antibody for psoriasis. *New England Journal of Medicine*, **366**, 1181–9.
9. Markmann JF and Fishman JA. (2011). Alemtuzumab in kidney-transplant recipients. *New England Journal of Medicine*, **364**, 1968–9.
10. Wallis RS. (2008). Tumor necrosis factor antagonists: structure, function and tuberculosis risks. *Lancet Infectious Diseases*, **8**, 601–11.
11. Cheson BD and Leonard JP. (2008). Monoclonal Antibody Therapy for B-Cell Non-Hodgkin's Lymphoma. *New England Journal of Medicine*, **359**(6), 613–26.
12. Connor, V. (2011). Anti-TNF therapies: a comprehensive analysis of adverse effects associated with immunosuppression. *Rheumatology International*, **31**(3), 327–37.

13. Copelan, E. A. (2006). Hematopoietic stem-cell transplantation. *New England Journal of Medicine*, **354**(17), 1813–26.
14. Di Giacomo AM, Biagioli M, and Maio M. (2010). The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. *Seminars in Oncology*, **37**(5), 499–507.
15. Manzano-Alonso ML and Castellano-Tortajada G. (2011). Reactivation of hepatitis B virus infection after cytotoxic chemotherapy or immunosuppressive therapy. *World Journal of Gastroenterology*, **17**(12), 1531–7.
16. Meyer KC, Decker C, and Baughman R. (2010). Toxicity and monitoring of immunosuppressive therapy used in systemic autoimmune diseases. *Clinical Chest Medicine*, **31**(3), 565–88.
17. Palumbo A, Freeman J, Weiss L, and Fenaux P. (2012). The clinical safety of lenalidomide in multiple myeloma and myelodysplastic syndromes. *Expert Opinion on Drug Safety*, **11**(1), 107–20.
18. Rezaei N, Abolhassani H, Aghamohammadi A, and Ochs HD. (2011). Indications and safety of intravenous and subcutaneous immunoglobulin therapy. *Expert Reviews in Clinical Immunology*, **7**(3), 301–16.
19. Teschner S and Burst V. (2010). Leflunomide: a drug with a potential beyond rheumatology. *Immunotherapy*, **2**(5), 637–50.
20. Wessels JA, Huizinga TW, and Guchelaar HJ. (2008). Recent insights in the pharmacological actions of methotrexate in the treatment of rheumatoid arthritis. *Rheumatology*, **47**(3), 249–55.

CHAPTER 291

HIV in the critically ill

Mark Hull and Steven C. Reynolds

Key points

- Human immunodeficiency virus (HIV) is increasingly a controllable disease in North America and life expectancy in patients adherent to combination antiretroviral therapy (cART) is similar to the general population.
- The majority of admissions of HIV positive patients to the ICU are for reasons unrelated to their HIV, although presentations due to opportunistic infections and malignancies must be considered in those with previously undiagnosed infection or in those patients non-adherent to cART.
- The CD4 count is critical in determining the degree of immune suppression in a patient and should be checked in all critically ill HIV-infected patients to determine appropriate work-up and management of HIV-related infections/complications.
- It is important to involve an infectious disease specialist familiar with HIV in the care of a critically ill HIV-infected patient, particularly if therapy requires alterations or cessation of cART or if the patient is found to be significantly immunocompromised.
- Antiretroviral agents have many potential drug interactions and rare toxicities which must be evaluated throughout the ICU stay as concomitant medications are introduced.

Introduction

It has been over 30 years since the identification of the first cases of unusual opportunistic infections and malignancies linked to infection with the human immunodeficiency virus (HIV). The use of combination antiretroviral therapy (cART) has been shown to halt progressive immunologic decline with concomitant improvement in morbidity and mortality due to HIV-related acquired immunodeficiency syndrome (AIDS). As a result, survival rates of HIV-infected individuals who are able to access cART approach those of the general population [1]. Management of patients presenting to the intensive care unit (ICU) must now encompass these expectations, and HIV infection alone should not affect decisions to pursue life-saving interventions. Reasons for admission to the ICU can include non-HIV-related conditions (including trauma or drug overdose), HIV-related infections, as well as infections similar to that of the general population. Physicians working in the ICU must have an awareness not only of the common opportunistic infections that remain a cause of hospitalization for HIV-infected individuals, but also be mindful of the possibility of causing inadvertent harm when altering or discontinuing antiretroviral therapies, their common toxicities and the importance of drug-drug interactions that can occur between antiretrovirals and other commonly used medications.

HIV epidemiology

There were an estimated 35 million individuals living with HIV/AIDS worldwide in 2013 [2]. The majority of individuals (24.7 million) reside in Sub-Saharan Africa, with an estimated 2–3 million individuals living in North America and Europe. Within the United States, by the end of 2011 there were an estimated 1.2 million individuals living with HIV—of whom 20% are thought to be undiagnosed [3]. Despite advances in therapy, individuals with undiagnosed HIV, and those with incomplete linkage to care may present with common opportunistic infections and morbidities related to untreated HIV.

The CD4 cell count is regarded as one of the key surrogate markers for prognostic staging and therapeutic monitoring of HIV-infected individuals (see Table 291.1). The CD4 count quantitates the magnitude of immune suppression and thus the array of opportunistic infections for which the patient might be at risk (Fig. 291.1). Plasma viral load has been shown to be an independent predictor of disease progression and death in untreated HIV-infected individuals [4].

Antiretroviral therapy in the ICU

Current recommendations for antiretroviral therapy

Therapeutic guidelines for the management of HIV-infected individuals are updated regularly by national and international organizations, and continue to evolve with time [5–7]. Individuals with symptomatic disease or AIDS-defining conditions require therapy regardless of CD4 cell count. At present, there is broad consensus that therapy should be initiated at a CD4 cell count threshold of 350 cells/mm^3 and is recommended at thresholds < 500 cells/mm^3 in most guidelines [5,7]. In addition, the presence of other co-infections (such as active hepatitis B) or comorbidities may be indicators for cART, regardless of CD4 cell count [5,6].

Antiretroviral drug classes

There are six major classes of antiretroviral therapy. Commonly available agents within each drug class are listed in Table 291.2.

Recommended regimens for first-line therapy include the combination of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with either a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI), or an integrase inhibitor. PIs require pharmacokinetic boosting with ritonavir, a potent cytochrome P450 3A4 inhibitor.

Table 291.1 Common laboratory evaluation of the HIV-infected patient

Test	Comment
HIV-specific tests	
Plasma HIV RNA (viral load)	
CD4+ lymphocyte count (absolute and percentage)	
Baseline HIV resistance testing (HIV genotype)	
HLA-B5701 assay	Presence of this marker is associated with increased risk of abacavir hypersensitivity reaction
Co-infection/opportunistic diseases assessment	
CD4 > 350	
Serological testing for syphilis	T.pallidum EIA or rapid plasma reagin (RPR)
Serological testing for Hepatitis A, B, and C	
Tuberculosis screen	
CD4 < 200	
Consider PJP	Bronchoscopy is required to confirm the diagnosis
CD4 < 100	
Toxoplasma Serology	Disease seen in those with CD4 < 100
Serum Cryptococcal Antigen	Sensitive screen for cryptococcal meningitis
CD4 < 50	
AFB blood cultures	Disseminated *Mycobacterium avium* complex seen with CD4 < 50
CMV	Serology and ophthalmology screen with CD4 < 50

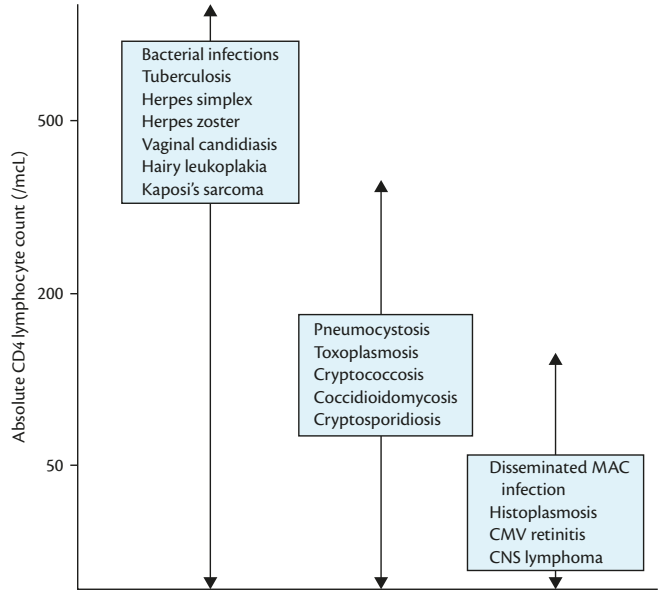


Fig. 291.1 Relationship of CD4 count and risk of opportunistic infections. CMV, cytomegalovirus; CNS, central nervous.
Reproduced from *Current Diagnosis and Treatment*, McPhee S et al., Figure 31-1, page 1350, Copyright 2007 McGraw-Hill Education.

Potential issues relating to cART in the ICU

When to start therapy/discontinuation of therapy

Initiation of antiretroviral therapy is rarely required on an urgent basis within the ICU for individuals who are newly diagnosed, or who have not previously been receiving treatment. In most circumstances, baseline HIV-related laboratory work (Table 291.1) can be completed to determine an optimal regimen. Consultation with an HIV-experienced physician/service may aide in selecting appropriate therapy and with linkage to care for long-term management.

In circumstances where the individual has presented with an opportunistic infection, early initiation of cART is desirable to prevent further morbidity. Results of an open-label trial have demonstrated fewer AIDS progression events/deaths in those initiating therapy after completing 14 days of treatment for the underlying infection [8].

A potential risk of early therapy is the development of immune reconstitution inflammatory syndrome.

Commonly, patients with underlying HIV may already be receiving antiretroviral therapy when admitted to the ICU. This poses concerns in terms of potential drug-drug interactions, poor absorption of medications in critically ill patients, and the risk of resistance if medications are abruptly discontinued. Agents such as the NNRTI class are known to have longer pharmacological half-life, leading to functional monotherapy if the cART regimen is stopped abruptly. This period of monotherapy is associated with the development of drug resistance [9]; if a regimen is to be discontinued due to NNRTI toxicity, then the offending agent should be substituted for another agent such as a PI if at all possible [10]. If the entire NNRTI-containing regimen or integrase inhibitor is to be discontinued, a staggered stop in which the nucleoside backbone is continued for an additional 7–10 days can be considered [6,7].

Both the NNRTI and PI classes are active at the level of the cytochrome P450 iso-enzyme system, with the potential to act either as potent inducers or inhibitors of metabolism of other medications, or conversely to have their levels affected by the action of other medications with similar properties. As such, use of certain anti-arrythmics, antihistamines, and even some benzodiazepines may be contraindicated, either relatively or absolutely [11].

Immune reconstitution syndrome

Suppression of HIV replication through the use of cART, and the associated CD4 cell count rebound, has led occasionally to exaggerated inflammatory responses to newly recognized antigens. This phenomenon has been named immune reconstitution inflammatory syndrome (IRIS). Proposed criteria include documented viral load decreases in addition to new or worsening symptoms of an infectious or inflammatory condition after initiation of HAART [12]. Currently IRIS is thought to be due to the interactions between the degree of immune recovery, previously unrecognized (subclinical or residual) antigenic burden and possible host genetic factors. Clinical management usually includes therapy with nonsteroidal

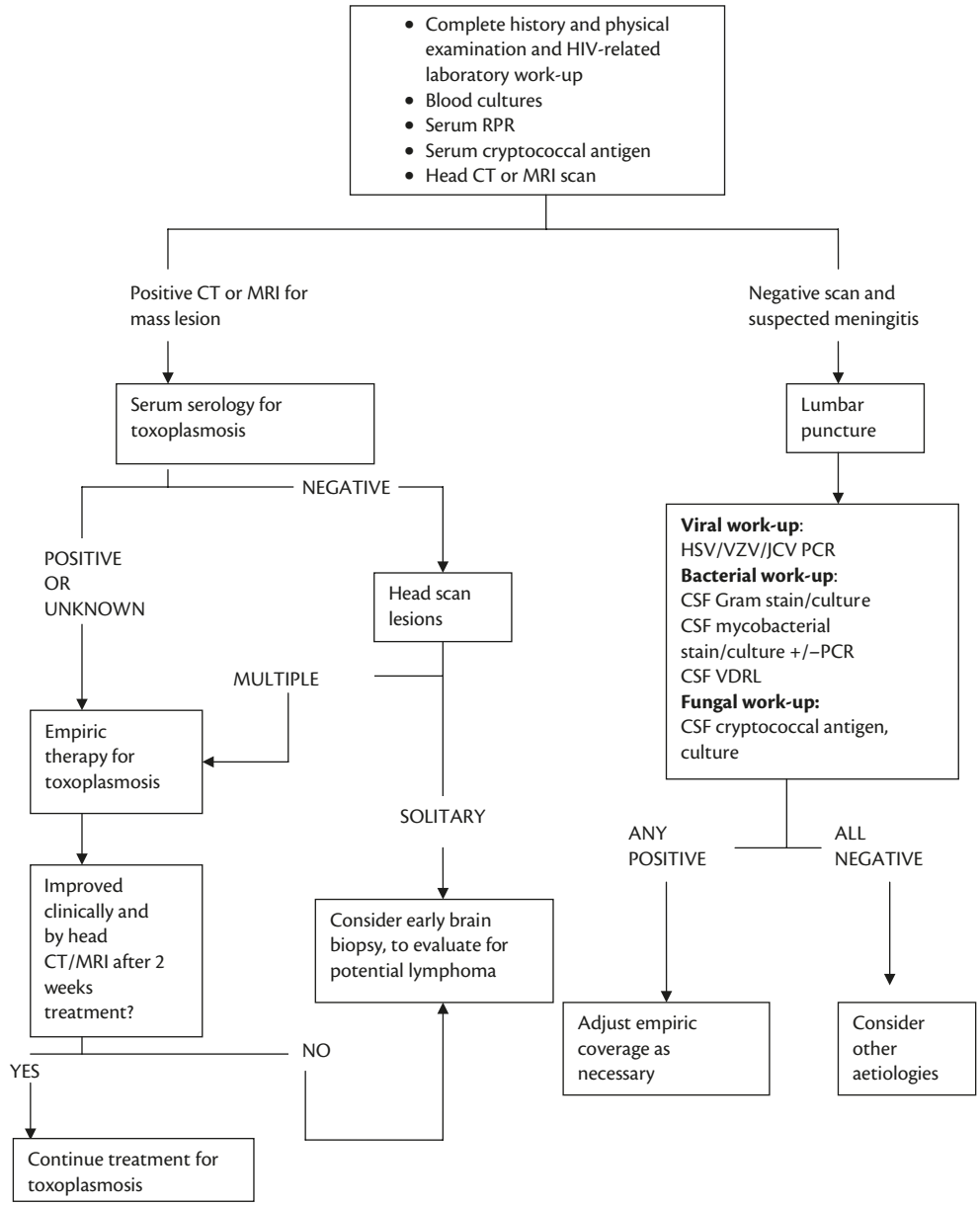


Fig. 291.2 Diagnostic algorithm for infectious aetiology of mental status changes in immunocompromised HIV-infected patients.

anti-inflammatories or corticosteroids, and antiretroviral therapy should be continued unless life-threatening features are present.

Approach to the HIV-infected patient in the ICU

The majority of presentations of HIV-infected patients to the intensive care unit are due to issues independent of their HIV such as trauma, neurological events, post-operative care, sepsis, and respiratory failure. One observational study from San Francisco found that only 21% of HIV positive patients admitted to the ICU over a 5-year period were admitted for HIV-related concerns. This was further reduced to 12% HIV associated admissions in those receiving cART [13].

Trauma-related outcomes amongst HIV-infected patients are similar to the general population, with the exception of increases in renal/respiratory and infectious complications [14,15]. In burn patients, HIV status does not affect outcome [16]. HIV-infected patients undergoing surgery (both general and orthopaedic) have been noted to have an increased risk for infection, and advanced disease with CD4 cell count <50 cells/mm^3 has been associated with an increased risk of complications [17].

Comorbidities related to the aging of the HIV-infected population including cardiovascular disease or end-stage liver disease related to hepatitis-C co-infection are also common reasons for ICU support.

It is important to identify HIV status early on in the history and locate the most recent CD4 count, CD4 percentage, and HIV viral

Table 291.2 Common antiretroviral agents by drug class

Class	Agent	Common side effects/comments
Nucleoside reverse transcriptase inhibitors (NRTIs)	Lamivudine (3TC)*	
	Emtricitabine (FTC)*	
	Tenofovir*	Renal impairment, classically Fanconi's syndrome with proximal tubular injury
	Abacavir*	Hypersensitivity reaction, requires prescreening with HLA B5701 assay
	Zidovudine (AZT)	Anaemia. An IV formulation is available
	Didanosine (DDI)	Pancreatitis, lactic acidosis
	Stavudine (D4T)	Pancreatitis, lactic acidosis
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz*	Potentially teratogenic, neuropsychiatric side effects common in first 4 weeks
	Nevirapine	Hypersensitivity reaction. Should not be used in men with CD4 > 400 and women with CD4 > 250 cells/mm^3
	Etravirine	
	Rilpivirine*	Should not be used if viral load > 100,000 copies/mL
Protease inhibitors These require boosting by ritonavir	Atazanavir*	Requires acid environment for absorption, concomitant proton pump inhibitor therapy should be avoided Causes indirect hyperbilirubinaemia
	Darunavir*	Potential cross-reactivity in severe sulpha allergy
	Lopinavir	Only agent co-formulated with ritonavir
	Saquinavir	
	Fosamprenavir	
Integrase inhibitors	Raltegravir*	Few side effects, but twice daily dosing recommended
	Elvitegravir*	Requires boosting with cobicistat
	Dolutegravir*	
Entry inhibitors	Enfuvirtide	Administered by subcutaneous injection twice daily
CCR5 antagonists	Maraviroc	Requires prescreening with viral tropism assay to evaluate if CCR5 coreceptor is utilized in binding process

*Common first-line agents.

load results. This essential information frames the subsequent clinical and investigational plan: a suppressed CD4 count may be indicative of opportunistic infections/malignancies which could account for the current presentation. The CD4 percentage is a useful adjunct as during acute illness the total lymphocyte population may be reduced, but the ratio will remain preserved and thus reflect more accurately the degree of immune suppression.

HIV associated reasons for ICU admission

Respiratory disease

Pulmonary manifestations of HIV infection are diverse, and include both infectious and non-infectious conditions (see Box 291.1) [18]. Opportunistic infections and malignancies should be considered when the CD4 cell count is below 200 cells/mm^3 although *Pneumocystis jirovecii* (formerly *carinii*) pneumonia (PJP) may occasionally present at higher CD4 thresholds.

Initial therapy should include broad-spectrum antimicrobial therapy, and empiric influenza coverage should also be considered during the winter seasons.

Empiric coverage for PJP is not unreasonable if the clinical or radiographic findings are suggestive of this diagnosis. PJP typically presents as a sub-acute condition, with a history of progressive exertional dyspnoea accompanied by fever, cough and, occasionally, spontaneous pneumothorax. Classically, radiographic imaging demonstrates bilateral interstitial infiltrates.

Laboratory abnormalities may include an elevated lactate dehydrogenase, although this is not diagnostic. Bronchoscopy with bronchial brushings and bronchoalveolar lavage (BAL) can be used to establish the diagnosis.

Intravenous trimethoprim-sulphamethoxazole is recommended for severely ill patients (e.g. PaO_2 <70 mmHg, A–a gradient >45 mmHg) for 21 days. Intravenous trimethoprim-sulphamethoxazole usually is associated with a daily volume of 1–2 litres of fluid as a diluent which can be problematic for the patient managed with a fluid restricted strategy which is standard of care in Acute Respiratory Distress Syndrome (ARDS) patients. Adjunctive corticosteroids are recommended in severe cases and have been shown to reduce mortality and morbidity [19].

Patients may worsen clinically during the initial 24–48 hrs of treatment, but usually show signs of improvement by about the 5th day. A meta-analysis of salvage therapy suggested that clindamycin in combination with primaquine was the most effective alternative

Box 291.1 Pulmonary conditions seen in HIV-infected patients

Viral infections

- Influenza.
- HSV.
- CMV.

Bacterial infections

- *Streptococcus pneumoniae.*
- *Haemophilus influenza.*
- *Pseudomonas aeruginosa.*
- *Legionella pneumonia.*
- *Rhodococcus equi.*

Mycobacterial infections

- *Mycobacterium tuberculosis.*
- *Mycobacterium avium complex.*

Fungal infections

- *Pneumocystis jiroveci.*
- *Cryptococcus neoformans.*
- *Histoplasma capsulatum.*
- *Coccidioides immitis.*
- *Aspergillus fumigatus.*

Malignancy

- Carcinoma of the lung.
- **Lymphoma**: Non-Hodgkin's lymphoma
- **Human Herpes 8 associated conditions:**
  - Kaposi's sarcoma.
  - Multicentric Castleman's disease.
  - Primary effusion lymphoma.

Other conditions

- Chronic obstructive pulmonary disease.
- Pulmonary hypertension.
- Bronchiectasis.

Adapted from Hull MW, Phillips P, Sin D, Man P, Montaner JSG. Pulmonary Manifestations of HIV. In *AIDS the First 30 Years*. Hall and Hall. 2011.

to the initially prescribed regimen [20], and older therapies such as pentamidine are not recommended unless allergy limits options.

Neurological manifestations

Causes of altered mental status in HIV infection in patients in the ICU may represent HIV-related opportunistic infection or associated systemic illness or may represent the many causes of altered mental status in the general ICU population. The prevalence of these opportunistic infections is dependent upon the level of immune suppression. In addition to standard viral and bacterial aetiologies of meningoencephalitis, opportunistic infections such as tuberculosis, *Cryptococcus neoformans* and Toxoplasma must be considered. With advanced disease (CD4 cell counts <50 cells/mm^3) progressive multifocal leukoencephalopathy (PML) associated with JC virus, and primary CNS lymphomas must be considered. An initial approach is suggested in Fig. 291.1.

Cryptococcal meningitis was seen in 5–10% of patients in the pre-cART era presenting as an acute or subacute onset meningitis with progressive symptoms of headache and often fever. Patients with cryptococcal meningitis may also have photophobia, drowsiness, reduced visual acuity, and papilloedema. Neuro-imaging may be normal or show parenchymal enhancement or cryptococcomas. A positive serum cryptococcal antigen has high sensitivity for diagnosis, however a lumbar puncture is mandatory to evaluate for an elevated opening pressure. Examination of the CSF may not reveal significant abnormalities other than elevated protein—in advanced HIV disease the CSF white blood count may be low, but may demonstrate lymphocytic predominance.

Therapy consists of amphotericin B (0.7 mg/kg/day) or liposomal preparations of amphotericin (4–6 mg/kg/day) in conjunction with flucytosine (100 mg/kg daily in four divided doses) for two weeks, followed by fluconazole once CSF sterilization is documented. If the opening pressure is elevated at presentation, daily lumbar punctures are recommended to decrease intracranial pressure. If this approach is unsuccessful, CSF shunt should be considered [19].

Conclusion

Antiretroviral therapy has provided major advances in the care of the HIV infected patients and increasingly transformed HIV into a chronic controllable disease in North America. HIV itself should not be considered a reason to limit provision of care as careful medical management of the acutely unwell HIV positive patients lead to outcomes that approach those of the general population.

References

1. Nakagawa F, Lodwick RK, Smith CJ, et al. (2012). Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS*, **26**(3), 335–43.
2. World Health Organization. (2014). *HIV/AIDS*, Fact Sheet 360, updated November 2014. Available at: http://www.who.int/mediacentre/factsheets/fs360/en/ (accessed 5 January, 2015).
3. Bradley H, Hall HI, Wolitski RJ, et al. (2014). Vital signs: HIV diagnosis, care, and treatment among persons living with HIV—United States, 2011. *Morbidity and Mortality Weekly Report*, **63**(47), 1113–17.
4. Mellors JW, Munoz A, Giorgi JV, et al. (1997). Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Annuals of internal medicine*, **126**(12), 946–54.
5. Gunthard HF, Aberg JA, Eron JJ, et al. (2014). Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel. *Journal of the American Medical Association*, **312**(4), 410–25.
6. Williams I, Churchill D, Anderson J, et al. (2014). British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (updated November 2013). *HIV Medicine*, **15**(1), 1–85.
7. Panel on Antiretroviral Guidelines for Adults and Adolescents (2014). *Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents*. Department of Health and Human Services. November 13, 2014. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf (accessed 5 January, 2015).

8. Zolopa A, Andersen J, Powderly W, et al. (2009). Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PloS One*, **4**(5), e5575.
9. Fox Z, Phillips A, Cohen C, et al. (2008). Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS*, **22**(17), 2279–89.
10. Taylor S, Boffito M, Khoo S, Smit E, and Back D. (2007). Stopping antiretroviral therapy. *AIDS*, **21**(13), 1673–82.
11. Lanoix JP, Andrejak C, and Schmit JL. (2011). Antiretroviral therapy in intensive care. *Médicines et Maladies Infectieuses*, **41**, (7),353–8.
12. Robertson J, Meier M, Wall J, Ying J, and Fichtenbaum CJ. (2006). Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. *Clinical Infectious Diseases*, **42**(11), 1639–46.
13. Powell K, Davis JL, Morris AM, Chi A, Bensley MR, and Huang L. (2009). Survival for patients With HIV admitted to the ICU continues to improve in the current era of combination antiretroviral therapy. *Chest*, **135**(1), 11–17.
14. Stawicki SP, Hoff WS, Hoey BA, Grossman MD, Scoll B, and Reed JF 3rd (2005). Human immunodeficiency virus infection in trauma patients: where do we stand? *Journal of Trauma*, **58**(1), 88–93.
15. Duane TM, Sekel S, Wolfe LG, Malhotra AK, Aboutanos MB, and Ivatury RR. (2008). Does HIV infection influence outcomes after trauma? *Journal of Trauma*, **65**(1), 63–5.
16. Edge JM, Van der Merwe AE, Pieper CH, and Bouic P. (2001). Clinical outcome of HIV positive patients with moderate to severe burns. *Burns*, **27**(2),111–4.
17. Wiseman SM, Forrest JI, Chan JE, et al. (2012). Factors predictive of 30-day postoperative mortality in HIV/AIDS patients in the era of highly active antiretroviral therapy. *Annuals of Surgery*, **256**(1), 170–6.
18. Hull MW, Phillips P, and Montaner JS. (2008). Changing global epidemiology of pulmonary manifestations of HIV/AIDS. *Chest*, **134**(6), 1287–98.
19. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, and Masur H. (2009). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *Morbidity and Mortality Weekly Report*, **58**(RR-4), 1–207; quiz CE1–4.
20. Smego RA, Jr., Nagar S, Maloba B, and Popara M. (2011). A meta-analysis of salvage therapy for *Pneumocystis carinii* pneumonia. *Archives of Internal Medicine*, **161**(12), 1529–33.

PART 13.4

Tropical diseases

CHAPTER 292

Diagnosis and management of malaria in the ICU

Christopher J. M. Whitty

Key points

- Malaria is a very common cause of severe infection from Africa, Asia, and Latin America. All severely-ill patients from these areas should have a malaria blood film.
- There is good evidence that artesunate reduces mortality compared to quinine, but do not delay treatment with quinine if artesunate is not available.
- Cerebral malaria, renal failure, and acute respiratory distress syndrome (ARDS) are the major syndromes in adults. There is little evidence for specific adjunctive treatments for these.
- Severe malaria is a significant risk factor for bacterial sepsis in children, but probably not adults.
- The prognosis for adult malaria patients if they survive is good.

Introduction

Malaria is the commonest life-threatening tropical infection. Diagnosed and treated early it will seldom require critical care and the outlook is good. Once severe malaria is established, it is a serious multi-system disease, which can continue to evolve even once the malaria parasites have cleared from the blood. This chapter is written for critical care physicians caring for predominantly adult patients. There are important differences from the management of severe childhood malaria, and as much of the data comes from children these are highlighted.

Epidemiology and when to suspect malaria

Malaria occurs in most countries in Africa, Asia, and Latin America, but incidence varies widely. In many parts of sub-Saharan Africa people can have clinical attacks of malaria four or more times a year. Malaria is much less common from most of Asia and Latin America, with many areas malaria-free. This can mean the diagnosis is not suspected and therefore delayed. The great majority of malaria that leads to critical illness is falciparum malaria, which causes around 95% of malaria in Africa. Vivax malaria is the most common form in much of Asia and Latin America, and relatively rarely causes critical illness, although severe cases have been more frequently recognized recently and a benign course cannot be assumed. In returning travellers presenting in non-endemic countries over 90% of cases of falciparum malaria will present within 3 months of return and most within a month, although delayed presentation of up to a year after return does occasionally occur. Very occasionally unexpected malaria is caused by blood transfusion, or sharing needles with intravenous drug use.

Diagnosis of malaria

Malaria can present in multiple ways; no clinical symptom or sign either proves or excludes the diagnosis. In a critically unwell patient with an exposure history fever, unconsciousness, or fitting, jaundice or splenomegaly are suggestive. Whilst a history of fever is usual, around half of patients with malaria are afebrile at the time of presentation. A malaria blood test is therefore essential.

For management of the critically-ill patient blood film microscopy for parasites remains the best test. It identifies the species of malaria, and importantly, the percentage of red cells parasitized. Rapid diagnostic tests for malaria are mostly as sensitive as microscopy, and may speed the diagnosis, but they are not a substitute for microscopy in severely ill patients as they give an all-or-nothing response. In critically-ill patients prior to treatment a sufficient number of parasites for diagnosis will almost always be present so microscopy is sensitive and specific.

Initial assessment of severity

Severe malaria can present with a number of syndromes. These may occur in isolation, or in any combination.

The most well-known is cerebral malaria. Strictly unrousable coma in the presence of asexual malaria parasites, any reduction of consciousness, neurological signs or fitting should be treated as cerebral malaria. It generally presents before starting antimalarial treatment, but especially in patients who present with very high parasite counts cerebral malaria may occur in the first 48 hours after starting treatment as parasites mature and begin to stick down (sequester) in the blood vessels in the brain.

Renal failure may present as oliguria or anuria, or be diagnosed from raised creatinine or blood urea. Renal failure may be present at initial diagnosis or develop in the first few days after treatment has started, including when parasites have cleared from the blood. There are potentially two components to renal failure in malaria; pre-renal failure in febrile patient not drinking adequately, and the direct effects of malaria on the kidney (the exact pathological mechanism is currently unknown). If there is any doubt whether prerenal failure is a major component rapid fluid challenges will help identify it. Renal failure is common in critically-ill adults with malaria (but rare in children) [1].

Malaria-associated respiratory distress in adults is usually due to problems in the lungs, with two potential causes. Pulmonary oedema, often caused or exacerbated by enthusiastic rehydration in patients with renal failure, is reversible. Adult respiratory distress syndrome (ARDS)/acute lung injury (ALI) often presents late in the course of severe malaria, including days after malaria parasites have cleared from the blood. In children respiratory distress is also a sign of severe disease, but is generally caused by acidosis rather than poor oxygen transfer and lungs are normal. In both adults and children coexisting pneumonia should be excluded.

Of the uncommon manifestations of severe malaria the most important is disseminated intravascular coagulation (DIC), and occasionally cerebral or other serious bleeds where there is no DIC due to the very low platelets which are commonly found in severe malaria.

In contrast to most critically-ill patients with sepsis, shock is relatively rare except when there is coexisting bacterial sepsis. Bilirubin is often raised due to massive haemolysis, but liver function rarely significantly impaired.

Two warning signs in otherwise well patient with malaria make it likely the patient will deteriorate even after starting treatment. The first is finding a high parasite count in the peripheral blood. Patients with parasite counts of greater than 10%, even if appearing initially well, have a very high chance of deteriorating over the next 48 hours as parasites mature. In high resource settings where malaria is not endemic, it is prudent to treat any patient with parasite count greater than 2% with parenteral drugs even if they are otherwise well as their risk of severe disease is significantly raised [2]. The second is jaundice which in the presence of malaria generally indicates massive haemolysis.

Three groups are at particular risk of poor outcomes; elderly patients as mortality increases steadily with age [3], pregnant patients where the risk of complications in the pregnancy are significant, and patients with AIDS.

Treatment

Antimalarial treatment

All patients with severe malaria should be treated rapidly with high doses of effective parenteral antimalarials, and this is by far the most important step in managing critically-ill patients. In practice the choice is between quinine (or in the USA quinidine) and artesunate. Quinine has been the mainstay of managing severe malaria for over a century, and remains an effective drug. In the last few years however there has been clear evidence from large randomized trials in children and adults in Africa and Asia that artesunate has a significant mortality advantage [4,5]. When both drugs are available therefore artesunate is preferable. No head-to-head comparisons of quinidine with artesunate have been undertaken, but there is no reason to believe that it would perform better than quinine so artesunate remains the best drug available. At present however stocks of artesunate are limited in many countries and the priority should be to treat as fast as possible with a high dose of an intravenous effective drug; better to use quinine (or quinidine) immediately than artesunate after several hours delay. In most non-endemic countries specialist centres hold critical stocks of artesunate.

A number of factors make artesunate particularly appropriate. Where patients have hyperparasitaemia (>10%) artesunate brings down parasite counts much faster than quinine, kills all ages of parasites, and it is in this group that the biggest survival advantage was found in trials in adults [4]. In patients who are at risk of arrhythmia quinine and quinidine are arrhythmogenic. Quinine has a number of unpleasant, but generally non-severe side-effects, but an important one is that it is hypoglycaemic, and in patients on quinine blood glucose must be monitored closely. The side effects of quinidine are very similar to those of quinine, but there is a roughly 2 times higher risk of arrhythmias with quinidine for the same malaria killing dose.

Quinine should have a loading dose of 20 mg/kg as a slow infusion, followed by 10 mg/kg 8–12-hourly. Artesunate is given at a dose of 2.4 mg/kg as a bolus, repeated at 12 and 24 hours, then daily. Both should be continued until either parasites have cleared from the blood, or the patient is able to take oral treatment and has no remaining signs of severe disease (again until parasites are clear). For oral follow-up a combination of two drugs should be used with either quinine or an artemisinin drug; most countries have local guidelines for oral treatment.

Treatment of complications

Other than rapidly treating malaria, the majority of the treatment of the critically-ill malaria patient is supportive, and does not differ significantly from the management of other critically-ill patients with multisystem disease. Many adjunctive therapies such as steroids have been tried, generally based on contemporary (often erroneous) beliefs about malaria pathophysiology, but almost all have fallen into disuse when proper clinical assessment demonstrated either they do not work or that they do harm. The evidence base for managing severe malaria in children is generally better than that in adults. Unfortunately, as the pathophysiology of the disease differs between adults and children, it is unwise to extrapolate between them.

Cerebral malaria

The most important thing in cases of reduced consciousness and malaria is to ensure that they do not have hypoglycaemia, which can be caused by the parasite and in patients on quinine the treatment.

In children in particular there is also risk of subclinical fitting for which the treatment is of complex partial status with antiepileptic drugs. This can manifest by subtle twitchings or, where available, EEG monitoring. Based on the finding that they reduce the risk of fitting, for a time prophylactic anticonvulsants were recommended for adults and children, but a trial in Kenyan children which demonstrated reduced fitting, but increased mortality means they are now generally only recommended in established fitting [6].

Because of evidence of some degree of brain oedema in cerebral malaria, steroids and mannitol have both been tried and seem to increase risks if anything.

In adults who recover even from prolonged (i.e. many weeks) unconsciousness in malaria, neurological deficits are surprisingly rare compared to other neurological infections. The great majority of patients with cerebral malaria will recover with no noticeable deficits. The rate of neurological sequelae is higher in children.

Renal failure

As with all acute renal failure the key is to minimize electrolyte disturbance, particularly high potassium and this may well require haemodialysis or haemofiltration. There is very weak evidence that early haemofiltration speeds recovery. Although renal support may be needed for some weeks following recovery from malaria, kidneys almost invariably recover back to their normal function with only a few case reports of persisting renal failure.

A very rare complication, although it used to be common when quinine was given in repeated low doses as prophylaxis, is blackwater fever (almost black urine). Almost all cases now are associated with G6PD deficiency, and are probably caused by quinine related drugs causing haemolysis. It is not a reason to stop therapy provided the haemoglobin is monitored and maintained when necessary.

Adult respiratory distress syndrome, disseminated intravascular coagulation

These are treated as with any other patients with these syndromes with no malaria-specific therapy proven to help other than treating the underlying condition.

Hyperparasitaemia and exchange transfusion

There is a logic that in patients treated with quinine who have very high parasite counts (>20% red cells) physically removing parasites will prevent them from developing into mature forms that sequester in vital organs. Quinine exerts the majority of its effect on mature parasites so many of these immature forms will progress if not removed even when on quinine treatment. In some centres it is therefore the practice with these very high parasite counts either to undertake an exchange transfusion where six units of blood are removed and six replaced simultaneously, or mechanical red-cell exchange. There is relatively little evidence either that this does any good, or any harm, beyond the usual risks of transfusion and substantial fluid shifts [7]. In patients treated with artesunate parasite counts drop rapidly, and the drug kills young parasite forms, so the logic of exchange transfusion largely disappears. Exchange transfusion is therefore now rarely recommended.

Fluid management

In adults, how best to manage fluids in malaria patients is hotly debated, largely because little convincing evidence exists. There is weak evidence that over hydration of patients leading to pulmonary oedema may increase the risk of ARDS. Malaria physicians are therefore usually cautious about minimizing the risk overhydration. In children a recent major trial showed convincingly that bolus fluids lead to increased mortality; it is not clear whether this is relevant to adults [8].

Shock, and coexisting bacterial sepsis

Shock is relatively rare in malaria except when patients are significantly dehydrated, there is coexisting bacterial sepsis (particularly Gram-negative sepsis) and in rare cases of occult gastrointestinal bleeds with DIC. Patients who become shocked with malaria therefore should be treated with broad spectrum antibiotics with Gram-negative cover in addition to supportive treatment. In children, severe malaria seems to increase substantially the risk of sepsis, but this association is less clear in adults [9]. It is therefore prudent to treat children prophylactically with antibiotics if they have severe malaria even without shock.

Anaemia and thrombocytopenia

Life-threatening anaemia is a common manifestation of malaria in children in low resource settings, but in non-pregnant adults it is rare, although some degree of anaemia is likely in all malaria cases because malaria destroys red cells. Transfusion is only likely to be useful in cases where haemoglobin has fallen substantially, or there is cardiovascular compromise. There is no consensus over what level of haemoglobin is appropriate treat in the absence of cardiovascular compromise, although in high resource settings Hb below 7 g/dL is a reasonable threshold. Thrombocytopenia is invariable in severe malaria. Except when coexisting with DIC it rarely causes significant clinical problems, and there is little association between scale of thrombocytopenia and severity of malaria. Platelet transfusions are probably only useful in the context of active bleeding where platelets fall below 30/L as hypersplenism means transfused platelets will be rapidly consumed.

Long-term prognosis

Depending on syndrome, mortality from severe malaria by the WHO criteria in adults is likely to be 5–15%. In a high resource settings childhood deaths from malaria are extremely rare [3] although in Africa childhood deaths are the great majority. In patients with isolated cerebral malaria and no other organ involvement, if the patient survives the first 48 hours the outlook is usually good. Deaths from isolated renal failure should not occur where haemodialysis and haemofiltration are available. The mortality from ARDS, the rarest of the major syndromes, is the highest with over 50% reported in some series.

The majority of those who die from malaria in well-resourced critical care settings do so from the complications associated with long intensive care unit stays, in particularly nosocomial infection once parasites have cleared. The great majority of patients with severe malaria will survive, even if unconscious for a long time, and their outlook for making a full recovery is good, with very rare cases of significant neurological impairment or other disability, although these do occur.

References

1. Marks ME, Armstrong M, Suvari M et al. (2013) Severe imported falciparum malaria among adults requiring intensive care: a retrospective study at the hospital for tropical diseases, London. *BMC Infectious Diseases*. **13**, 118.
2. Phillips A, Bassett P, Zeki S, Newman S, and Pasvol G. (2009). Risk factors for severe disease in adults with falciparum malaria. *Clinical Infectious Diseases*, **48**, 871–8.
3. Checkley AM, Smith A, Smith V, et al. (2012). Risk factors for mortality from imported falciparum malaria in the United Kingdom over 20 years: an observational study. *British Medical Journal*, **344**, e2116.
4. Dondorp A, Nosten F, Stepniewska K, et al. (2005). Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet*, **366**, 717–25.
5. Dondorp AM, Fanello CI, Hendriksen IC, et al. (2010). Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet*, **376**, 1647–57.

6. Crawley J, Waruiru C, Mithwani S, et al. (2000). Effect of phenobarbital on seizure frequency and mortality in childhood cerebral malaria: a randomised, controlled intervention study. *Lancet*, **355**,701–6.
7. Auer-Hackenberg L, Staudinger T, Bojic A et al. (2012) Automated red blood cell exchange as an adjunctive treatment for severe *Plasmodium falciparum* malaria at the Vienna General Hospital in Austria: a retrospective cohort study. *Malaria Journal*, **11**, 158.
8. Maitland K, Kiguli S, Opoka RO, et al. (2011). Mortality after fluid bolus in African children with severe infection. *New England Journal of Medicine*, **364**, 2483–95.
9. Nadjm B, Amos B, Mtove G, et al. (2010). WHO guidelines for antimicrobial treatment in children admitted to hospital in an area of intense *Plasmodium falciparum* transmission: prospective study. *British Medical Journal*, **340**, c1350.

CHAPTER 293

Diagnosis and management of viral haemorrhagic fevers in the ICU

Emersom C. Mesquita and Fernando A. Bozza

Key points

- Always suspect viral haemorrhagic fevers (VHFs) in a sick traveller from an endemic area in whom an alternative diagnosis cannot be established.
- Always perform a malaria test (thick blood films) in a VHF suspected case and, if not quickly available and/or reliable, start empirical antimalarial treatment.
- Immediately place the patient in a negative pressure room and alert local infection control unit, state, and national authorities.
- Health care professionals should always use appropriate barrier and aerosol precautions. Access to patient's room should be limited to only staff personnel.
- Supportive therapy is the main stay of treatment, but specific antiviral agent (ribavirin), preferably by intravenous (iv) route, should be started early in the diagnosing setting. Apply easily done diagnostic test (RT-PCR) and discontinue antiviral therapy if the diagnosis of filoviral or flaviviral infection is made.

Introduction

Viral haemorrhagic fevers (VHFs) represent a group of clinically indistinguishable diseases caused by four different families of small, enveloped, RNA virus: *Arenaviridae, Filoviridae, Bunyaviridae*, and *Flaviviridae*.

VHFs poses great medical challenge because:

- Diseases are associated with a high mortality rate.
- Many VHFs have the potential for person-to-person transmission (Filoviruses, Arenaviruses, and Bunyaviruses).
- Widespread international travel made possible for viral agents to migrate from endemic areas to non-endemic areas.
- Early diagnosis and treatment are paramount for improving clinical outcome and for minimizing health care associated transmission.

Main clinical and laboratory findings, major viral agents, as well as epidemiological characteristics of VHFs are depicted in Table 293.1.

VHFs are characterized by acute fever, coagulation disorders and organ specific syndromes such as encephalitis, pneumonitis, nephritis, and arthritis. The severity and clinical presentation of VHFs may vary from an unspecific febrile disease to severe forms with severe bleeding, intravascular coagulation, multiple organ dysfunctions and death. Often, the mechanisms of severe disease include a combination of endothelial dysfunction, causing capillary leak syndrome and bleeding disorders, associated with thrombocytopenia and disseminated intravascular coagulation. Different organ specific syndromes can be more associated to a specific virus family [1–6].

In the last years, a substantial progress in the understanding of pathogenesis and dissemination of VHFs has been made. However, to date, lack of available vaccines for most VHFs, absence of potent specific antiviral therapies and the potential for bioterrorism usage of these agents makes VHFs a major global public health concern [7].

Dengue is the most frequent haemorrhagic viral disease and re-emergent infection in the world. Currently, 25–30% of the world's population lives in areas at risk of dengue infection. It is estimated that there are 50 to 100 million cases of dengue infection per year, and the global incidence of dengue continues to increase. In the last decades a progressive global expansion of the disease including a higher frequency of severe forms (DHF/DSS) was observed. This expansion included tropical and subtropical areas in Americas, Europe, Asia, and Africa. Recently, the burden of dengue was reviewed as more than three times the previously estimated by World Health Organization (WHO). Due to its public health relevance, severe dengue will receive special attention in this chapter.

Pathogenesis

Information regarding the pathogenesis of VHF in humans is limited and, in general, comes from clinical observations and experimental infections in non-human primates (NHP). Careful interpretation of experimental studies is necessary due to virus type, viral load, administration route, host previous immunity, and animal species utilized in these studies.

Endothelial infection is a common finding among the diseases, but can be limited or widespread depending on the agent. In the case of Ebola haemorrhagic fever (EHF) and in severe forms of Rift Valley fever (RVF), the virus has a highly destructive interaction

Table 293.1 Main viral haemorrhagic fevers

Disease	Ebola HF	Marburg HF	Lassa HF	HFRS	CCHF	RVF	Severe dengue	Yellow fever
Causative virus (Family name)	Ebola (Filoviridae)	Marburg (Filoviridae)	Lassa (Arenadiridae)	Hantan (Bunyaviridae)	CCHV (Bunyaviridae)	RV (Bunyaviridae)	Dengue (Flaviviridae)	Yellow fever (Flaviviridae)
Distribution	Africa	Africa	West Africa†	Eastern Russia, Korea, China, and Balkans	Africa, Middle east, central Asia, Europe	Africa, Saudi Arabia and, subsequently, Yemen	Endemic in Asia, the Pacific, the Americas, Africa, and the Caribbean	Africa and tropical Americas
Transmission	Bat	Bat	Rodent	Rodent	Tick	Mosquito	Mosquito	Mosquito
Human-to-human transmission	Yes	Yes	Yes	Yes	Yes	No	No	No
Incubation (days)	2–21	2–21	7–21	7–21	3–12	2–10	3–10	3–6
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Haemorrhagic events	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Leucopenia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Thrombocytopenia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liver toxicity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Prominent
Renal impairment	Yes	Yes	Yes	Prominent	Yes	Yes	Yes	Yes
Mortality rate	High	High	High	High	High	High	High	High

†Other pathogenic members of the *Arenadiridae* family can also be found in the Americas.

with the endothelium leading to vascular leakage, disseminated intravascular coagulation (DIC), shock, and death. Arenaviruses and dengue, in contrast, infect the endothelium, but these cells are not the primary cellular targets and cause little direct damage to the endothelium; they may induce abnormal cytokine production and disrupt endothelial function, but this is in the absence of obvious morphologic signs. Other viruses, such as Hantaviruses, are virtually non-cytopathic, can infect cells in vitro without inducing any permeability or other major change, and depend on the host immune response to induce changes in vascular permeability [8–10].

All VHF induces thrombocytopenia. Different degrees of platelet dysfunction, including platelet activation, apoptosis, elevated clearance, and abnormal thrombopoiesis, are well documented in severe dengue, Ebola, Lassa fever, and Arenavirus infection. Decreased levels of coagulation factors, frequently observed and derived from hepatic failure or DIC, can be observed in yellow fever (YF) and RVF.

High concentrations of pro-inflammatory cytokines (cytokines storm) clearly play an important role in the different VHF infections, but the mechanisms for cytokine induction and their exact role are different and poorly understood among the infections. The clotting defects are also quite variable in both their obvious manifestations and their pathogeneses.

Most of the VHF produce very severe symptoms in their infections; however, dengue virus infections produce distinct disease outcomes. The immunopathological mechanisms responsible for the increased disease severity associated with severe dengue are only partially understood. Several lines of evidence have indicated that non-neutralizing anti-DENV antibodies play a modulatory role that involves antibody-dependent enhancement (ADE) of infection, via Fc-gamma receptor (FcγR)-facilitated virus entry. However, other factors, including altered T-cell responses, virus strain virulence, and innate immunity have been implicated in modulating the clinical outcome of the infection. These data support four non-mutually exclusive theories to explain the immune mechanisms leading to DHF [2,4,11,12]. The main theories are:

- **ADE**: anti-DENV antibodies can form non-neutralizing immune complexes with the virus and facilitate the infection of cells expressing FcγR.
- **Original antigenic sin (OAS)**: memory T-cells are abnormally activated by altered peptide epitopes that are capable of production of high levels of cytokines, but are not effective in killing infected cells.
- **Dengue strain virulence (DSV)**: specific strains of the dengue virus, of any of the serotypes, are more able to replicate in the human host tissues.
- **Host innate responses (HIR)**: the specific human genetic background influenced by environmental factors can result in inadequate innate responses, notably, dendritic cells, type I and II interferon responses and responses of the complement system.

Clinical presentation and laboratory findings

Describing in details clinical and laboratory findings of each viral agent is beyond the scope of this chapter and has been recently

reviewed elsewhere (WHO 2009 and 2013). Major clinical and laboratory features, shared by the four viral families aforementioned (*Filoviridae, Arenadiridae, Bunyaviridae, Flaviviridae*), are depicted here.

Patients usually become abruptly ill after an incubation period of 3–21 days. At presentation, fever, chills, headache, joint and muscle aches, fatigue, diarrhoea, nausea, vomiting, sore throat, and conjunctivitis can be present. Routine laboratory panel performed at this point should display leukopenia with lymphopenia, thrombocytopenia, and a mild to moderate elevation in liver enzymes (AST and ALT). Leukocytosis can also be observed usually after the second week of symptoms on filoviral infections. Prominent liver involvement is a common feature of YF and, together with patient's travel history, could help in distinguishing between different VHFs syndromes. Prominent renal impairment is a typical feature of haemorrhagic fever with renal syndrome (HFRS) and, together with a longer incubation period (usually 2 weeks) and patient's travel history, should point towards this diagnosis. As disease progresses, coagulopathy, with prolonged prothrombin (PT) and partial thromboplastin times (PTT), altered mental status, renal and liver , and DIC becomes evident. Haemorrhagic manifestations can include petechial skin rash, epistaxis, haematemesis, melena, conjunctival and venipuncture site bleeding and, finally, death.

Severe dengue is characterized by clinical and laboratorial evidence of increased capillary permeability and plasma leakage. After the febrile phase, patients experience sudden defervescence, circulatory and perfusion changes (hypotension and hypovolemic shock), ascites and pleural effusion, and organ dysfunctions such as liver failure, encephalitis, myocarditis, and clotting disorders. Usually a sudden drop of leucocytes and platelets precedes plasma leakage, and a progressive haematocrit increase can be observed reflecting the magnitude of haemoconcentration. The critical phase, which is evident in 10–15% of dengue cases, discloses the progression to severe disease. The duration of this phase is 1–3 days.

Differentials

Most important differentials are depicted in Table 293.2.

Diagnosis

Diagnosis should be considered in a sick traveller from an endemic area in whom an alternative diagnosis cannot be made (see Table 293.2 for relevant differential diagnosis). Malaria test (thick blood films) should always be performed in a suspected VHF case and, if not quickly available and/or reliable, empirical antimalarial treatment should be initiated. Lack of clinical and laboratory response to antimalarials and/or to the treatment of most common bacterial infections should raise suspicion of VHF in a patient returning from an endemic area. It is likely that most VHF suspected cases will end up with a more common definitive diagnosis; nevertheless, early diagnosis is paramount for achieving a better clinical outcome.

Table 293.2 Relevant differentials for VHFs

Bacterial and rickettsial infections	Viral and parasitic infections	Non-infectious conditions
◆ Leptospirosis ◆ Meningococcaemia ◆ Gram-negative bacterial septicaemia ◆ Typhoid fever ◆ Rocky Mountain spotted fever	◆ Malaria ◆ African trypanosomiasis ◆ Viral hepatitis	◆ Thrombotic or idiopathic thrombocytopenic purpura ◆ Haemolytic uraemic syndrome

Specific diagnoses of VHFs agents are usually obtained on blood samples by detecting specific antibodies, viral antigens (ELISA), viral nucleic acid (reverse transcriptase polymerase chain reaction (RT-PCR)) and virus isolation.

Detection of specific IgM antibodies or a four-fold increase in IgG antibody titres can be achieved by collecting acute-phase blood samples within 7 days of illness and convalescent-phase blood samples 8–20 days later. Detection of antibodies can be difficult because they are not easily detected early in the course of the diseases and some patients, usually associated with fatal outcome, fails to produce robust immune response. RT-PCR is an important diagnostic tool and offers the advantage of rapid detection with high sensitivity and specificity even in the first days of illness, when antibody titres are still low. Viral nucleic acid detected by RT-PCR can be performed even a few days after the viraemic period. Virus isolation should only be performed in laboratories biosafety level 3 or above.

Dengue infection can be firmed by detecting viral antigen (Ns1Ag), virus isolation, or RNA virus detection (RT-PCR). Around the fifth day, viremia and antigenemia disappear, which coincides with the appearance of specific antibodies. From the sixth day, IgM ELISA is the method of choice for diagnosis of dengue. High levels of IgM and low levels of IgG characterize primary infections, while low levels of IgM with high levels of IgG suggest secondary infections. In dengue endemic countries, acute clinical cases with a positive IgM are classified as probable dengue cases. The study of paired sera (acute and convalescent serum samples with the second sample being collected 15–21 days after the first sample), allows for serological confirmation of dengue infection.

Treatment in the intensive care setting

VHFs greatly resembles sepsis pathogenesis and their approach in the intensive care setting is quite similar. Intravenous volume replenishment, management of pain, anxiety and electrolyte imbalance is essential. Aggressive treatment of multi organ dysfunctions and haemorrhagic events frequently requires vasoactive drugs, haemodialysis, mechanical ventilation, platelet transfusion, and red blood cells transfusion.

Adjunctive antimicrobial therapy is usually implemented to treat coexisting or secondary infections. Antimalarial treatment should also be initiated if a malaria test (thick blood films) is not quickly available and/or reliable, and patients travel history is compatible.

Empirical antiviral treatment with Ribavirin should be started as soon as a case of VHF is suspected. Ribavirin (1-beta-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide) interfere with intracellular RNA and DNA synthesis and subsequently inhibits protein synthesis and viral replication of ribavirin-sensitive RNA or DNA viruses. Ribavirin should be preferably administered through iv route. Start with a loading dose of 30 mg/kg, followed by 16 mg/kg every 6 hours for 4 days, followed by 8 mg/kg every 8 hours for 5–10 days (Ribavirin treatment should be maintained if Arenavirus or Banyavirus infection). Ribavirin comes in vials of 1000 mg and

800 mg, to be diluted in 10 mL phosphate buffer solution. Infuse over 10–15 minutes. Major side effects and caution includes haemolytic anaemia, pancytopenia, pancreatitis, renal, and liver impairment.

The cornerstone for severe dengue therapy is a rapid recovery of the effective volaemia through an adequate fluid resuscitation (recently reviewed by WHO experts [6]). Briefly, a reference haematocrit (Ht) obtained before to start the fluid therapy, associated with the BP, will be major parameters to be used to evaluate the response to the therapy. To patients with shock, start iv fluid resuscitation with isotonic crystalloid solutions at 20 mL/kg as a bolus given over 15–30 minutes. If the patient's condition improves maintain the infusion at 10 mL/kg/hour for 1 hour more. Then gradually reduce to 5–7 mL/kg/hour for 1–2 hours, then to 3–5 mL/kg/h our for 2–4 hours, and finally to 2–3 mL/kg/hour (or less), which can be maintained for up to 24–48 hours.

When hypoperfusion signs persist after volume infusion in association with a drop in Ht it should be suspect bleeding complications. Red blood cell transfusion is indicted if there is severe overt bleeding, and transfusion of platelet concentrate is indicated for patients with lower than 50,000/mm^3 platelets with suspected severe bleeding.

If the Ht increases compared to the reference Ht or remains high continue fluid infusion at 10–20 mL/kg as a third bolus over 1 hour, colloid solution can be used. After this dose, reduce the rate to 7–10 mL/kg/hour for 1–2 hours, and then reduce the rate of infusion as mentioned previously when the patient's condition improves [15–18].

Biosafety measures

Installation of proper biosafety measures should not be delayed by any laboratory test. Notify local infection control unit and state and national authorities. All suspected cases of VHF should be immediately placed in a negative pressure room and access should be limited to necessary only staff personnel. Face shields, goggles, N-95 masks or powered air-purifying respirators, double gloves, impermeable gowns, leg, and shoe coverings should be worn while handling the patient. After handling the patient, it is mandatory to remove and discard gown, leg and shoe coverings, and gloves. Proper hand hygiene should be performed prior to the removal of facial protective equipment to minimize exposure of mucous membranes. Patient care equipment including thermometers, blood pressure cuffs and stethoscopes should be dedicated to the patient. If patient dies, handling of the body should be minimal.

Acknowledgements

The authors would like to acknowledge Ernesto Marques whose help in writing this chapter was greatly received.

References

1. Geisbert TW, Jahrling PB. (2004). Exotic emerging viral diseases: progress and challenges. *National Medicine*, **10**, S110–21.
2. Kortepeter MG, Bausch DG, Bray M. (2011). Basic Clinical and Laboratory Features of Filoviral Hemorrhagic Fever. *Journal of Infectious*, **204**(3), S810–6.
3. Meltzer E. (2012). Arboviruses and Viral Hemorrhagic Fevers (VHF). *Infectious Disease Clinic North America*, **26**(2), 479–96.
4. Paessler S, Walker DH. (2013). Pathogenesis of the Viral Hemorrhagic Fevers. *Annual Review of Pathology: Mechanisms of Disease*, **8**(1), 411–40.
5. Peters CJ, Zaki SR. (2002). Role of the endothelium in viral hemorrhagic fevers. *Critical Care Medicine*, **30**(5), S268–73.
6. Kunz S. (2009). The role of the vascular endothelium in arenavirus haemorrhagic fevers. *Journal of Thrombosis and Haemostasis*, [Internet.] Available from: http://www.schattauer.de/index.php?id=1214&doi=10.1160/TH09-06-0357 (accessed 22 April 2013)
7. Borio L, Inglesby T, Peters CJ, et al. (2002). Hemorrhagic fever viruses as biological weapons: medical and public health management. *Journal of the American Medical Association*, **287**(18), 2391–405.
8. Morens DM, Fauci AS. (2008). Dengue and hemorrhagic fever. *Journal of the American Medical Association*, **299**(2), 214–6.
9. Simmons CP, Farrar JJ, Nguyen van VC, Wills B. (2012). Dengue. *New England Journal of Medicine*, **366**(15), 1423–32.
10. Bhatt S, Gething PW, Brady OJ, et al. (2013). The global distribution and burden of dengue. *Nature*, **496**(7446), 504–7.
11. Towner JS, Khristova ML, Sealy TK, et al. (2003). Marburgvirus Genomics and Association with a Large Hemorrhagic Fever Outbreak in Angola. *Journal of Virology*, **80**(13), 6497–516.
12. Yun NE, Walker DH. (2012). Pathogenesis of Lassa fever. *Viruses*, **4**(10), 2031–48.
13. Special Programme for Research and Training in Tropical Diseases, World Health Organization, World Health Organization. (2009). Epidemic and Pandemic Alert and Response. *Dengue guidelines for diagnosis, treatment, prevention, and control*. Geneva: WHO [Internet.] Available from: http://site.ebrary.com/id/10363988 (accessed 15 April 2013).
14. World Health Organization (2015). *Handbook for Clinical Management of Dengue*. Geneva: WHO [Internet.] Available from: http://www.who.int/denguecontrol/9789241504713/en/ (accessed 8 December 2015).
15. Handy JM. (2004).Viral haemorrhagic fevers—implications in intensive care. *Current Anaesthesia & Critical Care*, **15**(3), 137–42.
16. Roddy P, Colebunders R, Jeffs B, Palma PP, Van Herp M, and Borchert M. (2011). Filovirus hemorrhagic fever outbreak case management: a review of current and future treatment options. *Journal of Infectious Diseases*, **204**(3), S791–5.
17. Marra A, de Matos G, Janeri R, et al. (2011). Managing patients with dengue fever during an epidemic: the importance of a hydration tent and of a multidisciplinary approach. *BMC Research Notes*, **4**(1), 335.
18. Hung NT. (2012). Fluid management for dengue in children. Paediatrics and International Child Health, **32**(1), 39–42.

CHAPTER 294

Other tropical diseases in the ICU

Arjen M. Dondorp

Key points

- A wide range of tropical infectious diseases can cause critical illness. Knowledge of the local epidemiology where the disease is likely acquired is essential.
- In addition, local resistance patterns of common bacterial pathogens can be very different in tropical countries, so that antibiotic regimens might need adaptation.
- The 'surviving sepsis' guidelines are not always appropriate for the treatment of tropical sepsis, including in dengue shock syndrome and severe malaria. Both diseases require a more restricted fluid management.
- Leptospirosis is another important (mainly) tropical disease that can cause sepsis with liver and renal failure or acute respiratory distress syndrome (ARDS) with pulmonary haemorrhages.
- Recent epidemics of respiratory viruses causing life-threatening pneumonia have had their origins in tropical countries, including Severe Acute Respiratory Syndrome (SARS), Influenza A subtype H5N1 ('avian influenza'), and recently Middle East respiratory syndrome coronavirus (MERS-CoV).

Introduction

In addition to severe malaria and viral haemorrhagic fevers (discussed in the previous chapters), there is a wide range of tropical diseases that might be encountered in the ICU setting. Knowledge about the local epidemiology of the area where the disease was most likely acquired is a prerequisite for the proper diagnostic work-up. For instance, a patient admitted with septicaemia acquired in north-eastern Thailand will have a high chance (20%) that this is caused by the soil-dwelling bacterium *Burkholderia pseudomallei*, whereas in Nepal *Salmonella typhi* or *paratyphi* will be the most common causes. These differences in a priori chances will have important consequences for the choice of initial empirical antibiotic therapy, e.g. *B. pseudomallei* should be covered by a carbamapenem or ceftazidim. HIV/AIDS is a very common disease in several tropical countries, especially in Sub-Saharan Africa, which will also affect the differential diagnosis in patients presenting with severe febrile illnesses.

It should also be realized that although a diagnosis of severe malaria often to be excluded first, the main causes for severe febrile illness acquired in tropical countries also include common bacterial pathogens like *Str. pneumoniae, Staph. aureus*, and Enterobacteriaceae. Resistance patterns of these bacteria acquired in tropical countries can, however, be very different, although good surveillance data from low-income countries are often lacking [1]. Methicillin resistant *Staph. aureus* infections in these tropical countries are often not only hospital associated, but now also widespread in community acquired infections (up to 20%) and reported from rural areas of both Asian and African countries [2]. Extended Spectrum β-lactamase (ESBL) producing Enterobacteriaceae (e.g. *E. coli*) have spread into the community in many low-income tropical countries, probably accelerated by increased consumption of 3rd generation cephalosporins. Fluoroquinolone resistance in typhoid in Asia has severely curtailed the usefulness of these drugs. More recently, and more worrying, carbapenemases producing Enterobacteriaceae (including NDM-1 producing *Klebsiella pneumonia*) have been identified in India and are increasingly reported in hospitals elsewhere [3].

Some other common tropical diseases that can present as severe sepsis include severe dengue (dengue haemorrhagic fever/dengue shock syndrome) and severe leptospirosis.

Dengue virus

Dengue virus (serotypes DENV 1,2,4, and 4) is transmitted through the bite of infected female *Aedes aegypti* mosquitoes and less common *Aedes albopticus*. The disease is widespread throughout the tropics and more than 1 billion people are at risk in over 100 countries. Although usually infections result after an incubation time of 4–7 days only in an uncomplicated undifferentiated fever, or a febrile illness with severe headache and generalized pains in muscles and bones ('breakbone fever'), a minority of patients develops severe disease typically starting at the time of defervescence. The hallmark of dengue haemorrhagic fever is an acute vascular permeability syndrome accompanied by abnormal haemostasis. Capillary leakage results in hypoproteinaemia, elevated haematocrit, pleural effusions, ascites, and a haemorrhagic diathesis aggravated by concomitant thrombocytopenia. In cases with more severe capillary leakage, haemodynamic shock can result called dengue shock syndrome (DSS). The relatively slow development of hypovolaemia and the prominent thrombocytopenia distinguishes DSS from other (bacterial) causes of septic shock. Treatment of DSS is supportive, with a particular focus on careful fluid management [4]. Because of the generalized capillary leakage, fluid volumes should be restricted, but sufficient to maintain cardiovascular stability and adequate renal function. Resuscitation with colloids rather than crystalloid solutions can be recommended for patients with hypotension [5]. The altered vascular permeability is short-lived and usually reversible after 48–72 hours [6]. As soon as re-absorption begins intravenous fluids should be stopped. Preventive transfusion of platelet concentrates in the absence of bleeding, even for profound thrombocytopenia, and the use of corticosteroids have not shown to improve outcome [7].

Leptospirosis

Leptospirosis is primarily a zoonosis affecting humans in both rural and urban settings in temperate and tropical climates. Human infection most often follows exposure to soil and water contaminated with excreta of animals infected with pathogenic species of *Leptospira*. Leptospirosis is an important cause of febrile illness in tourists returning from the tropics, and usually manifests as a mild febrile illness typically 7–12 days after exposure. However, a minority develops a severe systemic illness characterized by a systemic vasculitis resulting in a wide spectrum of clinical features. The major affected organs include the kidneys and liver ('Weil's disease') and the lungs, resulting in focal or massive intra-alveolar haemorrhage [8]. Haemodynamic shock is also common in severe leptospirosis and myocarditis, meningoencephalitis, and uveitis can also develop. Antibiotic treatment of severe disease is with penicillin G, cefotaxim, or ceftazidime [9]. Supportive treatment in the ICU will often have to include renal replacement therapy.

Therapy

Although many tropical infectious diseases in the ICU can present fulfilling the criteria for severe sepsis or septic shock, not all recommendations of the 'Surviving Sepsis Campaign' guidelines are always applicable. Fluid therapy in dengue shock syndrome should be much more careful then in septic shock from other causes, because of the generalized capillary damage and leakage. Fluids should also be restricted in patients with severe malaria, where hypotension is fortunately a rare event (10%) [10]. Permissive hypercapnia as a ventilation strategy in patients with cerebral malaria should be avoided because of the risk of herniation of the engorged brain. Corticosteroids are not recommended in patients with severe dengue or severe malaria.

Neurological syndromes

In addition to septic syndromes, severe neurological diseases might be encountered in the ICU in patients who resided in or visited the tropics. Again, in most cases, cerebral malaria will have to be excluded first. Meningitis caused by Neisseria meningitis is endemic in the so-called meningitis belt across central Africa, and it is important that travellers are asked whether they have received proper vaccinations before their trip to these areas.

Causes of meningitis and encephelitis

A large number of viruses with a prominent presence in tropical countries can cause meningitis, encephalitis, or meningo-encephelitis in humans [11]. Common examples include enteroviruses (including EV71 and polio, now close to eradication), Nippah virus, Herpes simplex virus, Rift Valley fever (caused by a phlebovirus (Bunyaviridae), and transmitted by mosquitoes), Japanese encephalitis (transmitted from cattle by culex mosquitoes and vaccine preventable), and West Nile virus infection (transmitted from birds by culex mosquitoes), some of the tick-borne encephalitides, and Venezuelan Equine Encephalitis (also mosquito borne). Except for the herpes viruses, no specific anti-viral treatment is available for these infections.

Rabies

Rabies causes between 40,000 and 70,000 deaths per year, mostly in Southeast Asia, Africa, and South America [12]. Although the majority (99%) is caused by dog bites, other terrestrial animals transmit the disease. Vampire bats can transmit the rabies related lyssaviruses. The incubation time is usually between 3 and 12 weeks, but can be as long as 19 years [13]. Disease can be prevented by post-exposure (bite) prophylaxis with vaccination and administration of human rabies immunoglobulin (HRIG). Once symptomatic disease develops, rabies is fatal. A rabies case related to bat transmitted lyssavirus has been reported who survived after treatment according to an experimental protocol ('Milwaukee protocol') including sedation with ketamine and midazolam and the antiviral drugs ribavirin and amantadine. This success has not been reproduced by other groups [14].

African trypanosomiasis

African trypanosomiasis (sleeping sickness) is endemic in most Sub-Saharan African countries (but not in South Africa, Namibia, and Botswana) and can occasionally affect travellers. The disease is a zoonosis transmitted to humans by the bite of the tsetse fly (*Glossina sp.*). The local skin lesion at the site of inoculation (chancre) is followed by the haemolymphatic stage of the disease (stage I) which may be followed by invasion of the central nervous system and cerebrospinal fluid, leading to a meningoencephalitis (stage II). *Trypanosoma b. gambiense* (Middle and West-Africa) causes a protracted illness over months, but *T.b. rhodesiense* (East-Africa) causes a severe acute febrile disease with rapid progression to meningoencephalitis. Treatment of stage II requires treatment of drugs that cross the blood-brain barrier, which include the toxic arsenic drug melarsoprol. Nifurtimox and eflornithine are less toxic, but only effective against *T. b. gambiense* [15].

Other causes

Other parasitic tropical diseases that can cause a meningoencephalitis include angiostrongyliasis, *Naegleria fowleri, Acanthamoeba castellani, Gnathostoma spinigerum, Trichinella spiralis*, and others.

Origins of epidemics

Many epidemics have their origins in tropical countries, and it is important for the treating physician to have up to date information, for instance through the Program for Monitoring Emerging Diseases—an Internet-based reporting system under the International Society of Infectious Diseases dedicated to rapid global dissemination of information on outbreaks of infectious diseases. Also many emerging or re-emerging infectious diseases have their origin in the tropics (see Fig. 294.1), and global spread is importantly facilitated by the nowadays intense global human movement through air traffic. Recent examples include Severe Acute Respiratory Syndrome (SARS), which originated in Hong Kong in 2002–2003, and quickly spread through the region and globally to a total of 37 countries. Acute respiratory distress syndrome (ARDS) caused by this SARS coronavirus, had a high case fatality rate and caused around 800 deaths globally [16]. Avian Influenza caused by *Influenza A* subtype H5N1 is an enzootic disease of many bird species including poultry, and can cause a rapidly progressive pneumonia in humans. It has caused over 100 outbreaks since 2003 with over 300 fatalities recorded [17]. Severe influenza with pneumonia caused by *Influenza A* subtype H1N1 caused a pandemic in 2009 which originated in Mexico [18]. Epidemics with other *Influenza A*

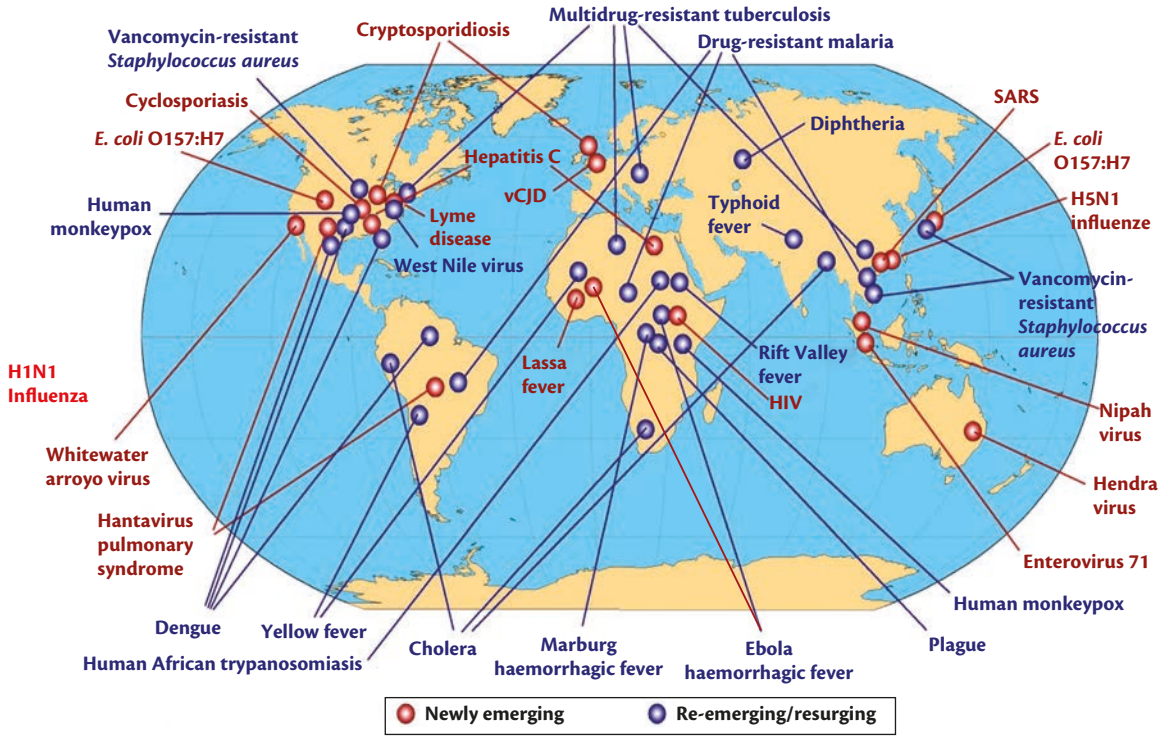


Fig. 294.1 Examples of emerging and re-emerging infectious diseases.
vCJD, variant Creutzfeldt Jacob disease; HIV, Human immunodeficiency virus; SARS, severe acute respiratory syndrome.
Reprinted by permission from Macmillan Publishers Ltd: Morens DM, Folkers GK, Fauci AS: The challenge of emerging and re-emerging infectious diseases. *Nature*, 2004, **430**(6996), 242–9.

subtypes have been reported since then. In 2012 a novel virus causing severe pneumonia with high mortality was reported from several countries in the Middle East. This epidemic caused by Middle East respiratory syndrome coronavirus (MERS-CoV) which was worrying because its virulence and ability of person-to-person transmission [19].

References

1. Ashley EA, Lubell Y, White NJ, and Turner P. (2011). Antimicrobial susceptibility of bacterial isolates from community acquired infections in Sub-Saharan Africa and Asian low and middle income countries. *Tropical Medicine International Health*, **16**(9), 1167–79.
2. DeLeo FR, Otto M, Kreiswirth BN, and Chambers HF. (2010). Community-associated methicillin-resistant *Staphylococcus aureus*. *Lancet*, **375**(9725), 1557–68.
3. Nordmann P, Poirel L, Walsh TR, and Livermore DM. (2011). The emerging NDM carbapenemases. *Trends in Microbiology*, **19**(12), 588–95.
4. WHO (2009). *Dengue: Guidelines for Treatment, Prevention and Control*. Geneva: World Health Organization.
5. Wills BA, Nguyen MD, Ha TL, et al. (2005). Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *New England Journal of Medicine*, **353**(9), 877–89.
6. Simmons CP, Farrar JJ, Nguyen vV, and Wills B. (2012). Dengue. *New England Journal of Medicine*, **366**(15), 1423–32.
7. Lye DC, Lee VJ, Sun Y, and Leo YS. (2009). Lack of efficacy of prophylactic platelet transfusion for severe thrombocytopenia in adults with acute uncomplicated dengue infection. *Clinical Infectious Diseases*, **48**(9), 1262–5.
8. Luks AM, Lakshminarayanan S, and Hirschmann JV. (2003). Leptospirosis presenting as diffuse alveolar hemorrhage: case report and literature review. *Chest*, **123**(2), 639–43.
9. Brett-Major DM and Coldren R. (2012). Antibiotics for leptospirosis. *Cochrane Database System Review*, **2**, CD008264.
10. Hanson JP, Lam SW, Mohanty S, et al. (2013). Fluid resuscitation of adults with severe falciparum malaria: effects on acid-base status, renal function, and extravascular lung water. *Critical Care Medicine*, **41**(4), 972–81.
11. Jmor F, Emsley HC, Fischer M, Solomon T, and Lewthwaite P. (2008). The incidence of acute encephalitis syndrome in Western industrialised and tropical countries. *Virology Journal*, **5**, 134.
12. Warrell M. (2010). Rabies and African bat lyssavirus encephalitis and its prevention. *International Journal of Antimicrobiology Agents*, **36**(1), S47–52.
13. Warrell MJ and Warrell DA. (2004). Rabies and other lyssavirus diseases. *Lancet*, **363**(9413), 959–69.
14. Jackson AC. (2011). Rabies in the critical care unit: diagnostic and therapeutic approaches. *Canadian Journal of Neurology Science*, **38**(5), 689–95.
15. Kennedy PG. (2013). Clinical features, diagnosis, and treatment of human African trypanosomiasis (sleeping sickness). *Lancet: Neurology*, **12**(2), 186–94.
16. Mazzulli T, Kain K, and Butany J. (2004). Severe acute respiratory syndrome: overview with an emphasis on the Toronto experience. *Archives of Pathology & Laboratory Medicine*, **128**(12), 1346–50.
17. Abdel-Ghafar AN, Chotpitayasunondh T, Gao Z, et al. (2008). Update on avian influenza A (H5N1) virus infection in humans. *New England Journal of Medicine*, **358**(3), 261–73.
18. Scalera NM and Mossad SB. (2009). The first pandemic of the 21st century: a review of the 2009 pandemic variant influenza A (H1N1) virus. *Postgraduate Medicine*, **121**(5), 43–7.
19. Assiri A, McGeer A, Perl TM, et al. (2013). Hospital outbreak of Middle East respiratory syndrome coronavirus. *New England Journal of Medicine*, **369**(5), 407–16.

PART 13.5

Sepsis

CHAPTER 295

Assessment of sepsis in the critically ill

Osamudiamen Idahosa and David T. Huang

Key points

- Sepsis is the presence of a known or suspected infection and a systemic inflammatory response.
- Severe sepsis is sepsis with acute organ dysfunction. Septic shock is a subset of severe sepsis characterized by systemic arterial hypotension or occult hypoperfusion.
- Severe sepsis is common, affecting more than 750 000 individuals in the United States each year with a hospital mortality of about 30%.
- Severe sepsis is a medical emergency that requires early identification, prompt evaluation, and treatment.
- The signs and symptoms of sepsis are influenced by the virulence of the pathogen, the portal of entry, the degree of organ dysfunction as well as the susceptibility and response of the host.

Definition

Sepsis is a clinical syndrome resulting from the presence of both an infection and a systemic inflammatory response. It can be complicated by organ dysfunction (severe sepsis) and shock (septic shock) [1,2]. Although the consensus definition for septic shock requires frank hypotension however, some have argued that evidence of hypoperfusion such as an elevated blood lactate ≥4 mmol/L should also be regarded as shock [3].

Epidemiology

In the United States, more than 750 000 individuals develop severe sepsis each year with a hospital mortality of about 30% [4]. Typically, about two cases per 100 hospital admissions develop severe sepsis, and about 10% of all ICU patients have severe sepsis on admission or during their ICU stay [5,6].

The Sepsis Occurrence in Acutely Ill Patients (SOAP) study across Europe reported that more than 35% of ICU patients had sepsis at some point during their ICU stay, with a mortality rate of 27% [7].

Nearly all microbes can cause sepsis. In immuno-competent hosts, typical causes are Gram-positive and Gram-negative bacteria, such as *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumonia*, Escherichia *coli* and *Pseudomonas* species [8]. In immunocompromised hosts, in addition to the usual pathogens, sepsis can also develop secondary to opportunistic organisms. The most frequent type of infection that leads to severe sepsis is pneumonia (44%), followed by primary bacteraemia (17%), genitourinary infection (9%), abdominal infection (9%), and, less commonly, wound and soft tissue infections (7%) [3]. Approximately one-third of septic patients are culture-negative [8]. Bacteria is the predominant cause of severe sepsis, with Gram-positive bacteria accounting for about 52% of cases, Gram-negative bacteria (38%), polymicrobial infections (5%), anaerobes (1%), and fungi (5%) [9].

When to suspect sepsis

Obvious sepsis cases with fever, leukocytosis, hypotension, and known infection require little skill to detect. The astute clinician recognizes that the initial presentation of sepsis can be subtle and non-specific, such as unexplained tachypnoea, altered mental status, hyperglycaemia, and diaphoresis. It is also important to recognize that elderly and immuno-suppressed patients with sepsis often do not have fever or leukocytosis. In such patients, hypothermia should specifically be sought for, and if found, treated seriously. Other physical and laboratory findings that prompt an experienced clinician to conclude that an infected patient 'looks septic' are outlined in Box 295.1. This list is by no means specific, but should help the clinician in identifying a septic patient and guide the early institution of adequate therapy including empiric antimicrobial therapy.

How to work up sepsis

History and physical

Determining the nature of the underlying infection and presence of organ dysfunction is critical. Presence of predisposing conditions such as advanced age, history of organ transplantation, immunosuppression, diabetes mellitus, trauma, and surgery should be quickly ascertained. Travel and pet exposure as well as history of intravenous drug and alcohol use should be obtained.

Vital signs need to be closely monitored. Although many patients with sepsis will be febrile, up to half of septic patients can be hypothermic or normothermic [10]. Tachycardia is a common sign as is tachypnoea and respiratory status needs to be closely monitored for evidence of respiratory failure. Blood pressure particularly diastolic pressure is usually lower than normal, with severe sepsis being the most common cause of vasodilatory shock [11].

A detailed examination could give you direct clues on the likely source of infection as well as the general clinical state of the patient.

Box 295.1 Diagnostic criteria for sepsis according to the sepsis definitions conference

Infection (documented or suspected) and some of the following:

General variables

- Fever (core temperature >38.3°C).
- Hypothermia (core temperature <36°C).
- Heart rate >90 min or >2 SD above normal value for age.
- Tachypnoea.
- Altered mental status.
- Significant oedema or positive fluid balance (>20 mL/kg over 24 hours).
- Hyperglycaemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes.

Inflammatory variables

- Leukocytosis (WBC count >12,000 μL).
- Leukopenia (WBC count <4000 μL).
- Normal WBC count with >10% immature forms.
- Plasma C-reactive protein >2 SD above the normal value.
- Plasma procalcitonin >2 SD above the normal value.

Haemodynamic variables

- Arterial hypotension—SBP <90 mm Hg, MAP <70 or an SBP decrease >40 mmHg in adults or <2 SD below normal for age.
- SvO2 >70%.
- Cardiac index >3.5 L/min.

Organ dysfunction variables

- Arterial hypoxaemia (PaO_2/FIO_2 <300).
- Acute oliguria (urine output <0.5 mL/kg/hour or 45 mmol/L for at least 2 hours).
- Creatinine increase >0.5 mg/dL.
- Coagulation abnormalities (INR >1.5 or a PTT>60 seconds).
- Ileus (absent bowel sounds).
- Thrombocytopenia (platelet count <100,000 μL).
- Hyperbilirubinaemia (plasma total bilirubin >4 mg/dL or 70 mmol/L).

Tissue perfusion variables

- Hyperlactataemia >1 mmol/L.
- Decreased capillary refill or mottling.
- Definitions of abbreviations: CRP, C-reactive protein; WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial pressure.

There may be evidence of depleted intravascular volume with dry mucous membranes and low jugular venous pressure as well as signs of impaired cutaneous perfusion with livedo reticularis and poor capillary refill. Altered mental status is often an important early indicator of sepsis with abnormalities in attention and cognition present especially in elderly patients. Careful attention should be paid to abnormalities in lung and abdominal examination such as asymmetric air entry and abdominal tenderness. Indwelling devices and surgical incisions should be closely examined for areas of tenderness, swelling, or erythema. Patients with diabetes mellitus are at risk for invasive polymicrobial infections such as necrotizing fasciitis and careful attention should be paid to the skin and soft tissues in such patients.

Laboratory

Patients with evidence of sepsis should have blood drawn for basic laboratory data including a complete blood count, complete metabolic panel as well as coagulation parameters. Leukocytosis, leucopenia, metabolic acidosis, renal or hepatic dysfunction should be sought. Abnormal liver function may also be a clue to the presence of acalculous cholecystitis, hepatic abscess, or biliary sepsis and further imaging may thus be useful. In addition, a blood lactate level should be obtained in the septic patient with an elevated level reflecting evidence of sepsis-related organ hypo perfusion. It is important to remember that except for immediate post-ictal patients and patients on an epinephrine infusion, an elevated lactate level, while not necessarily indicating sepsis, is always abnormal. Compensated cirrhotic have normal lactate levels. Only when they become ill do their lactate levels rise. Whenever possible, especially in the septic patient with tachypnoea or change in mental status, a blood gas should be obtained, as it provides a wealth of data in one simple test. If your facility's blood gas analyser allows it, always check a lactate level with the gas, as well as other useful basic laboratory indices such as haemoglobin, ionized calcium, and potassium. Early on in the septic process, an acute respiratory alkalosis will be apparent reflecting a state of increased minute ventilation. Metabolic acidosis occurs later in the septic process and thus if present, indicates greater severity. In patients who already have a central venous catheter, a venous blood gas sample is just as useful as an arterial gas, especially when combined with a working pulse oximetry value. Only if PaO2 is a specific concern is an arterial gas needed. The arterial pH as well as PCO2 can easily be inferred by adding ~0.05 to the venous pH and subtracting ~5 from the venous PCO2 levels [12]. In addition, a central venous blood gas can provide you central venous oxygen saturation, while an arterial gas cannot. Central venous lactate and arterial lactate are essentially equivalent.

Microbiology

In a patient with sepsis, all likely foci of infection should be cultured. Blood cultures should be routinely sent; however, 70% of patients with sepsis will not have organisms recovered from blood [8]. The Surviving Sepsis Campaign recommends obtaining appropriate cultures prior to antimicrobial therapy provided that such cultures do not cause a significant delay in antibiotic administration [13]. At least two sets of blood cultures should be obtained and if a vascular device is present, at least one is drawn percutaneously and one drawn through each vascular access device, unless the device was recently (<48 hrs) inserted. If the

same organism is recovered from both cultures, the likelihood that the organism is causing the severe sepsis is enhanced. In addition, if the culture drawn through the vascular access device is positive much earlier than the peripheral blood culture (i.e. >2 hrs earlier), the vascular access device is the likely source of infection [14]. If the likelihood that a vascular device is infected is felt to be high, it should be removed even before culture results are available. The search for the culprit pathogen should not be limited to blood alone, but depending on the clinical scenario could include examination and culture of materials from the lower respiratory tract, urine, cerebrospinal fluid, wounds, or other body fluids that may be the source of infection.

Imaging

Imaging studies should be geared towards localizing the source of infection and the pros and cons of various imaging modalities. Chest radiographs are routinely obtained, but are limited in critically ill patients with pneumonia. A portable supine chest film has a sensitivity of 0.60 and specificity of only 0.29 for the prediction of pneumonia in the critically ill patient with pneumonia [15]. Patients who are volume depleted or neutropenic may initially not have any detectable infiltrate on a chest radiograph. Generally, this becomes more obvious after hydration.

Ultrasounds are valuable particularly as they can be done at the bedside in unstable patients. It is commonly used to visualize the biliary tree and liver parenchyma in patients with unexplained abnormal liver function tests. It is also useful in viewing the renal parenchyma and the collecting system in the septic patient with suspected perinephric abscess and to exclude an obstructive uropathy. Importantly, bedside ultrasound may be of value for other diagnostic purposes such as estimating a patient's intravascular volume status. Both plain films and ultrasound have limited utility in establishing diagnosis of disease states like sinusitis, occult abscesses or fluid collections, ischaemic bowel or a perforated viscus. For such conditions, a computed tomographic (CT) scan is more useful.

Biomarkers

Many biomarkers have been evaluated for use in sepsis. Most have been evaluated as prognostic markers in sepsis; others for diagnosis. Thus far, none have been found to have sufficient specificity or sensitivity to be routinely employed. Procalcitonin has been the most widely studied, but has known false positives (e.g. massive trauma, burns, and severe shock) and false negatives (early infection, localized abscesses). As a prognostic marker, procalcitonin levels have been shown to correlate with mortality and some authors have proposed using procalcitonin levels to help decide on length of antibiotic treatment especially in culture negative sepsis [16]. The true clinical role of biomarkers remains to be determined.

Risk stratification

The extent of infection and the severity of organ failure have a significant impact on the prognosis of patients with sepsis. The site of infection also has a prognostic value. In the PROWESS (Protein C Worldwide Evaluation in Severe Sepsis) trial, patients with urinary tract infections as their source of severe sepsis had a 28 day mortality of 21% compared with patients with a pulmonary source who had a mortality rate of 34% ($p < 0.01$) [17]. Additionally, the response to infection varies among patients, reflecting the enormous heterogeneity in the patient population suffering from severe sepsis. While some patients have a marked systemic response, such as in patients with meningococcal sepsis, others often die of overwhelming infection with an inadequate host response for example neutropenic cancer patients with septic shock.

The PIRO model has recently been proposed as a way of stratifying septic patients according to their Predisposing condition, the severity of Infection, the host Response to infection, and the degree of Organ dysfunction [2]. PIRO is a staging score similar to the tumour nodes metastases (TNM) staging system in clinical oncology. The PIRO staging system could be used to assess risk and predict outcome in septic patients since the classification represents the different factors that contribute to the development of and outcome from sepsis. It could also help in early identification of those patients that need immediate ICU admission.

The degree of organ dysfunction can be assessed with various scoring systems, one of the most common being the Sequential Organ Failure Assessment (SOFA) score-a simple, but effective method to describe organ dysfunction or failure in critically ill patients [18]. Another prognostic scoring system, the Acute Physiology and Chronic Health Evaluation II (APACHE II), evaluates the risk of mortality, but however do not individualize the various degrees of organ dysfunction [19].

Conclusion

Severe sepsis is a medical emergency that is frequently fatal. It requires early identification, prompt evaluation, and treatment. The signs and symptoms of sepsis are influenced by the virulence of the pathogen, the portal of entry, as well as the susceptibility and response of the host. A quick and thorough history and examination with relevant ancillary studies are needed in evaluating a patient with sepsis. No biomarker has yet been found to have sufficient specificity or sensitivity to be routinely employed in the management of a septic patient.

References

1. Bone RC, Balk RA, Cerra FB, et al. (1992). ACCP/SCCM Consensus Conference Committee. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*, **101**(6), 1644–55.
2. Levy MM, Fink MP, Marshall JC, et al. (2003). 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Critical Care Medicine*, **31**, 1250–6.
3. Puskarich MA, Trzeciak S, Shapiro NI, et al. (2011).Outcomes of patients undergoing early sepsis resuscitation for cryptic shock compared with overt shock. *Resuscitation*, **82**(10), 1289–93.
4. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, and Pinsky MR. (2001). Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Critical Care Medicine*, **29**(7), 1303–10.
5. Sands KE, Bates DW, Lanken PN, et al. (1997). Academic Medical Center Consortium Sepsis Project Working Group. Epidemiology of sepsis syndrome in 8 academic medical centers. *Journal of the American Medical Association*, **278**(3), 234–40.
6. Linde-Zwirble WT and Angus DC. (2004). Severe sepsis epidemiology: sampling, selection, and society. *Critical Care*, **8**(4), 222–6.
7. Vincent JL, Sakr Y, Sprung CL, et al. (2006). Sepsis in European Intensive Care Units: Results of the SOAP study. *Critical Care Medicine*, **34**(2), 344–53.
8. Wheeler AP and Bernard GR. (1999). Treating patients with severe sepsis. *New England Journal of Medicine*, **340**(3), 207–14.

9. Martin GS, Mannino DM, Eaton S, and Moss M. (2003). The epidemiology of sepsis in the United States from 1979 through 2000. *New England Journal of Medicine*, **348**, 1546–54.
10. Rizoli SB and Marshall JC. (2002). Saturday night fever: finding and controlling the source of sepsis in critical illness. *Lancet Infectious Diseases*, **2**(3), 137–44.
11. Landry DW and Oliver JA. (2001). The pathogenesis of vasodilatory shock. *New England Journal of Medicine*, **345**(8), 588–95.
12. Treger R, Pirouz S, Kamangar N, and Corry D. (2010). Agreement between central venous and arterial blood gas measurements in the intensive care unit. *Clinical Journal of American Society of Nephrology*, **5**(3), 390–4.
13. Dellinger RP, Levy MM, Carlet JM, et al. (2008). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Critical Care Medicine*, **36**(1), 296–327.
14. Blot F, Schmidt E, Nitenberg G, et al. (1998). Earlier positivity of central-venous- versus peripheral-blood cultures is highly predictive of catheter-related sepsis. *Journal of Clinical Microbiology*, **36**(1), 105–9.
15. Lefcoe MS, Fox GA, Leasa DJ, Sparrow RK, and McCormack DG. (1994). Accuracy of portable chest radiography in the critical care setting. Diagnosis of pneumonia based on quantitative cultures obtained from protected brush catheter. Chest, **105**(3), 885–7.
16. Nobre V, Harbarth S, Graf JD, Rohner P, and Pugin J. (2008). Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *American Journal of Respiratory Critical Care Medicine*, **177**(5), 498–505.
17. Bernard GR, Vincent JL, Laterre PF, et al. (2001). Recombinant Human Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *New England Journal of Medicine*, **344**(10), 699–709.
18. Vincent JL, de Mendonça A, Cantraine F, et al. (1998). Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. *Critical Care Medicine*, **26**(11), 1793–800.
19. Vincent JL, and Abraham E. (2006). The last 100 years of sepsis. *American Journal of Respiratory Critical Care Medicine*, **173**(3), 256–63.
19. Knaus WA, Draper EA, Wagner DP, and Zimmerman JE. (1985). APACHE II: a severity of disease classification system. *Critical Care Medicine*, **13**, 818–29.

CHAPTER 296

Management of sepsis in the critically ill

Jon Sevransky

Key points

- Early identification of the patient with sepsis facilitates the delivery of appropriate treatment.
- The use of screening tools and algorithms may help with identification of sepsis patients.
- Delivery of rapid empiric antibiotics directed at the most likely source and organisms in conjunction with infection source control improves patient outcomes.
- Early aggressive therapy directed at targeted measures of perfusion do not provide additional benefit if early antibiotics and fluids are successfully delivered.
- Clinicians must be aware of potential complications of therapy, and should take precautions to limit nosocomial complications.

Introduction

The inciting insult that leads to sepsis necessarily involves an infection. Thus, the initial strategy for treating a patient with sepsis involves identifying the source and site of the infection, sending off cultures and rapidly treating with antibiotics [1,2]. In many patients, source control of the infection, such as removing an infected catheter or draining an abscess, is also required. As the previous chapter has noted, the absence of a biomarker for sepsis requires that the treating clinician have a high index of suspicion for sepsis in critically ill patients.

Antibiotic therapy

Sepsis patients require prompt delivery of antibiotics directed at the most likely causative organisms. It is useful to have appropriate cultures drawn to assist with subsequent tailoring of antibiotics, but delivery of such antibiotics should not be excessively delayed in order to obtain these cultures. Since the results from cultures take hours to days, the selection of antibiotics should be driven by the site of infection, host susceptibility, and the likelihood of exposure to resistant organisms. In general, patients with recent exposure to the health care system including hospitalization, nursing home residence, or visits to dialysis or chemotherapy clinics will be at risk for resistant organisms. The prevalence of resistant organisms in the community also needs to be considered when selecting initial empiric therapy, in addition to local sensitivity patterns. The site of infection: lungs, abdomen, urine, bloodstream, or central nervous system will also assist with the initial antimicrobial choice [3].

In general, most patients with sepsis require broad coverage including both Gram-positive and Gram-negative organisms. Using two different antimicrobial agents to 'double cover' Gram-negative organisms remains controversial, and, in the absence of extreme local resistance patterns or diseases such as cystic fibrosis, is not generally recommended [4].

Delay in appropriate antibiotic infusion has been associated with increased patient mortality [5]. Current treatment goals for hypotensive sepsis patients include the administration of effective antibiotics within an hour of hypotension for hospitalized patients [5]. This need for rapid delivery requires that the physician pay attention to the mechanics of ensuring that any order for antibiotics is expeditiously communicated to the nurse and pharmacy so that the medication ordered is delivered promptly to the patient.

Duration of antibiotic therapy should be driven by the site of infection, likely causative organisms, and clinical response to therapy. Patients who are in shock will often require longer courses of therapy than those patients who are clinically improving. In the absence of clinical deterioration, a shorter course of antibiotics of 7–8 days appears to be as effective as a longer course of 15 days for patients with ventilator associated pneumonia without resistant Gram-negative organisms [6]. Biomarkers such as procalcitonin are a potential option to use as part of an antibiotic de-escalation strategy [7]. Other strategies to limit length of therapy include use of clinical scores for pneumonia. While these strategies to limit antibiotic use have been clearly shown to decrease risk of complications and decrease exposure to antibiotics, they have not shown to effect patient mortality [3,7]. At this time, we do not recommend the use of biomarkers as a trigger to withhold antibiotics for critically ill patients with presumed sepsis. Most clinicians will, for patients with severe sepsis start broad spectrum antibiotics and modify the type and duration of antibiotics based on results from cultures and the patient's clinical response.

Infection source control

In conjunction with effective antibiotics, infection source control is an essential part of sepsis therapy. Both surgical and interventional radiological procedures should be considered in a patient with a closed space infection such as an abscess or empyema;

those patients with an indwelling catheter that is suspected of being infected should have it removed as soon as alternate access is obtained. Treating through an infected catheter without its removal in patients with severe sepsis or septic shock is not recommended. Some sepsis patients have co-morbidities such as coagulopathy or shock that may complicate the ability to achieve source control, and the treating clinician may need to treat these co-morbidities in order to facilitate source control

Early aggressive therapy

Supportive therapy buys time for the patient's host defence system to work in conjunction with antibiotic therapy to treat severe infections. Since the host response to infection often leads to vascular leak and decreased filling pressures, patients with sepsis require infusion of IV fluids to increase cardiac output and restore systemic perfusion of vital organs as a first line supportive treatment. There are many choices for types of fluid therapy: crystalloid fluids are most commonly used, and usually require higher doses than colloids [8]. Initial therapy of a severe sepsis patient should include a rapid infusion of crystalloids of at least 15–30 cc/kg, with many patients requiring additional boluses [3]. The largest randomized trial comparing crystalloid to colloid therapy in critically ill patients did not show a benefit to use of colloid therapy compared with crystalloids [9]. While no type of fluid therapy has been proven to be superior in patients with sepsis, the use of hydroxyethyl starches such as pentastarch and hetastarch have been shown to be harmful and are not recommended [8,10]. Patients with more severe forms of sepsis such as septic shock will require large amounts of fluid resuscitation both initially and over the first 24 hours of therapy, in doses that may approach 8–9 litres of crystalloid in over a 24 hour period [11].

In addition to following the patients vital signs in response to therapy, many patients receive assessment of filling pressures such as central venous pressure, and targets of resuscitation such as venous oxygen saturation or lactate (See Box 296.1). Use of early aggressive strategies based on treatment goals including specific targets do not provide additional benefit if early antibiotics and fluids have been effectively delivered.. Failure to reach treatment goals should prompt both re-evaluation of initial diagnosis, as well as consideration of additional therapy to both improve cardiac output and peripheral perfusion as well as limitation of oxygen consumption (See Fig. 296.1) [12,13]. While complicated algorithms have been used for acute care of the sepsis patient, it is not known which patient's part of the algorithms are most helpful. We therefore suggest using some clinical target such as lactate clearance or central venous oxygen saturations in addition to usual measures of vital sign monitoring such as following blood pressure, pulse, and urine output.

Delayed aggressive care of the sepsis patient that waits until the patient is stabilized in the ICU does not improve patient outcomes [14]. For most patients the aggressive phase of therapy should be continued for at least 6 hours and perhaps up to 24 hours. It is reasonable, if a patient is responding to fluid loading or additional therapies to increase oxygen delivery or decrease oxygen consumption, to continue these therapies beyond this 24 hour time point. If the patient does not respond to therapies to increase oxygen delivery such as adding additional fluids, transfusing packed red cells or adding an inotrope, the clinician will need to balance the risk of adding new goal directed therapies against any potential risks in an individualized fashion.

Box 296.1 Recommended treatment paradigm for severe sepsis patients

Early (hours 1–6)

- Make sepsis diagnosis.
- Send cultures from likely sites.
- Deliver antibiotics within 1 hour.
- Measure lactate.
- Obtain adequate access, including CVC for most patients.
- Ensure patient has adequate monitoring and nursing staffing.
- Follow measures of perfusion (urine output, capillary refill, pulse).
- Volume resuscitate.

Mid (hours 7–72)

- Monitor for signs of organ failure.
- Additional volume resuscitation if needed.
- **Follow-up cultures**: adjust antibiotics as needed.
- **Minimize nosocomial complications**: limit sedation, use lung protective ventilation.
- Wean supportive therapies as feasible.

Late (hours > 73)

- Wean supportive therapies as feasible.
- Remove unnecessary devices.
- **Minimize nosocomial complications**: limit sedation, use lung protective ventilation.
- Set endpoints for antibiotic therapy.

Supportive therapy for sepsis patients

Patients with sepsis are at risk for developing complications such as respiratory failure, acute respiratory distress syndrome (ARDS), acute kidney injury, disseminated intravascular coagulation, and delirium. Each of these complications of sepsis may require specific supportive therapy. Patients with sepsis who require positive pressure ventilation should receive therapy designed to both rest respiratory muscles and limit work of breathing including mechanical ventilation, pain and symptom control, and in many patients endotracheal intubation. Since sepsis patients who develop respiratory failure are at increased risk of developing ARDS, the clinician should choose a ventilator strategy that limits volumes and plateau pressures to decrease the likelihood of developing ventilator induced lung injury and ARDS [15].

The use of manoeuvers such as the straight leg raise may allow determination of whether additional fluid boluses might be helpful [16]. Once adequate volume resuscitation has occurred, there is little value in infusing additional IV fluids [16].

Some patients will require use of renal replacement therapy after the development of sepsis induced acute kidney injury. While dialysis will assist with fluid balance and potassium and solute clearance, the use of early or more intensive dialysis does not provide

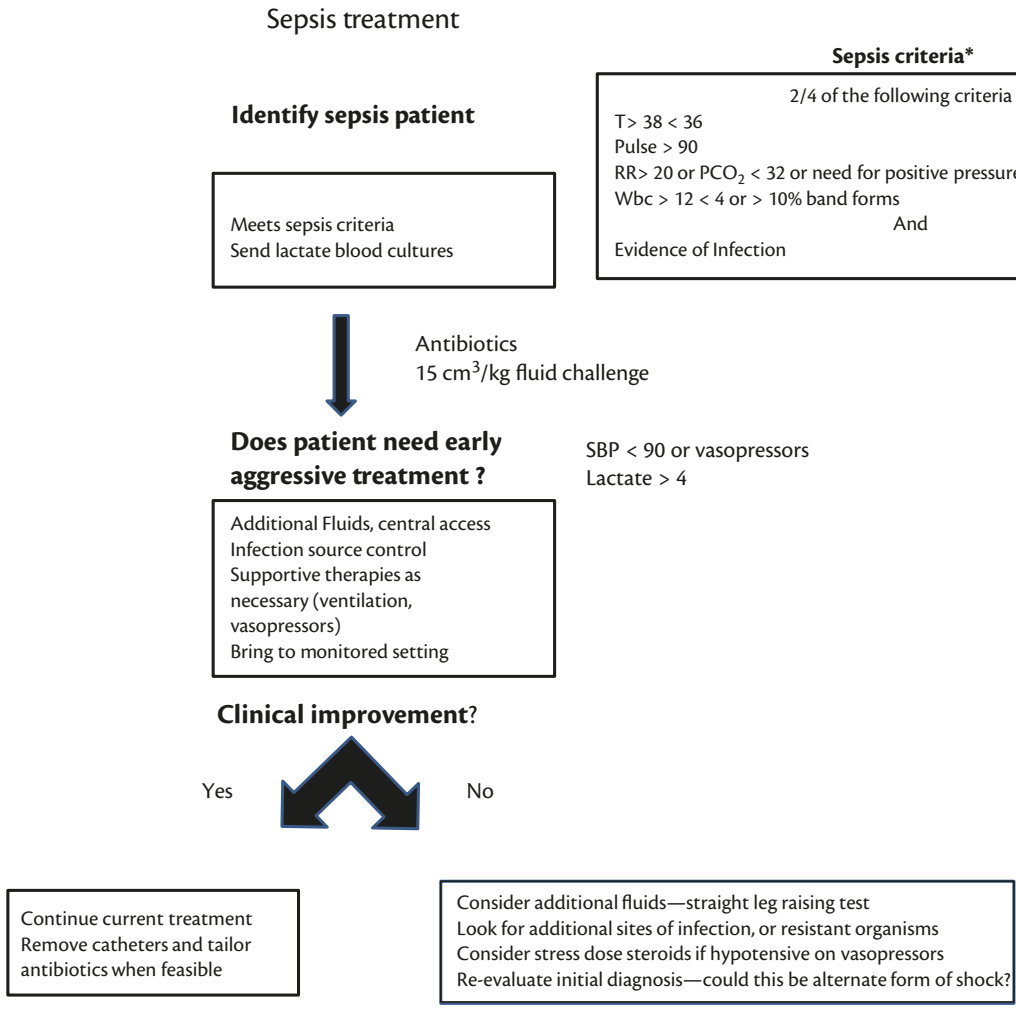


Fig. 296.1 Treatment pathway for sepsis.
*Will be updated in early 2016.

additional benefit over use for specific indications. There is no proven value in using dialysis therapies for clearance of specific inflammatory mediators. Additional support therapies such as nutritional are necessary in many patients, with the enteral route preferred for most.

Limitation of complications for sepsis patients

While early aggressive care of the sepsis patient in the emergency department and ICU may save lives, it is clear that these aggressive treatments are associated with risks including the development of nosocomial infections, delirium, critical illness weakness, stress ulceration, and ventilator induced lung injury [17]. It is important that the clinician carefully consider the risks of therapy when applying therapies. Strategies that may be useful in preventing ICU complications include limiting tidal volume in patients at risk for developing acute lung injury, limiting use of sedation and analgesics and mobilizing patients early in the course of sepsis. Avoidance of hyperglycaemia and hypoglycaemia are important ancillary goals, although the goal glucose level in a patient with sepsis remains controversial. Strategies to prevent nosocomial infections such as catheter checklists and ventilator bundles are also essential.

Response to treatment and continued care

Most patients with severe sepsis and septic shock will require treatment in an ICU where staffing ratios of nurses, physicians, and other caregivers will allow repeated and detailed observation of vital signs and organ perfusion. With early appropriate supportive care and antibiotics patients should demonstrate response to therapy including decreased fever, decreased pulse, and improved organ perfusion, and decreased need for supportive therapies such as mechanical ventilation and vasopressor support. If a patient does not show such clinical improvement, the clinician will need to reconsider whether there is an undrained infectious focus, whether the initial antimicrobial strategy was correct and whether there might be an alternate explanation for the patient's illness.

When available, culture results should allow tailoring antibiotics based on minimizing side effects, resistance, and costs. Use of clinical biomarkers such as procalcitonin may be helpful in limiting antibiotic length of therapy where available [7]. Since there is little guidance as to the length of therapy for most types of infections, it is reasonable to consider de-escalation of therapies when a patient is clinically improving

Once a sepsis patient with respiratory failure has been stabilized, the clinician needs to consider measures that will lead to

expeditious removal of endotracheal tubes and mechanical ventilation. Such measures would include a targeted sedation strategy, such as daily interruption of sedation, often in conjunction with early rehabilitation and mobility strategies, and fluid removal with diuretics in patients off vasopressor support for more than 12 hours [3,18]. Clinical improvement should also prompt consideration of whether other invasive devices such as arterial and venous catheters, as well as urinary catheters are still required. Use of cognitive aids such as checklists to remind clinicians about whether such devices are still required has been shown to be an effective technique.

Prevention of long-term complications of sepsis

While initial care of the sepsis patient requires aggressive and often invasive therapy, many sepsis patients will transition out of the ICU to regular wards. Many sepsis patients will develop ICU acquired weakness, delirium, and depression that will persist after ICU discharge [19]. While strategies designed to limit sedation and mobilize ICU patients may get them off the ventilator earlier, it is not yet known whether these strategies will limit the development of weakness or delirium [17].

References

1. Nguyen HB, Corbett SW, Steele R, et al. (2007). Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Critical Care Medicine*, **35**(4), 1105–12.
2. Moore LJ, Jones SL, Kreiner LA, et al. (2009). Validation of a screening tool for the early identification of sepsis. *Journal of Trauma*, **66**(6), 1539–46; discussion 46–7.
3. Dellinger RP, Levy MM, Rhodes A, et al. (2013). Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine*, **41**(2), 580–637.
4. Paul M, Silbiger I, Grozinsky S, Soares-Weiser K, and Leibovici L. (2006). Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database of Systematic Reviews*, **1**, CD003344.
5. Kumar A, Roberts D, Wood KE, et al. (2006). Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Critical Care Medicine*, **34**(6), 1589–96
6. Chastre J, Wolff M, Fagon JY, et al. (2003). Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *Journal of the American Medical Association*, **290**(19), 2588–98.
7. Tang BM, Eslick GD, Craig JC, and McLean AS. (2007). Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *The Lancet Infectious Diseases*, **7**(3), 210–17.
8. Perel P, Roberts I, and Ker K. (2013). Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database of Systematic Reviews*, **2**, CD000567.
9. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, and Norton R. (2004). A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *New England Journal of Medicine*, **350**(22), 2247–56.
10. Perner A, Haase N, Guttormsen AB, et al. (2012). Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *New England Journal of Medicine*, **367**(2), 124–34.
11. Packman MI and Rackow EC. (1983). Optimum left heart filling pressure during fluid resuscitation of patients with hypovolemic and septic shock. *Critical Care Medicine*, **11**(3), 165–9.
12. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, and Kline JA. (2010). Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *Journal of the American Medical Association*, **303**(8), 739–46.
13. Rivers E, Nguyen B, Havstad S, et al. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine*, **345**(19), 1368–77.
14. Gattinoni L, Brazzi L, Pelosi P, et al. (1995). A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *New England Journal of Medicine*, **333**(16), 1025–32.
15. Li G, Malinchoc M, Cartin-Ceba R, et al. (2011). Eight-year trend of acute respiratory distress syndrome: a population-based study in Olmsted County, Minnesota. *American Journal of Respiratory and Critical Care Medicine*, **183**(1), 59–66.
16. Coudray A, Romand JA, Treggiari M, and Bendjelid K. (2005). Fluid responsiveness in spontaneously breathing patients: a review of indexes used in intensive care. *Critical Care Medicine*, **33**(12), 2757–62.
17. Needham DM, Davidson J, Cohen H, et al. (2012). Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Critical Care Medicine*, **40**(2), 502–9.
18. Schweickert WD, Pohlman MC, Pohlman AS, et al. (2009). Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*, **373**(9678), 1874–82.
19. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, and Sevransky JE. (2010). Long-term mortality and quality of life in sepsis: a systematic review. *Critical Care Medicine*, **38**(5), 1276–83.

CHAPTER 297

Pathophysiology of septic shock

John M. Litell and Nathan I. Shapiro

Key points

- Sepsis results from a dysregulated homeostatic response to infection.
- Immune activation and immunosuppression are both present in sepsis syndromes.
- The host's inflammatory and coagulation systems are closely interrelated, and disruptions in both are central to sepsis pathophysiology.
- Abnormalities in macrovascular, microvascular, endothelial, and mitochondrial function all contribute to the haemodynamic changes and organ failures seen in septic patients.
- Sepsis mortality increases with successive organ failures.

Introduction

Sepsis is the result of a complex and dysregulated homeostatic response to infection. Untreated, sepsis progresses to hypoperfusion, hypoxia, and dysfunction at the level of cells, tissues, and organ systems, leading to death in at least 30% of cases [1]. The clinical syndrome of sepsis is a manifestation of pro- and anti-inflammatory intermediates and is intimately linked to disruptions in coagulation, microcirculatory flow, and mitochondrial function, leading to common pathways of failure in multiple organ systems. The severity of the response depends on both host and pathogen characteristics and the relevant underlying pathophysiology arises principally from interactions between an infectious agent and the host's innate immune system.

Innate immunity is characterized by a rapid response capability to novel insults, which results from an interaction between conserved molecular signals on pathogens and corresponding pattern recognition receptors on host immune cells. All non-vertebrate organisms—pathogenic, non-pathogenic, or commensal—express microbial-associated molecular patterns (MAMPs) [2]. These bind to pattern recognition receptors (PRR) expressed by host immune cells. The best-known human PRR are the ubiquitous toll-like receptors (TLR), a highly diversified family of cell surface and cytoplasmic receptors for an extraordinary number of microbial invaders and endogenous danger signals.

TLR activation, via multiple secondary signalling pathways, leads to translocation of nuclear factor kappa B (NF-κB), a central regulatory factor for several inflammatory target genes, including pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α) and interleukin 1 (IL-1). These trigger the cardinal pathophysiological manifestations of sepsis—leukocyte activation and transmigration, endothelial damage and dysfunction, and increased capillary permeability—resulting in hypovolaemia and exposure of tissue factor to circulating coagulation factors [3].

Circulating apoptotic or necrotic cell debris can initiate a similar response via damage-associated molecular pattern (DAMP) receptors. Since ischaemia and necrosis often accompany infection, these responses can coexist in positive feedback loops, wherein PRR are stimulated both by infectious agents and by damaged host cells resulting from the infection.

The pro-inflammatory cytokine high-mobility group box 1 protein (HMGB1) is also thought to play an important role late in the pathogenesis of sepsis. Several hours after exposure to infectious stimuli, macrophages, dendritic cells, and natural killer cells all release HMGB1, as do necrotic host cells. Apoptotic host cells may trigger release of HMGB1 from macrophages. The receptor for advanced glycation end-products (RAGE) may also contribute to pro-inflammatory signalling in sepsis. HMGB1 protein and several other endogenous ligands are recognized by RAGE, which may then activate NF-κB signalling pathways.

Historically, sepsis was thought to result from disproportionate release of pro-inflammatory mediators in response to infection. More recent work has identified features of both hyperinflammation and immunosuppression in sepsis [4]. That both are relevant is fairly clear, but the timing and relative contributions of their effects are uncertain.

Immune suppression in sepsis is partially due to elaboration of anti-inflammatory cytokines and likely also to lymphocyte apoptosis. TLR activation results in upregulation of signal transduction pathways, which lead to DNAse activation and apoptosis. Interestingly, although necropsy studies in septic patients reveal relatively little parenchymal cell death in failing organs, they do show profound apoptotic loss of components of cellular immunity. In addition to responding to anti-inflammatory cytokines, immune cells are also receptive to efferent vagal suppression via cholinergic receptors.

Inflammation and coagulation

There is substantial cross-talk between the inflammatory and coagulation systems, the full extent of which is still not elucidated. These systems are evolutionarily linked. Although they have diverged in humans and other vertebrates, in invertebrate species, inflammation and coagulation are performed by a single cell type, the haemocyte, reflecting an evolutionary precursor [5].

The coagulant response to an infectious insult is initiated by increased amounts of circulating tissue factor, which results from endothelial permeability as well as haematogenous spread of necrotic debris. This initiates a procoagulant response resulting in

thrombin generation and increased fibrin formation, balanced by early fibrinolysis via increased expression of plasminogen activator. Further counterbalance is provided by increased expression of plasminogen activator inhibitor.

These effects can proceed rapidly, and coagulation is an essential protective response to infection [6]. The formation of fibrin nets traps not only activated platelets, but also bacteria and leukocytes. By aggregating bacteria in a region of decreasing nutrient supply, bacterial trapping limits both haematogenous spread and local growth. The majority of known human bacterial pathogens employ fibrinolytic properties to evade these fibrin nets.

When overwhelmed, the pro- and anticoagulant responses to infection can accelerate to a consumptive coagulopathy and disseminated intravascular coagulation (DIC). Widespread microvascular thrombosis contributes to multi-organ failure, resulting in a progressive cycle of maladaptive immune response, dysregulated coagulation, and deepening critical illness.

Microcirculatory effects

Organ perfusion is impaired not only by abnormalities in macrovascular flow (oxygen circulation), but also by direct effects on the microcirculation (oxygen distribution) and the mitochondria (oxygen processing). A complex interplay between the endothelium, vascular smooth muscle, and the cellular components of blood is largely responsible for capillary blood flow, nutrient delivery, exchange of products of cellular respiration, and coagulation and immune function. The autoregulatory capability of the microcirculation, as well as arterial driving pressure and the physical characteristics of the blood, can all be adversely impacted in sepsis [7].

Toxic products of infection, pro-inflammatory mediators, reactive oxygen species (ROS), activated host leukocytes, and inducible nitric oxide synthase all exert direct effects on vascular tone, integrity, and endothelial cell signalling, leading to increased venous capacitance and massive capillary leak. Clinically, these contribute to impaired cardiac filling pressures that can be partially restored by volume resuscitation.

However, conventional measures of fluid balance and effective circulating volume do not fully reflect the substantial extravasation of fluids due to endothelial dysfunction, which can persist beyond initial resuscitation. Loss of normal autoregulatory function in end-organ tissue beds also contributes to maldistribution of blood flow, with hyperaemia at some sites and hypoperfusion at others.

Flow limitations are only part of the problem. Mitochondrial oxygen utilization is also disrupted, resulting in a cytopathic hypoxia even in regions with normal or supranormal blood flow [8]. Taken together, these changes result in a persistent anaerobic metabolism and lactic acidosis even after the restoration of adequate circulating volume. These microcirculatory and mitochondrial abnormalities are undetected by conventional haemodynamic measurements.

Organ system manifestations

Septic patients often manifest single or multiple organ failures, which share characteristic pathophysiological mechanisms. Mortality in these patients has been shown to roughly double for each additional organ system failure. Recovery of organ failures, where possible, is largely accomplished by reversal of the underlying insult and associated host inflammatory response.

Renal

Approximately one-third of critically ill patients experience AKI, with a mortality of 20–60% depending on the severity of the injury. Half of these cases are due to sepsis. For several reasons, the pathophysiology of septic AKI is incompletely understood. Ethical restrictions preclude widespread biopsy collection from critically ill patients, so histopathological data are limited. Most human data are flawed and over 30 years old [9]. Animal models created to fill this knowledge gap have largely relied upon mechanisms—such as ischaemia/reperfusion and drug toxicity—that are probably only indirectly relevant. More recent animal and human studies have called into question the theory that septic AKI involves renal hypoperfusion and tubular ischaemia.

Septic shock is typically a hyperdynamic hypotensive state. While septic AKI is typically attributed to renal hypoperfusion, this may not actually be the case. Animal data have revealed that hyperdynamic septic subjects often have increased renal blood flow, as the renal arterioles undergo the same dilation as the systemic vasculature. Septic AKI may therefore be misclassified, due instead to hyperaemic renal failure, with tubular cell injury and dysfunction due primarily to non-haemodynamic factors [10]. These may include the cytokines, coagulation factors, and other inflammatory and neuroendocrine mediators circulating in supranormal concentrations in septic patients.

Renal parenchymal cells express TLR, which may be directly activated by endotoxin. TNF, one of the principal inflammatory cytokines released after TLR activation, is also bound in increased quantities to renal parenchymal receptors in animals with experimentally induced septic AKI [10]. Thus, the dysfunction seen in septic AKI may result from both remote activation and local propagation.

Indirect evidence for this is seen in studies of remote effects of single organ injury, for example the development of AKI in rabbits with acute respiratory distress syndrome who are ventilated with injurious tidal volumes, or the initiation of in vitro apoptosis of renal tubular cells treated with plasma from burn patients [11]. This type of crosstalk between the kidneys and remotely failing organs suggests that our concept of AKI in sepsis as primarily a problem of renal perfusion is relatively rudimentary.

Renal tubular cell apoptosis is likely one of the non-haemodynamic mechanisms underlying septic AKI [12]. In contrast to ischaemic necrosis, apoptosis is triggered by intercellular signals and results in an organized sequence of steps that terminally extinguish cell function. Prevention of this sequence of events requires more than simply restoration of renal perfusion pressure. Identification of the signals responsible for the initiation of renal tubular cell death may allow the prevention of their release or blockade of their interaction with receptors in vulnerable renal tissues.

Pulmonary

Given its exposure to both the external environment and the systemic circulation, the lung can be both a primary site of infection or suffer collateral damage during sepsis. The extent and fragility of the pulmonary parenchyma renders it vulnerable to circulating mediators and chemical and mechanical disruption. Multiple direct and indirect inflammatory aetiologies can lead to acute pulmonary parenchymal injury, manifested by impaired alveolocapillary membrane integrity and non-cardiogenic pulmonary oedema.

In the case of acute lung injury as a secondary consequence of remote insults, systemically activated leukocytes traversing the pulmonary microcirculation migrate into the interstitium, where they perpetuate the inflammatory response locally via signalling intermediates. With local infections, TLR activation leads to microbial clearance or, if overwhelmed, necrosis and apoptosis of parenchymal cells. Since these processes result in DAMP release they are in themselves immunogenic [3]. This results in amplified local leukocyte activation, endothelial dysfunction, and interstitial oedema, as well as activation of platelets and coagulation factors. Progressive parenchymal dysfunction manifests as pulmonary shunt with refractory hypoxemia, contributing to multi-organ dysfunction.

Cardiac

Sepsis disrupts normal cardiovascular function through overlapping effects on myocardial function, vascular tone, and capillary integrity. Although commonly understood as a subtype of distributive shock, sepsis also involves features of hypovolemic and cardiogenic shock. Systemic presence of inflammatory cytokines contributes to peripheral arterial dilation, diffuse capillary leak, decreased contractility, and reflex tachycardia. Patients generally exhibit diastolic hypotension and decreased mean arterial pressure.

Myocardial dysfunction in sepsis manifests as biventricular dilation, decreased ejection fraction, diastolic dysfunction, and decreased cardiac output [13]. These reversible abnormalities are present even during the hyperdynamic phase of shock. Elevated concentrations of TNF-alpha, IL-2, and IL-6 may exert a direct myocardial depressant effect. Increased nitric oxide generation and dysregulation of intracellular calcium flux are theorized to contribute to cardiomyocyte dysfunction, via unclear mechanisms. Initial biventricular dilation is postulated as a compensatory Frank-Starling response to decreased vascular resistance. However, as with this and other changes in myocardial function during sepsis, it is not clear which are abnormal and which may be protective (e.g. energy-conserving).

Both left and right ventricular function can be impaired in sepsis, the latter being further compromised by increased pulmonary vascular resistance in the case of acute lung injury. To date, most studies of myocardial dysfunction in sepsis have evaluated systolic changes. Diastolic dysfunction also occurs, but it is technically more difficult to assess via echocardiography. As with other organ systems, myocardial dysfunction is likely not simply attributable to ischaemia, illustrated by thermodilution studies demonstrating normal or even supranormal coronary flow. Microcirculatory dysfunction is among the postulated mechanisms.

Structural myocardial structural changes also occur during sepsis, including leukocyte infiltration, interstitial oedema, collagen deposition, and mitochondrial damage, with unclear reversibility and functional consequences. As elsewhere, endothelial dysfunction and TLR activation on circulating leukocytes play central roles, as do locally generated ROS. The resultant interstitial oedema and inflammation are attributed to both leukocyte activation and the direct effects of toxic microbial products, though the degree to which each is responsible for myocardial dysfunction remains unclear. Furthermore, mitochondrial structural and functional abnormalities are seen in human autopsy specimens, though cardiomyocyte apoptosis has thus far primarily been seen in vitro.

Gastrointestinal

As little as one cell layer separates normally sterile tissues from a dense collection of faecal bacteria. Translocation of these microbes or their components is thought to play a role in the initiation or perpetuation of systemic inflammation in critically ill patients. Although the precise mechanisms remain unclear, hypomotility of the gut may contribute to this development [14].

Systemic effects of infection are known to affect gastrointestinal motility, likely due to a combination of effects on the enteric nervous system, sympathetic and vagal input, resident leukocytes, macrophages, and mast cells, and smooth muscle. It is not known whether these occur directly or are mediated by leukocyte signalling, and little is known about the specific associated TLR pathways. The presence of endotoxin and increased production of nitric oxide and prostaglandins are all implicated.

Sepsis-induced ileus likely contributes to a cycle of hypomotility, inflammatory cell recruitment and activation, and production of ROS and inflammatory cytokines. This may compromise the protective intestinal epithelial surface, with subsequent translocation of enteric flora or their PAMPs. The gut contains an unparalleled reservoir of potential pathogens. While some degree of translocation may serve an important immune function, in critically ill patients the homeostatic interplay among normal commensal enteric flora can become dysregulated, and the compromised gut wall may become a potent driver of systemic inflammation and multi-organ dysfunction. Translocation of gut flora and/or PAMPs may explain the delayed appearance of sepsis among some ICU patients, in whom progressive organ dysfunction includes deterioration of the gut mucosal protective barrier. Sepsis-induced ileus may also contribute to micro-aspiration and pulmonary infection, particularly in intubated patients.

Neurological

Among the neurological manifestations of sepsis, acquired delirium can complicate ICU outcomes and impact recovery. As many as 70% of patients with severe sepsis develop encephalopathy, which is associated with worsened outcomes [15]. Although initially attributed to toxic products of invading microorganisms, septic encephalopathy is now thought to result primarily from the systemic response to infection, including alterations in cerebral haemodynamics and the ratios of amino acid substrates for cerebral metabolism. Other potential causative factors include blood-brain barrier disruption, CNS inflammation, complement activation, increased production of nitric oxide and other vasoactive substances, neurotransmitter dysregulation, and leukocyte recruitment.

Endocrine

An association between sepsis and adrenal insufficiency has been recognized for over a century. As many as 60% of patients with sepsis and septic shock manifest a corticosteroid response that is apparently insufficient, given their severity of illness [16]. Critical illness-related corticosteroid insufficiency (CIRCI), results from decreased production of corticotropin-releasing hormone and its downstream products, as well as diminished sensitivity of peripheral tissues to activated glucocorticoid receptor [17]. The results include an impaired haemodynamic response to sepsis and insufficient downregulation of pro-inflammatory cytokines.

The diagnosis of CIRCI is complicated in part by the lack of an assay for corticosteroid activity at the level of the target tissue.

Clinicians must therefore rely on macroscopic features, as well as random measurements of absolute cortisol level and its response to stimulation by exogenous steroid, both of which are less accurate in the setting of sepsis.

The adverse effects of CIRCI seem to be due to its further perturbation of an imbalance between pro-inflammatory mediator overexpression and sepsis-related immune suppression. The optimal steroid replacement strategy must not further worsen this imbalance. Underdosing may allow the inflammatory vasoplegia and microvascular leak to persist, whereas overdosing may increase vulnerability to infectious insults, and can delay wound healing.

Glucose transporter (GLUT) dysfunction, insulin resistance, glucose intolerance, and hyperglycaemia commonly accompany critical illness. In sepsis, hyperglycaemia is likely due to pro-inflammatory cytokine-mediated GLUT dysfunction, sympathetic nervous system activation, and upregulation of counter regulatory hormones and insulin growth factor binding protein. Detrimental cytotoxic effects of hyperglycaemia appear to be mediated by cellular glucose overload and the accumulation of toxic products of glycolysis and oxidative phosphorylation. Multiple investigators have prospectively evaluated the association between glycaemic control and outcomes among critically ill patients, with largely mixed results [18]. For those limited populations in which tight glycaemic control has seemed beneficial, the purported benefits of insulin therapy may be directly due to glycaemic control or to salutary metabolic effects of insulin.

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, and Pinsky MR. (2001). Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Critical Care Medicine*, **29**(7), 1303–10.
2. van der Poll T, and Opal SM. (2008). Host-pathogen interactions in sepsis. *Lancet Infectious Diseases*, **8**(1), 32–43.
3. Denk S, Perl M, and Huber-Lang M. (2012). Damage- and pathogen-associated molecular patterns and alarmins: keys to sepsis? *European Surgery Research*, 48(4), 171–9.
4. Hotchkiss RS, and Karl IE. (2003). The pathophysiology and treatment of sepsis. *New England Journal of Medicine*, **348**(2), 138–50.
5. Opal SM. (2004). The nexus between systemic inflammation and disordered coagulation in sepsis. *Journal of Endotoxin Research*, **10**(2), 125–9.
6. Fourrier F. (2012). Severe sepsis, coagulation, and fibrinolysis. *Critical Care Medicine*, **40**(9), 2704–8.
7. Ince C. (2005). The microcirculation is the motor of sepsis. *Critical Care, BioMed Central*, **9**(4), S13.
8. Garrabou G, Moren C, Lopez S, et al. (2012). The effects of sepsis on mitochondria. *Journal of Infectious Diseases*, **205**(3), 392–400.
9. Zarjou A and Agarwal A. (2011). Sepsis and Acute Kidney Injury. *Journal of the American Society of Nephrology*, **22**(6), 999–1006.
10. Wan L, Bagshaw SM, Langenberg C, Saotome T, May C, and Bellomo R. (2008). Pathophysiology of septic acute kidney injury: What do we really know? *Critical Care Medicine*, **36**, S198–203.
11. Bhatia M and Moochhala S. (2004). Role of inflammatory mediators in the pathophysiology of acute respiratory distress syndrome. *Journal of Pathology*, **202**(2), 145–56.
12. Honore PM, Jacobs R, Joannes-Boyau O, et al. (2011). Septic AKI in ICU patients. Diagnosis, pathophysiology, and treatment type, dosing, and timing: a comprehensive review of recent and future developments. *Annals of Intensive Care*, **1**(1), 32.
13. Flynn A, Chokkalingam Mani B, and Mather PJ. (2010). Sepsis-induced cardiomyopathy: a review of pathophysiologic mechanisms. *Heart Failure Review*, **15**(6), 605–11.
14. Tsujimoto H, Ono S, and Mochizuki H. (2009). Role of Translocation of Pathogen-Associated Molecular Patterns in Sepsis. *Digestive Surgery*, **26**(2), 100–9.
15. Scalfani MT, and Diringer MN. (2011). Year in review 2010: critical care—neurocritical care. *Critical Care*, **15**(6), 237.
16. Annane D, Maxime V, Ibrahim F, Alvarez JC, Abe E, and Boudou P. (2006). Diagnosis of adrenal insufficiency in severe sepsis and septic shock. *American Journal of Respiratory Critical Care Medicine*, **174**(12), 1319–26.
17. Marik PE. (2009). Critical illness-related corticosteroid insufficiency. *Chest*, **135**(1), 181–93.
18. Ling Y, Li X, and Gao X. (2012). Intensive versus conventional glucose control in critically ill patients: a meta-analysis of randomized controlled trials. *European Journal of Internal Medicine*, **23**(6), 564–74.

CHAPTER 298

Management of septic shock in the critically ill

Sandra L. Peake and Matthew J. Maiden

Key points

- The pathophysiology of septic shock involves variable degrees of macrovascular, microvascular, and cellular dysfunction.
- Early recognition, resuscitation, appropriate antimicrobials, and source control are essential.
- Intravenous fluids are the first therapeutic strategy, but the optimal type and volume of fluid and resuscitation targets remain uncertain.
- If hypotension persists despite fluid resuscitation, noradrenaline is the currently recommended first-line vasopressor. If cardiac contractility is impaired despite adequate fluid replacement, consider adding dobutamine or adrenaline.
- Lactate and/or $ScvO_2$ can be used as a guide to adequacy of resuscitation. However, high $ScvO_2$ is associated with high mortality.

Introduction

Over the last 20 years, numerous clinical trials of novel therapeutic agents for septic shock have been evaluated. Nonetheless, conclusive evidence of a mortality benefit has not been forthcoming. Accordingly, the fundamental management principles of septic shock, namely early recognition, source control, appropriate and timely antibiotics, and haemodynamic resuscitation, remain the most important and effective therapeutic strategies.

The 2012 Surviving Sepsis Campaign (SSC) guidelines [1] recommend early (within 6 hours), protocolized resuscitation for septic patients with evidence of tissue hypoperfusion (hypotension despite an initial fluid challenge or blood lactate ≥4 mmol/L). Key recommendations and the levels of supportive evidence are outlined in Table 298.1.

Of note, the haemodynamic goals and the time frame for resuscitation were particularly influenced by one small, single-centre, randomized, controlled trial of protocolized early goal-directed therapy (EGDT) in patients presenting to the emergency department (ED) with severe sepsis or septic shock [2]. This trial, published in 2001, reported that delivery of EGDT for 6 hours was associated with a 16% reduction in hospital mortality. Implementation of 'bundled' care, incorporating the EGDT resuscitation algorithm, has been reported to improve survival in subsequent non-randomized studies. More recently, three randomized trials of protocol-based resuscitation for patients presenting to the ED with early septic shock in the United States (Protocol-based Care for Early Septic Shock, ProCESS) [3], Australasia (Australasian Resuscitation In Sepsis Evaluation, ARISE) [4] and England (Protocolised Management In Sepsis, ProMISe) [5] have failed to demonstrate a survival benefit with EGDT compared with non-protocolized usual care.

The aim of this chapter is to review the current management of septic shock, with particular emphasis on the importance of *early* infection control and haemodynamic resuscitation.

Infectious source identification and control

Urgent identification of the infectious focus should occur for all septic patients. If the source is not apparent clinically, imaging studies are often required to assist in site determination.

To help identify the infecting organism(s) and direct antimicrobial management, ≥2 sets of blood cultures (and other sites as appropriate) should be taken prior to commencing antimicrobials. Prospective data from >15,000 patients in the SSC performance improvement initiative demonstrated that mortality was lower for patients in whom blood cultures were obtained before starting antimicrobials (odds ratio [OR] 0.86, 95% Confidence Interval [CI] 0.79–0.93) [6]. Nevertheless, obtaining cultures must not unduly delay antimicrobial administration.

Although there are no, and unlikely to ever be, any randomized trials studying the effect of source control, once the site of infection is identified attention must be directed towards definitive treatment (e.g. drainage of collections, removal of infected tissue or intra-vascular devices). Highly lethal diseases like necrotising soft tissue infections and intestinal ischaemia require immediate intervention. Timing for other infections depends upon the type of infection, severity of physiological disturbance and the likely risk of deterioration.

Antimicrobial therapy

Timely administration of empirical broad-spectrum agents to cover all likely pathogens and susceptibility patterns (with subsequent narrowing of therapy) is vitally important. The importance of providing appropriate initial antimicrobials has been highlighted in a number of retrospective and observational studies in which delayed or inappropriate antimicrobial administration is associated with increased mortality [7,8]. Survival benefit with timely antimicrobials has also been described for immunosuppressed patients

Table 298.1 Summary of the key 2012 Surviving Sepsis Campaign guidelines recommendations for early infection control and haemodynamic resuscitation in patients with severe sepsis or septic shock#

Early resuscitation strategies	Level of evidence	Strength of recommendation
Determining infection source and causative organisms		
◆ Appropriate cultures before starting antimicrobials, provided administration not delayed	1	C
◆ ≥2 blood culture sets (other sites e.g. vascular access devices as clinically indicated)	1	C
Appropriate, timely antimicrobial therapy and source control		
◆ Broad-spectrum iv antimicrobials *within 1hr* of recognizing septic shock	1	B
◆ Broad-spectrum iv antimicrobials *within 1hr* of recognizing severe sepsis without shock	1	C
◆ Source identification and control *within 12hr* of diagnosis if feasible, including removal of potentially infected intravascular devices	1	C
Haemodynamic resuscitation		
◆ Goal-directed resuscitation for *first 6hr* after hypoperfusion recognized	1	C
◆ iv fluid to achieve CVP 8–12 mmHg (12–15 mmHg if mechanically ventilated or decreased ventricular compliance)	1	C
◆ Initial fluid resuscitation with crystalloids	1	A
◆ Minimum initial fluid challenge 30 mL/kg of crystalloids	1	C
◆ Suggest adding albumin for initial fluid resuscitation	2	B
◆ Noradrenaline as first-line vasopressor	1	B
◆ Adrenaline added or substituted to maintain MAP	1	C
◆ MAP target ≥65 mmHg	1	C
◆ Dobutamine if evidence of myocardial dysfunction or hypoperfusion	1	C
◆ PRBC transfusion (if Hct < 30%) and/or dobutamine to attain $ScvO_2$ ≥ 70% or SvO_2 ≥ 65%	1	C

#Quality of evidence assessed using the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. Evidence graded as high (A), moderate (B), low (C) and very low (D). Strength of recommendation graded as strong (1) or weak (2).

iv, intravenous; hr, hour; CVP, central venous pressure; MAP, mean arterial pressure; PRBC, packed red blood cells; Hct, haematocrit; $ScvO_2$, central venous oxygen saturation; SvO_2, mixed venous oxygen saturation (SvO_2) of ≥65%.

and for critically ill patients with specific infections such as candida, nosocomial infection, and ventilator-associated pneumonia.

Although delayed antimicrobial administration may be a critical determinant of outcome, the observed relationship does not necessarily imply causality. Early and appropriate antimicrobial therapy could simply be a surrogate marker for better overall processes-of-care and hence, better outcomes from septic shock. This provides impetus for processes-of-care that facilitate early recognition and definitive treatment of severe sepsis. A recent meta-analysis of providing 'bundled care' for sepsis, reported reduced time to antibiotic initiation (weighted mean difference –0.58 hrs [–0.85 to –0.33]) and increased likelihood of providing appropriate antimicrobials (OR 3.06, 95%CI 1.69–5.53) [9].

Haemodynamic resuscitation

Resuscitation of septic shock is a medical emergency. Early recognition is vital as survival is decreased if treatment is delayed. Resuscitation should occur in an environment with continuous physiological monitoring and close medical and nursing attention.

The fundamental disorder in septic shock is inadequate cellular oxygen delivery (DO_2) and/or impaired utilization. The circulatory disturbance involves decreased preload (secondary to increased capillary permeability, venodilatation, hypovolaemia), myocardial depression, arteriolar dilatation, and peripheral shunting. The causes of impaired cellular oxygen utilization remain unclear.

Whilst the resuscitation principles of optimizing preload, afterload, contractility, heart rate, haemoglobin concentration and oxygen saturation seem straightforward, a number of issues merit further consideration, including:

- The choice of resuscitation fluid.
- How much fluid to administer.
- Which vasoactive agent(s) to use.
- The best way to reliably guide resuscitation.

Resuscitation fluids

The predominant circulatory disturbance in septic shock is a maldistribution of circulating blood volume and inadequate preload. Myocardial dysfunction also occurs, but fluid resuscitation often increases stroke volume (SV), resulting in a hyperdynamic circulation. Hence, fluids are usually the first therapeutic strategy in the management of septic shock and an initial challenge with

≥500–1000 mL of either crystalloid or colloid should be immediately and rapidly infused.

However not all patients respond to fluid administration, particularly if the heart is fully loaded (Frank-Starling law). Of interest, results from the Fluid Expansion as Supportive Therapy (FEAST) trial even suggest that a fluid bolus (5% albumin or 0.9% saline) may be harmful; at least in children with severe infection in Africa [10]. A conservative approach to ongoing fluid management is also supported by a randomized trial of liberal versus restrictive fluid administration in mechanically ventilated patients with acute lung injury.

Unfortunately, there is little evidence to indicate how much fluid to give or what are the most appropriate end-point(s) to guide fluid resuscitation. For example, there are no large-scale randomized studies evaluating the recommended '≥30 mL/kg crystalloid as initial resuscitation'. In the absence of such a trial, we are left with clinical assessment of the heart rate and blood pressure (BP) response to fluid administration, indices of end-organ perfusion (e.g. urine output, capillary refill) and evidence of fluid overload (e.g. oedema).

Clinical assessment may be supplemented with invasive and/or non-invasive haemodynamic monitoring. Although the SSC guidelines recommend targeting a central venous pressure (CVP) of 8–12 mmHg (mechanically ventilated 12–15 mmHg), cardiac filling pressures often fail to discriminate when a patient will respond to a fluid challenge.

Repeated assessment of the ability to increase CO with fluid boluses or a passive leg-raise are more reliable than static measures such as CVP or pulmonary artery occlusion pressure (PAOP). Dynamic measures of systolic pressure variation, pulse pressure variation, and SV variation (using pulse contour analysis) are currently the most reliable techniques of assessing fluid responsiveness. However, these techniques have only been validated in patients in sinus rhythm and receiving positive-pressure ventilation. Other dynamic measurement techniques include ultrasound assessment of inferior vena cava diameter, left ventricle end-diastolic area (echocardiography), and global end-diastolic volume index (GEDVI) using transpulmonary thermodilution; albeit these techniques have proven too unreliable to adopt widely.

Which resuscitation fluid?

The choice of fluid has engendered considerable debate for many years and there is no evidence that one fluid is better than another for patients with septic shock. An international survey of resuscitation fluid use in 391 intensive care units (ICU) and 25 countries reported that whilst colloid is more commonly administered than crystalloid, considerable geographical variation is evident.

In principle, the choice of fluid should be determined by the type of fluid lost, adverse effects of the fluid administered, degree of peripheral/interstitial oedema, serum albumin, availability, and costs. Whilst crystalloids are cheap and readily available, the potential for interstitial oedema, electrolyte, and acid-base disturbances (e.g. hypernatraemia and hyperchloraemic acidosis with large volume 0.9% saline resuscitation) are considered problematic. Conversely, colloids restore circulating volume more quickly, but are more expensive than crystalloids, can accumulate in the interstitium contributing to persistent interstitial oedema and some solutions have specific side-effects.

In the Saline versus Albumin Fluid Evaluation (SAFE) study comparing 4% albumin and 0.9% saline for fluid resuscitation, albumin was associated with less fluid administration on days 1–4 (ratio 1:1.4). Over the same time-frame, no difference in mean arterial pressure (MAP) was observed, although CVP was statistically, but not clinically, significantly different (albumin ~1 mmHg higher). Twenty-eight-day mortality was also not different. Analysis of the pre-defined severe sepsis subgroup suggested that albumin improved survival (OR 0.71, 95% CI 0.52–0.97) [11]. A recent meta-analysis of albumin resuscitation in sepsis also supports a beneficial role (OR 0.82, 95% CI 0.67–1.0) [12].

Whilst hydroxyethyl starch (HES) is widely used in many countries, there is considerable concern regarding the safety profile, particularly with respect to renal function. The Intensive Insulin and Pentastarch Resuscitation in Severe Sepsis Randomized Trial reported a significant increase in renal dysfunction and a trend to increased 90-day mortality with 10% HES (200/0.5). The Scandinavian 6S Trial Group has also recently reported that resuscitation with 6% HES (130/0.42) is associated with both an increased mortality risk and requirement for renal-replacement therapy (RRT) compared with Ringer's acetate in a multi-centre, blinded trial of 798 severe sepsis patients [13]. However, a small, randomized trial of HES 130/0.4 versus 0.9% saline in severe sepsis (CRYSTMAS study) reported that HES was not associated with adverse outcomes. In contrast, the Crystalloid versus Hydroxyethyl Starch Trial (CHEST) trial involving 7000 ICU patients requiring fluid resuscitation reported that 6% HES was associated with increased requirement for RRT, although 90-day mortality was not different compared to patients receiving 0.9% saline for resuscitation [14].

Vasoactive agents

When fluid resuscitation alone fails to optimize end-organ perfusion, vasoactive agents should be commenced. As with the choice of resuscitation fluid, the optimal agent(s) is also controversial and the survival benefit of any particular agent has not been proven in large-scale trials.

The SSC guidelines advocate noradrenaline (predominantly α-agonist) as the initial vasopressor of choice to maintain a MAP ≥65 mmHg. Adrenaline has not been recommended as first-line therapy; in part because of concerns about tachycardia, hyperlactataemia and impaired organ perfusion. There is no evidence that adrenaline is associated with increased mortality and concerns are ameliorated by a recent blinded, randomized trial of adrenaline versus noradrenaline in patients with shock (57% septic shock), which reported that adrenaline-associated tachycardia and lactic acidosis were non-sustained and attainment of MAP goals was similar for both catecholamines. Mortality (secondary end-point) was also similar [15]. Haemodynamic end-points and survival were also similar in a randomized trial of septic shock patients comparing adrenaline with noradrenaline plus dobutamine.

Dopamine has often been considered an alternative first-line catecholamine for septic shock. A recent meta-analysis comparing dopamine and noradrenaline in septic shock suggested increased mortality and arrhythmias with dopamine. Accordingly, routine use of dopamine is not supported by the SSC guidelines.

Although the Vasopressin in Septic Shock Trial (VASST) failed to show a survival benefit for adding vasopressin (vs. noradrenaline) in septic shock patients, low-dose vasopressin administration may still be considered for catecholamine-resistant hypotension and tissue hypoperfusion [16]. Early, rather than late, administration may also be more beneficial.

Irrespective of the vasopressor choice, it is recommended that BP is continuously monitored using invasive measurement and that the MAP target is ≥65 mmHg. However, the appropriate BP target must be individualized to account for factors such as pre-morbid BP, vascular disease, and the clinical response to resuscitation. Although an increase in MAP from 65 to 85 mmHg with noradrenaline has been reported to improve the macrocirculation and microvascular blood flow, the ideal BP goal has never been formally evaluated in large-scale trials.

Finally, if MAP is restored, but signs of organ hypoperfusion remain, some authors advocate commencing an inotrope (generally dobutamine) to increase CO and improve DO_2. In particular, the Rivers' EGDT protocol calls for dobutamine commencement (≤20 μg/kg/min) if $ScvO_2$ is <70% and haematocrit is >30% despite intravenous (iv) fluid repletion and restoration of MAP [2]. Although the addition of dobutamine is recommended by the SSC guidelines, the level of evidence supporting its use is low.

Glyceryl trinitrate (GTN) has been reported to improve microvascular flow in a small observational study using sublingual orthogonal polarization spectral imaging in septic shock patients. A subsequent randomized, blinded trial of 70 severe sepsis patients demonstrated that whilst fluid resuscitation improved microvascular flow, GTN was not different to placebo and was associated with a trend to increased mortality.

Resuscitation targets

Tissue perfusion and O_2 utilization may remain inadequate despite seemingly normal global haemodynamic parameters. The ability to monitor adequacy of cellular resuscitation is becoming increasingly important. Given the complex and varied interplay of macro-vascular, micro-vascular, and cellular changes that occur in septic shock, it is unlikely that any one variable is reliable enough to guide resuscitation. Based on available evidence, a combination of clinical assessment, venous oxygen saturation monitoring, and/or lactate measurement provides the most useful guide to the adequacy of resuscitation.

Venous haemoglobin-O_2 saturation

Mixed venous oxygen saturation (SvO_2) monitoring provides information regarding the balance between DO_2 and global oxygen consumption. However, measurement requires pulmonary artery catheter placement. More recently, continuous central venous oxygen ($ScvO_2$) monitoring, with therapies titrated to achieve a $ScvO_2$ >70%, has been proposed as an alternative resuscitation target. Although $ScvO_2$ measurement does not include coronary venous blood, and in health is usually 5–20% higher than SvO_2, the two measures behave similarly in shock and $ScvO_2$ may be a useful surrogate marker.

Low $ScvO_2$ (<70%) suggests inadequate DO_2 and is associated with higher mortality rates. However high $ScvO_2$ (>85%) is also commonly encountered in septic shock and is associated with even higher mortality rates [17]. High $ScvO_2$ represents inadequate oxygen utilization or vascular shunting and how best to manage microvascular dysfunction and cellular dysoxia is an area of burgeoning research.

The utility of $ScvO_2$-guided resuscitation as described by Rivers' et al. has been investigated in three independent, multicentre, randomized trials of EGDT in the United States (ProCESS) [3], Australasia (ARISE) [4], and the United Kingdom (ProMISE) [5]. No evidence of a survival benefit has been demonstrated. Given concerns regarding the generalizability of Rivers' trial findings, the complexity and potential risks associated with elements of the resuscitation algorithm (e.g. blood, dobutamine), financial and infrastructure implications, and limited adoption despite incorporation into the SSC guidelines, widespread implementation of EGDT for the management of patients with septic shock cannot be recommended at this stage.

Lactate

Hyperlactataemia occurs in the setting of oxygen supply/demand imbalance and/or microcirculatory or cellular dysfunction. Serum lactate is a useful parameter to guide resuscitation as it is rapidly and easily measured at point-of-care and may be more readily available than continuous $ScvO_2$ monitoring. However, lactate is not specific for cellular hypoxia and can be elevated with β-agonists, some iv fluids and reduced hepatic clearance.

The utility of lactate as a marker of severity of sepsis has been reported by several investigators. In a retrospective study of 830 severe sepsis patients, adjusted mortality was increased with higher presenting lactate levels [18]. Normotensive septic patients with a lactate >4 mmol/L also have a similar mortality risk as hypotensive septic patients.

Lactate clearance may also provide a useful resuscitation guide in severe sepsis. Observational studies suggest that failure to achieve ≥10% lactate clearance during resuscitation is a better predictor of mortality than $ScvO_2$ or persistent hypotension. In controlled studies, lactate clearance was non-inferior to $ScvO_2$ as a resuscitation target and in a separate trial of ICU patients with lactate >3 mmol/L (39% sepsis), targeting therapy to achieve a ≥20% lactate clearance every 2 hours increased fluid administration and reduced mortality (hazard ratio 0.61, 95% CI 0.43–0.87) [19].

Other resuscitation tools

Monitoring venous–arterial CO_2 difference, tissue oxygenation, and sublingual micro-circulatory flow provide fascinating insights into the pathophysiology of septic shock. Currently, these techniques remain experimental.

References

1. Dellinger RP, Mitchell MM, Rhodes A, et al. (2013). Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine*, **41**(2), 580–637.
2. Rivers E, Nguyen B, Havstad S, et al. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine*, **345**(19), 1368–77.
3. The ProCESS Investigators (2014). A randomised trial of protocol-based care for early septic shock. *New England Journal of Medicine*, **370**(18), 1683–93.
4. The ARISE Investigators and the ANZICS Clinical Trials Group (2014). Goal-directed resuscitation for patients with early septic shock. *New England Journal of Medicine*, **371**(16), 1496–506.
5. Mouncey PR, Osborn TM, Power GS, et al. (2015). Trial of early, goal-directed resuscitation for septic shock. *New England Journal of Medicine*, **372**(14), 1301–11.
6. Levy MM, Dellinger P, Townsend SR, et al. (2010). The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Medicine*, **36**(2), 223–31.

7. Kumar A, Ellis P, Arabi Y, et al. (2009). Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest*, **136**(5), 1237–48.
8. Kumar A, Roberts D, Wood KE, et al. (2006). Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Critical Care Medicine*, **34**(6), 1589–96.
9. Barochia AV, Cui X, Vitberg D, et al. (2010). Bundled care for septic shock: an analysis of clinical trials. *Critical Care Medicine*, **38**(2), 668–78.
10. Maitland K, Kiguli S, Opoka R, et al. (2011). Mortality after fluid bolus in African children with severe infection. *New England Journal of Medicine*, **364**(26), 2183–95.
11. SAFE Study Investigators, Finfer S, McEvoy S, et al. (2011). Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Medicine*, **37**(1), 86–96.
12. Delaney AP, Dan A, McCaffrey J, and Finfer S. (2011). The role of albumin as a resuscitation fluid for patients with sepsis. A systematic review and meta-analysis. *Critical Care Medicine*, **39**(2), 386–91.
13. Perner A, Haase N, Guttormsen A, et al. (2012). Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *New England Journal of Medicine*, **367**(2), 124–34.
14. Myburgh JA, Finfer S, Bellomo R, et al. (2012). Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *New England Journal of Medicine*, **367**(20), 1901–11.
15. Myburgh JA, Higgins A, Jovanovska A, et al. (2008). A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Medicine*, **34**(12), 2226–34.
16. Russell J, Walley K, Singer J, et al. (2008). Vasopressin versus norepinephrine infusion in patients with septic shock. *New England Journal of Medicine*, **358**(9), 877–87.
17. Pope JV, Jones AE, Gaieski DF, et al. (2010). Multicentre study of central venous oxygen saturation (ScvO2) as a predictor of mortality in patients with sepsis. *Annuals of Emergency Medicine*, **55**(1), 40–6.
18. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. (2009). Serum lactate is a associated with mortality in severe sepsis independent of organ failure and shock. *Critical Care Medicine,* **37**(5), 1670-77.
19. Jansen TC, van Bommel J, Schoonderbeek FJ, et al. (2010). Early lactate-guided therapy in intensive care unit patients. A multicentre, open-label, randomised controlled trial. *American Journal of Respiratory Critical Care Medicine*, **182**(6), 752–61.

SECTION 14

Inflammation

PART 14.1

Physiology

CHAPTER 299

Innate immunity and the inflammatory cascade

Marianna Parlato and Jean-Marc Cavaillon

Key points

- Inflammation and innate immunity are two overlapping physiological processes aimed at addressing host tissue insults and infection.
- Interleukin-1 and tumour necrosis factor are the two main cytokines that orchestrate the inflammatory response.
- A cascade of mediators acting in synergy characterizes inflammation.
- Cytokines, free radicals, lipid mediators, coagulation factors, proteases, and neuromediators all contribute to the inflammatory process.
- Anti-inflammatory cytokines, specific IL-1 and TNF inhibitors, acute phase proteins, leukocyte reprogramming, neuromediators, and lipid mediators contribute to the resolution of inflammation.

Innate immunity and the inflammatory response

Inflammation and innate immunity are two overlapping processes aimed at addressing sterile insults of host integrity, and acts of aggression by infectious agents. In the case of trauma, burns, haemorrhage, surgery or ischaemia, endogenous mediators known as alarmins, or 'damage-associated molecular patterns' (DAMPs) are released by injured tissues and necrotic cells. DAMPs recognized by specific receptors initiate the production of inflammatory cytokines that orchestrate the inflammatory response. Similarly, in the case of infection, 'pathogen-associated molecular patterns' (PAMPs) derived from micro-organisms are the initiators of the cascade of events aimed at eliminating the pathogens. DAMPs and PAMPs are sensed by 'pattern recognition receptors' (PRRs), either at the cell surface (Toll-like receptors, scavenger receptors, C-type lectins) or expressed intracellularly (Nod-like receptors, Rig-like receptors) [1]. These receptors initiate a cascade of intracellular signalling events that lead to the synthesis and release of cytokines. Cytokines favour an anti-infectious response by boosting phagocytosis, enhancing haematopoiesis, favouring cell recruitment, and inducing fever. Their key roles in fighting infection have been demonstrated in numerous animal models. Enhanced protection can be achieved by pretreatment with cytokines such as interleukin-1 (IL-1), IL-12, tumour necrosis factor-α (TNF-α), gamma-interferon (IFN-γ), and the haematopoietic factors IL-3, granulocyte/macrophage colony-stimulating factor (GM-CSF), M-CSF, and G-CSF. Studies using neutralizing antibodies targeting endogenous cytokines, or mice lacking the functional gene for a given cytokine or cytokine receptor, have unravelled the role of these mediators. For example, the use of anti-TNF-α antibodies in a caecal ligature and puncture (CLP) model employed to mimic polymicrobial sepsis revealed the key role of tumour necrosis factor (TNF)-α in fighting the microbial insult. Of note is that the great number of pathogens that have developed strategies to inhibit cytokines further illustrates the central role of cytokines in the host defence against infection.

Cytokine storm and synergy

The physiological response can be associated with pathogenicity when the host is chronically exposed to inflammatory stimuli, or when the innate immunity response is overwhelmed and leads to a 'cytokine storm' as seen in severe malaria or sepsis. In septic patients, cytokines are overproduced and therefore detectable in the blood. Circulating cytokines are only the tip of the iceberg [2]. High plasma levels generally correlate with severity and poor outcomes, and this is true for both pro- and anti-inflammatory cytokines. Some inflammatory cytokines display side effects. For example, IL-1β injected into animals results in hypotension, increased cardiac output, tachycardia, leucopenia, thrombocytopenia, haemorrhage, and pulmonary oedema. TNF-α toxicity includes haemodynamic instability, fever, diarrhoea, metabolic acidosis, capillary leak syndrome, activation of coagulation, late hypoglycaemia, induction of a catabolic state, neurotoxicity, cachexia, and renal and haematological disorders, all phenomena associated with sepsis. The dark side of cytokines has been illustrated in humans with the so-called 'cytokine release syndrome' observed in patients treated with anti-CD3, anti-CD20 or anti-CD28 antibodies. Administration of endotoxin (lipopolysaccharide, LPS) to human volunteers induces significant amounts of circulating TNF-α, IL-6, and IL-8.

The production of inflammatory cytokines results from the synergy between numerous activating signals, such as PAMPs, DAMPs, anaphylatoxins (from complement activation), cytokines, haemoglobin, lipid mediators, neuromediators, and coagulation factors. Similarly, the severity of the clinical features reflects the synergy between the action of the inflammatory mediators (complement system, cytokines, free radicals, eicosanoids, neuromediators) and physiological events (coagulation, hypoxia, apoptosis,

viral reactivation). For example, co-injection of a non-lethal dose of TNF-α with a non-lethal dose of LPS, or co-injection of a non-lethal dose of IL-1β and IFN-γ, induces 100% mortality in mice.

Inflammatory cascade and regulatory loops

Cytokines and chemokines

IL-1β and TNF-α play a synergistic role in orchestrating the inflammatory response (Fig. 299.1). Their production in response to PAMPs and DAMPs can be amplified by other cytokines, such as IL-3, GM-CSF, or IFN-γ. IFN-γ is produced by T-cells and NK cells in response to other cytokines such as IL-2, IL-12, IL-15, and IL-18. IFN-γ possesses both pro-inflammatory and anti-bacterial properties. In particular, IFN-γ enhances phagocytosis and free radical production, thus increasing the bactericidal activity of macrophages and neutrophils. However, inhibition of IFN-γ is associated with a better prognosis in animal models of sepsis with a decrease in bacterial load and systemic inflammation. Among the IFN-γ inducing cytokines, neutralization of IL-18 protected mice against lethal endotoxaemia, while IL-18-deficient mice showed decreased sensitivity towards LPS-induced shock.

Sepsis and systemic inflammatory response syndrome (SIRS) are often associated with the development of the multiple organ dysfunction syndrome (MODS), and reflects the inflammatory processes occurring within the tissues. A major feature of this phenomenon is the recruitment of inflammatory leukocytes, which implies the adherence of circulating cells to the endothelium and their response to the locally produced chemokines. Endothelial cells are highly responsive to IL-1 and TNF-α in terms of adhesion molecule expression, cytokine production, and alteration of tight junctions. Endothelial cell wall integrity perturbed by these cytokines is illustrated by the absence of endothelial damage in IL-1 receptor type I deficient mice. Once immobilized on endothelium, leukocytes migrate towards the tissues in response to IL-8 and other chemokines. These can be directly induced by microbial agonists, as well as IL-1β and TNF-α. They contribute to the inflammatory cell infiltrate which, in turn, induces loss of tissue integrity. In acute respiratory distress syndrome (ARDS) patients, elevated levels of IL-8 in bronchoalveolar lavage correlated with poor outcomes. In sepsis, all plasma chemokine levels are enhanced with the exception of RANTES (CXCL5), of which levels are diminished. The inhibition of binding of CXCL chemokines to their receptors improved survival following CLP. The relative contribution of chemokines to the pathophysiological events associated with sepsis is linked to their capacity to recruit inflammatory cells within tissues. In contrast, their presence within the bloodstream may limit the inflammatory process by unpriming circulating cells to further chemoattractant signals. Notably, blocking CXCL receptors or giving anti-IFN-γ antibodies reduced levels of high mobility group box-1 (HMGB-1), a DAMP that is a late mediator of inflammation. Indeed, anti-HMGB1 antibodies improved gut dysfunction and were beneficial in a murine peritonitis model.

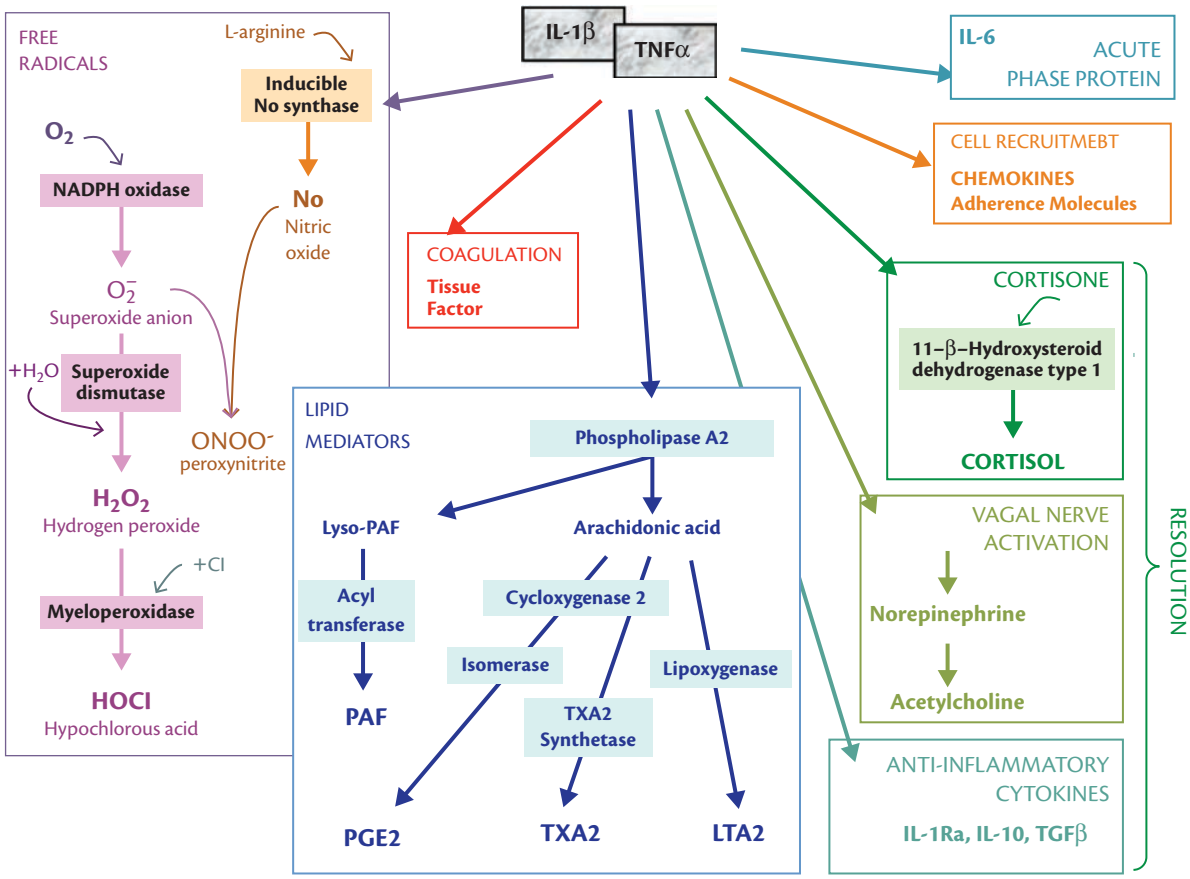


Fig. 299.1 Interleukin-1 (IL-1) and tumour necrosis factor (TNF) orchestrate a cascade of inflammatory events.

Macrophage migration inhibitory factor, produced in response to TNF-α, IFN-γ, IL-23 and IL-27, also contributed towards lethality in a CLP model. In contrast, conflicting reports have been published on the role of IL-17 and IL-33 during experimental sepsis. However, the role of IL-17 in the cross-talk between inflammatory tissues and in the perpetuation of the inflammatory process is now well established.

Among growth factors, vascular endothelial growth factor (VEGF) contributed to lethality in a CLP model by altering VE-cadherin expression and strength of tight junctions. Other mediators, e.g. the ligand of 'triggering receptor expressed on myeloid cells-1' (TREM-1), and the anaphylatoxin C5a act in synergy with TLR and NLR ligands favouring inflammatory cytokine production [3]. Finally, enhanced levels of programmed cell death 1 ligand (PD-1L) favour liver injury and lymphocyte apoptosis.

Free radicals

During inflammation, nitric oxide (NO) is produced in excess by inducible NO synthase (iNOS). Large amounts of NO are released after endotoxin exposure or cytokine-related stimulation of iNOS activity in inflamed tissues and vessels wall. NO production has been involved in many pathophysiological processes, including MODS. A major deleterious effect of NO is its ability to alter epithelial tight junctions, and this was shown to play an important role in the development of pulmonary, liver, and gut dysfunction in endotoxaemic mice. However, iNOS-deficient mice have a high mortality when exposed to polymicrobial sepsis, illustrating the fact that NO, as with many other mediators involved in both inflammation and innate immunity, has an ambiguous effect depending upon the experimental model or the timing of observation.

Upon activation by bacterial products or inflammatory cytokines, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase catalyses the production of superoxide anions. These are transformed by superoxide dismutase into H_2O_2, which, in turn, is converted into HOCl by myeloperoxidase (Fig. 299.1). These molecules are potent anti-microbial agents and probably contribute to tissue damage. Indeed, NADPH oxidase is involved in the impairment of capillary blood flow, lung injury, and intestinal damage.

Lipid mediators

Pro-inflammatory cytokines induce the synthesis of phospholipase-A2 (PLA2), inducible cyclooxygenase (COX2), 5-lipooxygenase, and acetyltransferase, which contribute to eicosanoid synthesis (Fig. 299.1). These factors promote inflammation, alter vasomotor tone, and increase blood flow and vascular permeability. PLA2-deficient mice are endotoxin-resistant while *in vivo* inhibition of PLA2 decreases neutrophil infiltration into the lungs and deterioration of gas exchange following endotoxin or zymosan challenge. COX-2 deficient mice are also resistant to endotoxin-induced inflammation and death. Blocking the synthesis of leukotrienes or using 5'-lipoxygenase deficient mice demonstrated the deleterious effect of this eicosanoid in vivo. Platelet activating factor (PAF) is released by a large amount of cell types such as platelets, endothelial cells, macrophages, and neutrophils. Blood levels of PAF are elevated during septic shock. In different animal models inhibiting or antagonizing PAF led to improved blood pressure, prevention of microvascular alterations, protection from gastrointestinal lesions, reduction in TNF-α levels, and protection against the lethal effects of LPS. All these data confirm the involvement of PAF within the network of inflammatory mediators. However, no significant beneficial effects of PAF antagonism could be observed in human settings.

Coagulation and fibrinolysis

Disorders of coagulation are common in sepsis; 30–50% of patients with the most severe clinical form have disseminated intravascular coagulation. Numerous animal models with tools aimed at inhibiting coagulation or enhancing fibrinolysis have been successful in improving outcomes. Tissue factor (TF) is the link between inflammation and coagulation. It interacts with factor VII and increases the production of fibrin through activation of prothrombin and thrombin. In healthy volunteers challenged with LPS and in sepsis patients, TF expression is enhanced; increased membrane expression by monocytes prognosticates for a poor outcome. IL-1 and TNF-α, IFN-γ, CD40L, VEGF and MCP-1 induce TF expression on both monocytes and endothelial cells, while IL-6 favours thrombin expression. In parallel, both IL-1 and TNF-α induced production of plasminogen activator inhibitor-1 (PAI-1), thus favouring microvascular thrombosis following depression of fibrinolysis and enhanced coagulation. Coagulation factors such as factor Xa or thrombin also display pro-inflammatory activities.

Proteases

During sepsis, proteases are released by activated leukocytes and play an important role in the inflammatory host response. However, excess levels of elastase are associated with organ dysfunction. Matrix metalloproteinases (MMP) are involved in tissue remodelling (degradation and remodelling of all components of extracellular matrix), as well as in various inflammatory processes. Plasma levels of MMP-1 and MMP-9 are enhanced in human sepsis, and correlate with both severity and mortality. Whereas MMP-9 deficiency protected mice against mortality in an endotoxin model, such a deficiency was associated with enhanced bacterial growth and bacterial dissemination following CLP. Blockade of MMP-1 activity suppressed endothelial barrier disruption, disseminated intravascular coagulation, lung vascular permeability, and the cytokine storm, and improved survival.

Neuromediators

Some neuromediators displays pro-inflammatory properties. Substance P and neurokin A are encoded by the preprotachykinin-A gene. In preprotachykinin-A deficient mice, mortality following CLP decreases compared with wild type. Substance P antagonists reduce stress-induced cytokine up-regulation. Finally, norepinephrine increases TNF-α production via α_2-adrenergic receptors.

Resolving mediators

Anti-inflammatory cytokines

The pro-inflammatory response is balanced by the release of cytokine inhibitors, such as interleukin-1 receptor antagonist (IL-1Ra), IL-10, transforming growth factor-β (TGF-β), and soluble IL-1 and TNF receptors. The capacity of these natural inhibitors to downregulate or counteract cytokines produced by activated monocytes, eosinophils, and polymorphonuclear leukocytes, has been well-established. For example, following endotoxin or staphylococcal enterotoxin B injection, IL-10 treatment reduced TNF-α production, hypothermia, and death. In addition, IL-10 deficient mice develop chronic inflammatory bowel disease, which could be reduced by IL-10 treatment. IL-10 deficient mice are also highly

susceptible to colitis leading to aberrant inflammation to commensal bacteria; this colitis is more severe when combined with deficiency in TGF-β signalling. Similarly, IL-1Ra treatment reduced lethality of endotoxin-induced shock in rabbits and mice [4]. Of note, IL-1Ra deficient mice are prone to develop certain chronic inflammatory disorders. Other cytokines have also been reported to display anti-inflammatory properties (i.e. IL-4, IL-13, IL-25, IL-27, IL-35, and IFNα). Similarly, other cytokine antagonists have been described (e.g. IL-18 binding protein, IL-38, IL36Ra).

Glucocorticoids

Glucocorticoids (GCs), steroid hormones produced by adrenal glands, elicit potent anti-inflammatory effects signalling through a ligand dependent transcription factor, GR (glucocorticoid receptor). Following translocation to the nucleus, GR binds to palindromic glucocorticoid response elements (GREs) or interacts with other transcriptional regulators such as activating protein-1 (AP-1) and nuclear factor kappa B (NF-κB). GCs also exert non-genomic anti-inflammatory effects, such as promoting apoptotic cell clearance by phagocytes. In vivo, the endogenous GC cortisone is converted into its active counterpart cortisol, by 11β-hydroxysteroid dehydrogenase type-1 (11β-HSD1; Fig. 299.1). Indeed, 11β-HSD1 deficient mice are unable to reactivate cortisone to the bioactive cortisol. In sterile peritonitis model, 11β-HSD1 deficient mice show an exacerbated inflammatory response and delayed resolution mechanisms. Moreover, 11β-HSD1 deficient mice are more susceptible to endotoxaemia, with increased weight loss and overproduction of pro-inflammatory cytokines such as TNF-α and IL-6 following LPS injection. Altered GC metabolism has been reported in sepsis and trauma patients who may display adrenal insufficiencies.

Acute phase proteins

Many inflammatory cytokines (e.g. IL-6, IL-1, TNF, IL-11, IL-22, leukocyte inhibitory factor, TGFβ) can induce the release of acute phase proteins by hepatocytes such as C-reactive protein (CRP). Acute phase proteins favour the elimination of debris and neutralize inflammatory mediators. CRP has also been shown to alter O_2- release by neutrophils and to limit their chemotaxis, and to be protective in varied in vivo models (e.g. C5a instillation, LPS, or histone injection)

Lipid mediators

Lipoxins, maresin, and members of the resolvin and protectin families act as pro-resolution molecules, providing signals that selectively reduce neutrophil and eosinophil infiltration to inflamed tissues, promoting macrophage clearance of apoptotic cells, and micro-organisms, favouring the exit of phagocytes from the inflamed site through the lymphatics, and stimulating the expression of antimicrobial molecules. For example, treatment with resolvin D2-enhanced macrophage-dependent bacterial clearance, reduced plasma levels of the pro-inflammatory cytokines IL-6, IL-1β and TNF-α, and increased survival rates following CLP. In addition, lipoxin A4 treatment promoted survival and stimulated IL-10 production [5].

Neuromediators

Epinephrine, via β_2-adrenergic receptors, decreases TNF, IL-6 and NO production in response to LPS and potentiates IL-10 production. Adrenomedullin is a neuropeptide, structurally related to corticotropin-releasing factor (CRF), which inhibits TNF expression and stimulates IL-6 production by macrophages in response to LPS. A growing number of observations implicate the vagus nerve in events associated with the down-regulation of inflammation. Acetylcholine produce by the vagus nerve and by norepinephrine activated T-cells can dampen inflammation via the α7-nicotinic receptor [6].

References

1. Kawai T and Akira S. (2011). Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity*, **34**, 637–50.
2. Cavaillon JM, Munoz C, Fitting C, Misset B, and Carlet J. (1992). Circulating cytokines: the tip of the iceberg? *Circulatory Shock*, **38**, 145–52.
3. Adib-Conquy M and Cavaillon JM. (2007). Stress molecules in sepsis and systemic inflammatory response syndrome. *FEBS Letters*, **581**, 3723–33.
4. Dinarello CA. (2010). Anti-inflammatory agents: present and future. *Cell*, **140**, 935–50.
5. Serhan CN, Chiang N, and Van Dyke TE. (2008). Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nature Review Immunology*, **8**, 349–61.
6. Andersson U and Tracey KJ. (2012). Neural reflexes in inflammation and immunity. *Journal of Experimental Medicine*, **209**, 1057.

PART 14.2

Organ-specific biomarkers

CHAPTER 300

Brain injury biomarkers in the critically ill

Patrick M. Kochanek and Rachel P. Berger

Key points

- The brain exhibits a secondary injury cascade that includes traditional, but also unique mechanisms, such as excitotoxicity, synaptic injury, axonal injury, and selective vulnerability. Quantification of brain injury biomarkers in serum and CSF has helped to define these biochemical, cellular, and molecular pathways.
- Three cellular targets, neurons, astrocytes, and axons have served as the principal cellular targets that have been used to develop brain injury biomarkers.
- Brain injury biomarkers have potential utility to aid in diagnosis and prognosis, guide therapy selection, and monitor therapeutic efficacy in acute brain injury in the intensive care unit (ICU).
- Protein biomarkers of brain injury such as NSE, S100B, GFAP, UCH-L1, and MBP, among others, have the potential for clinical use in the ICU, either alone or in combination. More novel brain injury biomarkers, such as oxidized cardiolipin and microRNAs deserve further exploration.
- Many factors can uniquely influence serum biomarker levels after brain injury, most notably the amount of disruption of the blood–brain barrier and the amount of cerebral blood flow in the injured tissue.

Introduction

Few areas in neurocritical care have attracted more attention recently than brain injury biomarkers. With the recent recognition of traumatic brain injury (TBI), particularly mild TBI, as a major public health problem, the search for reliable rapid diagnostic serum markers of brain injury has become a priority. Issues arising from sports concussion, blast TBI in combat casualty care, and abusive head trauma in infants and young children have driven this search. The development of one or more brain injury biomarkers would also have a broader impact, including utility in neurocritical care.

The roots of the potential use of serum or cerebrospinal fluid (CSF) biomarkers of brain injury in critical care medicine lie in seminal work of Vaagenes et al. in the early 1980s [1]. They examined the potential utility of CSF concentrations of the brain-specific isoform of creatine phosphokinase to identify morphological changes in the brain after experimental cardiac arrest. However, the use of brain injury biomarkers has a richer history than simply serving as a tool to identify brain injury. Serum and CSF biomarkers have been essential to understand the evolution of the unique secondary injury mechanisms occurring within the brain. Research linked to the search for brain injury biomarkers has yielded many dividends for the field of neurocritical care, notably in our understanding of the pathobiology of various acute insults [2].

Many things can serve as 'biomarkers'. A finding on cranial CT scan or brain MRI can serve as a biomarker of brain injury. Similarly, quantification of levels of various metabolites in brain tissue using magnetic resonance spectroscopy can aid in diagnosis or management in the ICU. This chapter focuses on brain injury biomarkers assessed in biological samples, such as serum or CSF, that are readily available in many intensive care unit (ICU) patients. This chapter will:

- Provide examples of how biomarkers of brain injury can be helpful in contemporary neurocritical care.
- Discuss the secondary injury mechanisms that represent the 'inflammatory response' to brain injury and the biological samples that are most often used to assess these biomarkers.
- Present key data on some of the biomarkers used to identify brain injury in research.
- Discuss novel brain injury biomarkers.
- Consider approaches that simultaneously evaluate multiple biomarkers.
- Briefly discuss innovative approaches to analysing biomarker profiles.
- Discuss factors that are relevant to neurocritical care that can influence the observed serum levels of brain injury biomarkers.

Table 300.1 identifies the biomarkers of acute brain injury discussed in this chapter.

The interface between critical care-relevant insults to the brain and brain injury biomarkers

The availability of reliable biomarkers could benefit ICU patients with a wide variety of acute brain injuries. For example, serum biomarkers could rapidly confirm the presence of acute brain injury in victims of polytrauma who are intoxicated and in whom a reliable

Table 300.1 Promising serum and/or cerebrospinal fluid biomarkers of acute brain injury relevant to critical care discussed in this chapter

Biomarker	Cellular source	References
Neuron specific enolase (NSE)	Neuron	[2, 3, 7, 8, 13, 15, 16]
Ubiquitin C-terminal hydrolase-1 (UCH-L1)	Neuron	[12, 13, 14]
α-Spectrin degradation products	Neuron	[6, 13, 16]
14-3-3-γ	Neuron	[16]
Glial fibrillary acidic protein (GFAP)	Astrocyte	[14, 15]
S100β	Astrocyte	[7, 8, 13, 15]
Myelin basic protein	Axon	[7, 9, 13]
Neurofilament-H	Axon	[16]
Cytochrome-C	Non-selective	[2, 4, 5]
High-mobility group protein B1 (HMGB-1)	Non-selective	[5]
Cardiolipin oxidation products	Brain mitochondria	[19]
MicroRNA let-7i	Unknown	[20]

Data from various sources (see references).

clinical exam is problematic. Similarly, biomarkers of brain injury could alert the physician to possible evolving brain injury in patients with status epilepticus, especially in cases where the admission CT scan is negative, but an acute injury is evolving. Serum or CSF biomarkers of brain injury could also aid in defining the severity of injury across various known neurocritical care disorders, such as TBI, cardiac arrest, stroke, meningitis, subarachnoid haemorrhage, and sepsis, and aid in prognostication. Serum levels of the brain injury biomarker, neuron specific enolase (NSE) have recently been incorporated into guidelines for prognostication in patients with hypoxic-ischaemic encephalopathy after cardiac arrest [3]. Finally, serum biomarkers might also be used in a theragnostic fashion, defining the response to treatments and/or guiding therapy selection. For example, recent studies suggest the possibility of using biomarkers to define the contribution of necrotic versus apoptotic neuronal death in patients with severe TBI or cardiac arrest. Two strategies in this regard are noteworthy. CSF levels of cytochrome C are strongly associated with neuronal death from apoptosis in children with severe TBI [4], while elevations in high mobility group box 1 (HMGB1) suggest alternative cell death pathways, such as necrosis, pyroptosis, or autophagy [5]. Assessing the breakdown products of the neuronal protein α-spectrin in CSF can similarly aid in this regard [6]. Caspase 3 cleaves α-spectrin to a 120 kDa fragment during apoptosis, while the enzyme calpain cleaves α-spectrin to 145 and 150 kDa fragments during necrosis. Examining the ratio of these two categories of products could thus help guide therapy.

The potential utility of serum biomarkers to evaluate the relative contributions of necrotic versus apopototic cell death as shown in a study assessing the neuronal injury biomarker NSE across three causes of brain injury in paediatric neurocritical care, namely, hypoxic-ischaemic encephalopathy from cardiopulmonary arrest, accidental TBI, and abusive head trauma [7]. In TBI, serum NSE levels were markedly increased, with peak levels seen on the initial day after TBI suggesting necrosis from the primary traumatic injury. In contrast, in both hypoxic-ischaemic encephalopathy and abusive head trauma, serum NSE generally peaked in infants and children in a delayed fashion, suggesting delayed neuronal death, probably from apoptosis. This illustrates the potential for serum biomarkers of brain injury both as a diagnostic tool and to potentially guide therapy. Similarly, in adults after cardiac arrest, serum NSE increased in a delayed fashion, suggesting delayed neuronal death from apoptosis. A marked attenuation of NSE levels was seen in patients treated with mild hypothermia, providing a biochemical correlate of beneficial effects of this therapy after cardiac arrest [8].

The use of biomarkers to assess mechanisms of secondary damage in brain in the ICU

The brain is complex and secondary damage after acute injury is multifaceted. The requisite mechanisms involved in injury cascades such as ischaemia/reperfusion, energy failure, and inflammation operate in the injured brain. However, after ischaemia, hypoxia, trauma, haemorrhage, or infection additional mechanisms are set into motion. Unique pathways linked to neurotransmission, connectivity (axonal and synaptic injury) and intracranial hypertension play significant roles (Fig. 300.1). Highlighting the complexity of the brain, after a hypoxic-ischaemic insult, such as cardiac arrest, delayed neuronal death occurs in selectively vulnerable regions, such as the CA1 region of the hippocampus, Purkinje cells in the cerebellum, and neurons in cortical layers. Yet neurons adjacent to these vulnerable cells and sharing the same blood supply are often not damaged. Similarly, highlighting the unique and complex injury cascades in brain, cognitive deficits can develop after mild TBI where no histopathological alterations are observed.

Several sources of biological samples are used to study secondary injury pathways in humans with severe brain injury. For example, the evolution of axonal injury after severe TBI can be monitored by assessing CSF levels of myelin basic protein (MBP) [9]. Similarly, assessment of the time course and magnitude of oxidative stress in brain can be accomplished by serially measuring CSF levels of markers such as ascorbate or F_2-isoprostane [10]. CSF is often available in patients with severe TBI, since ventricular catheters are placed to drain CSF in the treatment of raised intracranial pressure. Other methods, such as intracerebral microdialysis, which requires insertion of a probe directly into the brain, have allowed continuous sampling of brain interstitial fluid. Biomarkers of energy failure (lactate/pyruvate) or neurotransmitters (glutamate) have been assessed using this approach [11]. Microdialysis is a research tool, but has become standard care in several neurointensive care units.

Biomarkers to detect brain injury in the critically ill

Protein biomarkers: assessment of individual markers

A comprehensive review of protein biomarkers of brain injury is beyond the scope of this chapter, although several important markers will be discussed. In general, three categories of protein biomarkers—neuronal, astrocyte, and axonal—have been used. What is sought in a brain injury biomarker is a protein that is as unique as possible to brain as opposed to other tissues. However, few molecules are unique to brain. Individual brain injury biomarkers

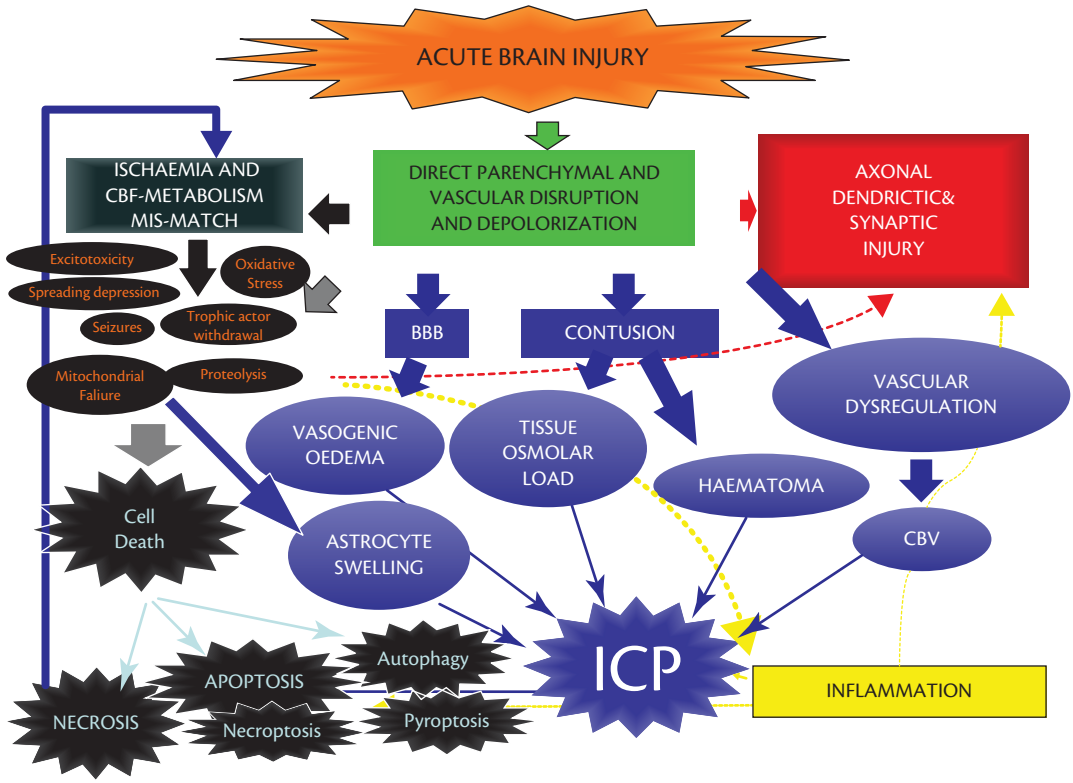


Fig. 300.1 Key mechanisms of secondary injury in the brain as defined by biomarker studies. In this example, traumatic brain injury is used as the example of acute brain injury. A vast array of biomarkers of acute brain injury in cerebrospinal fluid, serum, brain interstitial fluid, and brain tissue have been used to identify key mechanisms of secondary injury that evolve in the brain of critically-ill patients. Many of the biomarkers discussed in this chapter have contributed to current knowledge of these pathways. Secondary injury in the brain is notably more complex than in other organs related to several important factors including selective vulnerability of certain neurons to hypoxic-ischaemic insults, unique injury mechanisms, such as excitotoxicity, and unique and highly complex anatomical targets, such as synapses and axons. Please see text for details.

ICP, intracranial pressure; BBB, blood–brain barrier; CBV, cerebral blood volume.

as assessed in serum or CSF are generally quantified using ELISA or enzyme-linked immunofluorescence assays [2].

Neuronal injury markers

Several markers of neuronal injury have been studied extensively and have potential for clinical development. The most widely studied neuronal injury marker is NSE, a glycolytic enzyme localized predominantly in neuronal cytoplasm. It has a half-life of ~24 hours and has shown sensitivity and specificity in neurocritical care-relevant conditions, such as cardiac arrest and TBI [3]. A limitation of NSE is the occurrence of false positive values resulting from haemolysis due to the presence of enolase levels in erythrocytes and platelets. However, the level of NSE resulting from haemolysis in serum or CSF samples can be corrected. Two other neuronal injury markers have been the focus of investigation. Ubiquitin C-terminal hydrolase-1 (UCH-L1) is an abundant brain-specific protein involved in the addition or removal of ubiquitin from damaged proteins [12]. It has shown promise as both serum and CSF biomarker for mild and severe TBI, and may have broader utility in prediction of outcome after paediatric TBI [12]. As discussed previously, α-spectrin degradation products also show promise as serum and CSF biomarkers of brain injury. α-Spectrin is abundant in presynaptic terminals and, as previously discussed, the presence of its cleavage products in CSF or serum can suggest apoptotic versus necrotic injury pathways. Finally, other neuronal biomarkers have shown potential, including the protein 14-3-3-γ.

Astrocyte injury markers

Astrocytes are the most abundant cell type in brain and are a robust potential source for biomarkers. One promising biomarker is the astrocyte protein, glial fibrillary acidic protein (GFAP). It is almost exclusively found in brain and is released from the astrocyte cytoskeleton [13]. GFAP is showing promise as a brain injury biomarker in TBI, cardiac arrest, and stroke. Another marker studied extensively in brain injury is S100B, a calcium-binding protein found largely in astrocytes. This has shown effectiveness as a diagnostic marker in TBI, stroke, cardiac arrest, and subarachnoid haemorrhage [2]. Limitations of S100B include a short half-life, extracerebral sources, and high baseline levels in infants. Nevertheless, it has a substantial track record as a brain injury biomarker. Indeed, S100B is used as a standard of care in some European countries to exclude the need for a head CT scan in patients with mild TBI [14]. In a recent study comparing S100B, GFAP, NSE, and other biomarkers in adults after cardiac arrest, S100B exhibited the best sensitivity (87%) and specificity (100%) for predicting poor outcome [15].

Axonal injury markers

White matter is injured in various forms of acute brain injury. In diffuse axonal injury from certain forms of TBI, it can be selectively damaged. In contrast, in ischaemic brain injury from cardiac arrest, white matter is resistant to damage relative to gray matter. Thus, biomarkers of axonal injury can help differentiate brain injury mechanisms. MBP is an abundant protein in white matter that has been studied as a marker of axonal damage in acute brain injury. CSF levels of MBP increase >4000-fold in children after TBI [9].

Protein biomarkers: assessment of multiple markers

It is likely that multiple, rather than a single brain injury marker will be used in a panel to aid in diagnosis and patient management. The origins of this approach and indeed of much of the ultimate success in defining unique biomarkers came out of the use of 2D-gel and protein array approaches in TBI [16]. Multiplex bead technology was used to aid in the identification of silent brain injury with high sensitivity and specificity in infants and children who were victims of abusive head trauma [17].

Novel brain injury biomarkers

Although most clinical investigation has focused on the use of protein biomarkers of brain injury, two novel alternative acute brain injury biomarkers (oxidized cardiolipin and microRNA) are noteworthy. The mitochondria-specific lipid cardiolipin has special characteristics in brain that make it a potentially useful biomarker. Cardiolipin is a phospholipid with four fatty acid chains allowing for the existence of a diverse number of molecular species. In brain, there can be over 100 molecular species; markedly fewer species exist in other organs [18]. Many of these side chains contain unsaturated fatty acids and, given its mitochondrial location, aberrant oxidation can produce products that could serve as brain injury biomarkers. Similarly, recent work in TBI suggests there are unique microRNAs within brain that reflect injury; specifically, levels of the microRNA let-7i are elevated in serum and CSF [19]. These and other novel biomarkers merit additional investigation.

Novel analytical approaches to enhance the use of biomarkers in diagnostic, prognostic, and theragnostic applications

For diagnosis of brain injury, assessment of sensitivity and specificity, and identification of cut-off values for single point levels of biomarkers represent the standard approach to brain injury biomarker development and validation. For prognosis, what has served to be most useful is identification of cut-off values at a specific time point after a given insult. Other analytic approaches are also being used. Trajectory analysis incorporates all data collected over time by identifying subpopulations that follow specific paths of change in their biomarker levels. Once different subpopulations are identified, outcome of individual subjects can be successfully predicted based on subpopulation assignment [20].

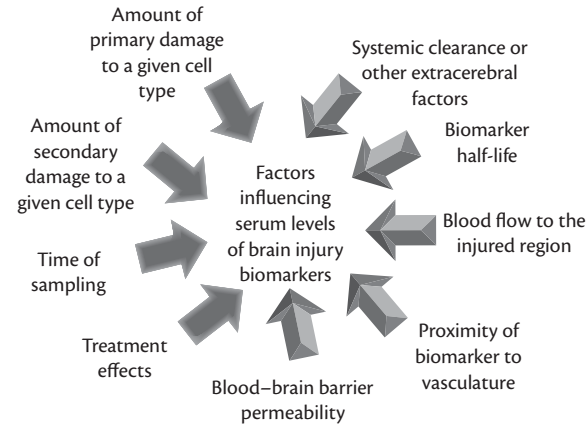


Fig. 300.2 Factors that affect serum levels of biomarkers of acute brain injury relevant to neurocritical care.

Factors that influence levels of brain injury biomarkers

Many factors influence the levels of brain injury biomarkers (Fig. 300.2). Factors such as the amount of primary and secondary damage, time of sampling, and treatment effects are important. The presence of the blood–brain barrier (BBB) and proximity of a given biomarker to the vasculature can also have special importance. For example, astrocyte foot processes represent a component of the BBB; thus, their proximity to the vasculature probably contributes to the value of astrocyte proteins as sensitive biomarkers. Blood flow to an injured brain region can also influence serum biomarker levels. In stroke, brain regions with extensive damage may have negligible perfusion and might be unable to transduce an increase in biomarker levels from tissue to blood. Finally, biomarker half-life and factors affecting clearance are important. In the setting of renal failure, sustained increases in serum levels of S100B could be observed after cardiac arrest despite its short half-life. Release of biomarkers from extracranial neuronal sites can also influence levels in diseases such as cardiac arrest and polytrauma.

Conclusion

The field of brain injury biomarkers is one of the most rapidly developing areas in contemporary neurocritical care. We expect that there will soon be one or more protein biomarkers of neuronal, astrocyte, and/or axonal injury available for routine diagnostic, prognostic, and/or theragnostic use in the ICU.

References

1. Vaagenes P., Kjekshus J, and Torvik A. (1980). The relationship between cerebrospinal fluid creatine kinase and morphologic changes in the brain after transient cardiac arrest. *Circulation*, **61**, 1194–9.
2. Kochanek PM, Berger RP, Bayır H, Wagner AK, Jenkins LW, and Clark RS. (2008). Biomarkers of primary and evolving damage in traumatic and ischemic brain injury: diagnosis, prognosis, probing mechanisms, and therapeutic decision making. *Current Opinion in Critical Care*, **14**, 135–41.
3. Widjicks EF, Hijdra A, Young GB, Bassetti CL, and Wiebe S. (2006). Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of

the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, **67**, 203–10.
4. Satchell MA, Lai Y, Kochanek PM, et al. (2005). Cytochrome C, a biomarker of apoptosis, is increased in cerebrospinal fluid from infants with inflicted brain injury from child abuse. *Journal of Cerebral Blood Flow Metabolism*, **25**, 919–27.
5. Au AK, Aneja RJ, Bell MJ, et al. (2012). Cerebrospinal fluid levels of high mobility group box 1 and cytochrome C predict outcome after pediatric traumatic brain injury. *Journal of Neurotrauma*, **29**, 2013–21.
6. Pike BR, Flint J, Dutta S, Johnson E, Wang KK, and Hayes RL. (2001). Accumulation of non-erythroid alpha II-spectrin and calpain-cleaved alpha II-spectrin breakdown products in cerebrospinal fluid after traumatic brain injury in rats. *Journal of Neurochemistry*, **78**, 1297–306.
7. Berger RP, Adelson PD, Richichi R, and Kochanek PM. (2006). Serum biomarkers after traumatic and hypoxemic brain injuries: insight into the biochemical response of the pediatric brain to inflicted brain injury. *Developmental Neuroscience*, **28**, 327–35.
8. Tiainen M, Roine RO, Pettilä V, and Takkunen O. (2003). Serum neuron-specific enolase and S-100B protein in cardiac arrest in patients treated with hypothermia. *Stroke*, **34**, 2881–6.
9. Su E, Bell MJ, Kochanek PM, et al. (2012). Increased CSF concentrations of myelin basic protein after TBI in infants and children. *Neurocritical Care*, **17**, 401–7.
10. Bayır H, Kagan VE, Tyurina YY, et al. (2002). Assessment of antioxidant reserve and oxidative stress in cerebrospinal fluid after severe traumatic brain injury in infants and children. *Pediatric Research*, **51**, 571–8.
11. Vespa P, Boonyaputthikul R, McArthur DL, et al. (2006). Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury. *Critical Care Medicine*, **34**, 850–6.
12. Berger RP, Hayes RL, Richichi R, Beers SR, and Wang KK. (2012). Serum concentrations of ubiquitin C-terminal hydrolase-L1 and αLL-spectrin breakdown product 145 kDa correlate with outcome after pediatric TBI. *Journal of Neurotrauma*, **29**, 162–7.
13. Mondello S, Jeromin A, Buki A, et al. (2012). Glial neuronal ratio: a novel index for differentiating injury type in patients with severe traumatic brain injury. *Journal of Neurotrauma*, **29**, 1096–104.
14. Muller K, Townend W, Biasca N, et al. (2007). S100B serum level predicts computed tomography findings after minor head injury. *Journal of Trauma*, **62**, 1452–6.
15. Mörtberg E, Zetterberg H, Nordmark J, Biennow K, Rosengren L, and Rubertsson S. (2011). S-100B is superior to NSE, BDNF and GFAP in predicting outcome of resuscitation from cardiac arrest with hypothermia treatment. *Resuscitation*, **82**, 26–31.
16. Gao W, Chadha MS, Berger RP, et al. (2007). A gel-based proteomic comparison of human cerebrospinal fluid between inflicted and non-inflicted pediatric traumatic brain injury. *Journal of Neurotrauma*, **24**, 43–53.
17. Berger RP, T'asan S, Rand A, Lokshin A, and Kochanek P. (2009). Multiplex assessment of serum biomarker concentrations in well-appearing children with inflicted traumatic brain injury. *Pediatric Research*, **65**, 97–102.
18. Ji J, Tyurina Y, Tang M, et al. (2012). Mitochondrial injury after mechanical stretch of cortical neurons in vitro: biomarkers of apoptosis and selective peroxidation of anionic phospholipids. *Journal of Neurotrauma*, **29**, 776–88.
19. Balakathiresan J, Bhomia M, Chandran R, Chavko M, McCarron RM, and Maheshwari RK. (2012). MicroRNA let-7i is a promising serum biomarker for blast-induced traumatic brain injury. *Journal of Neurotrauma*, **29**, 1379–87.
20. Berger RP, Bazaco MC, Wagner AK, Kochanek PM, and Fabio A. (2010). Trajectory analysis of serum biomarker concentrations facilitates outcome prediction after pediatric traumatic and hypoxemic brain injury. *Developmental Neuroscience*, **32**, 396–405.

CHAPTER 301

Cardiac injury biomarkers in the critically ill

Anthony S. McLean and Stephen J. Huang

Key points

- Only a few cardiac biomarkers have relevancy in the intensive care setting.
- The most useful cardiac injury marker is cardiac troponin, with recent high-sensitive assays being a significant advance.
- The cardiac stress biomarker B-type natriuretic peptide is useful for screening and diagnosis in the intensive care patient, although lacks specificity.
- Inflammatory markers for cardiac diseases are too non-specific.
- Although cardiac biomarkers are very helpful in the critically-ill patient, the presence of concomitant confounding factors requires considered interpretation.

Introduction

Despite an intensive search over many decades for accurate circulating cardiac biomarkers, only a handful have clinical relevance in the acute setting. Even this small number has been evaluated primarily in the setting of single organ dysfunction, such as a person presenting to hospital with chest pain, or for prognosticating in patients with known heart failure, and are thus not easily applicable to the intensive care unit (ICU) patient with multi-organ failure. The clinician also needs to clarify the reason for seeking biomarker levels, whether for screening, diagnosis, monitoring, or prognosis.

The evolution of most cardiac diseases involves three stages, beginning with inflammation, followed by acute injury to the myocardial cells and, finally, cardiac stress where the myocardium is subjected to pressure and/or volume overload. Parallel to this process is the sequential release of biomarkers reflecting each stage. Some overlap is to be expected (Fig. 301.1).

Inflammatory markers

Inflammation plays a key role in coronary artery disease—all stages of plaque development and eventual rupture leading to an acute coronary syndrome can be considered to be an inflammatory response [1]. Inflammation also plays an important role in heart failure and myocarditis. While inflammatory marker levels are increased in heart diseases, their uses as diagnostic markers and prognosticators are limited in the ICU due to various confounding inflammatory conditions (e.g. infection, trauma) often found in this setting. A summary of common inflammatory markers is provided in Table 301.1.

Markers of cardiac injury

Evaluating cardiac injury, especially where coronary artery occlusion has caused myocardial necrosis, has been at the forefront of medicine for the past 50 years. Creatinine phosphokinase (CPK), troponin, myoglobin, and heart-type fatty acid binding protein (H-FABP) have progressed to becoming useful clinical tools.

Cardiac troponins

Cardiac troponin (cTn) is the standout serum biomarker, past or present, in the evaluation of cardiac disease. Refinement of laboratory testing, now detecting a few ng per litre of serum, has increased diagnostic accuracy for identifying very small amounts of ischaemic/infarcted myocardium, greatly enhancing the diagnosis of underlying coronary artery disease in patients presenting with chest pain and/or other clinical features suggestive of a cardiac origin. The high sensitivity cardiac troponins (hs-cTn) can correctly be seen as a significant clinical advance, but challenges the physician dealing with the critically ill. Even with previous generations of less sensitive assays, the diagnostic potential was lessened by confounding factors. To optimize the benefit of hs-cTn testing, the clinician needs to: understand the analytical parameters of the actual cTn test used in their institution, know the serum half-life of troponin, consider more than a single static blood level, and be aware of both non-ischaemic cardiac pathology influences and non-cardiac pathologies. Furthermore, the result should be interpreted according to whether the test was performed for diagnostic or prognostic reasons.

Cardiac troponin assays

The troponin complex regulates striated muscle contraction by controlling the calcium-mediated interaction of actin and myosin. It consists of three subunits—T (tropomyosin binding), C (calcium binding) and I (inhibitory) (Fig. 301.2). T and I subunits are unique to cardiac muscle whereas the C subunit is found in both cardiac and skeletal muscle. The majority of cTnT and cTnI are bound to the myofibril with approximately 7% of cTnT and 3–5% cTnI free in the cytoplasm [2]. The biphasic rise in blood troponin following myocyte damage reflects this, with initial release of cytoplasmic troponin followed by gradual disengagement of the

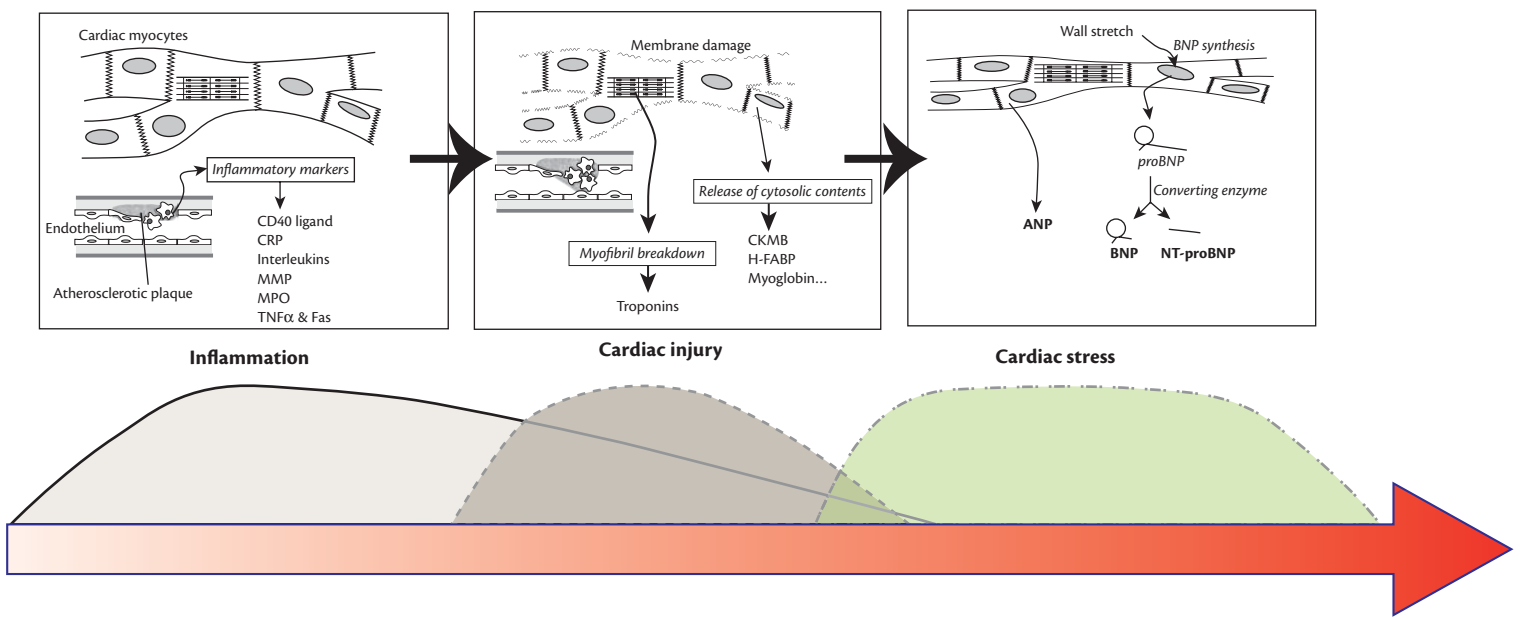


Fig. 301.1 Evolution of cardiac diseases. Most cardiac disease can be divided into three phases: inflammation, cardiac injury, and cardiac stress. There can be overlapping between the three phases.
ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CRP, C-reactive protein; H-FABP, heart-type fatty acid binding protein; MMP, matrix metalloproteinases; MPO, myeloperoxidases; TNF, tumour necrosis factor.

Table 301.1 Common inflammatory markers associated with coronary artery disease

Biomarker	Source(s)	Biological role or function	Uses
C-reactive protein (CRP)	Atherosclerotic plaque	◆ Pathophysiology of atherosclerosis ◆ Enhance macrophage uptake of lipids and formation of foam cell ◆ Causes plaque instability	◆ Elevated in patients with unstable angina, higher level is associated with worse outcome ◆ Also increased in patients with acute injury, infection and acute renal failure
Interleukins (IL) IL-6, IL-18	Atherosclerotic plaque and nucleated cells in the heart	◆ Pro-inflammatory cytokines ◆ Induce liver to produce all acute phase proteins, including CRP ◆ Destabilizes plaque	◆ Found in both stable and unstable atherosclerotic plaque ◆ Positively correlated with severity of decompensated heart failure ◆ Independent predictors of mortality
Tumour necrosis factor-α (TNFα) and FAS	TNFα: atherosclerotic plaque. Fas: cardiac myocytes and other cells	◆ TNFα induces left ventricular dilatation ◆ Fas mediates apoptosis and contributes to progression of heart failure	◆ TNFα is associated with higher incidence of heart failure ◆ Fas is positively associated with severity of heart failure
CD40 and soluble CD40 ligand (sCD40L)	Vascular cells, macrophages, platelets	Promotes degradation of fibrous cap	High sCD40L is associated with higher cardiovascular risk
Matrix metalloproteinases (MMPs)	Cardiac fibroblasts	◆ Pathophysiology of atherosclerosis and vascular disease ◆ May promote plaque rupture ◆ Take part in adverse remodelling in heart failure, hypertension, and MI	◆ MMP-9 is higher in CAD, and increases in acute MI ◆ MMP-9 is positively associated with risk of stroke or cardiovascular death
Myeloperoxidase (MPO)	Atherosclerotic plaque, activated neutrophils	◆ Pathophysiology of atherosclerosis ◆ Destabilizes plaque	◆ Predictor of MI ◆ Risk stratification for CAD ◆ Not specific for cardiac disease

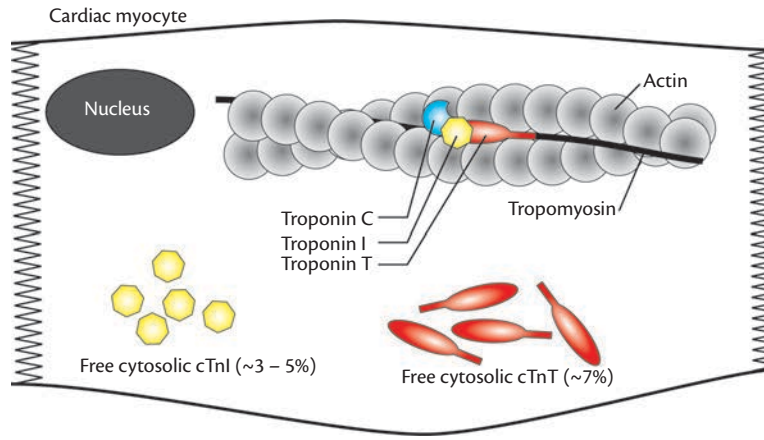


Fig. 301.2 The troponin complex and sources of troponin in cardiomyocytes.

myofibrillar-bound troponin. Elevation of serum cTn measured by conventional cTn assay can be detected 1–4 hours following myocardial damage, but with some uncertainty still surrounding the mechanisms by which it is cleared from the blood. Serum levels of cTnI remain elevated for 4–7 days following myocardial injury, whereas cTnT persists up to 10–14 days. cTn has a large molecular size and its clearance is believed to occur through the reticuloendothelial system.

Due to its release kinetics, the sensitivity of cTn as a diagnostic marker of myocardial infarction, increases with time; at the time of hospital admission conventional assays of cTnT and cTnI had sensitivities of 25–65% and 45%, respectively, but this increased to 100% by 6–12 hours later [3]. The introduction of hs-cTn assay, with detection limits as low as 3.0 ng/L for cTnT and 2.0 ng/L for cTnI, improved sensitivity and reduced the time to detection. In a study involving transcoronary ablation of septal hypertrophy, a

model of a diagnostic marker of myocardial infarction, hs-cTnT assay detected a significant cTnT rise (>50% above baseline) at 15 minutes after commencement and exceeded the 99th percentile after 30 minutes [4]. On the other hand, the first detectable significant change using cTnT was observed after 60 minutes, and this lagged behind myoglobin for which a rise was detected 30 minutes earlier. With increasingly sensitive assays, the number of healthy individuals with detectable troponin in the blood also increases, thereby changing the definition of abnormal serum levels. High sensitivity cTn assays are differentiated from contemporary ones in that detection of cTn is found in up to 90% of a reference population. This allows for a precise definition of abnormal by using a serum hs-cTn level above the 99th percentile of a normal reference population [5]. This renders hs-cTn as an ideal rule-out tool for a diagnostic marker of myocardial infarction within a shorter timeframe than standard assays. The clinician should be aware of the analytical quality and limitations of the particular assay used in their institution.

Applications of cTn assays

The diagnostic performance of hs-cTn outside the Emergency Department when assessing patients presenting with chest pain is uncertain. The debate about whether absolute or relative levels are better for rapid diagnosis of myocardial infarction is far from resolved [6].

In the ICU environment, where confounding factors are commonly found and adjuncts, such as complaints of chest pain or the typical electrocardiographic changes of acute coronary syndrome are often absent, moving from standard cTn to hs-cTn assays has compounded the interpretative challenges in an environment where multiple confounders are present. Interpretation is assisted by serial measurements and the use of relative rather than absolute levels (Fig. 301.3). Where very high serum cTn levels are identified, the diagnosis of coronary artery disease needs to be ruled out, usually by imaging of the coronary arteries. At the other end of the scale, a cTn level below the 99th percentile means myocardial necrosis is very unlikely, but a second sample 3–6 hours later may be of assistance. Intermediate values (e.g. 14–100 ng/L with cTnT) alerts to the evidence of myocardial damage or necrosis, but not the cause. If a rising or falling (>30% relative change) level is found over 3–6 hours then it is likely to be ischaemic necrosis; in the absence of classical electrocardiographic changes this may represent a Type II infarction where ischaemic damage is due to increased oxygen demand or decreased supply, and not necessarily a primary coronary artery event [7]. However, an elevated and rising serum cTn level informs the clinician that myocardial cell death has occurred,

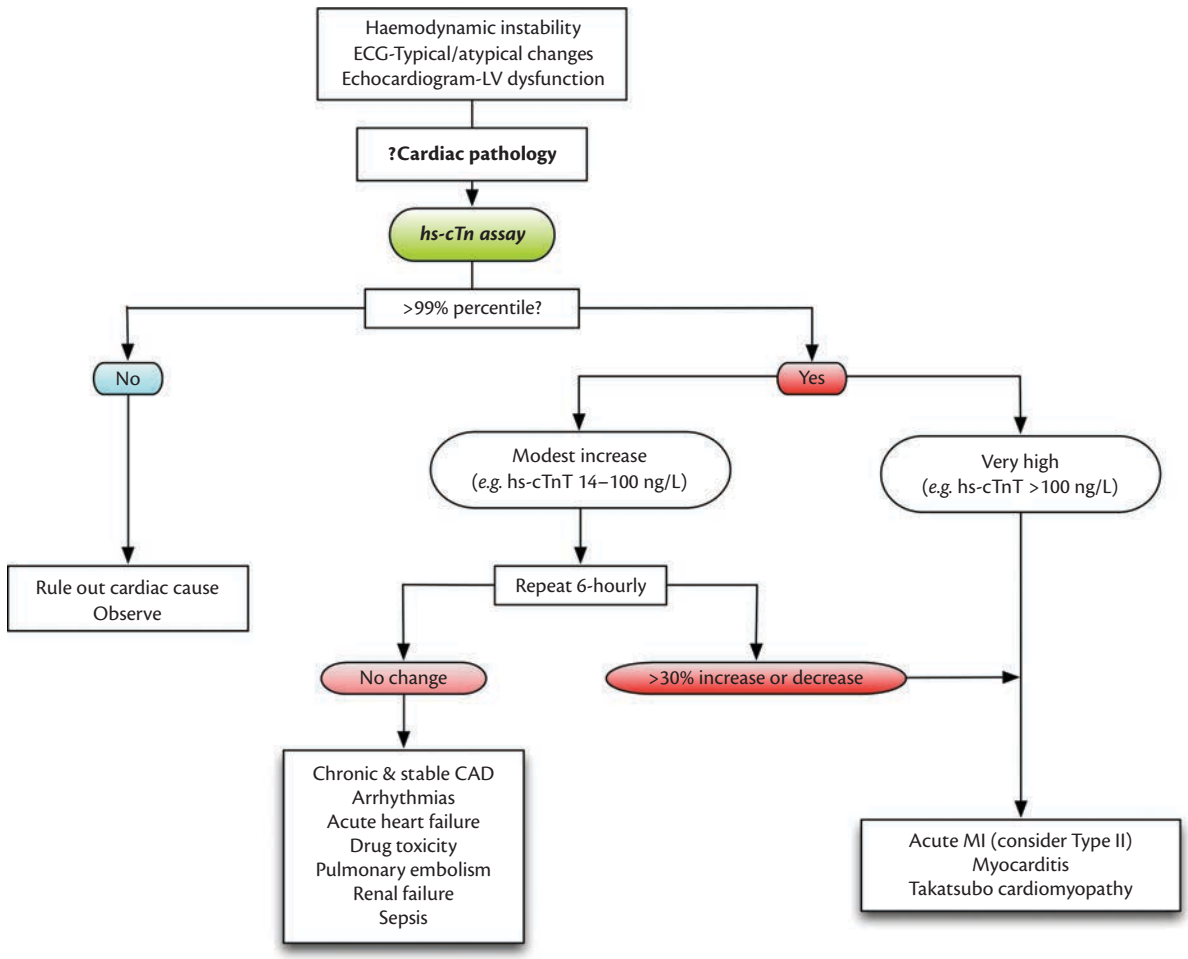


Fig. 301.3 Flow chart showing the possible use of hs-cTn in the ICU.

but not necessarily the cause of that necrosis. A slowly falling level over days raises the possibility of myocardial injury occurring some days previously. A steady level may implicate a non-ischaemic cause such as renal failure, pulmonary embolus, acute heart failure, or sepsis, for example.

Dismissing hs-cTn as having too low a specificity to be clinically useful, overlooks the gains in further understanding of the mechanisms and severity of cardiac damage in critically-ill patients that a simple blood test offers. In terms of prognosis, an elevated serum cTn levels is highly prognostic in the critically-ill population; future studies are likely to confirm these findings with hs-cTn. The translation of this information in improved patient care is implied, but not yet proven.

Box 301.1 Non-cardiac conditions known to alter BNP levels

- Sepsis.
- Inflammatory diseases.
- Pulmonary hypertension.
- Acute or chronic renal failure.
- Obesity.
- Embolic stroke.
- Liver cirrhosis.

Cardiac marker for cardiac stress: B-type natriuretic peptide

In contrast to cTn, which is a biomarker-related to myocardial cell injury, B-type natriuretic peptide (BNP) is best viewed as a biomarker of the physiological function of maintaining fluid homeostasis. In response to cardiac stress, such as volume and pressure overloading, *BNP* gene expression is induced in ventricular myocytes within an hour. The first product synthesized is a 132-amino acid preprohormone that is then processed into a 108-amino acid precursor protein (proBNP). ProBNP is cleaved into the biologically active 32-amino acid carboxyl-terminal peptide (BNP) and a 76-amino acid amino-terminal (N-terminal) fragment (NT-proBNP) by a converting enzyme. BNP contains a 17-amino acid ring structure common to the natriuretic peptide family.

Heart failure and other stimulants for BNP release

The low output state of heart failure leads to the adaptive activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). Although activation of both systems provides a short-term favourable haemodynamic response, if left unchecked their activation leads to worsening of heart failure. Tachycardia, increased peripheral resistance and volume overload are common amongst the heart failure population and are partly due to activation of RAAS and SNS. Other deleterious effects include rendering patients refractory to diuretics as a result of angiotensin II-induced increased Na^+ reabsorption, down-regulation of cardiac β_1-adrenoceptor leading to reduced contractility, tachycardia-induced cardiomyopathy, and myocardial remodelling. The end results of the maladaptive responses of the RAAS and SNS are deterioration of cardiac function and fluid retention (increase in preload and afterload).

The release of BNP is associated with an improvement in haemodynamics and reduction in cardiac stress. This is brought forth mainly by vasodilation (including both venous and arterial trees), and promoting natriuresis and diuresis. The vasodilatory effect not only reduces afterload but also improves the coronary circulation, and hence, oxygen supply to the myocardium. BNP, by inhibiting renin and aldosterone release, counteracts the deleterious effects of prolonged activation of the RAAS in decompensated heart failure [8]. This inhibitory effect on RAAS reduces both preload and afterload and lessens cardiac stress.

Cardiac stress is not the only stimulant for BNP release. Other factors, either directly or indirectly, also can cause an increase or decrease in BNP release (Box 301.1) [9]. For example, BNP concentrations are elevated in septic patients, even in those showing no symptoms or signs of myocardial dysfunction [10,11]. Inflammatory cytokines, lipopolysaccharide, mechanical ventilation, and catecholamines are known to interfere with BNP synthesis and release.

Clinical applications of BNP in critical care: screening and diagnosis

Approximately 30% of all patients admitted to a general ICU were identified by BNP to have some form of cardiac dysfunction, either overt or covert [12,13]. When BNP was used as a screening tool in the ICU, the concentration was significantly higher in patients with cardiac dysfunction. A cut-off value of 144 pg/mL offered 92% sensitivity and 86% specificity in predicting cardiac dysfunction. Most of these patients had subclinical signs of cardiac dysfunction, including left ventricular systolic and diastolic dysfunction, and right ventricular dysfunction. Early identification of these patients may prevent iatrogenic adverse events, such as pulmonary oedema as a result of fluid overload, and provide a better outcome [14].

The use of BNP for the diagnosis of heart failure is well established in the outpatient and emergency settings. In patients presenting to the Emergency Department with acute dyspnoea, a plasma BNP cut-off of 100 pg/mL had a sensitivity of 90% and a specificity of 76% in diagnosing heart failure [15]. NT-proBNP, at a cut-off of 300 pg/mL, is also useful in diagnosing acute heart failure in this setting [16]. To improve accuracy, age-related cut-offs for NT-proBNP are recommended: 450 pg/mL for people aged <50 years, 900 pg/mL for 50–75 years, and 1800 pg/mL for >75 years. Although diagnostic processes may be improved by measuring BNP and NT-proBNP levels, whether or not such tests confer significant clinical benefit remains questionable [17,18].

The future of cardiac biomarkers

The search for improved biomarkers continues unabated with ongoing publications on a myriad of potential candidates, very few of which appear to have clinical potential. One approach that offers potential is genetic markers. While the search for polymorphisms that may predispose an individual to certain cardiac diseases is yielding results, these are of little use to the practising intensivist. However, circulating microRNAs do have considerable potential. These are non-coding ribonucleic acids (RNA), 20–25 nucleotides long that bind to messenger RNA and play a role in gene silencing. The half-life of circulating miRNA is only a few hours and their disappearance from blood does not appear to be affected by the

presence of organ dysfunction, an advantage over cardiac troponins and natriuretic peptides. Some, like microRNA208a, are highly cardiac-specific and are associated with necrosis. In a study of 186 circulating microRNAs in patients with heart failure, elevated levels of microR-423–5p, microR320a, microR-22, microR-92b identified systolic heart failure patients and correlated with important clinical prognostic parameters [19].

References

1. Hansson GK. (2005). Inflammation, atherosclerosis, and coronary artery disease. *New England Journal of Medicine*, **352**, 1685–95.
2. Wu AH and Feng YJ. (1998). Biochemical differences between cTnT and cTnI and their significance for diagnosis of acute coronary syndromes. *European Heart Journal*, **19**(Suppl. N):N25–9.
3. Daubert MA and Jeremias AJ. (2010). The utility of troponin measurement to detect myocardial infarction: review of current findings. *Vascular Health Risk Management*, **6**, 691–9.
4. Liebetrau C, Mollmann H, Nef H, et al. (2012). Release kinetics of cardiac biomarkers in patients undergoing transcoronary ablation of septal hypertrophy. *Clinical Chemistry*, **58**, 1049–54.
5. Apple FS, Jesse RL, Newby LK, Wu AH, and Christenson RH. (2007). National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical issues for biochemical markers of acute coronary syndromes. *Circulation*, **115**, e352–5.
6. Reichlin T, Irfan A, Twerenbold R, et al. (2011). Utility of absolute and relative changes in cardiac troponin concentration in the early diagnosis of acute myocardial infarction. *Circulation*, **124**, 136–45.
7. Thygesen K, Alpert JS, and White HD. (2007). Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *European Heart Journal*, **28**, 2525–38.
8. Kalra PR, Anker SD, and Coats AJS. (2001). Water and sodium regulation in chronic heart failure: the role of natriuretic peptides and vasopressin. *Cardiovascular Research*, **51**, 495–509.
9. Wu AH, Jaffe AS, Apple FS, et al. (2007). National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Use of cardiac troponin and B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide for etiologies other than acute coronary syndromes and heart failure. *Clinical Chemistry*, **53**, 2086–96.
10. McLean AS, Huang SJ, Hyams S, et al. (2007). Prognostic values of B-type natriuretic peptide in severe sepsis and septic shock. *Critical Care Medicine*, **35**, 1019–26.
11. Shor R, Rozenman Y, Bolshinsky A, et al. (2006). BNP in septic patients without systolic myocardial dysfunction. *European Journal of Internal Medicine*, **17**, 536–40.
12. McLean AS, Tang B, Nalos M, Huang SJ, and Stewart DE. (2003). Increased B-type natriuretic peptide (BNP) level is a strong predictor for cardiac dysfunction in the intensive care unit patients. *Anaesthesia and Intensive Care*, **31**, 21–7.
13. McLean AS, Huang SJ, Nalos M, Tang B, and Stewart DE. (2003). The confounding effects of age, gender, serum creatinine, and electrolyte concentrations on plasma B-type natriuretic peptide concentrations in critically ill patients. *Critical Care Medicine*, **31**, 2611–18.
14. McLean AS, Huang SJ, and Ting I. (2004). B-type natriuretic peptide: Is there a place in the critical care setting? *Critical Care & Shock*, **7**, 117–24.
15. Maisel AS, McCord J, Nowak RM, et al. (2003). Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. *Journal of the American College of Cardiology*, **41**, 2010–17.
16. Januzzi JL, van Kimmenade R, Lainchbury J, et al. (2006). NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP study. *European Heart Journal*, **27**, 330–7.
17. Lam LL, Cameron PA, Schneider HG, Abramson MJ, Muller C, and Krum H. (2010). Meta-analysis: effect of B-type natriuretic peptide testing on clinical outcomes in patients with acute dyspnea in the emergency setting. *Annals of Internal Medicine*, **153**, 728–35.
18. Ambrosy AP, Fonarow GC, Albert NM, et al. (2012). B-type natriuretic peptide assessment in ambulatory heart failure patients: insights from IMPROVE HF. *Journal of Cardiovascular Medicine (Hagerstown)*, **13**, 360–7.
19. Goren Y, Kushnir M, Zafrir B, Tabak S, Lewis BS, and Amir O. (2012). Serum levels of microRNAs in patients with heart failure. *European Journal of Heart Failure*, **14**, 147–54.

CHAPTER 302

Renal injury biomarkers in the critically ill

John R. Prowle

Key points

- Acute kidney injury (AKI) is a complex clinical syndrome that is strongly associated with adverse outcomes in the critically ill.
- The traditional diagnosis of AKI, based on serum creatinine and urine output, is often delayed and imprecise, particularly in critical illness.
- Novel plasma and urinary biomarkers can diagnose AKI very early in its clinical course, and provide information on its nature and severity.
- Application of biomarker measurements may enable early identification of patients developing AKI for specific therapeutic interventions.
- Before widespread application, prospective interventional trials must demonstrate clinical benefits from biomarker-guided management.

Acute kidney injury: need for better diagnostics

Acute kidney injury (AKI) is independently associated with increased morbidity and mortality in hospitalized patients, and the critically ill in particular [1]. Its pathophysiology is complex—while 'pre-renal' acute haemodynamic changes can cause reversible falls in glomerular filtration rate (GFR), established AKI involves renal tubular injury leading to more sustained reductions in GFR. Inflammation plays a central role in the pathogenesis of tubular injury, which is often of multifactorial aetiology. Importantly, tubular injury can occur alongside or in the absence of prerenal changes in GFR, so renal injury may be well-established by the time it becomes clinically evident (Fig. 302.1) [1].

Conventional diagnosis of AKI is based upon an elevation of serum creatinine, reflecting reduced renal filtration of endogenously produced creatinine. Creatinine is thus a marker of GFR and does not directly distinguish tubular injury from rapidly reversible decreases in GFR, nor does it identify early stages of tubular injury when GFR may not have been affected. Importantly, when GFR decreases, time is required for creatinine to accumulate in the blood. This accumulation depends on the creatinine generation rate, which is depressed in acute and chronic, and may be masked by haemodilution during fluid resuscitation. Therefore, creatinine is a late and imprecise marker of AKI and performs less well in sicker patients [2].

Many specific interventions to avert or ameliorate AKI have proven ineffective in clinical practice. Therapeutic approaches thus remain essentially supportive. A delayed and imprecise diagnosis of AKI may preclude effective therapy to alter its natural history. This may explain our difficulty in applying specific interventions clinically. In addition, some treatments, such as vigorous fluid resuscitation or renal replacement therapy, may be beneficial or harmful depending on the point of intervention in the time-course of AKI. Finally, in the recovery period, recurrent tubular injury is difficult to detect, and therefore prevent, using conventional diagnostics. Consequently, there is a longstanding need for better diagnostic markers of AKI, particularly in the setting of critical illness.

Development and classification of novel biomarkers for AKI

Novel biological markers of AKI have been recently identified by proteomic analysis of urine or plasma [3], or by gene-expression analysis. These include urinary neutrophil gelatinase-associated lipocalin (NGAL) [4] and kidney injury molecule 1 (KIM-1) [5]. Other biomarkers have been identified by specifically examining mediators in the inflammatory pathogenesis of AKI, such as urinary IL-18, or more sensitive markers of changes in GFR, such as plasma cystatin-c (Cys-c). Most recently, two new AKI biomarkers, tissue inhibitor of metaloproteinase-7 (TIMP-7) and insulin-like growth factor binding protein-2 (IGFBP-2) have been identified from a pool of over 300 candidate molecules and validated as highly predictive of AKI in a separate validation study [6]. More data are likely to merge on these markers, which appear directly linked to the cellular response to tubular injury.

Novel biomarkers are in varying stages of development and validation (Table 302.1). Broadly, they can be classified into structural biomarkers that are specifically expressed or released from the kidney or other tissues in association with tubular injury, and functional biomarkers that accumulate in plasma or urine as a result of renal dysfunction. Structural biomarkers include substances directly released by injured tubular cells, but may also include markers of local or systemic inflammation that correlate with the occurrence of AKI. Functional biomarkers include measures of GFR, e.g. plasma creatinine and plasma Cys-c, as well as the appearance of filtered substances in the urine that would normally be removed by

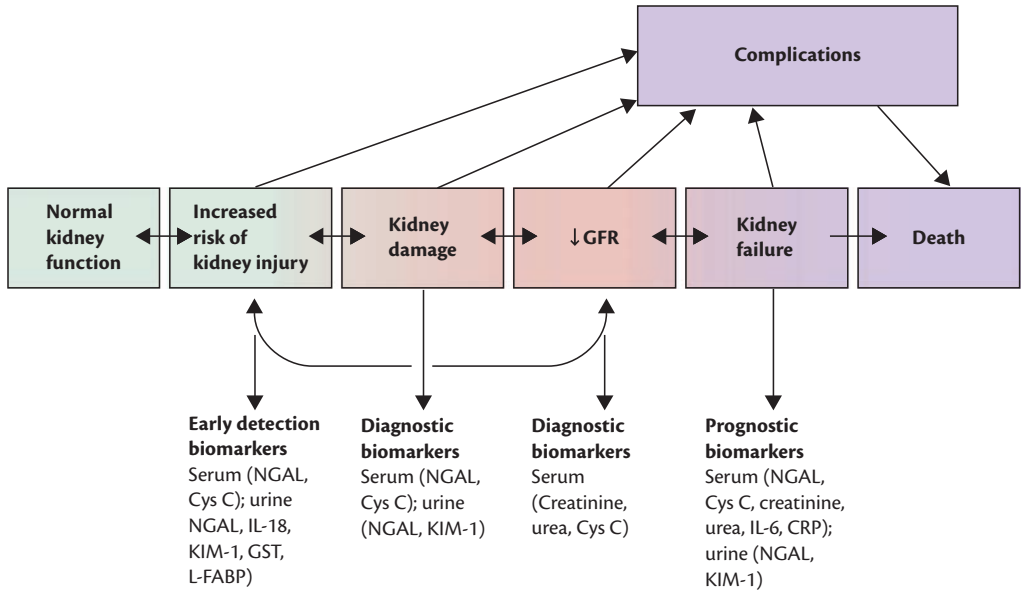


Fig. 302.1 Evolution of acute kidney injury. Injury begins before excretory function is lost (i.e. decreased GFR) and can, in some cases, be detected by measurement of biomarkers. Such biomarkers can also be used for diagnostic and prognostic assessment.

GFR, glomerular filtration rate; NGAL, neutrophil gelatinase-associated lipocalin; Cys C, cystatin C; KIM-1, kidney injury molecule 1; IL-18, interleukin-18; GST, glutathione-S-transferase; L-FABP, liver fatty-acid-binding protein; CRP, C-reactive protein; IL-6, interleukin-6.

Reprinted from *The Lancet*, **380**, Bellomo et al., 'Acute kidney injury', pp. 756–66, Copyright 2012, with permission from Elsevier.

Table 302.1 Some biomarkers of acute kidney injury currently under active clinical investigation

Biomarker	Structure	Source
NGAL: neutrophil gelatinase-associated lipocalin	25 kDa monomer with neutrophil gelatinase, an acute-phase, bacteriostatic protein that binds and sequesters iron-carrying siderophores	Produced in distal nephron, activated neutrophils, and other stimulated epithelia in response to inflammation, renal ischaemia, nephrotoxic or septic AKI
IGFBP-7 and TIMP-2: insulin-like growth factor binding protein-7 and tissue inhibitor of metalloproteinase-2	Involved in the process of G1 cell cycle arrest acting in an autocrine and paracrine mechanism via transmembrane receptors	Induced and released in response to tubular cellular injury
KIM-1: kidney injury molecule-1	Transmembrane phosphatidylserine receptor, which recognizes apoptotic cells	Specifically upregulated in de-differentiated proximal tubule cells after ischaemic or nephrotoxic AKI
IL-18: interleukin-18	Pro-inflammatory cytokine	Induced and cleaved in the proximal tubule and mediates ischaemic acute tubular injury in animal models. Systemic production in inflammatory diseases
L-FAB: liver-type fatty acid binding protein	One of a family of intracellular lipid chaperones	Cytoplasm of proximal tubular epithelial cells. Appears in the urine in association with AKI
GST: glutathione-S-transferases	Ubiquitous enzymes involved in the scavenging of free radicals	α and π forms are expressed in the renal tubules in a site-specific fashion. Appearance in urine may be related to different aetiologies of AKI
CysC: cystatin C	13-kDa endogenous cysteine proteinase inhibitor	Produced by all nucleated cells. Accumulates in the blood as GFR falls. Appears in the urine as a consequence of reduced proximal tubular catabolism of filtered CysC

functional proximal tubular cells, such as urinary Cys-c. Thus, different biomarkers may reflect different aspects of the pathogenesis of AKI, can be context-specific and may be informative at different points in the time-course of AKI (Fig. 302.1). An ideal biomarker would satisfy a number of unmet diagnostic needs (Box 302.1). While no individual biomarker may meet all of these requirements. a panel may provide complementary information on diagnosis and prognosis.

Box 302.1 Characteristics of an ideal biomarker of AKI

- Enables risk stratification for the development of overt AKI.
- Provides earliest possible diagnosis with high sensitivity and specificity enabling effective preventive intervention.
- Reliably distinguishes tubular injury from pre-renal causes of kidney dysfunction.
- Identifies the etiology of AKI.
- Prognosticates severity and duration of AKI, need for RRT, and risk of death.

Validation of biomarkers of AKI

Candidate renal biomarkers have been examined in observational studies assessing their ability to discriminate subsequent AKI, defined by consensus criteria based on serum creatinine and urine output. Combined sensitivity and specificity of biomarker measurements is often assessed by receiver-operating characteristic (ROC) analysis and expressed as the area under the curve (AUC). An AUC of 0.5 indicates no relationship between marker and outcome, while AUCs >0.8 and >0.9 represent, respectively, good and excellent predictive ability. Many biomarkers have been validated in the settings of predictable and time-defined risk in homogeneous populations, such as cardiopulmonary bypass in children [7]. Here, NGAL was exquisitely predictive of subsequent AKI as early as 2 hours after surgery with AUC values >0.9. However, the performance of NGAL and other biomarkers is not so strong in adults [8], in the presence of chronic kidney disease (CKD) [9], and in mixed critically-ill populations (8) with AUCs generally ranging between 0.7 and 0.8. NGAL measurements have been correlated with the severity of subsequent creatinine-defined AKI [10].

Any attempt to validate biomarkers of AKI is intrinsically limited by the use of a creatinine-based definition as a 'gold-standard' comparator [11]. Even the retrospective peak creatinine often underestimates the severity of AKI in patients with acute and chronic illness. Furthermore, kidney injury and tubular dysfunction could impact upon clinical outcomes that are not directly related to alterations in GFR. Apparent 'false negative' elevations in renal biomarkers may thus represent important biological phenomena. As a consequence, an important element of AKI biomarker validation is establishing an association with clinically relevant outcomes such as mortality and length of hospital or intensive care unit stay. In meta-analysis of prospective observational studies, plasma and urine NGAL predicted mortality with an AUC of 0.71 [8]. In an analysis of 2322 patients enrolled in these studies, increases in plasma or urinary NGAL were associated with increased hospital mortality in the absence of creatinine-defined AKI, while patients experiencing an elevation in creatinine without a raised NGAL had lower mortality [12]. These observations suggest that subclinical tubular injury may have a significant impact on outcomes, either because creatinine is imprecisely diagnosing renal dysfunction or because renal cellular injury affects organ function and survival by other processes. Novel biomarkers may thus allow definition of a new diagnostic category of sub-clinical AKI. It has been suggested that validated biomarkers may, in the future, be incorporated into consensus diagnostic criteria for AKI [13].

Experimental models may contribute to the validation of biomarkers. An NGAL reporter mouse has been developed that incorporates a fluorescent reporter protein for NGAL gene-expression. This model demonstrated a sensitive, rapid, dose-dependent, reversible, and organ—and cell-specific relationship between renal NGAL gene expression and tubular stress [14]. This elegant work further demonstrated that increases in creatinine induced by volume depletion were not associated with induction of renal NGAL, confirming its specificity for tubular injury.

Finally, validation of any novel diagnostic marker ultimately depends upon demonstration of clinical utility. To demonstrate that a biomarker provides a more effective diagnosis of AKI, evidence is required to show that measurements can be used to meaningfully improve patient outcomes.

Application of novel biomarkers of AKI

Renal biomarkers have been developed to detect patients with early AKI. After a timed insult, such as cardiac surgery, analysis of a panel of urinary biomarkers demonstrated sequential peaks in NGAL at 4 hours, liver fatty acid-binding protein (L-FAB) at 6 hours, interleukin-18 (IL-18) at 12 hours, and KIM-1 at 24 hours [7]. Very early prognostic information could identify patients at risk for continued close monitoring, avoidance of nephrotoxins, and/or haemodynamically-targeted therapy. In a cardiac surgery population, biomarker measurements significantly improved risk classification over conventional diagnostic models for AKI in the early post-operative setting [7]. Many specific interventions for early AKI that have not previously been proven to be clinically effective could be re-investigated if a homogenous patient population could be identified very early in the time course. Given that production of biomarkers such as NGAL has been associated with AKI severity [4] and predicts later use of renal replacement therapy (RRT) [8], there is also the potential to individualize treatment according to biomarker levels. These strategies will need investigation and validation in prospective randomized controlled trials.

There is significant clinical interest in the use of renal biomarkers to risk-stratify patients presenting to hospital or intensive care. In a study of 635 patients presenting to an emergency department [15], urinary NGAL was significantly better than serum creatinine at predicting AKI, the need for RRT, and intensive care unit admission. Urinary NGAL also successfully discriminated between groups of patients with normal renal function, stable CKD, pre-renal AKI, and sustained AKI. In a subsequent study of 1635 unselected emergency hospital admissions [16] that examined a panel of biomarkers, both urinary NGAL and urinary KIM-1 predicted a composite outcome of RRT or death in hospital. This study also identified a substantial sub-population with low serum creatinine at admission that was at risk of adverse events. These results suggest that patients could be risk-stratified to observation in a critical care area or to specific therapeutic interventions based on biomarker measurements taken at hospital admission.

As well as providing information on the timing of injury, measurements of multiple biomarkers may give useful clues to the quality and quantity of injury. In a study of 489 mixed intensive care unit admissions [17], prerenal AKI (defined as recovery within 48 hours and a fractional sodium excretion <1%) was associated with significant elevations in urinary KIM-18, IL-18 and Cys-c, but not urinary NGAL, which was only significantly elevated in patients

who developed sustained AKI. These observations suggest that a biomarker panel could be used to individualize therapy, but also that 'prerenal' AKI is likely to involve a degree of covert tubular injury.

Renal biomarkers are also being examined as outcome measures. KIM-1 has been suggested screening for nephrotoxicity in drug development [18]. This approach could be extended to monitoring sub-clinical nephroxicity from treatments such as chemotherapy or radiological contrast, allowing modification of subsequent treatment to reduce the risk of AKI. Biomarkers can also be used as secondary outcomes in interventional studies. This may be particularly beneficial in pilot studies of preventative interventions for AKI, where a positive effect on an AKI biomarker could justify larger trials to confirm a true clinical benefit.

Finally, biomarkers are being examined as markers of renal prognosis and recovery. A higher plasma NGAL at diagnosis of severe AKI correlated with non-recovery of renal function in survivors in a large cohort of patients with AKI following community-acquired pneumonia [19]. Biomarkers could thus provide information on renal prognosis and recurrent renal injury to aid ongoing management. Further data are required in this group of patients; it is also possible that novel biomarkers will be developed that are specific for the recovery phase of AKI.

Limitations of biomarkers

Interest in the use of renal biomarkers should be tempered by consideration of their limitations. For many, a direct causal link in the pathogenesis of AKI is unproven, and the mechanisms by which they are raised in AKI are uncertain or multifactorial. For instance, urinary NGAL is predominantly derived from the distal nephron [14], despite this not being the main site of pathological tubular injury. Furthermore, the majority of plasma NGAL is not renally-derived [4], but may arise from leukocytes, lungs, and other tissues. The relationship between biomarkers and AKI is thus complex and may reflect the strong link between local or systemic inflammation and AKI, and also the bi-directional interaction between AKI and distant organ injury. This suggests that renal biomarker performance will be highly dependent upon the clinical context with critical illness, age and CKD significantly impacting predictive ability [7,9]. In particular, as a marker of systemic inflammation, plasma NGAL correlates poorly with AKI in sepsis [20]. Monomeric NGAL may be more renal-specific, but does not enhance AKI discrimination in sepsis. Another factor in interpretation of urinary biomarkers is the variable effect of the urine concentration; conventionally, this is handled by expression of biomarker measurements as ratios to urinary creatinine concentration. However, soon after a decrease in GFR, creatinine excretion will fall. This will potentially cause an elevation in urinary biomarker:creatinine ratio unrelated to increased biomarker release. Finally, while many biomarkers have been strongly statistically associated with the occurrence of AKI in specific populations, such association does not prove that they are useful clinical tools. Utility very much depends upon the likelihood ratio for the outcome in question (ratio of post- to pretest odds). For many biomarkers this may be poor, particularly if AKI is relatively infrequent in a heterogeneous population. It is useful to consider the intensive care unit experience with well-established biomarkers in other areas of adult medicine. Cardiac troponins, brain natriuretic peptide, and D-dimers are excellent markers of, respectively, unstable coronary artery disease, cardiogenic pulmonary oedema and venous thromboembolism. However, interpretation crucially depends upon clinical context, history and ancillary investigation. All may be significantly elevated in septic multi-organ failure, but may be associated with different pathologies and not have their usual therapeutic implications. Thus, useful clinical application of renal biomarkers may require incorporation into risk prediction models for the occurrence or progression of AKI, allowing prospective validation of biomarker-led therapy in populations of critically-ill patients.

References

1. Bellomo R, Kellum JA, and Ronco C. (2012). Acute kidney injury. *Lancet*, **380**, 756–66
2. Endre ZH, Pickering JW, and Walker RJ. (2011). Clearance and beyond: the complementary roles of GFR measurement and injury biomarkers in acute kidney injury (AKI). *American Journal of Physiology and Renal Physiology*, **301**, F697–707.
3. Bennett MR and Devarajan P. (2011). Proteomic analysis of acute kidney injury: biomarkers to mechanisms. *PROTEOMICS—Clinical Applications*, **5**, 67–77.
4. Devarajan P. (2010). Neutrophil gelatinase-associated lipocalin: a promising biomarker for human acute kidney injury. *Biomarkers in Medicine*, **4**, 265–80.
5. Bonventre JV and Yang L. (2010). Kidney injury molecule-1. *Current Opinion in Critical Care*, **16**, 556–61.
6. Kashani K, Al-Khafaji A, Ardiles T, et al. (2013). Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Critical Care*, **17**, R25.
7. Parikh CR, Devarajan P, Zappitelli M, et al. (2011). Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. *Journal of the American Society of Nephrology*, **22**, 1737–47.
8. Haase M, Bellomo R, Devarajan P, Schlattmann P, and Haase-Fielitz A. (2009). Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *American Journal of Kidney Disease*, **54**, 1012–24.
9. McIlroy DR, Wagener G, and Lee HT. (2010). Neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery: the effect of baseline renal function on diagnostic performance. *Clinical Journal of the American Society of Nephrology*, **5**, 211–19.
10. de Geus HR, Bakker J, Lesaffre EM, and le Noble JL. (2011). Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. *American Journal of Respiratory and Critical Care Medicine*, **183**, 907–14.
11. Waikar SS, Betensky RA, Emerson SC, and Bonventre JV. (2012). Imperfect gold standards for kidney injury biomarker evaluation. *Journal of the American Society of Nephrology*, **23**, 13–21.
12. Haase M, Devarajan P, Haase-Fielitz A, et al. (2011). The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. *Journal of the American College of Cardiology*, **57**, 1752–61.
13. Ricci Z, Cruz DN, and Ronco C. (2011). Classification and staging of acute kidney injury: beyond the RIFLE and AKIN criteria. *Nature Review: Nephrology*, **7**, 201–8.
14. Paragas N, Qiu A, Zhang Q, et al. (2011). The NGAL reporter mouse detects the response of the kidney to injury in real time. *Nature: Medicine*, **17**, 216–22.
15. Nickolas TL, O'Rourke MJ, Yang J, et al. (2008). Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. *Annals of Internal Medicine*, **148**, 810–19.
16. Nickolas TL, Schmidt-Ott KM, Canetta P, et al. (2012). Diagnostic and prognostic stratification in the emergency department using urinary

biomarkers of nephron damage: a multicenter prospective cohort study. *Journal of the American College of Cardiology*, **59**, 246–55.
17. Nejat M, Pickering JW, Devarajan P, et al. (2012). Some biomarkers of acute kidney injury are increased in pre-renal acute injury. *Kidney International*, **81**, 1254–62.
18. Vaidya VS, Ozer JS, Dieterle F, et al. (2010). Kidney injury molecule-1 outperforms traditional biomarkers of kidney injury in preclinical biomarker qualification studies. *Nature Biotechnology*, **28**, 478–85.
19. Srisawat N, Murugan R, Lee M, et al. (2011). Plasma neutrophil gelatinase-associated lipocalin predicts recovery from acute kidney injury following community-acquired pneumonia. *Kidney International*, **80**, 545–52.
20. Martensson J, Bell M, Oldner A, Xu S, Venge P, and Martling CR. (2010). Neutrophil gelatinase-associated lipocalin in adult septic patients with and without acute kidney injury. *Intensive Care Medicine*, **36**, 1333–40.

PART 14.3

Host response

CHAPTER 303

The host response to infection in the critically ill

W. Joost Wiersinga and Tom van der Poll

Key points

- Toll-like receptors (TLRs) are the first to sense invading pathogens and initiate the immune response.
- Pattern recognition receptors (PRRs) such as TLRs and Nod-like receptors (NLRs) recognize pathogen-associated-molecular patterns (PAMPs) such as LPS, peptidoglycan, lipopeptides, lipoteichoic acid, flagellin, and bacterial DNA, as well as danger-associated-molecular patterns (DAMPs) such as heat shock proteins, fibrinogen, hyaluronic acid and high-mobility group box-1 protein (HMGB-1).
- The systemic host response to infection results in activation of coagulation, due to tissue factor-mediated thrombin generation, downregulation of physiological anticoagulant mechanisms, and inhibition of fibrinolysis.
- Sepsis can be viewed as a PRR-mediated dysregulation of the immune system following pathogen invasion in which a careful balance between inflammatory and anti-inflammatory responses is vital.
- Severe sepsis (sepsis and organ dysfunction) and septic shock (severe sepsis plus fluid-refractory hypotension) are progressively severe stages of the host's immune response to infection.

Introduction

Among the many challenges facing the critically ill, infectious diseases stand out for both their omnipresence and their ability to have a profound impact on morbidity and mortality. When the body's response to an infection injures one's own tissues and organs it can become a life-threatening condition called sepsis [1]. Severe sepsis (sepsis and organ dysfunction) and septic shock (severe sepsis plus fluid-refractory hypotension) are progressively severe stages of the host's immune response to infection.

Moving away from the SIRS versus CARS dogma

The systemic inflammatory response syndrome (SIRS) is the predominantly cytokine-mediated, pro-inflammatory host response to invading pathogens that has always been considered the hallmark of sepsis [2]. Its molecular components can be divided into cytokines, plasma cascades, and acute phase proteins, while the cellular components include leukocytes and endothelium. However, simple inhibition of pro-inflammatory cytokines, such as tumour necrosis factor (TNF)-α and interleukin (IL)-1 has not provided clinical benefit to patients with severe sepsis [3]. Clearly, the hypothesis that excessive inflammation is the basis for adverse outcomes in sepsis requires reconsideration: the host response includes multiple concurrent and subsequent processes that involve both exaggerated inflammation and immune suppression. In general, pro-inflammatory reactions are held responsible for 'collateral' tissue damage in severe sepsis, whereas anti-inflammatory responses (meant to limit excessive activity of inflammation) may promote the development of secondary infections (Fig. 303.1) [4]. Anti-inflammatory cytokines, particularly IL-10 and transforming growth factor (TGF)-β, negative regulators of Toll-like receptor (TLR) signalling and various inflammatory mediators, such as prostaglandin E_2, epinephrine, and glucocorticoids are all likely to contribute to this inhibition of inflammation during severe infection. However, a clear separation between SIRS and the 'compensatory anti-inflammatory response syndrome' (CARS) does not seem to exist.

Historical perspective

Sir William Osler (1849–1919) was among the first to recognize that morbidity and mortality from sepsis were not directly caused by the invading pathogens, but mainly by the body's response. The original notion that sepsis mortality was due to an excessive stimulation of the immune system by high bacterial loads was based upon studies in animals infused with large doses of bacteria or bacterial products, in particular lipopolysaccharide (LPS), the toxic component of the Gram-negative bacterial cell wall. Such infusions result in a strong activation of different pro-inflammatory protein cascades that, although designed to protect the host against invading pathogens, can cause damage to tissues when produced in high amounts. In a landmark article published in 1985 Beutler and colleagues reported that neutralization of TNF-α, secreted after intravenous injection of an otherwise lethal dose of LPS, prevented death in mice [5]. Nearly two decades later, in 2011, the Nobel Prize in Medicine was awarded to Beutler and Hoffmann for their role in the discovery of the TLRs that form the front line of the host defences against invading pathogens.

The tremendous increase in our understanding of the interactions between the microbial world and our host defence system has led to the notion that sepsis is now considered an imbalance between pro-inflammatory reactions (designed to kill invading pathogens but, at the same time, responsible for tissue damage) and anti-inflammatory responses (designed to limit excessive inflammation but, at the same time, making the host more vulnerable to secondary infections) [3]. Here, the key components that define the host response to infection are discussed.

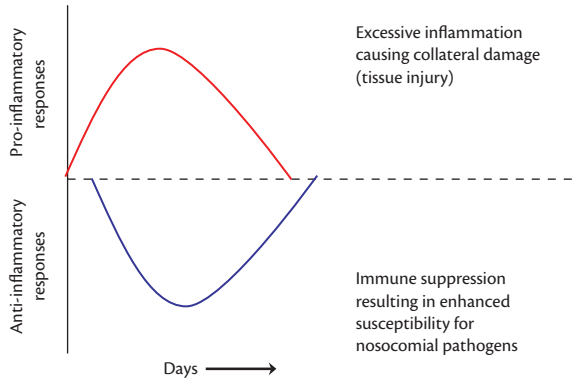


Fig. 303.1 The host response to infection during sepsis. The host response to sepsis is characteristically seen as an exaggerated pro-inflammatory response to invading pathogens. This tumour necrosis factor (TNF)-α and interleukin (IL)-1-driven early response is associated with fulminant sepsis and early mortality. In recent years more attention has been paid to the immunosuppressive phase in which IL-10 serves as an important anti-inflammatory cytokine; this phase of the septic response is associated with nosocomial infections, viral reactivation, and late mortality.

Data from Hotchkiss RS et al., 'The sepsis seesaw: tilting toward immunosuppression', *Nature Medicine*, 2009, **15**, pp. 496–7.

The virulence of invading pathogens

Gram-positive bacteria (e.g. *Streptococcus pneumoniae, Staphylococcus aureus*) have overtaken Gram-negative bacteria (e.g. *Escherichia coli, Klebsiella* spp., *Pseudomonas aeruginosa*) as the leading cause of sepsis. Polymicrobial infections, anaerobes and yeasts constitute <10% of responsible pathogens. These invading microorganisms have an impressive armoury of virulence factors to assault the host. To be successful, pathogens must adhere, traverse the mucosal barrier and multiply, while overwhelming the antimicrobial host defence systems [3,6]. Individual bacteria can affect the behaviour of surrounding bacteria by making use of the quorum sensing apparatus to coordinate their gene expression according to the density of their local population. This utilizes signalling molecules such as the *N*-acyl-homoserine-lactones (AHLs). Quorum sensing also plays an important role in the production and maintenance of biofilms; these slimy layers of bacteria are well-organized communities that can protect themselves against the immune system and antibiotics. Activation of quorum sensing can ultimately lead to production of proteins needed for tissue invasion and activation of toxins. Bacterial toxins are important mediators of sepsis by their capacity to damage natural barriers such as the mucosa to enable further bacterial spread. A well-known example is the toxin-mediated toxic shock syndrome caused by *S. aureus* and *S. pyogenes*. Bacterial toxins can be injected into the cytosol of host immune cells by specialized nanosyringes called type-III secretion systems. All these molecular components of invading pathogens that are recognized by host defence receptors are called pathogen-associated-molecular-patterns (PAMPs). Examples of bacterial PAMPs are LPS, peptidoglycan, lipopeptides (constituents of many pathogens), lipoteichoic acid (a cell wall component of Gram-positive bacteria), flagellin (factor in the mobility of bacteria) and bacterial DNA (Fig. 303.2) [7].

Pattern recognition receptors and the initiation of the immune response

The innate immune system can detect pathogens via a limited number of pattern-recognition receptors (PRRs) that recognize PAMPs

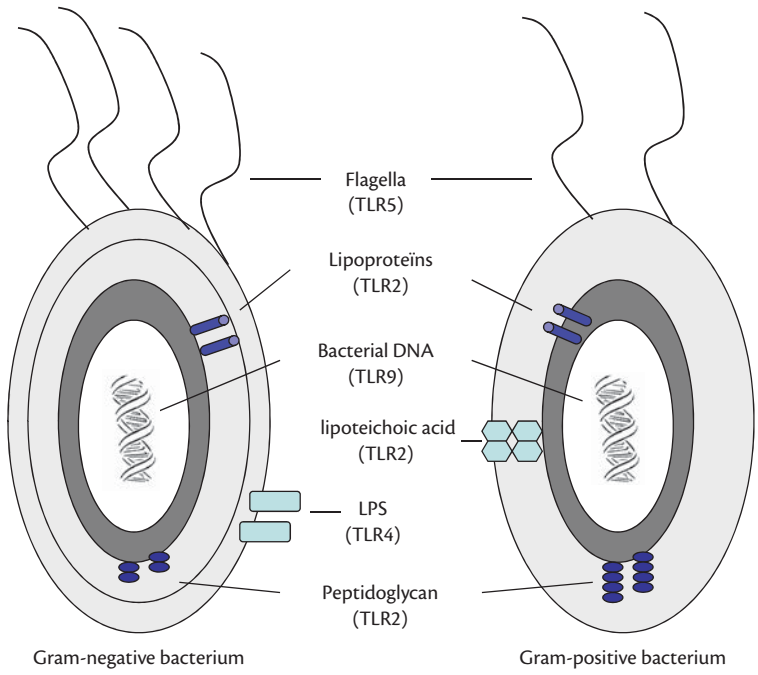


Fig. 303.2 Innate recognition of pathogens by Toll-like receptors (TLRs). Gram-positive and Gram-negative bacteria express distinct pathogen-associated molecular patterns (PAMPs) that are recognized by various, partly overlapping, TLRs. Lipoteichoic acid is exclusively expressed by Gram-positive pathogens, and lipopolysaccharide (LPS) by Gram-negative pathogens. Common PAMPs include peptidoglycan, lipoproteins, flagellin, and bacterial DNA.

Adapted from *The Lancet Infectious Diseases*, 8, 1, van der Poll and Opal SM, 'Host-pathogen interaction in sepsis', pp. 32–43, copyright 2008, with permission from Elsevier.

(Fig. 303.2) [7]. The TLRs and intracellular (NOD)-like receptors (NLRs) are considered the most important PRRs.

Toll-like receptors

TLRs play a central role in the initiation of cellular innate immune responses during infection. Thirteen TLRs (TLRs 1–13) have been identified in mammals. Bacterial ligands have been described for most TLRs (Table 303.1). For instance, TLR4 functions as the LPS receptor (Fig. 303.3). The entire TLR family signals via four adaptor proteins, namely myeloid differentiation primary-response protein 88 (MyD88), TIR-domain-containing-adaptor-protein (TIRAP), TIR-domain-containing-adaptor-protein-inducing-IFN-β (TRIF) and TRIF-related-adaptor-molecule (TRAM). Together with a number of protein kinases, these take care of the recognition and response to microbial molecules. While TLRs are essential for the early detection of pathogens, they may also cause excessive inflammation after uncontrolled stimulation. As an example, TLR4-deficient mice are fully protected against LPS-induced lethality, but display an enhanced susceptibility to several Gram-negative infections. The clinical relevance of TLR signalling is reflected by the recent description of marked vulnerability to purulent infections in children with a genetic deficiency for MyD88 or IL-1 receptor-associated kinase (IRAK)-4, a kinase acting directly downstream from MyD88 [8]. Several single nucleotide polymorphisms in genes encoding TLRs have also been associated with an altered susceptibility to bacterial infections [9]. Of note, PRRs can also recognize endogenous mediators released upon injury, thereby warning the host of imminent danger. Such endogenous danger signals are called 'alarmins' or 'danger-associated molecular patterns' (DAMPs) (Table 303.1) [3,7]. Heat shock proteins, fibrinogen, hyaluronic acid, and high-mobility group box-1 protein (HMGB-1) are examples of DAMPs that cause further amplification of the pro-inflammatory response through PRRs.

Table 303.1 Important ligands for Toll-like receptors (TLRs) during the host response to infection. PAMPs (pathogen-associated molecular patterns) and DAMPs (danger-associated molecular patterns) with relevance to the host response against bacterial infection. endogenous mediators identified as TLR4 ligands

	Species	TLR
PAMPs		
LPS	Gram-negative bacteria	TLR4
LTA	Gram-positive bacteria	TLR2*
Peptidoglycan	Most bacteria	TLR2
Triacyl lipopeptides	Most bacteria	TLR1/TLR2
Diacyl lipopeptides	*Mycoplasma* spp.	TLR2/TLR6
Porins	*Neisseria*	TLR2
Flagellin	Flagellated bacteria	TLR5
CpG DNA	Bacteria	TLR9
Unknown	Uropathogenic bacteria	TLR11**
DAMPs**		
Heat shock proteins	Host	TLR4
Fibrinogen, fibronectin	Host	TLR4
Hyaluronan	Host	TLR4
Biglycans	Host	TLR4
HMGB-1	Host	TLR4, TLR2

*For detection of LTA from some pathogens TLR6 functions as a co-receptor for TLR2.

**TLR11 is not functional in humans.

***Recent studies describe a role for TLRs in acute injury using rodent models of haemorrhagic shock, ischaemia and reperfusion, tissue trauma, and wound repair, and various toxic exposures; these studies have implicated TLR4 as a major factor in the initial injury response.

Adapted from *Lancet Infectious Diseases*, **8**(1), van der Poll T and Opal SM, 'Host-pathogen interactions in sepsis', pp. 32–43, copyright 2008, with permission from Elsevier.

The inflammasome

Whereas TLRs detect pathogens at either the cell surface or in lysosomes/endosomes, micro-organisms that invade the cytosol can be recognized by cytoplasmatic PRRs such as the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) [10]. Several members of the NLR family can assemble multimolecular complexes termed 'inflammasomes' in response to various activators. Activation of the NLRP3 inflammasome by PAMPs or DAMPs induces activation of caspase-1, which stimulates processing of the pro-inflammatory cytokines IL-1β and IL-18 [10]. Although NLRs

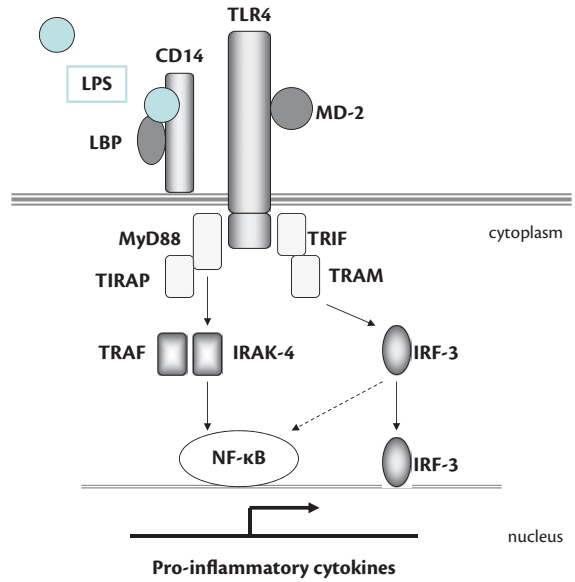


Fig. 303.3 The Toll-like receptor (TLR)-4 complex. The TLR family discriminates between specific patterns of microbial components. TLR4 recognizes lipolysaccharide (LPS). LPS first binds to LPS-binding-protein (LBP), which transfers LPS to CD14. Binding of LPS to CD14 leads to the association of CD14 with MD-2 and TLR4. After TLR stimulation, the adaptor molecule myeloid differentiation primary-response protein 88 (MyD88) is recruited. MyD88 associates with IL-1 receptor-associated kinase (IRAK)-4. This leads to release of nuclear-factor-κB (NF-κB), resulting in the transcription of a whole range of inflammatory genes. Next to MyD88, the adaptor molecules TIR-domain-containing-adaptor-protein (TIRAP), TIR-domain-containing-adaptor-protein-inducing-IFN-β (TRIF) and TRIF-related-adaptor-molecule (TRAM) have been identified. TIRAP is essential for MyD88-dependent signalling through TLR2 and TLR4. IRF-3 regulated TRIF is essential for TLR3—and TLR4-mediated activation of the MyD88-independent pathway. TRAM is involved in TLR4 mediated MyD88-independent/TRIF-dependent signalling pathways.

are of utmost importance for recognition of bacteria by the innate immune system, their exact role in sepsis pathophysiology is far from clear.

Regulation of the host response to infection

TLR signalling must be tightly regulated since a constant balance needs to found between activation and inhibition of the inflammatory response to avoid a detrimental inappropriate response [11]. Triggering receptor expressed on myeloid cells-1 (TREM-1) is an important amplifier of the TLR-and NLR-mediated inflammatory response to invading pathogens [12]. TREM-1 is specifically expressed on monocytes and neutrophils from patients with sepsis. Negative regulators of the TLRs designated to prevent excessive TLR signalling have been identified, including MyD88 short (MyD88s), ST2, single-immunoglobulin-interleukin-1 receptor-related (SIGIRR) molecule, toll-interacting protein (TOLLIP), suppressor-of-cytokine signalling (SOCS), A20, and IRAK-M [11].

Host–response proteins released upon infection

The interaction between pathogens and innate immune receptors triggers the release of a myriad of inflammatory mediators.

Cytokines

Cytokines are small proteins produced by various cell types (e.g. monocytes and macrophages) during infection that coordinate both local and systemic inflammation. In addition to TNF-α and IL-1, many other cytokines play an important role in regulating the septic host response. Many other cytokines are also important in regulating the septic host response. Novel cytokine mediators implicated in sepsis pathogenesis include IL-17, IL-33, and macrophage migration inhibitory factor (MgIF). Serum MgIF levels are elevated in patients with sepsis [13]. MgIF regulates innate immune responses through modulation of TLR4 [3,13]. MgIF-deficient mice challenged with LPS showed a defective response as a direct result of decreased TLR4 expression.

HMGB-1 and Mrp8/14

Cytokine activation trigger the release of numerous inflammatory response proteins, of which HMGB-1 and Mrp8/14 are prime examples. HMGB-1 is a nuclear protein released upon cell activation or injury [14]. Patients with sepsis have elevated circulating levels of HMGB-1. In preclinical sepsis models, HMGB-1 blockade protected against LPS-induced lethality, even when administration was delayed until after peak TNF-α and IL-1 levels had been reached [14]. Several receptors can mediate (directly or indirectly) the cellular effects of HMGB-1, including TLR2, TLR4, and the receptor for advanced glycation end-products (RAGE) [14]. RAGE is a promiscuous receptor that interacts with diverse ligands, such as advanced glycation end products (hence its name), S100 proteins, amyloid A, leukocyte adhesion receptors, and certain components of *E. coli*. It play various roles in the host defence against bacteria. Myeloid-related protein-8 (Mrp8 also called S100A8) and Mrp14 (also called S100A9) are members of the S100 protein family. Mrp8 and Mrp14 can form heterodimers that elicit a variety of inflammatory responses. Mrp8/14 complexes can activate TLR4 and amplify the LPS-triggered inflammatory responses of phagocytes [15]. In patients with sepsis and in healthy humans injected with LPS elevated Mrp8/14 plasma levels have been observed. Mice lacking Mrp8-Mrp14 complexes had increased survival following LPS-induced lethal shock and bacterial sepsis [15]. They displayed a reduced bacterial dissemination after intraperitoneal infection with *E. coli*.

Activation of complement

Complement factors are released as part of the inflammatory reaction to infection. Although the complement system has traditionally been considered a central part of the protective immunity against bacteria, complement activation may also contribute to an adverse outcome from sepsis [16]. Indeed, infusion of anti-C5a antibodies improved haemodynamic parameters in pigs infused with LPS or live *E. coli*, and reduced mortality in primates with *E. coli* sepsis and rats subjected to caecal ligation and puncture [16].

Bilateral interaction between inflammation and coagulation during infection

Sepsis is associated with multiple alterations in pro- and anticoagulant mechanisms [17]. The systemic host response to infection results in activation of coagulation, downregulation of physiological anticoagulant mechanisms, and inhibition of fibrinolysis. Coagulation activation in sepsis is primarily driven by tissue factor (TF). TF is a potent stimulator of the extrinsic coagulation cascade, and an essential mediator of coagulation. TF is not exposed to circulating blood in a resting state, but becomes exposed on the surface of mononuclear cells and endothelial cells when these cells are stimulated by bacteria or bacterial products such as LPS, or pro-inflammatory cytokines such as TNF-α. TF binds and activates factor (F)VII. The TF/VIIa complex so generated initiates coagulation activation by activation of FX, producing FXa that finally results in prothrombin conversion to thrombin. Procoagulant events are controlled by three major anticoagulant proteins: tissue factor pathway inhibitor (TFPI), antithrombin and activated protein C (AP-C) [17]. During severe sepsis the activities of TFPI, antithrombin and the protein C–AP-C system are impaired, together with enhanced TF-dependent coagulation, this results in a shift toward a net procoagulant state. The capacity of APC to control coagulation depends on inactivation of cofactors Va and VIIIa by this protease, while the anti-inflammatory effects of APC rely on its interaction with the protease-activated receptor-1 (PAcR-1). Proteolytic cleavage of PAcR-1 by APC induces genes known to downregulate pro-inflammatory signalling pathways and inhibit apoptosis. The relative contribution of the cytoprotective and anticoagulant effects of APC in the host defence against severe infections remains to be elucidated. PAcR-1 is a member of a family of receptors that also includes PAcR-2 to PAcR-4. Whereas APC signals through PAcR-1, the TF-FVIIa-FXa complex can activate PAcR-2. PAcRs can be activated by multiple other proteases (both host- and pathogen-derived), thereby markedly influencing inflammatory responses. PAcR-1 activation may be harmful during the early phases of endotoxaemia and sepsis, facilitating pulmonary leak and disseminated intravascular coagulation, but may be beneficial at later stages [17].

Conclusion

Taken together, the host response to infection can be seen as a PRR-mediated dysregulation of the immune system following pathogen invasion in which a careful balance between inflammatory and anti-inflammatory responses is vital (Fig. 303.4). A measured and rapid response to microbial invasion is essential to health; yet, the same immunological and coagulation systems that protect against localized infection can act to our disadvantage when these systems are activated systemically during generalized microbial infection [3]. Although systemic inflammation likely contributes to sepsis-induced death in some patients, recent insights have forced us to rethink the pure hyperinflammatory sepsis paradigm as many patients die during an extended period of immune suppression accompanying and/or following the initial septic response. Detailed knowledge of the interconnections between the host immune response programs will be essential in order to assist patients to prevent microbial invasion, limit the damage created by pathogens, and attenuate the injurious effects of the systemic host response. Further dissection of the role of host-pathogen interactions, the cytokine response, the coagulation cascade and their multidirectional interactions in sepsis should lead towards the development of new therapeutic approaches in the critically ill who are faced with infection. However, new approaches in clinical trial designs are also needed that take into account the considerable patient

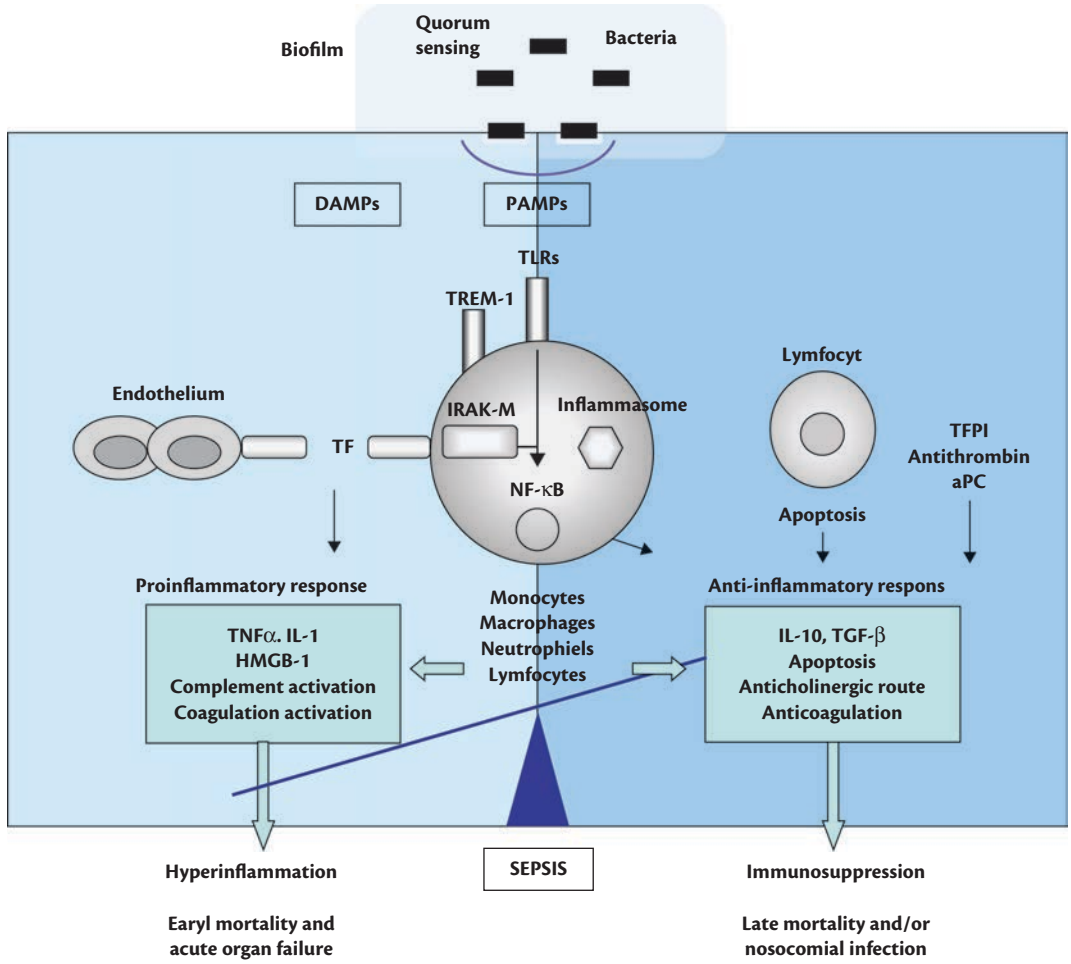


Fig. 303.4 The pro- and anti-inflammatory response during sepsis. The host response to infection starts with the initial interaction between PAMPs (pathogen-associated molecular pathogens) and pattern recognition receptors (PRR) such as the Toll-like receptors (TLR) and the inflammasome. Invading pathogens can communicate with each other via 'quorum sensing'. Biofilms are well-organized layers of micro-organism communities in which bacteria can protect themselves against the host's immune system and antibiotics. The PRR-initiated immune response can result in release of alarmins or DAMPs (danger-associated molecular patterns), e.g. high-mobility group box-1 protein (HMGB-1), that can further amplify the inflammatory response, at least in part via PRR. Pro-inflammatory cytokines, e.g. tumour necrosis factor (TNF)-α, interleukin (IL)-1, lead to hyperinflammation, initiation of the immune response and tissue factor (TF)-induced activation of coagulation. The directly activated anti-inflammatory response is characterized by upregulation of negative regulators of the TLR cascade e.g. IL-1 receptor-associated kinase (IRAK)-M, anti-inflammatory cytokines, e.g. IL-10 and transforming growth (TGF)-β, apoptosis of mainly lymphocytes, activation of a cholinergic anti-inflammatory response and the release of anticoagulant proteins. The resulting innate response of immune cells can result in a balanced reaction leading to pathogen elimination and tissue recovery or an unbalanced reaction that, on the one hand, can lead to exaggerated inflammation and tissue injury or, alternatively, to immune suppression caused by immune cell apoptosis and enhanced expression of negative regulators of TLR signalling.

Data from van der Poll T and Opal SM, 'Host-pathogen interactions in sepsis', *The Lancet Infectious Diseases*, 2008, **8**, pp. 32–43.

heterogeneity, the differences in causative organisms and the various phases of the individual immunological response [18].

References

1. Dellinger RP, Levy MM, Rhodes A, et al. (2012). Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine*, **41**, 580–37.
2. de Jong HK, van der Poll T, and Wiersinga WJ. (2010). The systemic pro-inflammatory response in sepsis. *Journal of Innate Immunology*, **2**, 422–30.
3. van der Poll T and Opal SM. (2008). Host-pathogen interactions in sepsis. *Lancet: Infectious Diseases*, **8**, 32–43.
4. Hotchkiss RS, Coopersmith CM, McDunn JE, and Ferguson TA. (2009). The sepsis seesaw: tilting toward immunosuppression. *Nature: Medicine*, **15**, 496–7.
5. Beutler B, Milsark IW, and Cerami AC. (1985). Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. *Science*, **229**, 869–71.
6. Merrell DS and Falkow S. (2004). Frontal and stealth attack strategies in microbial pathogenesis. *Nature*, **430**, 250–6.
7. Kawai T and Akira S. (2010). The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nature: Immunology*, **11**, 373–84.
8. von Bernuth H, Picard C, Jin Z, et al. (2008). Pyogenic bacterial infections in humans with MyD88 deficiency. *Science*, **321**, 691–6.
9. Schroder NW and Schumann RR. (2005). Single nucleotide polymorphisms of Toll-like receptors and susceptibility to infectious disease. *Lancet: Infectious Diseases*, **5**, 156–64.
10. Franchi L, Munoz-Planillo R, and Nunez G. (2012). Sensing and reacting to microbes through the inflammasomes. *Nature: Immunology*, **13**, 325–32.
11. Liew FY, Xu D, Brint EK, and O'Neill LA. (2005). Negative regulation of toll-like receptor-mediated immune responses. *Nature Review: Immunology*, **5**, 446–58.
12. Klesney-Tait J, Turnbull IR, and Colonna M. (2006). The TREM receptor family and signal integration. *Nature: Immunology*, **7**, 1266–73.
13. Calandra T, Echtenacher B, Roy DL, et al. (2000). Protection from septic shock by neutralization of macrophage migration inhibitory factor. *Nature: Medicine*, **6**, 164–70.
14. Lotze MT and Tracey KJ. (2005). High-mobility group box 1 protein (HMGB1): nuclear weapon in the immune arsenal. *Nature Review: Immunology*, **5**, 331–42.
15. Vogl T, Tenbrock K, Ludwig S, et al. (2007). Mrp8 and Mrp14 are endogenous activators of Toll-like receptor 4, promoting lethal, endotoxin-induced shock. *Nature: Medicine*, **13**, 1042–9.
16. Guo RF and Ward PA. (2005). Role of C5a in inflammatory responses. *Annual Review of Immunology*, **23**, 821–52.
17. Levi M and van der Poll T. (2010). Inflammation and coagulation. *Critical Care Medicine*, **38**(2 Suppl.), 26–34.
18. Angus DC. (2011). The search for effective therapy for sepsis: back to the drawing board? *Journal of the American Medical Association*, **306**, 2614–15.

CHAPTER 304

The host response to trauma and burns in the critically ill

Edward A. Bittner and Shawn P. Fagan

Key points

- Critical illness is associated with a broad spectrum of immunological derangements that defy simple characterization. Recent genomic studies have challenged the systemic inflammatory response syndrome/ compensatory anti-inflammatory syndrome paradigm regarding how the adult human responds to severe injury.
- Severe injury, whether a result of trauma, infection or burn, produces a genomic reprioritization ('genomic storm') in which up to 80% of the leukocyte transcriptome involving cell functions and pathways is altered. These changes occur rapidly after injury and can persist for days to weeks.
- Changes in both innate and adaptive immunity are established soon after injury; early, targeted therapy to either or both immune pathways may be the approach with the best possibility of improving patient outcomes.
- The prevailing assumption—molecular derangement results from current mouse models developed to mimic human diseases translate directly to human conditions—is challenged by recent genomic studies. New approaches should be explored to improve current models.
- Analysis of gene expression profiles may be useful in identifying not only patients at risk for complications after trauma, but also in allowing clinicians to focus on prevention of complications and identify those patients most likely to benefit from interventions.

Introduction

Following severe traumatic injury, patients enter a state of immune dysregulation consisting of both exaggerated inflammation and immune suppression with significant changes in inflammatory mediators and leukocyte cell populations. Many immune responses are common to trauma, burns, and sepsis; immunological dysregulation is thought to contribute to poor outcomes in these patient populations. The inflammatory response to trauma involves a wide variety of mediators (cytokines, chemokines, complement, oxygen radicals, eicosanoids, and nitric oxide) and effector cells (neutrophils, monocytes/macrophages, and endothelial cells). All these factors are interrelated and interconnected by up- and downregulatory mechanisms, leading to the systemic inflammatory response syndrome (SIRS). After massive trauma, uncontrolled systemic inflammation and an imbalance of these inflammatory factors results in organ dysfunction. The level of immunological alteration that leads to SIRS-associated multiple organ failure (MOF) is regulated by the degree of injury, the type of tissue injured, and various other factors including age, sex, genetics, and premorbid medical conditions.

Traumatic injury profoundly affects both innate and adaptive immune responses. The marked suppression in cell-mediated immunity following an excessive inflammatory response appears responsible for the increased susceptibility to subsequent sepsis. These responses are initiated and modulated by both pathogen- and damage-associated molecular pattern molecules detected through pattern-recognition receptors. Suppression of cell-mediated immunity may be caused by multifaceted cytokine/inhibitor profiles in the circulation and other compartments of the host. These may include excessive activation and dysregulated recruitment of neutrophils, induction of alternatively activated or regulatory macrophages that have anti-inflammatory properties, a shift in the T-helper (Th)1/Th2 balance toward Th2, appearance of regulatory T cells (potent suppressors of the innate and adaptive immune system), and lymphocyte apoptosis.

With recent advances in molecular biology and genetics, it is now possible to both characterize the inflammatory response to injury, and quantify the molecular mediators involved in this dynamic evolving process. Release of these mediators is dependent primarily on the severity of the 'first hit phenomenon' (injury) and, secondarily, on activation of the various molecular cascades during therapeutic or diagnostic interventions, surgical procedures and post-traumatic/post-operative complications ('second' or 'third' hits). Mediators involved in the sequelae of post-traumatic events are released from the cellular populations locally at the site of injury and, subsequently, systemically. The sequestration and activation of mainly neutrophils, monocytes, and lymphocytes triggers a multifocal molecular and pathophysiological process.

In addition to our capacity to evaluate the molecular events governing the immuno-inflammatory response to trauma, a growing body of evidence now suggests that genetic susceptibility influences the development of post-trauma complications. It is therefore possible that individual patients will react differently to major injury depending on their underlying genotype. Mapping of the actual gene information of each trauma patient and correlating this profile to the post-traumatic clinical course appears to be of paramount importance. DNA-chip technology is being used to clarify the different responses to the traumatic primary, secondary,

or tertiary hits, and to elucidate possible reasons for the transition of some patients towards complications and undesirable clinical outcomes.

SIRS/compensatory anti-inflammatory or immune-suppressive response syndrome/ multiple organ dysfunction syndrome paradigm

Injury due to major trauma or burns produces profound immunological dysfunction resulting in tissue injury, post-operative infection, and multiple organ dysfunction syndrome (MODS). The traditional paradigm of the host response has been viewed as an early SIRS followed temporally by a compensatory anti-inflammatory or immune-suppressive response syndrome (CARS). SIRS is mediated primarily by cells of the innate immune system, while CARS is primarily mediated by the adaptive immune system. This traditional paradigm argues that exaggerated inflammation contributes to early mortality. Complicated clinical courses are commonly associated with second hits or multiple inflammatory events induced by clinical episodes of infection or surgical stress. Much of this work is based on murine models of trauma, burns, and sepsis. Another component of the traditional SIRS-CARS paradigm is that the pro-inflammatory response occurs early and is terminated by the development of CARS. A model of early and late MODS based on the initial degree of injury severity has been described. An initial massive traumatic insult can create an early vigorous pro-inflammatory response and severe SIRS independent of infection ('one-hit' model), resulting in early MODS. In the 'two-hit' scenario, initially less severely-injured patients eventually develop late MODS as a result of the reactivation of their inflammatory response caused by an adverse and often minor intercurrent event, such as additional surgical stress, bacterial infections, or ischaemia/reperfusion injury. CARS often accompanies late MODS. An unbalanced compensatory anti-inflammatory response can result in anergy and immunosuppression, predisposing the host to opportunistic infection.

'Genomic storm' paradigm

Only recently has the human injury response been studied systematically at the genomic level. The 'Glue Grant' collaborative research programme (**Inflammation and the Host Response to Injury**) was the brainchild of its principal investigator, Tompkins, whose years of innovation in this field have contributed much to our present thinking [1]. Its investigators examined genome-wide expression patterns of blood leukocytes in the immediate post-injury period to better understand the overall priorities and patterns of gene expression. These patterns underlie not only the initial injury response, but also the development of complications and delayed clinical recovery [2]. The Glue Grant investigators have challenged the SIRS/CARS paradigm as to how the adult human responds to severe injury (Fig. 304.1). Major findings of their work include:

- Severe injury, whether as a result of trauma, infection, or burn injury produces a genomic reprioritization ('genomic storm') in which up to 80% of the leukocyte transcriptome involving cell functions and pathways is altered. These changes occur rapidly (within 4–12 hours) after injury, and can be prolonged from days to weeks.
- Similarities in gene expression patterns between different injuries (i.e. trauma, burns, and sepsis) reveal an apparently fundamental response to severe inflammatory stress, with genomic signatures that are surprisingly far more common than different.
- At the level of the leukocyte transcriptome, alterations in expression of classical inflammatory and anti-inflammatory, as well as adaptive immunity genes occur simultaneously, not sequentially after severe injury. Transcriptomic changes in the adaptive immune response occur very early and, often, simultaneously with the pro-inflammatory reactions found in innate immunity.
- The temporal nature of the current SIRS/CARS paradigm is not supported at the level of the leukocyte transcriptome. Complications such as nosocomial infections and organ failure are not associated with any genomic evidence of a 'second hit' and differ only in the magnitude and duration of this genomic reprioritization. Furthermore, the delayed clinical recovery with organ

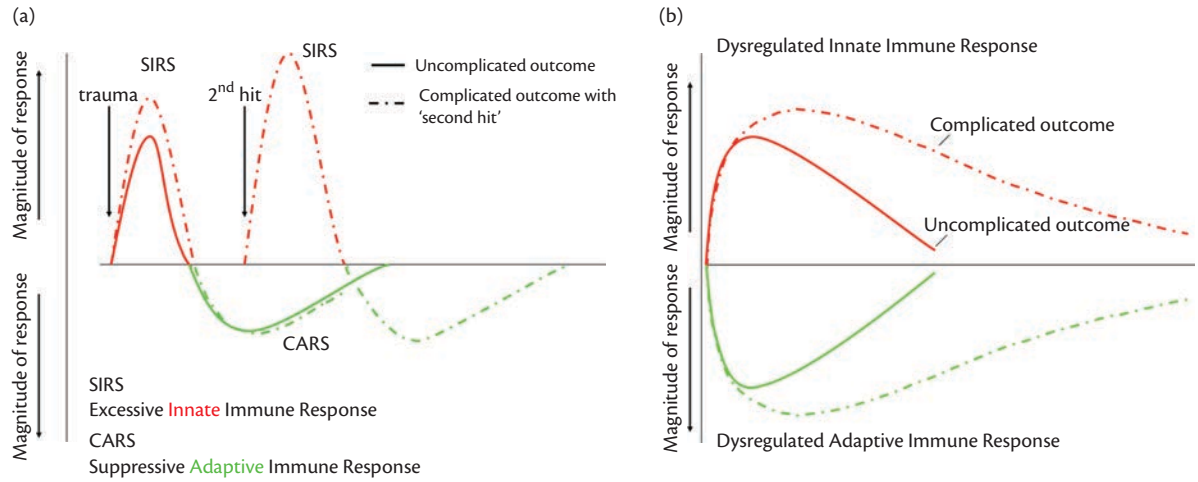


Fig. 304.1 Trauma-induced 'genomic storm': (a) Classic SIRS/CARS paradigm. (b) New paradigm of human response to injury. Genomic wide expression patterns of blood leukocytes following initial injury and the relationship between recovery and complications.

injury is not associated with dramatic qualitative differences in the leukocyte transcriptome. In examining recovery from injury, all genes moved in the same direction regardless of how complicated the patient's clinical course had been. There was no evidence of a single gene or cluster of genes whose expression changed uniquely, or any that dropped out in trauma patients with a complicated recovery versus those with an uncomplicated recovery.

Implications of the 'genomic storm' paradigm

Critically-ill patients with different underlying acute injuries have similar appearing physiological reactions, a condition known by consensus definition as SIRS. An unproven hypothesis central to the pursuit of drug targets for this syndrome has been that the molecular mechanisms underlying this syndrome are similar, regardless of initiating aetiology. The very high correlation in response between trauma, burns, and sepsis in humans strongly supports this hypothesis and suggests that such an approach may be possible. Furthermore, the commonality of genomic patterns in the human leukocyte transcriptome in patients with burn injury, trauma, and sepsis suggests a fundamental response to severe inflammatory stress in humans regardless of its origin, with far more similarities than differences. These findings are consistent with a genomic storm that is neither chaotic nor erratic, but rather highly coordinated and reproducible. This new paradigm has profound implications regarding the direction of future research, prediction of outcome, and the development of new therapeutics.

Need for new models of disease

A cornerstone of modern biomedical research is the use of murine models to explore basic pathophysiological mechanisms, evaluate new therapeutic approaches, and make decisions regarding whether to carry new drug candidates forward into clinical trials. An inherent assumption in the use of murine models to mimic human systemic inflammation is that the time course of injury and repair between the species is similar. Until recently, systematic studies evaluating how well murine models mimic human inflammatory diseases were non-existent. The Glue Grant collaborative research programme investigators performed a systematic comparison of the genomic response between human inflammatory diseases and murine models. This comparison challenges the assumption that mouse models developed to mimic human diseases translate directly to human conditions [3]. In their study, the investigators:

- Compared the correlations of gene expression changes with trauma, burns and endotoxaemia between human subjects and corresponding mouse models.
- Characterized and compared the temporal gene response patterns seen in these human conditions and models.
- Identified the major signalling pathways significantly regulated in the inflammatory response to human injuries and compared them against the human *in vivo* endotoxaemia model and three murine models.
- Evaluated patient and murine studies of several representative acute inflammatory diseases.

The study found that acute inflammatory stresses from different aetiologies resulted in highly similar genomic responses in humans, although the responses in the corresponding mouse models correlated poorly with the human conditions and with one another (Fig. 304.2). Among genes changed significantly in humans, the murine orthologs were close to random in matching their human counterparts.

Although there are many inherent flaws to using animal models in translational research, it is the reality of today's environment that they must be used. Therefore, existing animal models should be improved as new human data become available so that the models more closely mimic human immune responses. To date, many anti-inflammatory approaches to treat severe trauma and subsequent multi-organ failure have succeeded in mice, but failed in humans, probably due to differences in the complex nature of protective immunity between species.

As virtually every drug and drug candidate functions at the molecular level, one practical forward approach is to require molecular detail in the animal model studies. This would indicate whether the model mimics or fails to mimic the molecular behaviour of key genes, key pathways, or the genome-wide level thought to be important for the relevant human disease. These might first include requiring comprehensive genomic descriptions in patient studies to define the human disease, then using these as a guide to develop the animal model. The quality of the animal model could then be determined by how well it reproduces the human disease on a molecular basis, rather than simply phenotype. In addition, the development of synthetic human models by in vitro reconstitution of disease-related cell types or tissues might similarly improve current disease models. Furthermore, new genomic information, such as the availability of personal genomes or exomes to capture the disease heterogeneity directly from patients, or systematic interpretation of genome-wide signatures in human diseases, will probably complement or reduce the need for mouse models in disease discovery and drug development.

Prediction of outcome

Many patients have complicated recoveries following severe trauma due to the development of organ injury. Predictive models based on physiological and clinical parameters have had limited success in predicting clinical trajectories of individual patients at risk of developing organ injury or sepsis. Since changes in both innate and adaptive immunity are established soon after injury, early identification of severely injured patients who may have a complicated clinical course and targeting therapy to either or both immune pathways may be the approach with the best possibility of improving outcomes.

It is generally accepted that early interventional trials in trauma and sepsis patients have failed in large part due to the heterogeneity of the patient population. This is combined with the inability to select the sickest patients with the highest mortality, who are perhaps most likely to benefit from such therapy. Study inclusion criteria are primarily physiological and are often limited to non-specific inflammatory responses and overall organ injury, which may be too delayed to permit intervention to affect outcomes. Furthermore, the use of clinical criteria to enter patients into trauma or sepsis clinical trials inevitably results in the inclusion of individuals who will either not benefit from the therapy or may actually be harmed. The ability to identify and exclude those patients who will recover and not require intervention, while identifying those who may have

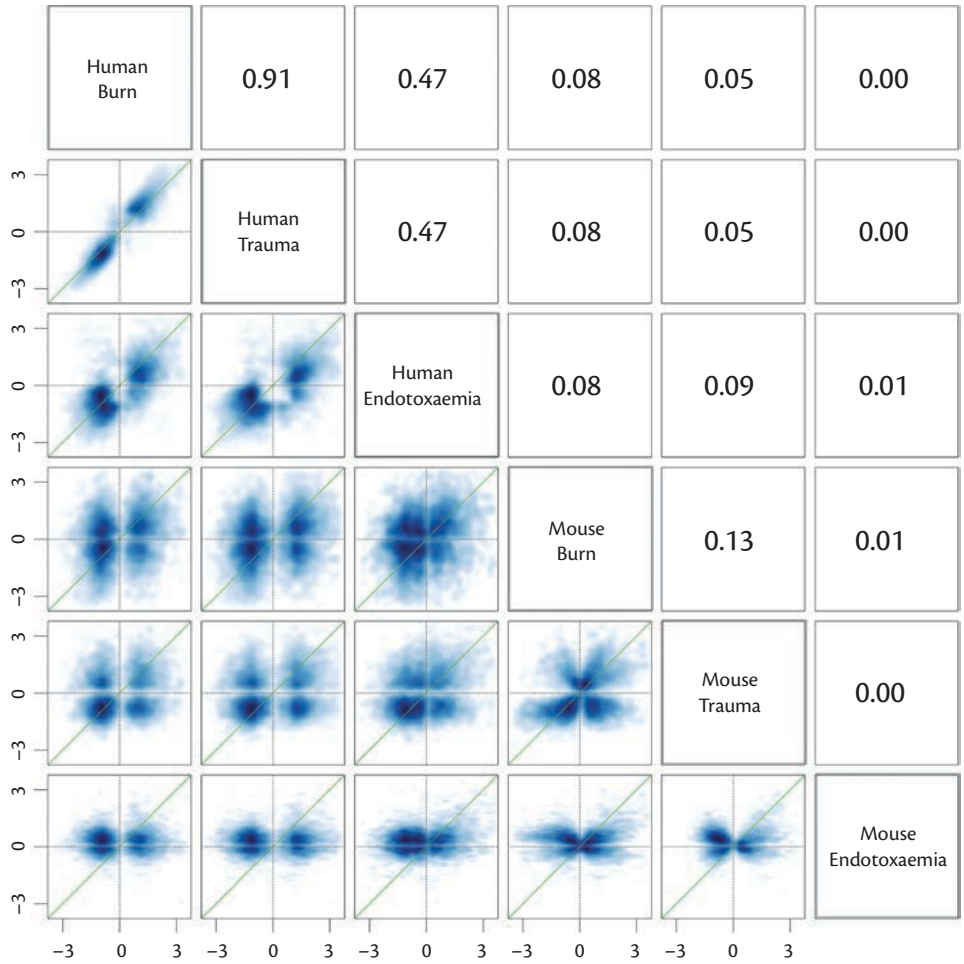


Fig. 304.2 Comparison of inflammation-induced genomic responses (burns, trauma, and endotoxin) between humans and their corresponding murine models. Scatter plots are presented of $\log_2$ changes of 4918 genes and their corresponding Pearson correlation coefficients (r).
Reproduced from Seok J et al., 'Genomic responses in mouse models poorly mimic human inflammatory diseases', *Proceedings of the National Academy of Sciences*, 2013, **110**, pp. 3507–12, doi 10.1073/pnas.1222878110.

a poor outcome and benefit from intervention would be a useful tool for future trials.

The development of prognosticators based on immunological measures has shown promise. The Glue Grant collaborative research program (**Inflammation and the Host Response to Injury**) developed and retrospectively validated a simple genomic composite score that can be rapidly used to predict clinical outcomes [4]. From previously identified families of genes involved in inflammation, antigen presentation and T-cell responses, the investigators identified 63 genes from 167 severely injured patients. The leukocyte gene expression in these patients was significantly different depending on whether the course was uncomplicated or complicated. The investigators then used a genomic tool to consolidate the gene expression profile of each patient into a single genomic score, which was able to discriminate patients that developed a poor clinical outcome from those who recovered. Based on the their findings, such a genomic score may be feasible as a prognostic tool in the clinical setting to identify trauma patients at risk for developing organ injury and adverse outcomes, and theoretically, identify those patients most likely to benefit from interventions. In the Glue Grant study, two-thirds of the 63 genes identified as being differentially expressed between uncomplicated and complicated trauma patients were genes associated with adaptive immunity in general, and specifically with interferon signalling. The expression of this subgroup of genes was suppressed in trauma patients with complicated courses, suggesting that this battery of genes may be useful in identifying not only patients at risk for complications after trauma, but also those who are responsive to biological response modifiers. This would allow the clinician to identify patients at risk of developing adverse clinical outcomes and focus care on the prevention of complications, such as secondary infections and multisystem organ failure.

References

1. Tompkins RG. (2011). Administration—inflammation and the host response to injury. Boston: Massachusetts General Hospital. Available at: https://www.gluegrant.org/administration.htm (accessed 2 September 2015).
2. Xiao W, Mindrinos MN, Seok J, et al. (2011). A genomic storm in critically injured humans. *Journal of Experimental Medicine*, **208**, 2581–90.
3. Seok J, Warren HS, Cuenca AG, et al. (2013). Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proceedings of the National Academy of Sciences, USA*, **110**, 3507–12.
4. Cuenca AG, Gentile LF, Lopez MC, et al. (2013). Development of a genomic metric that can be rapidly used to predict clinical outcome in severely injured trauma patients. *Critical Care Medicine*, **41**, 1175–85.

CHAPTER 305

The host response to hypoxia in the critically ill

Raghavan Raju and Irshad H. Chaudry

Key points

- Severe haemorrhage causes whole body hypoxia.
- Hypoxia-inducible factor (HIF-1), an oxygen-sensing transcription factor, regulates the cellular response to hypoxia.
- The HIF-1 level is controlled by intracellular oxygen concentration.
- Hypoxia causes a decrease in mitochondrial oxidation, resulting in decreased adenosine diphosphate (ATP) production.
- Hypoxia also triggers endoplasmic reticulum stress.

Introduction

According to the US Centers for Disease Control, injury is a leading cause of death, while haemorrhage is the most common cause of preventable death [1]. Soft-tissue trauma and haemorrhage lead to decreased organ blood flow. The reduced tissue supply of nutrients and oxygen results in hypoxia, metabolic dysregulation, and organ dysfunction. Conditions such as trauma-haemorrhage (T-H) cause whole body hypoxia. Severe tissue hypoxia is also a frequent pathophysiological abnormality in severe sepsis [2]. The hypoxic response of the host is complex—during hypoxia, the oxygen-sensing intracellular machinery within mammals attempts to restore homeostasis by augmenting respiration and blood flow [3]. Although hypoxia plays an important role in various conditions, such as heart and lung diseases, cancer and stroke, contributing to the majority of deaths in the United States, this chapter will focus upon hypoxia produced by low flow conditions following T-H, and its consequences.

Hypoxia and haemorrhagic shock

Sustained tissue hypoxia contributes to the initiation of inflammatory processes, generation of excessive free radicals, and cellular apoptosis [4]. Specifically within the immune compartment, hypoxia modulates differentiation and function of T cells, dendritic cells and macrophages, as well as their cytokine profiles [5,6]. Hypoxia may also contribute to lipid accumulation within different cell types, including macrophages [7]. Serious immunological perturbations may occur following haemorrhagic shock in animal models, contributing to increased susceptibility to sepsis [8]. Our T-H animal model, wherein 60% of the blood volume is withdrawn in 45 minutes to induce haemorrhagic shock, induces severe hypoxia. Data from this model show significant reductions in blood flow in several organs, including liver, heart, kidney, and intestine, at 2 hours following haemorrhage and resuscitation. Haemorrhagic shock leads to increased production of pro-inflammatory cytokines, such as tumour necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1. Hypoxaemia (low O_2 level in the circulation) has been suggested to be one of the reasons for this immunological response. When mice were exposed to low oxygen (95% N_2–5% O_2) for 60 minutes, significant hypotension occurred followed by an inflammatory cytokine release [9]. Thus, even in the absence of any blood loss or tissue injury, hypoxaemia induced systemic inflammation as evidenced by a significant rise in plasma TNF-α and IL-6 levels, and a significant decrease in antigen presentation capacity of peritoneal macrophages. This immune response is gender-dependent, with females in the pro-oestrus state being resistant to a pro-inflammatory response [8]. Indeed, oestrogen pretreatment protected males against a hypoxia-induced immune depression [8]. Hypoxaemia in male mice resulted in markedly depressed proliferation and IL-2 release capacity of splenocytes. However, in male mice pretreated with 17β-oestradiol, splenocyte function was preserved. Numerous studies have demonstrated a sex-dependent host response to T-H. This dichotomy was further confirmed by the finding that MyD88 and Src expression in Kupffer cells were significantly decreased after hypoxia in pro-oestrus females, but not in males. Elevated IL-6 production by Kupffer cells in response to hypoxia may be mediated by p38MAPK activation via a Src-dependent pathway [9].

Role of HIF-1 in hypoxia

As mentioned previously, haemorrhage and soft-tissue trauma impair tissue perfusion and cause microvascular injury, increased interstitial pressure, thrombosis, and local hypoxia [10]. Although some data show that hypoxia enhances macrophage phagocytosis, suppression of Kupffer cell phagocytosis has also been observed [11,12]. We compared the similarity of cellular hypoxia observed in T-H with that of a hypoxaemic animal model exposed to 5% O_2 for 2 hours. Using Pimonidazole as a marker of hypoxia, a similar percentage (80%) of Kupffer cells from T-H and hypoxia groups demonstrated a comparable hypoxic effect [11]. In another study, peritoneal macrophage phagocytosis was enhanced in animals subjected to hypoxia, but a reversed effect was seen when hypoxia-inducible factor (HIF)-1α mRNA was disrupted [12]. HIF-1α is an oxygen-sensing protein, the intracellular level of which is

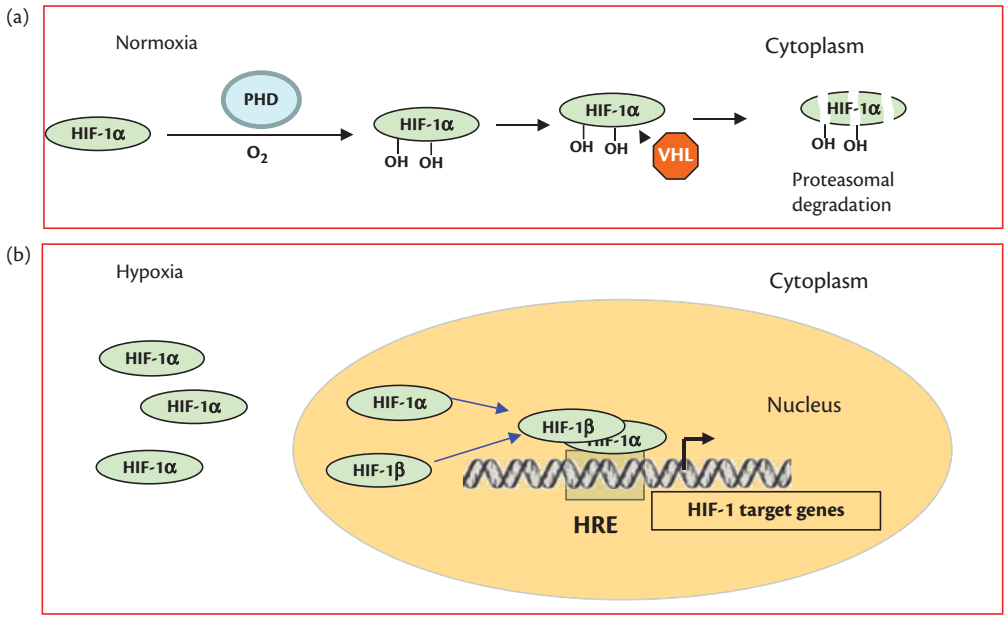


Fig. 305.1 Oxygen-regulated HIF-1 dynamics. (a) In the presence of oxygen, HIF-1α protein subunit is hydroxylated on one or two proline residues. The process is catalysed by the enzyme, prolyl hydroxylase (PHD) utilizing O_2. Hydroxylated HIF-1α, bound by von Hippel-Lindau protein (VHL) recruits E3 ubiquitin-protein ligase to the complex and targets for proteosomal degradation. (b) With deficiency of oxygen, hydroxylation of HIF-1α is inhibited, resulting in the build-up of HIF-1α in the cytosol. HIF-1α forms a heterodimer with HIF-1β in the nucleus, binds to hypoxia response elements (HRE) on gene promoters and regulates gene transcription. Over 100 genes are known to be regulated by HIF-1α.

Adapted from Carroll VA and Aschcroft M, 'Targeting the molecular basis for tumour hypoxia', Expert *Reviews in Molecular Medicine*, 2005, **7**, pp. 1–16, with permission from Cambridge University Press.

controlled by the oxygen level. When the mRNA was overexpressed there was a further increase in phagocytosis, demonstrating a direct relationship between the observed phenotypic effects and HIF-1α expression [12]. However, alongside the significant increase in HIF-1α expression, there was a marked reduction in mitochondrial function.

HIF-1 is a transcription factor, a heterodimer of HIF-1α and HIF-1β. Whereas HIF-1β expression is constitutive, the intracellular level of HIF-1α is highly regulated by the cellular oxygen concentration. In the presence of adequate oxygen, HIF-1α undergoes an oxygen-dependent hydroxylation at one or two proline residues, at positions 402 or 564. The hydroxylated HIF-1α is bound by von Hippel-Lindau (pVHL) protein and eventually targeted for proteosomal degradation (Fig. 305.1a). As the activity of the enzyme that hydroxylates HIF-1α is tightly dependent on oxygen availability, during oxygen deficiency the hydroxylation of HIF-1α declines. This results in an increased intracellular concentration of HIF-1α, allowing it to pair with HIF-1β. The dimer binds to promoter regions of more than 100 different genes (Fig. 305.1b). The nucleotide sequence on the promoters that bind HIF-1 is termed the hypoxia-responsive element (HRE) and is determined to be (A/G)CGTG [13]. HIF-2 and HIF-3 are also heterodimeric proteins with similar functions to HIF-1; however, HIF-1 is the most studied oxygen-sensing transcription factor.

Effect of hypoxia on cellular energetics

A primary role of HIF-1 is to assist a hypoxic cell to shift its energy reliance from aerobic respiration to glycolysis. Indeed, significant increases in HIF-1α expression have been observed in several organs after ischaemia-reperfusion injury, T-H, or soft tissue injury [7]. Mitochondrial ATP production relies on oxidative phosphorylation, which slows down under hypoxic conditions. The effect of hypoxia in promoting glycolysis, while reducing ATP production through decreased mitochondrial oxidation in cardiomyocytes subjected to hypoxia is well documented [14]. Anaerobic metabolism due to a low flow condition produces lactate as a by-product. This process is akin to the Warburg effect proposed in cancer, wherein oxygen-deprived cancer cells drive the less efficient glycolytic mechanism, with inhibition of fatty acid oxidation, conversion of acetyl CoA to pyruvate and mitochondrial oxidative phosphorylation, for survival. Decreased levels of the mitochondrial biogenesis factors, PGC-1α, PPAR, and NRF are reported following T-H. Consistent with this observation, decreased ATP and mitochondrial function have been observed in several organs. Hypoxia amplifies mitochondrial inhibition induced by nitric oxide during an inflammatory response [15]. To further understand mitochondrial gene expression changes following hypoxia, we studied the mitoscriptome profile (i.e. the transcriptome of mitochondrial DNA and nuclear DNA that play a role in the structure and function of mitochondria) in cardiomyocytes subjected to hypoxia [16]. A significant increase was observed in expression of aldolase (Aldoc) and another key glycolytic enzyme, hexokinase (HK1) in neonatal cardiomyocytes subjected to hypoxia. Expression of seven of the 10 tested genes involved in glycolysis was significantly increased. A key cellular response related to HIF-1 expression in hypoxia is facilitating a metabolic shift from oxidative phosphorylation to glycolytic production of ATP. Of note, expression of pyruvate dehydrogenase kinase, iso-enzyme 1 (Pdk1) also increased following hypoxia. Pdk1 phosphorylates the pyruvate

dehydrogenase complex (Pdh), which catalyses the conversion of pyruvate to acetyl CoA. The inhibition of Pdh therefore limits availability and entry of acetyl CoA into mitochondrial oxidation.

Among the genes upregulated following hypoxia were the HIF target genes, *Bnip3, HK1*, and *Pdk1*. Expression and accumulation of *Bnip3* mRNA and overexpression of *Bnip3*-activated cardiomyocyte death have been observed in chronic hypoxia [17]. *Bnip3* has also been implicated in hypoxia-mediated autophagy, although a recent study suggested that hypoxic induction of *Bnip3* may not be directly mediated by HIF-1 [18]. Nonetheless, *Bnip3* may play an important role in hypoxia-induced cell death.

Neutrophils are among the first responders and important mediators of any innate immune response. The dominant glycolytic metabolism of neutrophils allows these cells to function in hypoxic inflammatory foci. Furthermore, a hypoxic environment inhibits constitutive neurophil apoptosis. Murine neutrophils deficient in HIF-1α had decreased survival in oxygen deficiency conditions [19]. In addition, specific *in vivo* deletion of HIF-1α in myeloid cells resulted in reduced ATP pools and impairment of myeloid cell aggregation, motility and invasiveness, and reduced bacterial killing, further highlighting the need for hypoxic adaptation as part of the functional requirement of myeloid cells [19].

Another important cellular response to hypoxia is the induction of endoplasmic reticulum (ER) stress [20]. ER stress is one of the first and foremost responses of a cell in response to conditions such as hypoxia or hyperglycaemia; most injury situations elicit these conditions requiring the initiation of ER stress. ER is the first compartment of the protein secretory pathway; folding and post-translational modifications of newly-synthesized and transmembrane proteins are carried in this compartment. In response to ER stress-inducing signals, cells initiate an unfolded protein response. When misfolded or unfolded proteins accumulate, ER stress sensors IRE1, PERK, and ATF6 perched on the ER membrane activate various signalling pathways in order to restore cellular homeostasis. However, sustained stress may lead to apoptosis. Activation of the ER stress pathway has been observed following injuries such as T-H and burns.

Overall, there is a profound effect of hypoxia on metabolic homeostasis in the target tissues. The initial host response to hypoxia may be characterized as a survival response, although a sustained hypoxic condition may be suicidal to the host cells.

References

1. Curry N, Hopewell S, Doree C, Hyde C, Brohi K, and Stanworth S. (2011). The acute management of trauma hemorrhage: a systematic review of randomized controlled trials. *Critical Care*, **15**, R92.
2. Bozza FA, Carnevale R, Japiassu AM, Castro-Faria-Neto HC, Angus DC, and Salluh JI. (2011). Early fluid resuscitation in sepsis: evidence and perspectives. *Shock*, **34**(Suppl.1), 40–3.
3. Eltzschig HK and Carmeliet P. (2011). Hypoxia and inflammation. *New England Journal of Medicine*, **364**, 656–65.
4. Melillo G. (2011). Hypoxia: jump-starting inflammation. *Blood*, **117**, 2561–2.
5. Bosco MC, Pierobon D, Blengio F, et al. (2011). Hypoxia modulates the gene expression profile of immunoregulatory receptors in human mature dendritic cells: identification of TREM-1 as a novel hypoxic marker in vitro and in vivo. *Blood*, **117**, 2625–39.
6. Palazon A, Aragones J, Morales-Kastresana A, de Landazuri MO, and Melero I. (2012). Molecular pathways: hypoxia response in immune cells fighting or promoting cancer. *Clinical Cancer Research*, **18**, 1207–13.
7. Nath B and Szabo G. (2012). Hypoxia and hypoxia inducible factors: diverse roles in liver diseases. *Hepatology*, **55**, 622–33.
8. Raju R, Bland KI, and Chaudry IH. (2008). Estrogen: a novel therapeutic adjunct for the treatment of trauma-hemorrhage-induced immunological alterations. *Molecular Medicine*, **14**, 213–21.
9. Thobe BM, Frink M, Choudhry MA, Schwacha MG, Bland KI, and Chaudry IH. (2006). Src family kinases regulate p38 MAPK-mediated IL-6 production in Kupffer cells following hypoxia. *American Journal of Physiology and Cell Physiology*, **291**, C476–82.
10. Nizet V and Johnson RS. (2009). Interdependence of hypoxic and innate immune responses. *Nature Review: Immunology*, **9**, 609–17.
11. Hsieh CH, Nickel, EA, Hsu, JT, Schwacha MG, Bland KI, and Chaudry IH. (2009). Trauma-hemorrhage and hypoxia differentially influence Kupffer cell phagocytic capacity: role of hypoxia-inducible-factor-1alpha and phosphoinositide 3-kinase/Akt activation. *Annals of Surgery*, **250**, 995–1001.
12. Anand RJ, Gribar SC, Li J, et al. (2007). Hypoxia causes an increase in phagocytosis by macrophages in a HIF-1alpha-dependent manner. *Journal of Leukocyte Biology*, **82**, 1257–65.
13. Semenza GL. (2010). Vascular responses to hypoxia and ischemia. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **30**, 648–65.
14. Jian B, Wang D, Chen D, Voss J, Chaudry I, and Raju R. (2010). Hypoxia-induced alteration of mitochondrial genes in cardiomyocytes—role of Bnip3 and Pdk1. *Shock*, **34**, 169–75.
15. Frost MT, Wang Q, Moncada S, and Singer M. (2005). Hypoxia accelerates nitric oxide-dependent inhibition of mitochondrial complex I in activated macrophages. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, **288**, R394–400.
16. Raju R, Jian B, Hubbard,W, and Chaudry I. (2011). The mitoscriptome in aging and disease. *Aging Diseases*, **2**, 174–80.
17. Kubasiak LA, Hernandez OM, Bishopric NH, and Webster KA. (2002). Hypoxia and acidosis activate cardiac myocyte death through the Bcl-2 family protein BNIP3. *Proceedings of the National Academy of Sciences, USA*, **99**, 12825–30.
18. Namas RA, Metukuri MR, Dhupar R, et al. (2011). Hypoxia-induced overexpression of BNIP3 is not dependent on hypoxia-inducible factor 1alpha in mouse hepatocytes. *Shock*, **36**, 196–202.
19. Walmsley SR, Cadwallader KA, and Chilvers ER. (2005). The role of HIF-1alpha in myeloid cell inflammation. *Trends in Immunology*, **26**, 434–9.
20. Jian B, Hsieh C-H, Chen J, et al. (2008). Activation of endoplasmic reticulum stress response following trauma-hemorrhage. *Biochimica Biophysica Acta*, **1782**, 621–6.

CHAPTER 306

Host–pathogen interactions in the critically ill

Guillaume Geri and Jean-Paul Mira

Key points

- Host–pathogen interactions are complex, precise, and varied.
- The innate immune response involves numerous pattern recognition receptors that detect pathogen-associated molecular patterns, leading to the production of cytokines, chemokines, and the development of adaptive immunity.
- Host–pathogen interaction diversity is increased by microbial variability.
- Genetic deficiencies may help physicians to understand and validate innate immune responses.
- Future therapeutic applications should be studied to adapt standard therapeutics to individual patients.

Introduction

Infection by a pathogenic micro-organism triggers a coordinated activation of both innate and adaptive immune responses that aim to control microbial growth and protect the host. The innate immune response, the first line of defence against micro-organisms, is either non-specific or directed against a group of micro-organisms, while the adaptive immune response is specific and targets a given pathogen. The innate immune response quickly triggers an antimicrobial response through the induction of various inflammatory cytokines and chemokines, and this will initiate development of a pathogen-specific, long-lasting adaptive immune response. Accurate recognition of microbial-associated molecular patterns (MAMPs) by pattern-recognition receptors (PRRs) is the cornerstone of this immediate response. PRRs are not only expressed on dendritic cells, macrophages and neutrophils, but also on endothelial and epithelial cells. These receptors sense various classes of molecules and activate different intracellular signalling pathways to produce an adequate initial response to the pathogen's aggression.

The importance of host genetics in the immune response is unequivocal. Hence, the same infectious challenge does not create a similar clinical phenotype in both humans and animal models. Familial clustering of severe infections, such as meningococcal disease, also argues for some inherited genetic susceptibility. Since the discovery of the double helical structure of DNA by Crick and Watson in 1953 to the completion of the human genome project, major advances have been realized in genetic medicine. These have allowed the rapid expansion of genetic-association, genome-wide association (GWA) and sequencing studies, leading to numerous publications on the host's genetic susceptibility. However, the two-way interactions that occur between host and pathogen also suggest that pathogen variability is another important piece of the puzzle, leading to a very complex two-sided relationship with numerous combinations. While immune-related genes are promising candidates for any infectious disease, genes encoding proteins involved in the pathogen life cycle within the host or in other pathways should also be considered.

This review aims to first describe the multiple determinants of the host's immune response and the influence of pathogen variability, and then to consider potential therapeutic applications for individualized medicine.

Host recognition of microbial-associated molecular patterns

Toll-like receptors

Toll-like receptors (TLRs) are major PRRs that trigger kinase cascades to activate nuclear transcription factors that induce gene expression and cytokine production. The TLR structure is composed of an extracellular domain that contains several leucine-rich repeats and an intracytoplasmic domain that shares significant sequence similarities with the corresponding domain of the interleukin-1 receptor. Myeloid differentiation factor-88 (MyD88) is the cornerstone protein for most of the pathways induced by the TLRs, with the exception of TLR-3. In particular, stimulation of TLRs triggers an intracellular signalling cascade leading to activation of NFκ-B, the central transcription factor of inflammation.

Thirteen TLRs have been described in mammalians. All these receptors act either as homo—or heterodimers with other members of the TLR family. The TLR-2/6 and TLR-1/2 heterodimers recognize Gram-positive bacteria through sensing of different bacterial surface lipoproteins. TLR-5 recognizes flagellin from both Gram-positive and Gram-negative bacteria, while TLR-7 detects bacterial RNA. CpG bacterial DNA stimulates only TLR-9. TLR-4 was initially described as recognizing lipopolysaccharide (LPS), a major pathogenic component of Gram-negative bacteria, although recent studies show that LPS does not bind directly to TLR4, but rather to a protein complex composed of LPS bound to MD2 and LPS-binding protein, which in turn activates TLR-4. The TLRs do not only recognize bacteria, but also fungi, parasites, and viruses. TLR-2 and TLR-4 recognize multiple ligands shared by different parasites. Viruses are recognized

by intracytoplasmic TLRs, namely TLR-3, -7, and -8 as they need to have access to viral nucleic acids.

In young children, rare autosomal MyD88 deficiencies lead to recurrent pyogenic infections and invasive pneumococcal diseases, including meningitis [1]. Similarly, serine-threonine kinase IRAK-4 (interleukin-1 receptor-associated kinase-4) deficiencies that affect TLR signalling also predispose to the same bacterial infections [2]. The common point between these two different genetic deficiencies is the host's inability to activate NF- κB and induce downstream cytokine release in response to TLR stimulation. Genetic mutations are also involved in severe viral infections. Hence, mutations in TLR-3 or in UNC93B1 (a protein involved in TLR-3 signalling) predispose to recurrent herpes virus encephalitis [3,4].

Other pattern recognition receptors

Besides TLRs, three others PRR families have been described. Two intracytoplasmic PRR families (RIG-I helicase receptors and NOD-like receptors (NLRs)) may be distinguished from C-type lectin receptors (CLRs), which constitute an extracellular PRR family like the TLRs.

CLRs recognize microbial polysaccharides and are important for recognition of bacteria and fungi [5]. The dectin-1 receptor is the major PRR for the beta-1,3-glucan, an important component of the fungal wall. This triggers phagocytosis and production of various inflammatory chemokines and cytokines via activation of the NLRP3 inflammasome. Dectin-1 deficient mice show great susceptibility to systemic fungal infections that is related to an impaired pro-inflammatory cytokine production and a decrease in neutrophil-mediated fungal killing [6]. However, patients with dectin-1 deficiency appear not to be more susceptible to severe fungal infections, even if they are more likely to colonized by fungi when undergoing stem-cell transplantation [7]. Hence, they are likely to need more frequent antifungal therapy than patients without dectin deficiency.

Intracytoplasmic RIG-1 receptors are efficient receptors for RNA viruses. The two main receptors of the RIG-1 family are retinoic acid-inducible gene 1 (*RIG-1*) and melanoma differentiation-associated gene 5 (*MDA5*), which are very efficient receptors for hepatitis C, Japanese encephalitis virus, dengue, and West Nile viruses. Until now, no mutation in this PRR family has been associated with an altered susceptibility to sepsis. NLRs are the second intracellular PRR family and play a major role in inflammasome activation. The inflammasome is a multiprotein complex that leads to production of inflammatory cytokines, such as IL-1ß, IL-18, and IL-33. The NOD receptors 1 and 2 (NOD1 and NOD2), are members of the NLR family and recognize the muramyl peptide moieties of the peptidoglycans of Gram-negative and Gram-positive bacteria [8].

Interactions between the different PRRs pathways are essential for optimal anti-pathogen responses. Synergy between the TLRs and NOD2, for example, is crucial for activation of defence system against mycobacteria and *Staphylococci*, while cross-talk between TLRs and CLRs is necessary for optimal antifungal responses [8].

Complement system

The complement system is a complex and diversified system composed of over 32 proteins. Complement is activated *via* three different pathways—classical, alternative, and lectin pathways—that activate C3 derived-components. C3 is the cornerstone of the complement system with activation leading to the release of C3a and C5a. These active forms have numerous functions, such as stimulating the inflammatory process, leucocyte chemotaxis, phagocytic cell degranulation, and an increase in vascular permeability. During complement activation, a membrane attack complex is formed allowing cell lysis. This system is tightly controlled and several inhibitors such as complement receptors 1 and 2 (CR1 and CR2), decay-accelerating factors (DAF) and membrane cofactor proteins (MCP) regulate this activation cascade. Factor H or factor I also inhibit complement system activation by shortening the half-life of the C3 and C5 convertases.

The absolute importance of the complement system in innate immunity is illustrated by recurrent and severe infectious events in patients carrying genetic deficiencies of some components of this system. Hence, recurrent meningococcal disease is frequently reported in patients with various complement deficiencies [9]. For example, factor H inhibits alternative pathway spontaneous activation and its deficiency leads to decreased C3 concentrations and an increased susceptibility to *Neisseria meningitidis* infections [10]. Host genetic variations of factor H, factor H receptor, and factor H-related protein-3 have been also reported in GWA studies (GWAS) performed on cohorts of patients with meningococcal infections, confirming the predominant role of these regulators in the pathogenesis of invasive meningococcal disease. Similar findings have been recently described for factor H in *Streptococcus pyogenes* infection [11].

Inflammatory host response after MAMPs recognition

Numerous factors mediate the inflammatory response after initial contact between the host and pathogen.

In viral infections, type 1 interferons are key cytokines inducing an antiviral response. Viral activation of TLRs and RLRs induce production of type 1 interferons and IL-12 to trigger specific antiviral actions.

Interaction between the host and bacteria leads to release of numerous pro-inflammatory cytokines (e.g. tumour necrosis factor-α (TNF-α), IL-1, IL-6, IL-17) but also neutrophil proteases, lactoferrin, myeloperoxidase, and specific antimicrobial peptides. The primordial role of these antimicrobial peptides has been seen in knock-out mice which are more susceptible to bacterial infections than their wild-type counterparts. TNF-α is a central pro-inflammatory cytokine involved in most of the antimicrobial defence processes. Patients carrying the TNF2 allele (a common G→A single nucleotide polymorphism (SNP) located at -308 from the transcription initiation site) have an increased risk of developing severe cerebral malaria and purpura fulminans [12]. TNF2 has also been associated with susceptibility of septic shock and is an independent risk factor for death due to septic shock [13].

Another part of the primary response to a host–pathogen interaction is the production of numerous chemokines that induce chemotaxis in target cells that express appropriate chemokine receptors. Apart from immune cell homing and maintaining inflammation, chemokines also have important antibacterial activity.

Influence of pathogen variability on infectious diseases presentation

Apart from host genetic variability, pathogen diversity also influences the phenotypic features of various infectious diseases. To illustrate this important aspect of the host-pathogen relationship, the pathogen diversity of *Pneumococcus, Meningococcus*, and *Plasmodium* will be briefly highlighted.

Genomic diversity of *Streptococcus pneumoniae*

Streptococcus pneumoniae may cause invasive lethal infectious diseases (bacteraemic pneumonia, septicaemia, and meningitis) or uncomplicated pneumonia, sinusitis, and acute otitis media. To partially explain this large diversity of invasiveness, immunochemical differences of the polysaccharide capsule have been performed, revealing approximately 90 different serotypes. Many of these strains are rarely recovered from serious diseases, and only 15 serotypes are implicated in the vast majority of invasive infections. Sandgren et al. evidenced 34 different serotypes out of 273 invasive isolates and 246 colonizing isolates—one group of serotypes was predominantly found in invasive isolates (type 1, 3, 4, 7F, and 9V serotypes), while another group was associated with both invasive pneumococcal disease, as well as carriage (type 6A, 6B, 14 and 19F isolates) [14]. More recently, multilocus sequence typing studies have revealed that one serotype does not really correspond to only one bacterium. In reality, it may contain bacteria from diverse ancestries, each having different consequences on the clinical phenotype. Interestingly, highly invasive isolates are less diversified than those isolated from carriage [15]. This diversity of pneumococcal invasiveness also includes varying susceptibility to antibiotics. In Sandgren's study, a decreased susceptibility to penicillin was most frequently observed in carriage-related compared to highly invasive isolates [14].

Hyperinvasive genotypes of *Neisseria meningitidis*

Neisseria meningitides is a frequent commensal bacterium of the human nasopharynx. It can be involved in severe, and sometimes fatal, disseminated disease. As with *Streptococcus pneumoniae*, the capsule is an important virulence factor in meningococci. To date, few genotypes of *Neisseria meningitidis* are known to be prominent in invasive infections. A strong association between invasive meningococcal disease and expression of serogroup C has been shown, with an odds ratio of 27.4. In the same study, ST-11, ST-41/44 and ST-269 clone complexes were strongly associated with invasive disease [16]. These findings have been confirmed in some subsequent reports. The ST-11 clonal complex has been specially reported to correlate with fatal outcome, higher virulence, more damage to human epithelial cells, and induction of apoptosis in epithelial cells.

Plasmodium diversity and severe malaria

As severe *Plasmodium falciparum* malaria is observed in only a small percentage of the infected population, this has led to a search for particular genotypes of the parasite. In parasite polymorphisms in Dakar (Senegal) a higher rate of *Pfdhfr* mutation was reported in severe compared with moderate malaria. An association was also noted between the presence of the msp-1 locus and malaria severity. Although the role of this gene product in malaria pathogenesis remains unclear, msp-1 is associated with greater plasma levels of TNF-α, which is central to the inflammatory response [17]. Similarly, increased expression of the *var-D* gene, involved in the primordial phase of parasite cyto-adherence, was also associated with malaria severity. On the other hand, some protective polymorphisms have been described. Some mutations in the control region of nitric oxide synthase-2 have been reported as protective and associated with less severe *P. falciparum* malaria.

Therapeutic applications and future challenges

In addition to improving our understanding of host-pathogen interactions, genomic analysis may assist in the development of targeted therapies or new therapeutic strategies based on the patient's genotype.

In HIV patients, a conformational change of the CC chemokine receptor CCR5 (CCR5Δ32) led to an inability for the receptor to be expressed on the cell surface, thus preventing virus entry into lymphocytes. Genetic studies revealed that patients who are homozygous for this genetic variant were resistant to HIV entrance, maintained a normal lymphocyte count for a long time after infection, and were long-term survivors even in the absence of treatment. This enabled the development of new drug specifically targeting the CCR5 co-receptor. Another example of genomic analysis application in clinical practice is the use of abacavir in HIV patients. Abacavir is a reverse transcriptase inhibitor used to treat HIV-1 infection and is responsible for severe adverse hypersensitivity reactions that are clearly linked with the *HLAB5701* allele [18], leading to screen this allele before prescription in order to reduce the risk of hypersensitivity reactions

Genomic knowledge may also increase the development of prophylactic strategies for infectious diseases. Indeed, several studies have shown that HLA subgroups may influence the response to immunization. This is most clearly illustrated by the responses to hepatitis B and measles immunization. A significant association was seen between HLA II (in particular HLA DRB1) and the response to primary hepatitis B vaccination, with HLADRB1*07 being strongly associated with a non-response to a full-dose immunization [19]. Likewise, some familial clusters of measles vaccination failures suggest that some HLA polymorphisms lead to different responses to immunization [20]. Identification of groups of patients with similar genotype risk may also improve outcomes through the use of specific targeted therapies such as anti-TNF-α for high TNF secretor patients.

Genomic medicine will play an increasingly larger role in clinical practice in the years ahead. In addition to becoming familiar with genetic analysis techniques, physicians should also look to adopt these new tools to improve patient outcomes.

References

1. Von Bernuth H, Picard C, Jin Z, et al. (2008). Pyogenic bacterial infections in humans with MyD88 deficiency. *Science*, **321**, 691–6.
2. Picard C, Puel A, Bonnet M, et al. (2003). Pyogenic bacterial infections in humans with IRAK-4 deficiency. *Science*, **299**, 2076–9.
3. Zhang S-Y, Jouanguy E, Ugolini S, et al. (2007). TLR3 deficiency in patients with herpes simplex encephalitis. *Science*, **317**, 1522–7.

4. Casrouge A, Zhang S-Y, Eidenschenk C, et al. (2006). Herpes simplex virus encephalitis in human UNC-93B deficiency. *Science*, **314**, 308–12.
5. Drummond RA and Brown GD. (2011). The role of dectin-1 in the host defence against fungal infections. *Current Opinion in Microbiology*, **14**, 392–9.
6. Taylor PR, Tsoni SV, Willment JA, et al. (2007). Dectin-1 is required for beta-glucan recognition and control of fungal infection. *Nature: Immunology*, **8**, 31–8.
7. Plantinga TS, van der Velden WJFM, Ferwerda B, et al. (2009). Early stop polymorphism in human DECTIN-1 is associated with increased *Candida* colonization in hematopoietic stem cell transplant recipients. *Clinical Infectious Diseases*, **49**, 724–32.
8. Netea MG and van der Meer JWM. (2011). Immunodeficiency and genetic defects of pattern-recognition receptors. *New England Journal of Medicine*, **364**, 60–70.
9. Fijen CA, Kuijper EJ, te Bulte MT, Daha MR, and Dankert J. (1999). Assessment of complement deficiency in patients with meningococcal disease in the Netherlands. *Clinical Infectious Diseases*, **28**, 98–105.
10. Schneider MC, Exley RM, Chan H, et al. (2006). Functional significance of factor H binding to *Neisseria meningitidis. Journal of Immunology*, **176**, 7566–75.
11. Haapasalo K, Vuopio J, Syrjänen J, et al. (2012). Acquisition of complement factor H is important for pathogenesis of *Streptococcus pyogenes* infections: evidence from bacterial in vitro survival and human genetic association. *Journal of Immunology*, **188**, 426–35.
12. Nadel S, Newport MJ, Booy R, and Levin M. (1996). Variation in the tumor necrosis factor-alpha gene promoter region may be associated with death from meningococcal disease. *Journal of Infectious Diseases*, **174**, 878–80.
13. Mira JP, Cariou A, Grall F, et al. (1999). Association of TNF2, a TNF-alpha promoter polymorphism, with septic shock susceptibility and mortality: a multicenter study. *Journal of the American Medical Association*, **282**, 561–8.
14. Sandgren A, Sjostrom K, Olsson-Liljequist B, et al. (2004). Effect of clonal and serotype-specific properties on the invasive capacity of *Streptococcus pneumoniae. Journal of Infectious Diseases*, **189**, 785–96.
15. Brueggemann AB, Griffiths DT, Meats E, Peto T, Crook DW, and Spratt BG. (2003). Clonal relationships between invasive and carriage Streptococcus pneumoniae and serotype- and clone-specific differences in invasive disease potential. *Journal of Infectious Diseases*, **187**, 1424–32.
16. Yazdankhah SP, Kriz P, Tzanakaki G, et al. (2004). Distribution of serogroups and genotypes among disease-associated and carried isolates of *Neisseria meningitidis* from the Czech Republic, Greece, and Norway. *Journal of Clinical Microbiology*, **42**, 5146–53.
17. Robert F, Ntoumi F, Angel G, et al. (1996). Extensive genetic diversity of Plasmodium falciparum isolates collected from patients with severe malaria in Dakar, Senegal. *Transactions of the Royal Society for Tropical Medicine & Hygiene*, **90**, 704–11.
18. Mallal S, Nolan D, Witt C, et al. (2002). Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*, **359**, 727–32.
19. Wang C, Tang J, Song W, Lobashevsky E, Wilson CM, and Kaslow RA. (2004). HLA and cytokine gene polymorphisms are independently associated with responses to hepatitis B vaccination. *Hepatology*, **39**, 978–88.
20. Ovsyannikova IG, Pankratz VS, Vierkant RA, Jacobson RM, and Poland GA. (2006). Human leukocyte antigen haplotypes in the genetic control of immune response to measles-mumps-rubella vaccine. *Journal of Infectious Diseases*, **193**, 655–63.

CHAPTER 307

Coagulation and the endothelium in acute injury in the critically ill

Marcel Levi and Tom van der Poll

Key points

- Endothelial cells have a central role in the bidirectional relationship between inflammation and coagulation.
- Expression of tissue factor is the pivotal initiating event in the coagulation response occurring with systemic inflammation.
- Regulation of coagulation activation through physiological anticoagulant mechanisms occurs in large part at the endothelial cell surface.
- Activated coagulation proteases may bind and activate protease-activated receptors expressed by endothelial cells, and may elicit a pro-inflammatory effect.
- The endothelial cell-related glycocalyx is an important interface in modulation of the activation of coagulation and systemic inflammation.

Introduction

Acute inflammation, as a response to severe infection or trauma, results in systemic activation of the coagulation system [1].The principal initiator of inflammation-induced thrombin generation is tissue factor (TF). Since TF is expressed on cytokine-activated mononuclear cells, which play a pivotal role in the host response to infection, it was hypothesized that micro-organism-induced activation of mononuclear cells resulted in TF-mediated activation of coagulation. Cytokines mediate many of the responses triggered by severe inflammation, thereby placing cells other than circulating mononuclear cells in the spotlight. More complex mechanisms could thus be involved in the relationship between inflammation and activation of coagulation [2]. This relationship is not uni-directional; activation of coagulation will also affect inflammatory activity. In particular, vascular endothelial cells play a pivotal mediatory role in the procoagulant response to systemic inflammation and the cross-talk between coagulation and inflammation [3]. Endothelial cells respond to cytokines expressed and released by activated leukocytes, but can also release cytokines themselves. Furthermore, endothelial cells can express adhesion molecules and growth factors that may not only promote the inflammatory response further, but also amplify the coagulation response.

In addition to these mostly indirect effects of the endothelium, endothelial cells can also interfere directly with initiation and regulation of fibrin formation and removal during severe infection. In fact, endothelial cells play a prominent role in all three major pathogenetic pathways associated with coagulopathy in sepsis: TF-mediated thrombin generation, dysfunctional anticoagulant pathways, and blocked fibrinolysis.

Role of endothelial cells in the initiation of coagulation

TF plays a central role in the initiation of inflammation-induced coagulation. Blocking TF activity completely inhibits inflammation-induced thrombin generation in models of experimental endotoxaemia or bacteraemia [4]. The vast majority of cells constitutively expressing tissue factor are found in tissues not in direct contact with blood, such as the adventitial layer of larger blood vessels. However, TF comes into contact with blood when the integrity of the vessel wall is disrupted, or when endothelial cells and/or circulating blood cells start expressing tissue factor. The in vivo expression of TF is mostly dependent on IL-6, as studies show that inhibition of IL-6 completely abrogates TF-dependent thrombin generation in experimental endotoxaemia, whereas specific inhibition of other pro-inflammatory cytokines had less or no effect. Inflammatory cells in atherosclerotic plaques produce abundant TF; upon plaque rupture there is extensive TF exposure to blood [5].

In severe sepsis, mononuclear cells, stimulated by pro-inflammatory cytokines, express TF, thus leading to systemic activation of coagulation [6]. However, endothelial cells also play an important role in TF generation during severe infection. Under *in vitro* conditions, various cytokines (e.g. TNF-α and IL-1) induce TF expression in vascular endothelial cells. Ex vivo observations also support the notion of endothelial cell involvement in TF-mediated activation of coagulation during severe infection. The demonstration of circulating endothelial cells expressing TF in patients with sickle cell disease also suggests endothelial involvement in TF production.

Expression of TF by endothelial cells appears confined to certain organs and vascular beds [3]. It remains uncertain whether this

is genetically controlled in an organ-specific manner. Differential activation of endothelial cell TF expression may occur, in particular, during severe infection. Although not yet directly demonstrated, it is likely that in situations of tissue trauma (such as extensive surgery, brain trauma or burns) TF expressed constitutively at the site of injury (such as in subcutaneous tissue) contributes to, or is the primary source of, the procoagulant stimulation underlying disseminated intravascular coagulation (DIC).

Direct interaction between micro-organisms and endothelial cells can also occur, especially in the case of viral infections. Endothelial cell perturbation is a common feature of viral infection and can alter haemostasis both directly and indirectly. Endothelial cells can be directly infected by various viruses, e.g. Herpes simplex virus, adenovirus, parainfluenza, polio, echo, measles, mumps, cytomegalovirus, HTLV-1, human immunodeficiency virus, and in particular, by viruses causing haemorrhagic fevers, e.g. dengue, Marburg, ebola, Hanta, lassa.

Role of endothelial cells in the regulation of coagulation

Thrombin generation is limited by antithrombin (AT), the protein C system, and tissue factor pathway inhibitor (TFPI). During injury and inflammation, all three regulatory systems are defective, primarily as a result of endothelial dysfunction.

Antithrombin system

AT is the main inhibitor of thrombin and factor Xa. Endogenous glycosaminoglycans on the vessel wall, such as heparin sulphates, promote AT-mediated inhibition of thrombin and other coagulation enzymes. During severe inflammatory responses, AT levels are markedly decreased due to impaired synthesis (negative acute phase response), degradation by elastase from activated neutrophils, and—quantitatively the most important—consumption as a consequence of ongoing thrombin generation [2]. Pro-inflammatory cytokines can also cause reduced synthesis of glycosaminoglycans on the endothelial surface. This contributes to reduced AT function since these glycosaminoglycans can act as physiological heparin-like cofactors of AT.

Protein C system

Activated protein C (AcPC) plays a central role in the pathogenesis of sepsis and associated organ dysfunction [7]. Insufficient functioning of the protein C pathway contributes to coagulation derangement in sepsis [8]. The circulating zymogen, protein C is activated by endothelial cell-bound thrombomodulin once this itself is activated by thrombin. AcPC acts in concert with its co-factor, protein S, to proteolytically degrade the essential coagulation cofactors Va and VIIIa; in this manner, it functions as an effective anticoagulant. The endothelial protein C receptor (EPCR) not only accelerates activation of protein C several-fold, but also serves as a receptor for AcPC; binding of AcPC to this receptor may amplify its anticoagulant and anti-inflammatory effects. In patients with severe inflammation, the protein C system malfunctions at virtually all levels. First, plasma levels of protein C are (very) low due to impaired synthesis, increased consumption, and degradation by proteolytic enzymes, such as neutrophil elastase. Secondly, a significant downregulation of thrombomodulin, caused by pro-inflammatory cytokines, such as TNF-α and IL-1, has also been demonstrated, resulting in diminished protein C activation [9]. Low levels of free protein S may further compromise adequate functioning of the protein C system. Finally, but importantly, the EPCR is downregulated in sepsis, and this may further negatively affect functioning of the protein C system. Apart from these effects, sepsis may also cause resistance towards AcPC by other mechanisms that are dependent in part on a sharp increase in factor VIII levels (released from endothelial cells), but also through as yet unidentified mechanisms.

Tissue factor pathway inhibitor (TFPI)

A third inhibitory mechanism of thrombin generation involves TFPI, the main inhibitor of the tissue factor-factor VIIa complex. The role of TFPI in the regulation of inflammation-induced coagulation activation is not completely clear. Administration of recombinant TFPI (thereby achieving supra-physiological plasma concentrations of TFPI) blocked inflammation-induced thrombin generation in humans. Furthermore, the observation that pharmacological doses of TFPI can prevent mortality during systemic infection and inflammation suggests that high TFPI concentrations are capable of modulating TF-mediated coagulation [10].

Role of endothelial cells in fibrinolytic activity

Central regulators of plasminogen activators and inhibitors during inflammation are TNF-α and IL-1β. The presence of these cytokines in the circulation leads to release of plasminogen activators, in particular tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA), from storage sites in vascular endothelial cells. However, this increase in plasminogen activation, and subsequent plasmin generation, is counteracted by a delayed but sustained increase in plasminogen activator inhibitor type 1 (PAI-1). The resulting effect on fibrinolysis is a complete inhibition and, as a consequence, inadequate fibrin removal that contributes to microvascular thrombosis. Experiments in mice with targeted disruptions of genes encoding components of the plasminogen-plasmin system confirm that fibrinolysis plays a major role in inflammation. Mice deficient in plasminogen activators have more extensive organ fibrin deposition when challenged with endotoxin; on the other hand, PAI-1 knockout mice, in contrast to wild-type controls, exhibit no microvascular thrombosis upon endotoxin administration [11].

Cross-talk between coagulation and inflammation at the endothelial interface

Communication between inflammation and coagulation is bidirectional such that coagulation can also modulate inflammatory activity. Coagulation proteases and protease inhibitors not only interact with coagulation protein zymogens, but also with specific cell receptors to induce signalling pathways (Fig. 307.1). In particular, protease interactions that affect inflammatory processes may be important in the critically ill.

The pivotal mechanism by which coagulation proteases modulate inflammation is via binding to protease-activated receptors (PARs). Four types (PAR 1–4) have been identified, all belonging

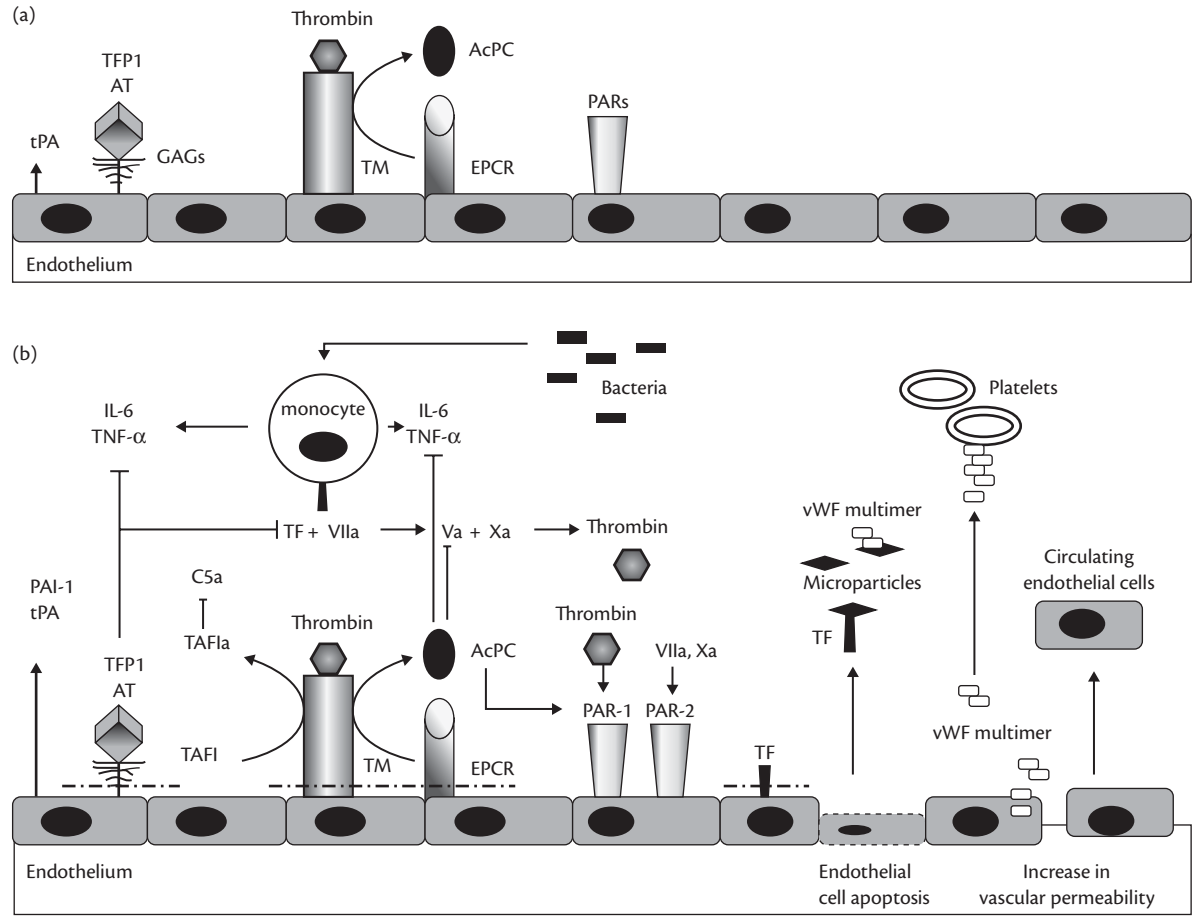


Fig. 307.1 Endothelium-associated mediators of coagulation and inflammation. (a) The normal situation by which the endothelium expresses thrombomodulin (TM) (activated by thrombin) and the endothelial PC receptor (EPCR), which then generate activated PC (AcPC). Other anticoagulant factors include tissue factor pathway inhibitor (TFPI) and antithrombin (AT), which attach to the endothelial surface, and endothelium-released tissue-type plasminogen activator (tPA), which promotes fibrinolysis. (b) Systemic activation of inflammation leads to cytokine release and endothelial perturbation, resulting in release of microparticles (MPs), apoptosis, detachment of endothelial cells, and loss of barrier function. Coagulation is activated by induction of tissue factor (TF) on monocytes, MPs, and endothelium, and by release of von Willebrand factor (vWF), which increases platelet adhesion to the subendothelial surface. Production of glycosaminoglycans (GAGs) is downregulated, and the anticoagulant proteins TFPI, AT, EPCR, and TM are cleaved from the endothelial surface, thus impairing their action. Fibrinolysis is impaired as a result of a rise in the main inhibitor of PA (PAI-1), which outweighs the rise in tPA. Complement activation is enhanced by loss of activation of thrombin-activatable fibrinolysis inhibitor (TAFI), which normally inhibits the complement factors C3a and C5a, and by increased bradykinin activity. In turn, anticoagulant proteins modulate cytokine release: tissue factor-factor VIIa (TF-FVIIa), factor (F) Xa, and thrombin exert pro-inflammatory activity by cleaving mainly protease-activated receptor (PAR)-1 and PAR-2. AcPC cleaves PAR-1 in an EPCR-dependent manner, thereby modulating inflammation and apoptosis.

to the family of transmembrane domain, G-protein-coupled receptors [12]. A typical feature of the PARs is that they serve as their own ligand. Proteolytic cleavage by an activated coagulation factor leads to exposure of a neo-amino terminus which activates the same receptor and, possibly, adjacent receptors, initiating transmembrane signalling. PARs are localized in the vasculature on endothelial cells, mononuclear cells, platelets, fibroblasts, and smooth muscle cells [12]. PARs 1, 3, and 4 are thrombin receptors, while PAR-1 can also serve as a receptor for the tissue factor-factor VIIa complex and factor Xa. PAR-2 cannot bind thrombin, but can be activated by the tissue factor-factor VIIa complex or factor Xa. Binding of thrombin to its cellular receptor may induce production of several cytokines and growth factors. Binding of tissue factor-factor VIIa to PAR-2 also results in upregulation of inflammatory responses (production of reactive oxygen species and expression of MHC class II and cell adhesion molecules) in macrophages, as well as modulating neutrophil infiltration and pro-inflammatory cytokine (TNF-α, IL-1β) expression. The *in vivo* relevance of the PARs has been confirmed in studies using PAR inhibitors or PAR-deficient mice [13].

Coagulation inhibitors regulate inflammation at the endothelial surface

Physiological coagulation inhibitors can also modulate inflammation. Antithrombin possesses anti-inflammatory properties, many of which are mediated by its actions in the coagulation cascade. Most importantly, thrombin inhibition by AT blunts activation of

many inflammatory mediators. For example, thrombin activates platelets and endothelial cells that, in turn, contribute to local inflammation. Activated platelets secrete inflammatory mediators such as IL-1, which stimulate leukocyte activity. In particular, recruitment and adhesion of neutrophils and monocytes to blood vessels within the microcirculation promote inflammation. Perhaps most importantly, AT induces prostacyclin release from endothelial cells. Prostacyclin inhibits platelet activation and aggregation, blocks neutrophil tethering to blood vessels, and decreases endothelial cell production of various cytokines and chemokines. Thus, AT directly hinders leukocyte migration and adhesion to endothelial cells and this, in turn, impacts upon the severity of capillary leakage and subsequent organ damage.

Components of the protein C system are also important modulators of inflammation [14,15]. AcPC plays an important role in attenuating the systemic inflammatory response in sepsis; indeed, blocking the protein C pathway exacerbated the inflammatory response in septic baboons. In contrast, AcPC administration ameliorated the inflammatory activation following intravenous infusion of *E. coli* [16]. Support for the notion that AcPC has anti-inflammatory properties comes from in vitro observations demonstrating an AcPC binding site on monocytes that may mediate downstream inflammatory processes, and from experiments showing that AcPC can block NF-kB nuclear translocation, a prerequisite for increases in pro-inflammatory cytokines and adhesion molecules. These in vitro findings are supported by in vivo studies in mice with targeted disruption of the protein C gene in whom endotoxaemia produced a greater increase in pro-inflammatory cytokines and other inflammatory responses, as compared with wild-type controls [17]. The effects of AcPC on inflammation are likely mediated by the EPCR [14]. Binding of AcPC to the EPCR influences gene expression profiles of cells by inhibiting endotoxin-induced calcium fluxes in the cell and by blocking NF-κB nuclear translocation. EPCR binding of AcPC may result in PAR-1 activation, and thereby affect cytokine responses [18]. In contrast, other experiments suggested a significant physiological role for PAR-1 activation by AcPC was less likely. Like AcPC, the EPCR itself may have anti-inflammatory properties. Soluble EPCR, the extracellular domain of the cell-associated EPCR shed from the cell surface by the action of an inducible metalloproteinase can bind to proteinase 3, an elastase-like enzyme. The resulting complex binds to the adhesion integrin macrophage 1 antigen (Mac-1). AcPC may protect against disruption of the endothelial cell barrier in sepsis, probably by interfering with the EPCR and PAR-1 on endothelial cells. Finally, AcPC can inhibit endothelial cell apoptosis, which also appears to be mediated by an EPCR-PAR-1-dependent mechanism [19].

The glycocalyx mediates coagulation in endothelial injury

Recent research points to an important role of the inner (luminal) layer of the endothelium, i.e. the glycocalyx, in the interaction between inflammation and coagulation. In sepsis, glycosaminoglycans are downregulated as a result of pro-inflammatory cytokines. This can impact on the function of antithrombin and TFPI, and on leukocyte adhesion and transmigration. Besides glycosaminoglycans and highly sulphated polysaccharides, the glycocalyx consists of glycoproteins, hyaluronic acid, and membrane-associated proteins. The glycocalyx may also play a role in other endothelial functions including maintenance of vascular barrier function, nitric oxide-mediated vasodilation and antioxidant activity, all processes known to be involved in sepsis. Specific disruption of the glycocalyx results in thrombin generation and platelet adhesion within a few minutes [20]. Moreover, loss of glycocalyx in vivo has been associated with subendothelial oedema formation. The role of the glycocalyx in modulating endothelial function, including anticoagulation, and the role of the endothelium in modulating the glycocalyx in situations of vascular injury and systemic inflammation suggest this may be an interesting point of impact for future therapy.

References

1. Levi M and van der Poll T. (2010). Inflammation and coagulation. *Critical Care Medicine*, **38**, S26–34.
2. Levi M, van der Poll T, and Buller HR, (2004). Bidirectional relation between inflammation and coagulation. *Circulation*, **109**, 2698–704.
3. Aird WC. (2001). Vascular bed-specific hemostasis: role of endothelium in sepsis pathogenesis. *Critical Care Medicine*, **29**, S28–34.
4. Levi M, ten Cate H, Bauer KA, et al. (1994). Inhibition of endotoxin-induced activation of coagulation and fibrinolysis by pentoxifylline or by a monoclonal anti-tissue factor antibody in chimpanzees. *Journal of Clinical Investigations*, **93**, 114–20.
5. Libby P and Aikawa M. (2002). Stabilization of atherosclerotic plaques: new mechanisms and clinical targets. *Nature: Medicine*, **8**, 1257–62.
6. Osterud B, Rao LV, and Olsen JO. (2000). Induction of tissue factor expression in whole blood—lack of evidence for the presence of tissue factor expression on granulocytes. *Thrombosis and Haemostasis*, **83**, 861–7.
7. Levi M and van der Poll T. (2007). Recombinant human activated protein C: current insights into its mechanism of action. *Critical Care*, **11**(Suppl. 5), S3.
8. Esmon CT (2001). Role of coagulation inhibitors in inflammation. *Thrombosis and Haemostasis*, **86**(1), 51–6.
9. Faust SN, Levin M, Harrison OB, et al. (2001). Dysfunction of endothelial protein C activation in severe meningococcal sepsis. *New England Journal of Medicine*, **345**, 408–16.
10. de Jonge E, Dekkers PE, Creasey AA, et al. (2000). Tissue factor pathway inhibitor (TFPI) dose-dependently inhibits coagulation activation without influencing the fibrinolytic and cytokine response during human endotoxemia. *Blood*, **95**, 1124–9.
11. Yamamoto K and Loskutoff DJ. (1996). Fibrin deposition in tissues from endotoxin-treated mice correlates with decreases in the expression of urokinase-type but not tissue-type plasminogen activator. *Journal of Clinical Investigations*, **97**, 2440–51.
12. Coughlin SR. (2000). Thrombin signalling and protease-activated receptors. *Nature*, **407**, 258–64.
13. Camerer E, Cornelissen I, Kataoka H, Duong DN, Zheng YW, and Coughlin SR. (2006). Roles of protease-activated receptors in a mouse model of endotoxemia. *Blood*, **107**, 3912–21.
14. Esmon CT. (2002). New mechanisms for vascular control of inflammation mediated by natural anticoagulant proteins. *Journal of Experimental Medicine*, **196**, 561–4.
15. Okajima K. (2001). Regulation of inflammatory responses by natural anticoagulants. *Immunological Review*, **184**, 258–74.
16. Taylor FBJ, Chang A, Esmon CT, D'Angelo A, Vigano-D'Angelo S, and Blick KE. (1987). Protein C prevents the coagulopathic and lethal effects of Escherichia coli infusion in the baboon. *Journal of Clinical Investigations*, **79**, 918–25.

17. Levi M, Dorffler-Melly J, Reitsma PH, et al. (2003). Aggravation of endotoxin-induced disseminated intravascular coagulation and cytokine activation in heterozygous protein C deficient mice. *Blood*, **101**, 4823–7.
18. Riewald M, Petrovan RJ, Donner A, Mueller BM, and Ruf W. (2002). Activation of endothelial cell protease activated receptor 1 by the protein C pathway. *Science*, **296**, 1880–2.
19. Cheng T, Liu D, Griffin JH, et al. (2003). Activated protein C blocks p53-mediated apoptosis in ischemic human brain endothelium and is neuroprotective. *Nature: Medicine*, **9**, 338–42.
20. Nieuwdorp M, van Haeften TW, Gouverneur MC, et al. (2006). Loss of endothelial glycocalyx during acute hyperglycemia coincides with endothelial dysfunction and coagulation activation in vivo. *Diabetes*, **55**, 480–6.

CHAPTER 308

Ischaemia-reperfusion injury in the critically ill

Mitchell P. Fink

Key points

- Although ischaemia is intrinsically deleterious, restoration of adequate blood flow, i.e. reperfusion can, paradoxically, make matters worse.
- ROS are capable of covalently modifying and damaging nearly all cellular constituents, including nucleic acids, proteins, and lipids.
- The electron transport chain in mitochondria is the principal source of ROS production, although cytosolic reactions catalysed by enzymes, such as xanthine oxidase, are probably also important under some conditions.
- Conflicting, but generally disappointing, results have been obtained in clinical trials of various ROS scavengers, such as tirilizad and edavarone, for the treatment of stroke.
- A small clinical trial of cyclosporin for acute myocardial infarction yielded encouraging results.

Introduction

Ischaemia describes a reduction in blood flow to a tissue or organ, leading to an inadequate supply of oxygen and glucose to support normal metabolism. If inadequate perfusion persists, then ischaemia can lead to cell death. This process occurs in commonly encountered conditions, such as myocardial infarction (MI) or stroke. Although ischaemia per se is intrinsically deleterious, restoration of adequate blood flow, i.e. reperfusion can, paradoxically, make matters even worse. Ischaemia/reperfusion (I/R) injury is an important pathophysiological process implicated in early and late graft dysfunction after solid organ transplantation. I/R injury is also an important cause of organ dysfunction after therapeutic interventions for stroke or MI, such as thrombolysis or coronary angioplasty. I/R injury involving multiple organs may play a role in the pathogenesis of critical illness after resuscitation from haemorrhagic shock.

Redox stress

The pathophysiology of I/R injury is complex and remains incompletely understood. However, redox-mediated events play a crucial role in the pathogenesis of cellular death or dysfunction related to I/R injury.

The term **redox** is a contraction of **reduction** and **oxidation**. A redox reaction involves transfer of electrons from a reducing agent to an oxidizing agent. Good reducing agents are elements or compounds that have a strong propensity to donate electrons. Conversely, good oxidizing agents avidly accept electrons. Molecular oxygen (O_2) is a very potent oxidizing agent. Two strong reducing agents, namely the reduced forms of nicotine adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$), are produced during glycolysis and the citric acid cycle. In mitochondria, these two reducing agents are oxidized by O_2, and the energy released is used to drive formation of adenosine triphosphate (ATP), the primary 'energy currency' of all cells. Substrate level phosphorylation of adenosine diphosphate (ADP) to form ATP during glycolysis also depends upon NADH oxidation. Thus, redox reactions are responsible for the generation of energy that drives all cellular processes. Redox reactions also play a key role in activation and modulation of key intracellular signalling pathways. While life is crucially dependent on various biochemical redox reactions, these are also capable of damaging cellular constituents or activating various maladaptive physiological responses, and thus can play an important role in disease pathogenesis.

Reactive oxygen and nitrogen species (NOS)

Reactive oxygen species (ROS) are reactive, partially reduced derivatives of O_2. Examples include superoxide anion radical ($O_2^{-}\cdot$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH\cdot$). Closely related are various RNS, exemplified by the weak acid, peroxynitrous acid (ONOOH), and its anion, peroxynitrite ($ONOO^-$). Free radicals are atoms or molecules that contain an unpaired electron in an outer (bonding) atomic or molecular orbital. This usually renders such species extremely reactive. While many free radicals are ROS (e.g. $O_2^{-}\cdot$), not all ROS or reactive nitrogen species (RNS) are free radicals, e.g. H_2O_2 and $ONOO^-$.

Although many enzymatic processes can lead to ROS formation, the mitochondrial electron transport chain is considered the principal source of partially reduced forms of oxygen, at least in cell types richly endowed with these organelles, such as neurons, cardiomyocytes, and hepatocytes. Approximately 0.2% of cellular O_2 consumption is converted into ROS, and 90% of ROS generated are derived from mitochondria [1].

In addition to intramitochondrial reactions, various other enzymatic processes can generate ROS, including reactions catalysed by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase

and xanthine oxidase. NADPH oxidase catalyses the one-electron reduction of O_2 to form $O_2^{-}\cdot$, using NADPH as the electron donor. NADPH oxidase is an enzyme complex that is assembled after activation of phagocytes by microbes or microbial products, such as lipopolysaccharide (LPS), pro-inflammatory mediators, such as tumour necrosis factor (TNF), or exposure to ROS. The reaction catalysed by NADPH oxidase is critical for the formation of ROS in macrophages and polymorphonuclear neutrophils (PMNs). NADPH oxidase isoforms are also present in other cell types, including vascular smooth muscle cells, neurons, epithelial, and endothelial cells [2].

XO catalyses the oxidation of xanthine (or hypoxanthine) to form uric acid and $O_2^{-}\cdot$. XO is a post-translationally modified form of another closely-related enzyme, xanthine dehydrogenase (XD), which utilizes NAD^+ as a cofactor, and coverts xanthine (or hypoxanthine) to uric acid without forming ROS. Conditions associated with XD-to-XO conversion include cellular hypoxia and/or exposure to various pro-inflammatory mediators [3].

The enzyme, nitric oxide synthase (NOS), is crucial for formation of RNS. NOS catalyses the formation of L-citrulline and a gaseous free radical, nitric oxide (NO·) from L-arginine in a complex five-electron redox reaction that requires O_2 and several co-factors. If L-arginine availability is limiting, NOS can generate $O_2^{-}\cdot$ [4]. Three isoforms of NOS have been identified: NOS-1 (neuronal NOS or nNOS), NOS-3 (endothelial NOS or eNOS), and NOS-2 (inducible NOS or iNOS). Both nNOS and eNOS are constitutively expressed, and their production of NO· is tightly regulated by changes in intracellular Ca^{2+} concentration. In contrast, iNOS, is expressed only after induction by various cytokines or microbial products. A fourth isoform, mitochondrial NOS (mtNOS), has been postulated, but this entity is probably a cytoplasmic isoform (mostly probably nNOS), which has been transported into mitochondria. Increased iNOS expression occurs when murine macrophages or PMN are stimulated by LPS and/or pro-inflammatory cytokines, e.g. interferon-γ (IFN-γ). Appropriately stimulated human macrophages can also produce NO· via an iNOS-dependent mechanism, as can other human cell types, such as intestinal and alveolar epithelial cells.

Although not exceptionally reactive per se, $O_2^{-}\cdot$ occupies a central place in the biochemistry of redox stress. It participates in the Haber–Weiss reaction ($O_2^{-}\cdot + H_2O_2 \rightarrow O_2 + OH\cdot + OH^-$), which combines a Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\cdot + OH^-$) and reduction of ferric iron (Fe^{3+}) by $O_2^{-}\cdot$, yielding ferrous iron (Fe^{2+}) and oxygen ($Fe^{3+} + O_2^{-}\cdot \rightarrow Fe^{2+} + O_2$). The hydroxyl radical is extremely reactive, combining very rapidly (~10^{-9} sec) with other molecules physically colocated. Under conditions commonly associated with upregulated iNOS expression, cells can produce both NO· and $O_2^{-}\cdot$ that can react with each other to produce the potent oxidizing and nitrosating agent, $ONOO^-$.

Molecular targets for ROS and RNS

General processes whereby ROS cause pathological changes in cells and tissues are collectively referred to as oxidative (or oxidant or redox) stress. Since ROS are being produced continuously, oxidative stress occurs not as a result of ROS production per se, but rather when ROS biosynthesis exceeds the detoxifying capacity of various intrinsic anti-oxidant (and free radical scavenging) defence systems.

At high concentrations, ROS can covalently modify most cell structures, including nucleic acids, lipids and proteins [6]. The hydroxyl radical reacts with all components of the DNA molecule, damaging both purine and pyrimidine bases and the deoxyribose backbone [6].

ROS also attack carbon-carbon double bonds in the polyunsaturated fatty acid (PUFA) residues of phospholipids, leading to formation of peroxyl radicals (ROO·). These can attack other targets (e.g. other PUFA residues), propagating a chain reaction and widespread damage to cellular constituents. ROS also oxidize sulphydryl groups of cysteine residues within proteins, forming intramolecular disulphides or mixed disulphides with other –SH-containing small molecules, notably glutathione. RNS, such as $ONOO^-$ can S-nitrosylate cysteine residues, leading to loss of function of key proteins.

Intrinsic anti-oxidant defence mechanisms

In view of the myriad potential deleterious effects of ROS and RNS, it is not surprising that eukaryotic cells have evolved various mechanisms to detoxify these reactive species. A key defence against oxidant stress is glutathione (GSH). Its oxidized form is glutathione disulphide. GSH is the major soluble antioxidant in cytosol, nuclei and mitochondria, offering protection against redox stress by acting as a co-factor for several ROS detoxifying enzymes, e.g. glutathione peroxidase, directly scavenging certain highly reactive species (e.g. OH·), and participating in the regeneration of other key endogenous antioxidants, e.g. ascorbate, vitamin E.

Another key group of endogenous ROS scavengers are the isoforms of superoxide dismutatase (SOD). These enzymes dismutate $O_2^{-}\cdot$, into O_2 and H_2O_2 at rates faster than $O_2^{-}\cdot$ can react with other potential targets [7]. There are three known SOD isoforms: the manganese-containing enzyme, SOD2 (localized to mitochondria); the copper and zinc-containing enzyme, SOD1 (localized to cytosol); and SOD3, which is present in the extracellular milieu. Knocking out SOD2 is lethal in mice, emphasizing its critical importance [7].

In addition to GSH-dependent and SOD-dependent mechanisms, other important cellular buffers against redox stress include small molecules such as ascorbate, vitamin E, carotenoids, and lipoic acid. Catalase, which catalyses the conversion of H_2O_2 to water and O_2, is also important.

Pathophysiology of I/R injury

The concept was first advanced by Jennings et al. in 1960 using a canine model of coronary occlusion. They showed that a short period of ischaemia followed by a short period of reperfusion produced as much histological damage as a much more prolonged period of ischaemia without reperfusion. For many years, experts debated whether reperfusion is independently responsible for tissue injury or simply hastens the demise of cells otherwise destined for necrosis. During the early 1980s, landmark publications led to the recognition that tissue injury caused by 'ischaemia' was also dependent on ROS production, notably $O_2^{-}\cdot$.

The McCord hypothesis and the role of XO

McCord hypothesized a central role for XO. While ATP is degraded in steps to hypoxanthine during tissue ischaemia, XDH is converted to XO, setting the stage for a burst of ROS production. On reperfusion the supply of abundant O_2 leads to oxidation of the accumulated store of hypoxanthine leading to $O_2^{-}\cdot$ formation. This hypothesis was supported by various studies showing organ protection in I/R injury utilizing intravenous SOD, molybdenum-depleted, and/or tungsten-rich diets (leading to loss of XD and XO activity) or XO

inhibitors (e.g. allopurinol, oxypurinol). Repine's group reported that XO released into the circulation after reperfusion of a previously ischaemic organ, such as the intestine, could lead to distant organ injury, e.g. lung [8]. This could be ameliorated by pretreatment with an allopurinol- or tungsten-enriched diet.

The PARP hypothesis

Single-strand breaks in nuclear DNA can activate poly(ADP-ribose) polymerase-1 (PARP-1), catalysing cleavage of NAD^+ into nicotinamide and ADP-ribose, with polymerization into branching poly(ADP-ribose) homopolymers. Simultaneously, poly-ADP ribose is degraded by poly(ADP-ribose) glycohydrolase. The concurrent actions of PARP-1 and poly(ADP-ribose glycohydrolase) constitute the functional equivalent of an NADase, thus massive activation of PARP-1 can lead to marked intracellular NAD^+ depletion.

In states of acute inflammation or after I/R, ROS and RNS, including H_2O_2 and $ONOO^-$, can induce single strand breaks in nuclear DNA, thereby activating PARP-1 and depleting cellular NAD^+/NADH content. Since NADH is the main reducing equivalent that supports oxidative phosphorylation, PARP-1 activation can markedly impair the ability of cells to utilize O_2 to support ATP synthesis. The notion that redox stress can lead to PARP-1 activation and metabolic inhibition was first articulated by Schraufstatter et al. [9]. Szabó et al. subsequently showed that both endogenous and exogenous $ONOO^-$ activated PARP-1 resulting in impaired mitochondrial respiration [10]. Genetic or pharmacological means of decreasing or ablating PARP-1 activity protected organs in various I/R injury models [7].

Role of the mitochondrial permeability transition pore

Mitochondria play a crucial role in cell death pathways. One key mechanism is the 'intrinsic' apoptosis pathway, whereby toxic events, such as overwhelming redox stress, induce translocation and integration of prodeath members of the Bcl-2 family of proteins (e.g. Bax, Bak, Bid) into the outer mitochondrial membrane [11]. Membrane permeability is increased, permitting the leakage of several pro-apoptotic proteins, including cytochrome c, Smac/DIABLO, and htrA2/Omi, into the cytosol which, in turn, activates the proteolytic enzymes, caspase-9, -3, and -8.

Severe redox stress secondary to I/R injury (or other triggers) also promotes opening of a large, non-specific channel in the inner mitochondrial membrane, the mitochondrial permeability transition pore (MPTP). MPTP opening leads to dissipation of the electrochemical gradient ($\Delta\Psi m$), normally present across the inner mitochondrial membrane, thereby decreasing ATP synthesis, further increasing ROS production, and ultimately causing swelling and rupture of the organelle. Mitochondrial rupture can lead to release of pro-apoptotic proteins and activation of the intrinsic apoptosis cascade. As the apoptosis programme requires ATP, MPTP opening of the MPTP can (somewhat paradoxically) inhibit apoptosis and instead promote necrosis.

During ischaemia mitochondria are damaged by various mechanisms, including overloading of the matrix with Ca^{2+} ions. Mitochondria, can no longer efficiently transfer electrons so components of the mitochondrial electron transport chain, notably complexes I and III, 'leak' electrons and generate $O_2^{-}\cdot$, particularly during reperfusion when abundant O_2 is available [11]. Thus, reperfusion is associated with the production of a burst of mitochondria-derived ROS.

The structure of MPTP remains controversial. A voltage-dependent anion channel (VDAC) in the outer membrane, an adenine nucleotide translocase (ANT) in the inner membrane and a protein, cyclophilin-D (CypD), in the matrix have been described. Three isoforms of VDAC are known called VDAC1, VDAC2 and VDAC3. Inhibitors of ANT, such as bongkrekic acid, CypD, such as cyclosporin or VDAC inhibitors inhibit MPTP function and protect against I/R injury. VDAC inhibitors also have been shown to block opening of the MPTP. However, the importance of the VDAC and ANT components have recently been called into question.

Role of the innate immune response

Microbial components—the so-called pathogen-associated molecular patterns (PAMPs)—are recognized by cells of the innate and acquired immune system, primarily through interaction with Toll-like receptors (TLRs) and other receptors. The interaction of a PAMP, e.g. lipopolysaccharide, with a TLR (TLR4 in this example) leads to activation of numerous intracellular signalling pathways and key cells, including macrophages and PMNs, which are recruited to the site of infection to destroy the invading pathogen and/or pathogen-infected cells. Additionally, an adaptive immunological response is initiated to produce and select specific T cell receptors and antibodies for pathogen recognition on a future occasion.

The innate and adaptive immune systems can also be activated by I/R injury. Cell and/or tissue damage leads to release of endogenous molecules, called damage-associated molecular patterns (DAMPs) or alarmins, which can activate inflammatory or immune responses. Like PAMPs, many alarmins can also interact with TLRs.

High mobility group box (HMGB)1 is an important alarmin. HMGB1 is released by necrotic, but not apoptotic, cells, and by immunostimulated macrophages, endothelial and intestinal epithelial cells. HMGB1 is both a chemotactic factor and activating agent for leukocytes, and can mediate key events in sterile inflammation. Activation of the complement system, another component of the innate immune system, has also been implicated in the pathogenesis of I/R-induced injury to the heart, intestine, kidneys, brain, and lungs. Pharmacological approaches for inhibiting complement activity, such as treatment with recombinant soluble human complement receptor type 1, have been efficacious in preclinical models.

Results from key clinical trials of interventions to ameliorate I/R injury

Unfortunately, efforts to translate our improved understanding of the pathophysiological mechanisms underlying I/R injury into interventions that clearly benefit patients have been largely unsuccessful. A few notable exceptions exist and are highlighted in the following sections.

Allopurinol

Allopurinol, which inhibits XO activity, ameliorates I/R injury in myriad animal models (*vide infra*). Apart from studies of ex vivo organ preservation solutions (not discussed here), most randomized clinical trials (RCTs) have been relatively small, mostly single-centre, and have focused on patients undergoing

cardiopulmonary bypass surgery. Pre-treatment with allopurinol before bypass provided significant benefit, as evidenced by lower mortality rate [12], higher post-operative cardiac index and a reduced need for post-operative inotropic support. Other studies, however, have reported no benefit. A recent meta-analysis of three small RCTs in perinatal hypoxia found insufficient data to determine whether allopurinol was beneficial or not [13].

Free radical scavengers

Three chemically dissimilar, but uniformly potent, free radical scavengers have been studied extensively for the treatment of stroke (Fig. 308.1). Edavarone (MCI-186), a lipophilic substituted 3-pyrazalone compound, was approved by the Japanese Ministry of Health, Labor, and Welfare in 2001 for treating acute ischaemic stroke, and was recommended as therapy by the Japanese Guidelines for the Management of Stroke 2004. A meta-analysis of clinical trials of edaravone for stroke concluded that 'edaravone appeared to increase the proportion of participants with marked neurological improvement' [14]. Phenyl-t-butylnitrone (PBN), a so-called 'spin trap', is protective in myriad animal models of I/R injury. A water-soluble derivative of PBN, NXY-059, was evaluated in a trial of 1722 patients with ischaemic stroke. While NXY-059 significantly reduced disability at 90 days, other outcome measures, such as neurological functioning, were not improved. A repeat study in 3195 patients, using a similar design, also found no difference between drug- and placebo-treated groups for any important outcome measure, including mortality or disability score at 90 days. Tirilazad (U74006F), a 21-aminosteroid devoid of classical steroid hormonal activities, can potently inhibit radical-mediated lipid peroxidation. Tirilazad and related compounds ameliorated I/R injury in animal models. However, a meta-analysis of six double-blind RCTs that enrolled a total of 1747 patients with presumed ischaemic stroke found no survival benefit and a worsening of functional outcomes [15].

Complement inhibitors

Two agents that target the complement system, namely TP10 and pexelizumab, have been investigated. Complement receptor 1 (CR1) is a cell surface glycoprotein expressed on erythrocytes, leukocytes and other cell types. CR1 inhibits both the classic and alternative pathways of complement activation. The soluble form of CR1 inhibits both complement pathways in a manner similar to that of the cell-bound protein. The recombinant form of soluble CR1, TP10, inhibits C3 and C5 activation and enhances proteolysis of activated C3b and C4b by plasma factor I. A double-blind RCT that enrolled 564 high-risk patients undergoing cardiac surgery and CPB showed no difference between TP10 and placebo in the primary composite endpoint (death **or** post-operative MI **or** requirement for prolonged support with an intra-aortic balloon pump **or** requirement for prolonged mechanical ventilation). Pexelizumab is a neutralizing humanized monoclonal antibody against C5. More than 15,000 patients undergoing treatment for ST segment elevation MI (STEMI) or coronary artery bypass graft surgery were enrolled in seven RCTs of pexelizumab. A meta-analysis showed no benefit from pexelizumab in rates of adverse events, death, MI, stroke, or heart failure [16]. Although pexiluzimab was associated with a significant (26%) reduction in risk of death after cardiac bypass surgery ($p = 0.01$), the number needed to treat was 100.

Ischaemic post-conditioning

Post-conditioning, i.e. deliberately causing short periods of ischaemia during the reperfusion phase of an I/R insult, ameliorated organ damage in various animal models. Mechanism(s) remain poorly understood, but probably involve inhibition of apoptosis, possibly by promoting activation of signalling via the phosphatidylinositol 3-kinase pathway. Several recent studies have yielded encouraging results in terms of infarct size, ejection fraction, cardiac enzyme rise, and long-term complications from post-conditioning after percutaneous coronary intervention (balloon angioplasty and stent placement) for the treatment of STEMI [17]. In contrast, negative results were reported from two other relatively small studies and one 700 patient RCT [18]. In view of these conflicting findings, the value, if any, of post-conditioning in the management of STEMI remains to be elucidated.

Therapeutic hypothermia

Hypothermia, i.e. deliberate lowering of core temperature to subnormal levels, is another therapeutic intervention extensively evaluated in various forms of I/R injury. Abundant evidence from preclinical studies support the value of therapeutic hypothermia in

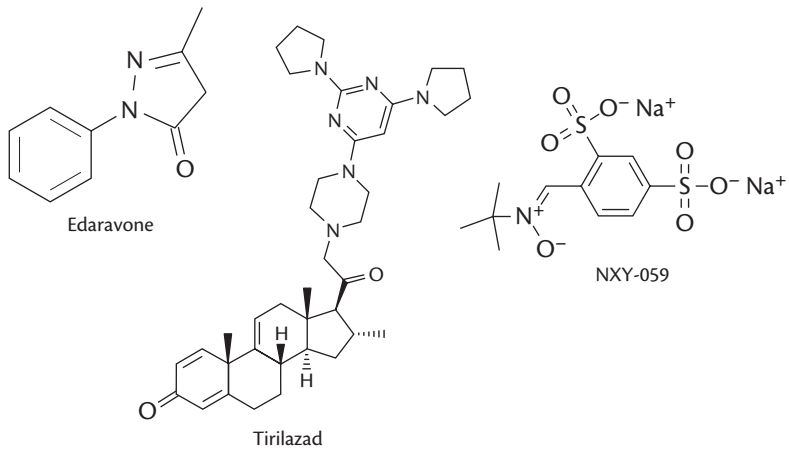


Fig. 308.1 Chemical structures of three free radical scavengers that have been evaluated in clinical trials for the treatment of stroke.

conditions including stroke, cardiopulmonary arrest and MI. Until the recent publication of negative data from a large RCT [19] induction of therapeutic hypothermia was a component of the standard management of patients, who have return of circulation, but loss of consciousness after successful resuscitation from cardiopulmonary arrest. Data are lacking from clinical trials of therapeutic hypothermia for stroke and results from several trials of therapeutic hypothermia for STEMI, mostly using endovascular cooling, have yielded largely negative results.

Cyclosporin

This compound was developed as an immunosuppressive agent in the 1970s, but is now known to exert its immunological effects by inhibiting signalling mediated by calcineurin. In 1988, cyclosporin was shown to block opening of the MPTP, acting by binding to cyclophyllin D. In various preclinical models of, treatment with cyclosporine- improved post-reperfusion myocardial performance and/or inhibited cell death. The positive results with cyclosporin in animal models of cardiac I/R injury have been supported by a small RCT of 58 patients with acute STEMI which showed superior outcome advantages [20].

Acknowledgements

The editors were saddened to hear of the death of Dr Mitchell P. Fink since writing this chapter of the book.

References

1. Balaban RS, Nemoto S, and Finkel T. (2005). Mitochondria, oxidants, and aging. *Cell*, **120**, 483–95.
2. Bedard K and Krause KH. (2007). The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. *Physiological Reviews*, **87**, 245–313.
3. Meneshian A and Bulkley GB. (2002). The physiology of endothelial xanthine oxidase: from urate catabolism to reperfusion injury to inflammatory signal transduction. *Microcirculation*, **9**, 161–75.
4. Pou S, Keaton L, Surichamorn W, and Rosen GM. (1999). Mechanism of superoxide generation by neuronal nitric-oxide synthase. *Journal of Biological Chemistry*, **274**, 9573–80.
5. Zaobornyj T and Ghafourifar P. (2012). Strategic localization of heart mitochondrial NOS: a review of the evidence. *American Journal of Physiology—Heart and Circulatory Physiology*, **303**, H1283–93.
6. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, and Telser J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *International Journal of Biochemistry and Cell Biology*, **39**, 44–84.
7. Cuzzocrea S, Riley DP, Caputi AP, and Salvemini D. (2001). Antioxidant therapy: a new pharmacological approach in shock, inflammation, and ischemia/reperfusion injury. *Pharmacology Review*, **53**, 135–59.
8. Terada LS, Dormish JJ, Shanley PF, Leff JA, Anderson BO, and Repine JE. (1992). Circulating xanthine oxidase mediates lung neutrophil sequestration after intestinal ischemia-reperfusion. *American Journal of Physiology*, **263**, L394–401.
9. Schraufstatter IU, Hyslop PA, Hinshaw DB, Spragg RG, Sklar LA, and Cochrane CG. (1986). Hydrogen peroxide-induced injury of cells and its prevention by inhibitors of poly(ADP-ribose) polymerase. *Proceedings of the National Academy of Sciences of the United States of America*, **83**, 4908–12.
10. Szabo C, Zingarelli B, O'Connor M, and Salzman AL. (1996). DNA strand breakage, activation of poly (ADP-ribose) synthetase, and cellular energy depletion are involved in the cytotoxicity of macrophages and smooth muscle cells exposed to peroxynitrite. *Proceedings of the National Academy of Sciences of the United States of America*, **93**, 1753–8.
11. Baines CP. (2009). The mitochondrial permeability transition pore and ischemia-reperfusion injury. *Basic Research in Cardiology*, **104**, 181–8.
12. Johnson WD, Kayser KL, Brenowitz JB, and Saedi SF. (1991). A randomized controlled trial of allopurinol in coronary bypass surgery. *American Heart Journal*, **121**, 20–4.
13. Chaudhari T and McGuire W. (2012). Allopurinol for preventing mortality and morbidity in newborn infants with hypoxic-ischaemic encephalopathy. *Cochrane Database of Systematic Reviews*, **7**, CD006817.
14. Feng S, Yang Q, Liu M, et al. (2011). Edaravone for acute ischaemic stroke. *Cochrane Database of Systematic Reviews*, **12**, CD007230.
15. Bath PM, Iddenden R, Bath FJ, Orgogozo JM, and Tirilazad International Steering C. (2001). Tirilazad for acute ischaemic stroke. *Cochrane Database of Systematic Reviews*, **4**, CD002087.
16. Testa L, Van Gaal WJ, Bhindi R, et al. (2008). Pexelizumab in ischemic heart disease: a systematic review and meta-analysis on 15,196 patients. *Journal of Thoracic Cardiovascular Surgery*, **136**, 884–93.
17. Thuny F, Lairez O, Roubille F, et al. (2012). Post-conditioning reduces infarct size and edema in patients with ST-segment elevation myocardial infarction. *Journal of the American College of Cardiology*, **59**, 2175–81.
18. Kloner RA. (2013). Current state of clinical translation of cardioprotective agents for acute myocardial infarction. *Circulatory Research*, **113**, 451–63.
19. Nielsen N, Wetterslev J, Cronberg T, et al. (2013). Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *New England Journal of Medicine*, **369**, 2197–206.
20. Piot C, Croisille P, Staat P, et al. (2008). Effect of cyclosporin on reperfusion injury in acute myocardial infarction. *New England Journal of Medicine*, **359**, 473–81.

CHAPTER 309

Repair and recovery mechanisms following critical illness

Geoffrey Bellingan and Brijesh V. Patel

Key points

- Critical illness represents a perpetuated state of inflammation and injury, with abnormal resolution and recovery.
- Resolution of inflammation is an active process involving a highly coordinated series of events, involving multiple molecular and cellular mediators.
- Stages of resolution and recovery involve the prevention of further insults, timely removal of infiltrated immune cells, clearing up of debris, and ultimately, recovery of tissue structure and function.
- The enhancement of proresolving mechanisms, rather than anti-inflammatory strategies may be a more amenable therapeutic strategy in critical illness.
- Abnormal resolution of inflammation may also lead to long-term functional deficits seen after critical illness.

Introduction

The ideal response to injury should ensure removal of any harmful stimuli, followed by a decline in the inflammatory response limiting damage to the host. In parallel, there should be successful repair of tissue(s) enabling return to normal structure and function. There is now convincing evidence that inflammation does not just simply 'fizzle out'. In contrast, resolution of inflammation and recovery involves a highly coordinated and actively controlled series of events. States such as sepsis and the acute respiratory distress syndrome (ARDS) show overwhelming inflammation due to disturbances in mechanisms that control the resolution of inflammation.

Injury, inflammation, and resolution

The cascade of events that govern inflammation, injury and resolution are showcased using an experimental model of resolving ARDS (Fig. 309.1) [1]. Injurious insults such as infection and acid aspiration lead to (**A**) classical activation of tissue macrophages through pathogen—and damage-associated molecular patterns (PAMPs and DAMPs). Activated macrophages release a host of pro-inflammatory mediators including cytokines, reactive oxygen/nitrogen species (ROS/RNS) and lipid mediators (**B**) (listed in Box 309.1), which upregulate cell adhesion molecules on the endothelium of the microcirculation triggering the rolling, activation, and firm adhesion of blood leukocytes (neutrophils and monocytes) (**C**). Barrier dysfunction occurs due to epithelial and endothelial disruption leading to the translocation of serum proteins and oedema (**D**). Migrated blood-derived leukocytes release opsonins (e.g. complement), which facilitate the recognition and phagocytic removal (**E**) of the offending trigger. The ideal inflammatory response should be confined to the affected region, be specific, and terminate after the injurious stimulus has been cleared, with little collateral damage.

This termination of the immune response is typically deranged in critical illness. The hallmarks for tissue recovery and resolution of inflammation can be described in three overlapping phases.

Phase 1: 'The stop signal'

First, the early phase of resolution removes the inciting stimulus, ceases further pro-inflammatory leucocyte recruitment, and promotes the reduction of pro-inflammatory mediators with a controlled anti-inflammatory response.

Increasing evidence exists that this phase of resolution is triggered earlier than previously thought. Within hours of the initial stimulus there is a switch from formation of pro-inflammatory eicosanoids (e.g. prostaglandins, leukotrienes, and platelet activating factor) to anti-inflammatory eicosanoids (including lipoxins, resolvins, and protectins). This switch is triggered by the neutrophils themselves (via neutrophil-platelet interactions) in an attempt to limit the inflammatory response (**F**). More importantly, these mediators also prevent further neutrophil trafficking, reduce vascular permeability, promote exudative monocyte entry, and the ingestion/clearance of debris and apoptotic neutrophils, which are integral to the later stages of resolution.

The ability to initiate this shutdown of pro-inflammatory leukocyte activity is an important checkpoint for the resolution of inflammation. Indeed, the resolution interval is an experimental index defined by the time taken for numbers of infiltrated neutrophils in the inflamed tissue to decline by half [2]. This decline depends upon constitutive apoptosis of neutrophils that consequently imparts a limited lifespan of ≤24 hours. Perpetuated neutrophil-mediated inflammation as a result of abnormal (delayed) apoptosis can

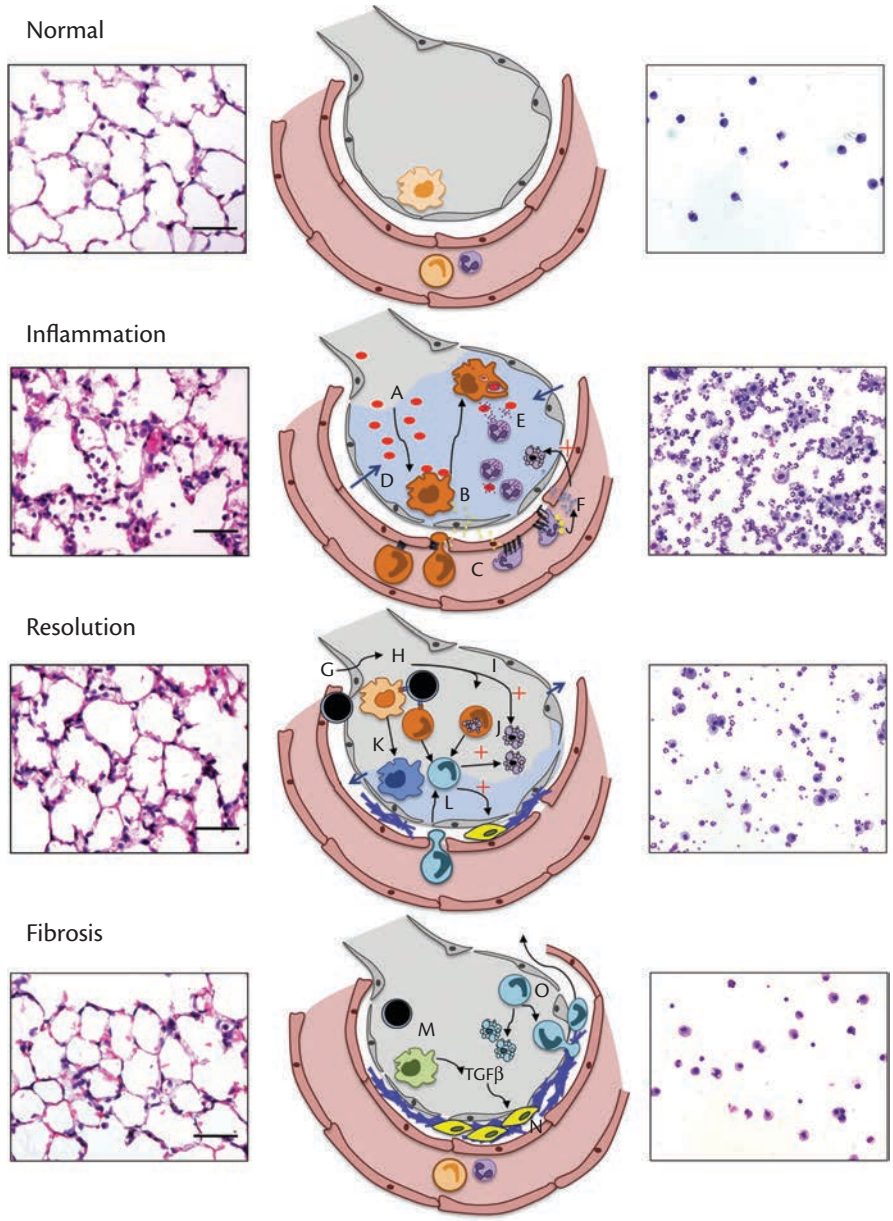


Fig. 309.1 Histology (left) and bronchoalveolar lavage cytology (right) after acid-induced lung injury to represent the events of injury, inflammation, resolution and fibrosis (middle). The events A-O are described in the main text. Scale bar represents 50 μm.

Reproduced with permission of the European Respiratory Society. *European Respiratory Journal*, May 2012, **39**, 1162–70, doi:10.1183/09031936.00093911.

indeed be detrimental in the overzealous inflammatory processes that occur in critical illness. For example, bronchoalveolar lavage fluid from patients with established ARDS prolongs the survival of neutrophils through disrupted apoptosis [3].

Various cytokines and their receptors are implicated in this phase, including IL-1 receptor antagonist, soluble TNF receptors, IL-4, IL-10, and IL-13. One of the most studied, IL-10, blocks the synthesis of various pro-inflammatory cytokines (including IFN-γ, IL-1, TNF, IL-12) and chemokines (e.g. IL-8, CCL2), and is often released from macrophages that have changed their phenotype response having ingested debris and apoptotic neutrophils [4,5] (Fig. 309.2). IL-4 and IL-13 also influence the monocyte/macrophage phenotype by increased endocytic activity through increased expression of scavenger receptors to recognize and increase parasite killing, and stimulation of mRNA of proteins such as matrix metalloproteinases and collagen types, all of which are crucial in enhancing tissue repair and fibrosis. IL-10 and TGF-beta can deactivate monocytes and reduce expression of MHC class II molecules used for antigen presentation to cytotoxic T-cells.

Phase 2: 'Clearing up the mess'

A clearance phase of resolution is then initiated. Shortly after neutrophil infiltration into damaged/infected tissue the adaptive system is activated with T-cell infiltration (**G**). A cell–cell interaction with resident macrophages, exudative monocytes, and dendritic cells (DC) (**H**) leads to the release of mediators such as TGF-β and IL-10, promoting apoptosis of neutrophils (**I**) and their uptake by macrophages (**J**).

Box 309.1 Pro-inflammatory and proresolving mediators during inflammation.

Pro inflammatory mediators

- Coagulation products: fibrin.
- Fibrinolytic products.
- Amines: histamine, bradykinin, serotonin.
- Complement system: C3a, C5a.
- Eicosanoids: PGE_2, PGI_2, leukotrienes, thromboxane A_2, PAF.
- Cytokines: TNF, IL-1, IL-6.
- Chemokines: IL-8, CCL-2.
- Cell adhesion molecules: E-/P-selection, ICAM.
- Reactive oxygen species.
- Reactive nitrogen species: NO, peroxynitrite.

Anti-inflammatory/proresolving

- Cytokines: TGFβ, IL-10, IL-1RA, IL-6.
- Eicosanoids: lipoxins, resolvins, protectins.
- Transcription factors: NF-κB, FoxP3.
- Cell adhesion molecules: $\alpha_v\beta_3$ integrin, thrombospondin, phosphatidylserine.
- Glucocorticoid/annexin A1 pathway.

Adapted by permission from Macmillan Publishers Ltd: *Nature Reviews Drug Discovery*, Gilroy et al., 'Inflammatory resolution: new opportunities for drug discovery', 2004, **3**, pp. 401–16, copyright 2004.

Cell death can proceed through a spectrum ranging from the programmed form (apoptosis) to a less ordered process (necrosis). Apoptosis is the ideal way for cells to die as it prevents activation of a pro-inflammatory response against intracellular molecular patterns released with necrotic cell death. Neutrophil apoptosis can be modulated by various agents, including granulocyte-macrophage colony-stimulating factor, lipopolysaccharide, and TNF-alpha, all of which are upregulated in sepsis and initially delay apoptosis. Mechanisms that dictate neutrophil apoptosis are beyond the scope of this chapter, but it is important to recognize that apoptotic neutrophils are non-functional, yet retain their histotoxic cellular constituents.

More importantly, apoptotic cells upregulate recognition signals facilitating their uptake by macrophages. These include thrombospondin-1, annexin-1, phosphatidylserine, and lysophosphatidylcholine. Indeed, mechanisms through which apoptotic cells signal their own disposal is crucial for the macrophage switch from pro-inflammatory to pro-resolving phenotypes (**K**) [6]. This plasticity to their environment makes macrophages vital regulators and effectors of local immune responses (Fig. 309.2). Influx of blood-derived monocytes (**L**) increases total tissue macrophage numbers to help initially fight the inflammatory battle, but then to subsequently switch their phenotype to clear debris and apoptotic neutrophils (**J**).

After clearance of neutrophils and debris, T-cells continue to be present, producing T_H2 cytokines such as IL-4 and IL-13 that regulate resident tissue macrophages (**M**). As a consequence, these resident macrophages take on a wound-healing phenotype leading to myofibroblast proliferation and collagen deposition (**N**). The extent is most likely dependent on the severity of damage. The fate of these exudative macrophages is still uncertain, but there is

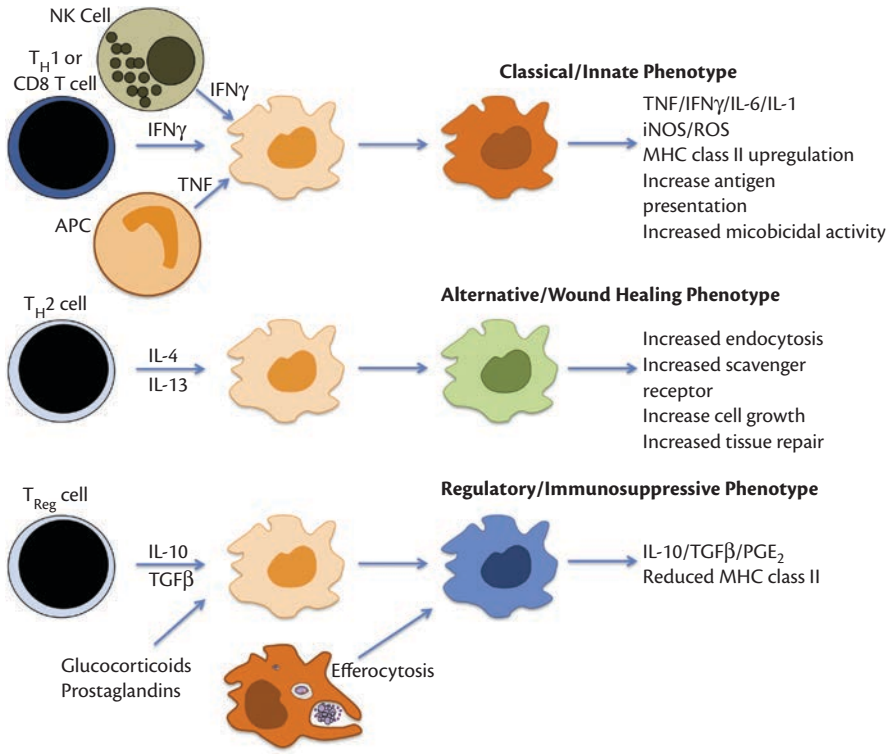


Fig. 309.2 The interactions and plasticity of activated macrophages.
Adapted by permission from Macmillan Publishers Ltd: *Nature Reviews Immunology*, Mosser and Edwards, 'Exploring the full spectrum of macrophage activation', 2008, **8**, pp. 958–69, copyright 2008.

evidence to suggest that they too undergo constitutive apoptosis, and that this may occur either locally or after migration to local lymph nodes (**O**).

Phase 3: 'Re-establishing order and function'

So, once the battlefield has been cleared, we return to the overall goal, i.e. functional recovery and catabasis, which requires recovery of cellular bio-energetics, controlled apoptosis and proliferation of damaged parenchymal cells. It remains unclear as to why certain patients heal while others repair through fibrosis. For instance, ARDS can lead to a protracted fibrotic phase. It is also clear that fibrosis occurs much earlier (at the onset of inflammation) and, factors such as TGF-β that regulate resolution, also influence fibrosis. Increasing evidence suggests that parenchymal cell death may dictate acute and chronic fibrotic responses. Hence, while leukocyte apoptosis is crucial for inflammatory resolution, parenchymal apoptosis also influences whether the tissue heals or is scarred. Furthermore, inflammation can worsen parenchymal cell death perpetuating fibrotic responses.

Translational avenues promoting resolution therapies in critical care

It is unclear why an initial focused inflammatory response goes awry in critical illness. There are significant challenges to bedside translation of biological therapies to treat conditions, such as sepsis and ARDS. A major hurdle is that patients do not present at time zero and often have overwhelming inflammation on presentation.

Prevention is better than cure

Much of the recent improvement in mortality is a result of improved delivery of care attenuating perpetuated inflammation as a result of iatrogenic insults, such as ventilation, invasive monitoring and nosocomial infection. The first significant breakthrough was the use of low tidal volumes to prevent iatrogenic ventilator-induced lung injury.

Anti-inflammatory strategies

A major focus of research over the past few decades has been to elucidate effective anti-inflammatory strategies. This has been fraught with difficulty, as such agents may promote an immunocompromised state with augmentation of an uncontrolled 'compensatory anti-inflammatory response syndrome'. For instance, low levels of pro-inflammatory mediators such as nitric oxide, TNF-alpha and IL-6 are pro-resolving and reparative. This may explain why the bench-to-bedside translation of cytokine-based therapies in the absence of mechanistic insights has increased mortality in some sepsis studies. The temporal relationship between this initial anti-inflammatory response and the progression of the first and second phases of resolution may determine susceptibility to nosocomial infection.

Enhancing active resolution phase mediators

The notion of active resolution mechanisms is so recent that well-known agents, such as glucocorticoids and aspirin have been labelled as anti-inflammatory, whereas in actual fact, they are significantly proresolving in nature. For instance, glucocorticoids delay neutrophil apoptosis yet influence the macrophage phenotype and have important resolving effects through induction of annexin A1. Overall, this leads to reduced pro-inflammatory cytokine release, reduced neutrophil trafficking and thus, overall, promotes the resolution of inflammation [7].

More recent advances have discovered the lipoxin, resolvin, and protectin classes of the eicosanoid family, which serve to actively promote homeostasis and resolution of inflammation. For instance, lipoxin A2 restitutes epithelial barrier function in experimental ALI [8], while resolvin D2 improved survival in a model of polymicrobial sepsis [9]. Hence, enhancing the effects of endogenous proresolving mediators may prove a better therapeutic option. Interestingly, aspirin influences resolution within hours of the onset of inflammation through the production of lipoxin A4 precursors.

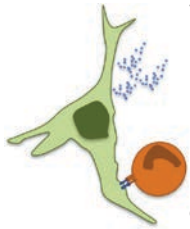
In addition to molecular mediators, cellular mediators also direct the path through which inflammation may proceed. This involves a concerted cross-talk between the acute innate and the regulatory adaptive arms of the immune system. More recently, regulatory T-cells, which are identified by the cell surface markers CD4, CD25 and the transcription factor FoxP3, have recently been shown to reduce pro-inflammatory cytokine production, increase TGF-β levels and increase neutrophil apoptosis in experimental ALI, and were also found to be present in human ALI [10].

Further insights into mechanisms through which infiltrating cells die have also improved understanding as to how leukocyte apoptosis can be manipulated to promote resolution. There is potential scope for manipulating neutrophil apoptosis and enhancing their uptake by macrophages, thus promoting proresolving reparative macrophage phenotypes. Additionally, the diagnostic evaluation of the macrophage phenotype may give insights into the immune status of patients allowing the implementation of personalized therapies to promote resolution.

Most excitingly, the future role of cell therapy has been significantly fuelled by the application of mesenchymal stem cells (MSCs) in experimental models of critical illness (Fig. 309.3). The heterogeneous and plastic nature of these cells, allowing them to adapt and respond appropriately to various inflammatory milieus in a reparative fashion, has shown significant therapeutic potential. MSCs have improved experimental ALI, bacterial pneumonia, and Gram-negative sepsis. Unfortunately, the application of MSCs in critical illness is still relatively devoid of mechanisms. There is emerging evidence that these may include paracrine effects such as secretion of growth factors (e.g. keratinocyte growth factor) and anti-bacterial proteins, as well as immunomodulatory effects on circulating monocytes, tissue macrophages and T-cells [11].

Aiming for full functional recovery

Mitochondrial dysfunction is integral to the pathogenesis of sepsis and multi-organ failure, and can be induced by various soluble mediators including nitric oxide and reactive oxygen species (ROS), as well as through activation of apoptosis signalling. Mitochondrial biogenesis most likely occurs at a transcriptional level involving nuclear regulators such as PGC-1alpha [12], which integrates multiple external signals including ROS and reactive nitrogen species (RNS). Furthermore, endocrine factors, such as thyroid hormones also influence mitochondrial recovery. Hence, strategies aimed at 'jump-starting' mitochondria are attractive as repair and recovery would undoubtedly require energy [13]. Another approach involves mesenchymal stem cells that have more recently been visually captured to adopt a 'trojan horse' strategy to deliver mitochondria, packaged in microvesicles, to injured alveolar epithelial cells, improving tissue bioenergetics, and thereby preventing injury and promoting recovery [14].



Soluble mediators released by MSCs

- IL-6 inhibits neutrophil respiratory burst and prevents DC maturation
- Stem cell factor
- GM-CSF
- VEGF promotes angiogenesis
- Hepatocyte growth factor
- Adrenomedillin
- PGE_2 inhibition of proliferation and cytotoxicity of NK cells

Cellular interactions with MSCs

- Monocytes – inhibited differentiation into mature DCs.
- DC – reduced TNF production and reduced antigen presentation.
- Reduces CD8 T-cell cytotoxicity.
- DC induced IL-10 production increases regulatory T-cell differentiation.
- Parencymal cells – mitochondrial transfer.

Fig. 309.3 The heterogeneous resolving and reparative potential of mesenchymal stem cells.

Conclusion

Despite discharge from critical care and hospital, many patients continue to have significant underlying physiological and chronic organ dysfunction. These have been particularly highlighted in ICU-acquired weakness post-ARDS [15], the risk of chronic kidney disease after sepsis-induced AKI [16], and neuropsychiatric complications including post-ICU delirium [17]. Future work to investigate the extent of underlying chronic immune activation and its resolution in patients post-ICU may uncover insights into the full temporal course of ICU-acquired inflammation.

References

1. Patel BV, Wilson MR, and Takata M. (2012). Resolution of acute lung injury and inflammation: a translational mouse model. *European Respiratory Journal*, **39**, 1162–70.
2. Serhan CN and Savill J. (2005). Resolution of inflammation: the beginning programs the end. *Nature: Immunology*, **6**, 1191–7.
3. Matute-Bello G, Liles WC, Radella F, et al. (1997). Neutrophil apoptosis in the acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **156**, 1969–77.
4. Voll RE, Herrmann M, Roth EA, Stach C, Kalden JR, and Girkontaite I. (1997). Immunosuppressive effects of apoptotic cells. *Nature*, **390**, 350–1.
5. Fadok VA, Bratton DL, Konowal A, Freed PW, Westcott JY, and Henson PM. (1998). Macrophages that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-beta, PGE2, and PAF. *Journal of Clinical Investigation*, **101**, 890–8.
6. Mosser DM and Edwards JP. (2008). Exploring the full spectrum of macrophage activation. *Nature Review: Immunology*, **8**, 958–69.
7. Perretti M and D'Acquisto F. (2009). Annexin A1 and glucocorticoids as effectors of the resolution of inflammation. *Nature Review: Immunology*, **9**, 62–70.
8. Bonnans C and Levy BD. (2007). Lipid mediators as agonists for the resolution of acute lung inflammation and injury. *American Journal of Respiratory Cell and Molecular Biology*, **36**, 201–5.
9. Spite M, Norling LV, Summers L, et al. (2009). Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis. *Nature*, **461**, 1287–91.
10. D'Alessio FR, Tsushima K, Aggarwal NR, et al. (2009). CD4 + CD25 + Foxp3 + Tregs resolve experimental lung injury in mice and are present in humans with acute lung injury. *Journal of Clinical Investigations*, **119**, 2898–913.
11. Matthay MA, Goolaerts A, Howard JP, and Lee JW. (2010). Mesenchymal stem cells for acute lung injury: preclinical evidence. *Critical Care Medicine*, **38**, S569–73.
12. Tran M, Tam D, Bardia A, et al. (2011). PGC-1α promotes recovery after acute kidney injury during systemic inflammation in mice. *Journal of Clinical Investigation*, **121**, 4003–14.
13. Protti A and Singer M. (2006). Bench-to-bedside review: potential strategies to protect or reverse mitochondrial dysfunction in sepsis-induced organ failure. *Critical Care*, **10**, 228.
14. Islam MN, Das SR, Emin MT, et al. (2012). Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. *Nature: Medicine*, **18**, 759–65.
15. Herridge MS, Tansey CM, Matté A, et al. (2011). Functional disability 5 years after acute respiratory distress syndrome. *New England Journal of Medicine*, **364**, 1293–304.
16. Murugan R and Kellum JA. (2011). Acute kidney injury: what's the prognosis? *Nature Review: Nephrology*, **7**, 209–17.
17. Iwashyna TJ, Ely EW, Smith DM, and Langa KM. (2010). Long-term cognitive impairment and functional disability among survivors of severe sepsis. *Journal of the American Medical Association*, **304**, 1787–94.

CHAPTER 310

Neural and endocrine function in the immune response to critical illness

Gareth L. Ackland

Key points

- Bidirectional links between neurohormones and immune effectors contribute essential mechanisms that limit organ dysfunction.
- The persistence of the 'fight or flight' response is increasingly seen as a detrimental feature of critical illness.
- Iatrogenic factors introduced by critical care therapy may exacerbate neurohormonal dysregulation.
- Neurohormonal responses are dysregulated in chronic diseases, predisposing patients to an increased risk of sepsis and multi-organ failure.
- Off-target local immune effects may explain the failure of clinical trials aimed at altering systemic neurohormonal physiology.

Introduction

The neurohormonal physiological response is pivotal for effective defence against a range of insults that trigger critical illness, in an effort to maintain homeostasis. The acute and chronic phases of critical illness are characterized by distinct neurohormonal and immune profiles. While Cannon pioneered the concept that stressors elicit a coordinated response to maintain homeostasis, the advent of modern critical care has generated an entirely new (patho)physiological embodiment involving both direct and off-target effects of neurohormonal control on immune function, and vice versa [1]. Selye provided a prescient conceptual biological framework for established critical care states. He suggested that maladaptive responses to triggers of critical illness follow an initial phase of alertness, leading to habituation processes that may either not resolve, or become dysregulated. In turn, this leads to a prolonged or irreversible pathophysiological phenotype (Fig. 310.1).

The first phase of the effector response requires detection of afferent signals through various non-exclusive pathways [2]. Peripheral immunogenic stimuli activate neurons of the circumventricular organs, via fenestrated endothelium, or trigger phylogenetically-conserved immune signalling pathways in 'hard-wired' components of the afferent autonomic nervous system that detect both pathogen- and danger-associated molecular patterns (Fig. 310.2). The molecular mediators of acute critical illness are detected by both the carotid body and vagus nerves, which transduce inflammatory mediators and/or pathophysiological derangements into neural signals to key central nervous system substrates, such as the nucleus tractus solitarius. Afferent neural pathways mediated by pain (c-fibres) may also play an important role in conveying molecular information from damaged remote tissue, initiating CNS autonomic reflex neuro-immunomodulatory mechanisms.

The medial parvocellular region of the paraventricular nucleus within the hypothalamic pituitary axis integrates various afferent signals, or through direct/indirect neuronal activation via a pathologically compromised blood–brain barrier, to trigger the release of glucocorticoids [3]. Corticotropin-releasing factor is released into the portal circulation of the anterior pituitary gland, stimulating the systemic secretion of the melanocortin adrenocorticotrophic hormone by pituitary corticotrophs. Concomitantly, neural reflex circuits are activated that innervate the principal organs of the immune system, including spleen, lymph nodes, and reticuloendothelial organs.

The adrenal gland consists of two functional units—the medulla and cortex. Production of sympathetic system hormones (epinephrine and norepinephrine) is localized within the medulla. The adrenal cortex consists of three zones:

- The superficially located zona glomerulosa produces mineralocorticoids (aldosterone and, to a lesser extent, corticosterone).
- The zona reticularis produces androgens (dehydroepiandrosterone, dehydroepiandrosterone sulphate, and 11β-hydroxyandrostenedione).
- The zona fasciculata generates glucocorticoids (cortisol and cortisone).

Once adrenocorticotropic hormone (ACTH) reaches the zona fasciculata, cortisol and cortisone are released into the bloodstream to limit synthesis of pro-inflammatory mediators by various effector cells. The neurohypophysial hormones vasopressin and oxytocin maintain cardiovascular and metabolic homeostasis through central and peripheral sites of action. Arginine vasopressin stimulates ACTH secretion weakly, but strongly promotes CRH action.

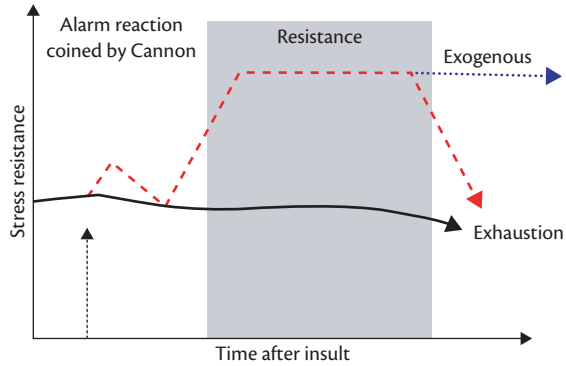


Fig. 310.1 Conceptual framework for neuroendocrine dysregulation in response to critical illness. Acute pathological insults trigger a coordinated neuroendocrine alarm reaction, as described by Cannon. In chronic pathologies characterized by persistent neuroendocrine activation, e.g. heart failure, the alarm reaction is muted (solid black line), leading to rapid exhaustion of cellular signalling in the presence of dysregulated pathophysiological control mechanisms (e.g. hypocortisolaemia). In patients without major chronic morbidity (dashed red line), the alarm reaction triggers a coordinated neuroendocrine response, which may become exhausted in the face of additional or iatrogenic insults, or downregulation of cellular signalling and metabolic pathways, leading to immunosupression. Apparent continued resistance (dotted blue line) achieved by exogenous delivery of various neuroendocrine modulators may perpetuate the resistance phase, often at the expense of off-target effects including immunosuppression.

Catecholamines, angiotensin II, serotonin, and vasoactive intestinal peptide also stimulate ACTH secretion.

The dysregulation of this initial neuroendocrine response, and the persistent failure to regulate the reciprocal exchange of signals between the immune, endocrine, and nervous systems that is required for effective immunoregulation and central nervous system function, is associated with the establishment of chronic critical illness [4]. While acute mechanisms regulating neuroendocrine control of immunity are becoming clearer, the habituation phenotype is less well understood. Furthermore, the acutely critically-ill patient frequently presents with this chronically disordered neuroendocrine phenotype prior to the onset of further acute deterioration as a feature of underlying co-morbidity: established neurohormonal dysregulation is a core feature of cardiac failure, diabetes mellitus, and malignancy.

Central and cellular autonomic regulation of immunity

Immunomodulatory neurotransmitters rapidly fine-tune the spatial and temporal control of innate and adaptive immune cellular function by specific molecular mechanisms. Catecholamines modulate immune function through both local cellular and neural origins. In addition to catecholamines derived from the adrenal medulla and presynaptic neurons, T lymphocytes, macrophages, and neutrophils synthesize and release catecholamines [5]. Autocrine/paracrine regulation by such diverse effectors provides a complex catecholaminergic influence on inflammatory mediators. Some of the deleterious effects of acute sympatho-excitation may result from direct tissue injury releasing danger-associated molecules, for example, from cardiomyocyte injury. While experimental and clinical models provide conflicting results, the detrimental effects of hyperacute and/or prolonged beta-adrenergic receptor stimulation may be targeted to ameliorate dysglycaemia, and hepatic and immune cell generation of inflammatory mediators. Sympatholysis with alpha-2 agonists, such as the sedative dexmedetomidine, reduces systemic inflammation, while a similar potential protective role for beta-1 blockade beyond cardioprotection is also plausible [6]. Consistent with the deleterious effects of catecholamines, dopamine predominantly exerts immunosuppressive effects, including inhibition of phagocytic chemotaxis and impaired T cell proliferation. The lack of clinical benefit with beta-2 agonists in acute lung injury, despite

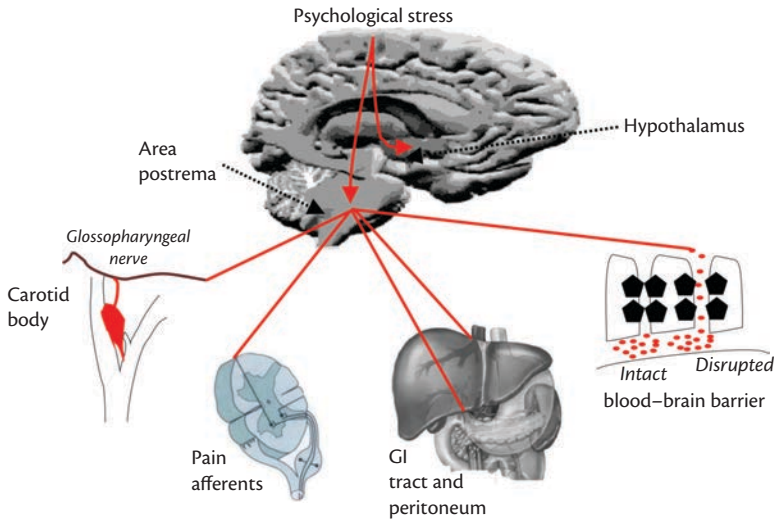


Fig. 310.2 Afferent detection by the neuroendocrine system of inflammation. Acute critical illness is detected by both central and peripheral substrates. The carotid body chemoreceptor, vagus nerve, and pain afferents nerve can directly detect cytokines. The carotid body can also detect neurohormones, danger-associated molecular patterns, and metabolic dysregulation. The area postrema and other circumventricular organs (characterized by their extensive vasculature and lack of a normal blood–brain barrier) permit inflammatory mediators to central nervous system neuroendocrine responses directly, as does breakdown of the blood–brain barrier. Psychological stress, a common feature to acute critical illness regardless of aetiology, also drives neuroendocrine activation.

cellular anti-inflammatory effects, illustrates the complex interplay between sympathetic modulation of immunity and off-target effects.

Parasympathetic neuromodulation

Similar to catecholamines, parasympathetic neurotransmitters innervate immune cells following both neural and local immune cell release [7]. Upregulation of endogenous acetylcholine synthesis in mononuclear leukocytes occurs following pathophysiological insults in vivo. Through nicotinic alpha-7 receptors, acetylcholine reduces the release of pro-inflammatory cytokines by human macrophages via inhibition of NF-κB and Janus kinase (JAK) and Signal Transducer and Activator of Transcription pathways (JAK–STAT). Human peripheral blood lymphocytes also possess M2-M5 muscarinic cholinergic receptors, in addition to the full range of neuronal cholinergic synthetic machinery. The activation of neural-immune reflexes appears to be a strongly conserved evolutionary mechanism to enable rapidly controlled immune responses to pathogens, chiefly through the release of acetylcholine from the vagus nerve to attenuate the release of pro-inflammatory mediators [8]. Central activation of the peripheral anti-inflammatory actions of cholinergic ligands, mediated by the vagus nerve, limit the pathological sequelae of a range of pathologies that leads to acute critical illness. Activation of central nervous system pathways by distant tissue injury or inflammation results in efferent neural regulation of infiltrative immune cell function through diverse signalling and effector molecules acting through the cholinergic anti-inflammatory pathway. Adrenocorticotropin (ACTH-1–24), another melanocortin endogenously produced from pro-opiomelanocortin in the anterior pituitary gland, reverses organ dysfunction after haemorrhagic shock, the benefit of which is lost in vagotomized animals [9]. Ghrelin is an endogenous orexigenic neurohormone produced chiefly by gastric endocrine cells [10], but also within the hypothalamus. Ghrelin inhibits pro-inflammatory cytokine production in experimental intra-abdominal sepsis. This anti-inflammatory effect is abrogated by surgical vagotomy, which is consistent with the potent pro-kinetic properties of ghrelin. However, as with many of these neural-immune interactions, ghrelin also directly inhibits cytokine release from monocytes and T cells. Several, as yet unidentified, clinically relevant triggers are likely to contribute to the vagal immunomodulatory release of acetylcholine, including gut-mediated afferent pathways through which enteral lipids release cholecystokinin [11].

The loss of parasympathetic activity in critically ill patients is associated with increased mortality. The vagus nerve also releases vasoactive intestinal peptide (VIP), a potent anti-inflammatory molecule that promotes Th2 cytokine production while reducing proliferation of activated Th1 cells [12]. Macrophage phagocytic activity, migration, and release of nitric oxide and prostaglandins are inhibited by VIP. The principal cyclic AMP/protein kinase A-mediated anti-inflammatory pathway activated by VIP is shared by other non-related neuropeptides, including pituitary adenylate cyclase-activating polypeptide, urocortin, adrenomedullin, cortistatin and ghrelin, all of which are GPCR-ligands produced by various immune cells. The pleiotropic immunomodulatory properties of these neuropeptides, including direct antibacterial actions in the case of adrenomedullin and ghrelin, and the induction of regulatory T cells that suppress activity against autoreactive T cell effectors, suggests that complex time and location specific functional changes drive the development, resolution and persistence of critical illness [13].

Hypothalamic regulation of immunity

Under normal conditions, glucocorticoids are secreted in a pulsatile fashion, driven by circadian and ultra-radian patterns in hypothalamic pituitary neuronal activity. Once released from the adrenal cortex, apparently normal or frequently elevated circulating levels of glucocorticoids may fail to execute normal physiological actions due to the development of glucocorticoid resistance. Reduced expression or binding affinity of glucorticoid receptor, and interference by other transcription factors may impair counter-regulatory control of the immune response. Epigenetic changes in the glucorticoid receptor gene, precipitated by common comorbidities including chronic exposure to inflammation and exogenous glucocorticoids, induce glucocorticoid resistance. Acute infections, including bacterial toxins, also directly impair glucocorticoid receptor function [14].

Glucocorticoids exert an ubiquitous, anti-inflammatory effect on immune function, driving a Th2 adaptive immune phenotype and suppressed cellular immunity characterized by decreased interferon-γ synthesis and promotion of interleukin-4 secretion. This anti-inflammatory profile extends to reducing adhesion molecule expression on endothelial cells. Consistent with this immunosuppressive phenotype, the CORTICUS trial in septic shock patients demonstrated that exogenous supplementation with hydrocortisone increased the risk of subsequent infection and failed to reduce mortality [15].

Leptin

Glucocorticoids are also potent regulators of leptin expression, an adipocyte-secreted hormone that links nutritional status with neuroendocrine and immune function. Leptin reduces cortisol synthesis by downregulating the steroid-producing enzyme cascade in the adrenal cortex, and also counteracts glucocorticoid-induced apoptosis of lymphocytes. Circulating leptin levels increase early during infection and inflammation, with direct stimulatory effects on chemotaxis and bactericidal capacity in phagocytes, enhanced production of pro-inflammatory cytokines, and the promotion of survival of thymic T cells accompanied by a switch to Th1-cell immune responses characterized by IFN-γ and TNFα secretion [16]. Acute starvation and reduced caloric intake, common features of both critical illness and comorbidities that predispose to its development, result in leptin deficiency and impaired immunity. Genetic ablation of leptin increases mortality in experimental murine sepsis, chiefly through impaired neutrophil function. Exogenous leptin administration can restore immune competence, reinforcing the link between energy homeostasis and immune function. Compatible with a critical neural mechanism, genetic rescue of leptin signalling specifically within the CNS improves mortality and dampens inflammation following experimental sepsis. Notably, acute elevations in plasma leptin that may occur at the onset of critical illness contrast with the suppression of leptin in established critical illness.

Vasopressin

Preprovasopressin is synthesized within magnocellular neurohypophyseal neurons, but stored and released from axonal

terminals in the posterior pituitary gland. Vasopressin is synthesized as a prohormone, which is then cleaved to form the mature active hormone. The release of vasopressin is triggered by hypotension and hyperosmolality of extracellular fluid, both familiar clinical features of acute critical illness. Regulatory changes in synthesis, release, and metabolism control serum levels of vasopressin. Feedback to the corticosteroid axis is mediated by the AVPR1b receptor, the stimulation of which releases ACTH. Thus, vasopressin and corticotrophin-releasing hormone synergistically promote ACTH release, albeit through distinct cellular signalling. This accounts, in part, for the preservation of vasopressin stimulation of corticotrophic cells in response to increased cortisol levels, in contrast to concomitant downregulation of the corticotropin-releasing hormone/ACTH response. A further bidirectional control mechanism is conferred by corticosteroids increasing vasopressin mRNA, with the preservation, or restoration, of circulatory pressor responses to vasopressin. Interestingly, the Vasopressin and Septic Shock Trial (VASST) study suggested a clinically relevant, physiological interaction between the vasopressin-corticosteroid axis, since low-dose vasopressin infusions combined with corticosteroid treatment decreased mortality compared to corticosteroids plus norepinephrine [17]. In established critical illness, including sepsis, vasopressin receptor expression is downregulated.

Consistent with the remarkable parallels between neural and cellular immunoregulatory control by many neurohormones, vasopressin is expressed and release from immune cells, including T cells, B cells and monocytes/macrophages [18]. Furthermore, vasopressin interacts with the CRH/ACTH axis within immune cells to potentiate CRH-induced ACTH release from peripheral blood monocytes. Pulmonary inflammation in experimental sepsis is decreased by administration of vasopressin. However, the precise contributions of systemic (particularly circulatory) effects of vasopressin and local immune actions remain unclear.

Conclusion

The complex, bi-directional interplay between neural and humoral influences on immune function impacts on the development and resolution of critical illness. There is increasing recognition that apparently acutely beneficial neurohormonal anti-inflammatory mechanisms may become deleterious during the progression to established critical illness. The loss of immunoregulatory function through impaired CNS and local cellular signalling, combined with the dysregulation of counter-regulatory mechanisms between various neurohormones, is likely to underpin several key features of the chronic critical illness phenotype.

References

1. Cuesta JM and Singer M. (2012). The stress response and critical illness: a review. *Critical Care Medicine*, **40**, 3283–9.
2. Sternberg EM. (2006). Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. *Nature Review: Immunology*, **6**, 318–28.
3. Rivest S. (2010). Interactions between the immune and neuroendocrine systems. *Progress in Brain Research*, **181**, 43–53.
4. Beishuizen A and Thijs LG. (2004). The immunoneuroendocrine axis in critical illness: beneficial adaptation or neuroendocrine exhaustion? *Current Opinion in Critical Care*, **10**, 461–7.
5. Flierl MA, Rittirsch D, Huber-Lang M, Sarma JV, and Ward PA. (2008). Catecholamines-crafty weapons in the inflammatory arsenal of immune/inflammatory cells or opening pandora's box? *Molecular Medicine*, **14**, 195–204.
6. Barnes SJ and Ackland GL. (2010). Beta-adrenoreceptor modulation of metabolic, endocrine and immunologic function during critical illness. *Endocrine, Metabolic & Immune Disorders—Drug Targets*, **10**, 292–300.
7. Andersson U and Tracey KJ. (2012). Reflex principles of immunological homeostasis. *Annual Review of Immunology*, **30**, 313–35.
8. Tracey KJ. (2011). Cell biology. Ancient neurons regulate immunity. *Science*, **332**, 673–4.
9. Guarini S, Altavilla D, Cainazzo MM, et al. (2003). Efferent vagal fibre stimulation blunts nuclear factor-kappaB activation and protects against hypovolemic hemorrhagic shock. *Circulation*, **107**, 1189–94.
10. Deane A, Chapman MJ, Fraser RJ, and Horowitz M. (2010). Bench-to-bedside review: the gut as an endocrine organ in the critically ill. *Critical Care*, **14**, 228.
11. Luyer MD, Greve JW, Hadfoune M, Jacobs JA, Dejong CH, and Buurman WA. (2005). Nutritional stimulation of cholecystokinin receptors inhibits inflammation via the vagus nerve. *Journal of Experimental Medicine*, **202**, 1023–9.
12. Delgado M and Ganea D. (2013). Vasoactive intestinal peptide: a neuropeptide with pleiotropic immune functions. *Amino Acids*, **45**, 25–39.
13. Delgado M and Ganea D. (2008). Anti-inflammatory neuropeptides: a new class of endogenous immunoregulatory agents. *Brain, Behavior, and Immunity*, **22**, 1146–51.
14. Busillo JM and Cidlowski JA. (2013). The five Rs of glucocorticoid action during inflammation: ready, reinforce, repress, resolve, and restore. *Trends in Endocrinology and Metabolism*, **24**, 109–19.
15. Sprung CL, Annane D, Keh D, et al. (2008). Hydrocortisone therapy for patients with septic shock. *New England Journal of Medicine*, **358**, 111–24.
16. Tschop J, Dattilo JR, Prakash PS, Kasten KR, Tschop MH, and Caldwell CC. (2010). The leptin system: a potential target for sepsis induced immune suppression. *Endocrine, Metabolic & Immune Disorders—Drug Targets*, **10**, 336–47.
17. Russell JA, Walley KR, Singer J, et al. (2008). Vasopressin versus norepinephrine infusion in patients with septic shock. *New England Journal of Medicine*, **358**, 877–87.
18. Russell JA and Walley KR. (2010). Vasopressin and its immune effects in septic shock. *Journal of Innate Immunity*, **2**, 446–60.

CHAPTER 311

Adaptive immunity in critical illness

Sean F. Monaghan and Alfred Ayala

Key points

- Genomic responses after critical illness simultaneously include changes to the innate and adaptive immune responses, thus suggesting they are not unique events, but intertwined.
- B and T cells play a critical role in the development of many critical illnesses.
- Human lymphocyte antigen (HLA) is a biomarker implemented in critical illness that bridges the innate and adaptive immune response.
- Immune modulating proteins, such as CTLA-4 and PD-1, lead to alterations in the adaptive immune response in critical illness.
- Targeted immune modulating therapies may reverse the immune suppression seen after critical illness. They can target the adaptive immune response potentially leading to improved outcomes.

Normal adaptive immunity

Adaptive (acquired) immunity is an evolutionarily young system that appears to be restricted to vertebrates. It relies on the function of recombinase (RAG) genes for somatic recombination of gene segments that code for antigen receptors, i.e. novel immunoglobulin (Ig) by/on B-lymphocytes and/or unique T-cell receptor (TCR) molecules on T-lymphocytes. Clonal distribution/selection from randomly generated/highly diverse repertoire of specificities allows for development of selective 'memory' (vaccination). This 'memory' is in the form of specific antibodies (humoral immunity) to a given microbe (vaccine target) and/or selective cytotoxic effector lymphocytes (cell-mediated immunity) against viral and/or cancer cells (tumour proteins or non-self-proteins). The development of such memory allows for selective targeting of specific pathogens (especially upon their re-appearance), as well as the host cells infected with them, thereby leading to their rapid clearance via orchestrated effector systems.

Importantly, the activation/initiation of an adaptive immune response is intimately linked to activity and function of cellular components of the innate arm of the immune response. This is because microbial pathogens and their respective proteins must be captured/cleared (phagocytosed) by antigen-presenting cells, such as macrophages, dendritic cells, etc., and those pathogen proteins dissociated/fragmented and presented to CD4 T cells in a process called antigen presentation (Fig. 311.1). Typically, after such a microbial challenge, there is an initial expansion and differentiation of the CD4+ T-lymphocyte/cell into a T-helper-type 1 (Th1) cell. This supports not only the selective development of humoral and/or cell-mediated immune memory required to clear the foreign pathogen/antigen providing sterile immunity, but also for ensuring the innate immune system adequately handles the initial insult [1]. However, over time, even as a memory response is developing, there is a shift from the Th1 response toward a Th2 response that is orchestrated by sub-populations of 'regulatory' CD4+ T cells. The best known of these cell types are the Th17 and T regulatory cell subpopulations (Fig. 311.1) [2]. It is important to appreciate that, as foreign antigens are processed by macrophages/dendritic cells and presented to cells of the adaptive immune system, a Th2 (anti-inflammatory) response allows the development of memory of the event [3].

From a temporal/theoretical perspective the adaptive response was thought to occur in a sequential manner after the innate response. However, recent genomic studies of severely-injured patients have shown that both systemic inflammatory response syndrome (SIRS) and compensatory anti-inflammatory response syndrome (CARS) involve both innate and adaptive systems, and appear to occur simultaneously during critical illness [4].

Adaptive immune cells in critical illness

Although changes in total white blood cell count and neutrophils have been previously described, little has been written specifically on the role of lymphocytes in critical illness. The typical response for leukocytes and neutrophils are elevations in order to respond to the acute insult. In trauma patients who survived at least three days, three distinct patterns of lymphocyte (T and B cells) expression are noted. One-third never alter their lymphocyte count. Most, however, suffer a loss of lymphocytes (lymphopenia), of whom half show a recovery of lymphocyte count to normal levels within 4 days whereas the other half remain lymphopenic and have an increased mortality at 21 days. This inability of the critically ill patient to replenish cellular components of the adaptive immune response, such as T and/or B cells, suggests a need to retain such immunological capacity if the individual is to survive [5]. The accepted explanation for loss of these cells is through the process of lymphoid apoptosis.

From a functional perspective the development of immune suppression/anergy in critically ill patients (while not a routinely

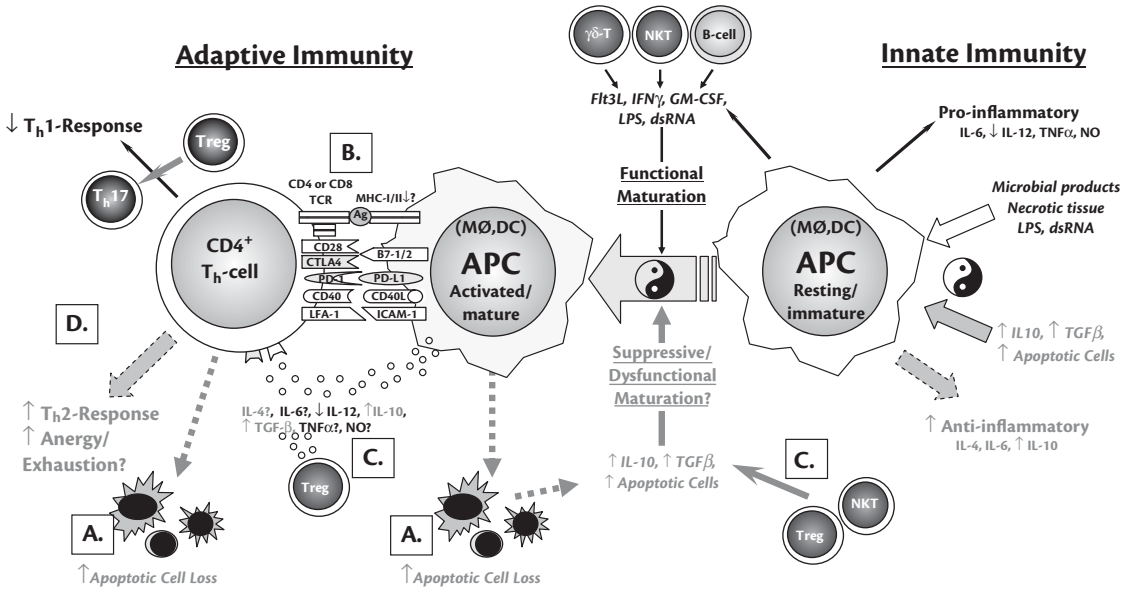


Fig. 311.1 The antigen presenting cell (APC, which could be a dendritic cell [DC] or macrophage/monocyte [MØ]):T cell interaction plays a major role in determining the type of T lymphocyte immune response that predominates following an antigen challenge/presentation. This is highly dependent on initial stimuli present at the time of APC maturation/activation. On the one hand, inflammatory stimuli such as microbial products may induce pro-inflammatory cytokine production by DC/MØ s (IL-12), as well as up-regulation of co-stimulatory receptors on their surface (B7–1/2). This may lead to a shift towards the Th1 type of immune response. On the other hand, anti-inflammatory/deactivating stimuli may induce incomplete maturation of DCs, their production of anti-inflammatory cytokines (IL-10, TGF-β, etc.) and expression of regulatory receptors such as PD-L1 at their surface. This type of stimulation may rather induce a Th2 type of immune response; this latter quiescent/suppressive state is often the default condition for the APC normally. After sepsis, APCs exhibit several alterations of both their phenotype and function: (A) increased apoptosis of both CD4 T-cells as well as mature/activated and immature/resting DC/MØs; (B) changes in surface molecule expressions (e.g., ↑co-inhibitory molecules vs. ↓co-stimulatory molecules); (C) changes in cytokine production, and; (D) impairment in capacity to induce Th1 type/pro-inflammatory T cell activation (reduced Cell-Mediated Immune responsiveness). Other Abbreviations: Flt-3L, Fms-like tyrosine kinase ligand 3; GM-CSF, granulocyte-macrophage colony stimulating factor; LPS, lipopolysaccharide.

measured outcome) has been described thirty years ago [6]. While apoptotic cell loss was identified as a contributor to this response, there are several other secreted and/or cell-associated mediators and regulatory cell types that also contribute to this state of immune suppression (Fig. 311.1)).

In patients with sepsis, the role of the adaptive immune cells is ever-expanding. The innate and adaptive responses were previously considered to be distinctly separate. However, both B and T cells (and their subtypes) are now recognized to play a prominent role in the clearance of pathogens (innate immune process) and the transition to the adaptive response. CD4+ cells, particularly the Th1 subset, are key players in the clearance of pathogens by providing cytokines, and these are known to undergo apoptosis in sepsis [7]. Spleens from patients who died from sepsis show a decrease in CD4 and CD8 cells; this correlates with data seen in trauma patients, further implicating the role of adaptive immune cells in sepsis [8].

At the far end of the spectrum of critical illness is end-organ failure such as acute respiratory distress syndrome (ARDS). Like sepsis, this was once thought to be caused only by an uncontrolled innate immune response. Again, recent research has demonstrated a role for the adaptive immune response in ARDS. In an animal model (haemorrhagic shock followed by polymicrobial sepsis via caecal ligation and puncture), CD4 cells were specifically recruited to the lung and this was regulated by T regulatory cells [9]. In human acute lung injury, T regulatory cells also appear to play a role in the pathophysiology of the end-organ disease (Fig. 311.1)) [10].

Immune modulating proteins in the adaptive immune system

Although the impact of cell types from the adaptive response have been studied in critical illness, numerous molecules such as cytokines, steroids and catecholamines have been studied extensively regarding their role in critical illness. Much of the work has focused on the shift towards a Th2 response, particularly in sepsis (Fig. 311.1)). The cytokines interleukin (IL)-4 and IL-13 shift the immune system towards the Th2 response. In addition soluble receptor antagonists, such as tumour necrosis factor (TNF) and IL-1, can block the primary function of the cytokine (Th1 response for TNF and IL-1), thereby shifting to the adaptive Th2 response [11]. Catecholamines and steroids (both endogenous and exogenous) shift the immune system towards a Th2 response [12].

Recent work has focused on specific cell-surface proteins that alter the immune response. Human leukocyte antigen (HLA) is the monocyte protein that presents antigens to the T cells, and is the bridge between the innate and adaptive immune response. HLA is decreased in patients who die from sepsis [8], however its utility as a biomarker has been questioned even though patients with critical illness have decreased levels of HLA [13].

As an appropriate adaptive immune response to a foreign antigen requires the T cell to receive proper co-stimulation during antigen presentation, there has been growing interest in understanding how cell-surface co-stimulatory molecules are antagonized by

co-inhibitory cell surface molecules such as CTLA-4 and PD-1 (Fig. 311.1)). These have been shown in other disease states to have the capacity to produce a state of T and B cell anergy/exhaustion that looks similar to what is encountered in the critically ill. CTLA-4 levels in human sepsis correlated with CD4 cell apoptosis [14]. In mice who underwent caecal ligation and puncture to model polymicrobial sepsis, increased expression of CTLA-4 was seen on adaptive cells; when CTLA-4 antibodies were given survival was improved [15]. Interestingly, this survival benefit was seen in a dose-dependent manner where survival was improved at low dose, but worsened with high doses. This finding speaks to the delicate balance of the immune system in critical illness.

In critically-ill surgical patients (from either trauma or surgical stress), PD-1 expression was significantly increased on T cells in those patients with severe physiologic dysfunction as noted by an APACHE II score >20 [16]. In an animal model of sepsis (caecal ligation and puncture) PD-1 expression was increased on adaptive immune cells while administration of an anti-PD-1 antibody improved survival [17]. Survival was also increased in mice lacking PD-1 who underwent caecal ligation and puncture compared with wild type animals. However, this benefit was attributed to the expression of PD-1 on macrophages, a cell of the innate immune system [18]. This again shows the cross-talk between adaptive and innate immune systems. In humans, increased PD-1 expression was seen in CD4 T cells in the days soon after onset of sepsis. Interestingly, this increased expression also correlated with an increased risk of nosocomial infection, highlighting the immune suppressive effects of PD-1 [19]. In animal models of ARDS (haemorrhagic shock followed by caecal ligation and puncture) PD-1 expression was increased on both innate and adaptive cells in the lung. In addition, lack of PD-1 was associated with improved survival when compared to wild-type mice. In humans with ARDS, those who survived had reduced expression of PD-1 on T cells compared to those who died [20].

Future directions

HLA, CTLA-4 and PD-1 have an impact on the adaptive immune system in critical illness. Other immune modulating proteins, such as BTLA, may also have similar effects. These proteins can enhance our understanding of the immune system in ICU patients, however, they may also provide an opportunity for therapeutic intervention.

Past efforts to treat critical illness, particularly sepsis, have failed in part due to the limited nature of the targeted therapy. When an antibody to one cytokine was given, the native immune system adapted with compensation by another combination of cytokines. This is evident by the long list of failed therapies [7]. Targeting immune modulating proteins such as PD-1 may be better able to treat a critical illness such as sepsis. Antibodies to both CTLA-4 and PD-1 have been trialled for cancer treatments and a CTLA-4 antibody has been approved for melanoma treatment. It is thus tempting to speculate about their potential application in the critically-ill patient sometime in the future.

References

1. Perl M, Chung CS, Garber M, Huang X, and Ayala A. (2006). Contribution of anti-inflammatory/immune suppressive processes to the pathology of sepsis. *Frontiers in Bioscience*, **11**, 272–99.
2. Mai J, Wang H, and Yang XF. (2010). Th 17 cells interplay with Foxp3+ Tregs in regulation of inflammation and autoimmunity. *Frontiers in Bioscience*, **15**, 986–1006.
3. Marshall JC, Charbonney E, and Gonzalez PD. (2008). The immune system in critical illness. *Clinics in Chest Medicine*, **29**, 605–16.
4. Xiao W, Mindrinos MN, Seok J et al. (2011). A genomic storm in critically injured humans. *Journal of Experimental Medicine*, **208**, 2581–90.
5. Heffernan DS, Monaghan SF, Thakkar RK, Machan JT, Cioffi WG, and Ayala A. (2012). Failure to normalize lymphopenia following trauma is associated with increased mortality, independent of the leukocytosis pattern. *Critical Care*, **16**, R12.
6. Winchurch RA and Munster AM. (1980). Post-traumatic activation of suppressor cells. *Journal of Reticuloendothelial Society*, **27**, 83–8.
7. Larosa SP and Opal SM. (2012). Immune aspects of sepsis and hope for new therapeutics. *Current Infectious Disease Reports*, **14**, 474–83.
8. Boomer JS, To K, Chang KC, et al. (2011). Immunosuppression in patients who die of sepsis and multiple organ failure. *Journal of the American Medical Association*, **306**, 2594–605.
9. Venet F, Chung CS, Huang X, Lomas-Neira J, Chen Y, and Ayala A. (2009). Lymphocytes in the development of lung inflammation: a role for regulatory CD4+ T cells in indirect pulmonary lung injury. *Journal of Immunology*, **183**, 3472–80.
10. D'Alessio FR, Tsushima K, Aggarwal NR, et al. (2009). CD4 + CD25 + Foxp3 + Tregs resolve experimental lung injury in mice and are present in humans with acute lung injury. *Journal of Clinical Investigations*, **119**, 2898–913.
11. Shubin NJ, Monaghan SF, and Ayala A. (2011). Anti-inflammatory mechanisms of sepsis. *Contributions to Microbiology*, **17**, 108–24.
12. Elenkov IJ. (2004). Glucocorticoids and the Th1/Th2 balance. *Annals of the New York Academy of Sciences*, **1024**, 138–46.
13. Trimmel H, Luschin U, Kohrer K, Anzur C, Vevera D, and Spittler A. (2012). Clinical outcome of critically ill patients cannot be defined by cutoff values of monocyte human leukocyte antigen-DR expression. *Shock*, **37**, 140–4.
14. Roger PM, Hyvernat H, Ticchioni M, Kumar G, Dellamonica J, and Bernardin G. (2012). The early phase of human sepsis is characterized by a combination of apoptosis and proliferation of T cells. *Journal of Critical Care*, **27**, 384–93.
15. Inoue S, Bo L, Bian J, Unsinger J, Chang K, and Hotchkiss RS. (2011). Dose-dependent effect of anti-CTLA-4 on survival in sepsis. *Shock*, **36**, 38–44.
16. Monaghan SF, Thakkar RK, Tran ML, et al. (2012). Programmed death 1 expression as a marker for immune and physiological dysfunction in the critically ill surgical patient. *Shock*, **38**, 117–22.
17. Brahmamdam P, Inoue S, Unsinger J, Chang KC, McDunn JE, and Hotchkiss RS. (2010). Delayed administration of anti-PD-1 antibody reverses immune dysfunction and improves survival during sepsis. *Journal of Leukocyte Biology*, **88**, 233–40.
18. Huang X, Venet F, Wang YL, et al. (2009). PD-1 expression by macrophages plays a pathologic role in altering microbial clearance and the innate inflammatory response to sepsis. *Proceedings of the National Academy of Sciences, USA*, **106**, 6303–8.
19. Guignant C, Lepape A, Huang X, et al. Programmed death-1 levels correlate with increased mortality, nosocomial infection and immune dysfunctions in septic shock patients. *Critical Care*, **15**, R99.
20. Monaghan SF, Thakkar RK, Heffernan DS, et al. (2012). Mechanisms of indirect acute lung injury: a novel role for the coinhibitory receptor, programmed death-1. *Annals of Surgery*, **255**, 158–64.

CHAPTER 312

Immunomodulation strategies in the critically ill

Aline B. Maddux and Gordon R. Bernard

Key points

- Severe sepsis is the result of an infectious stimulus that triggers a hyper-inflammatory response and results in multiple organ failure. This hyperimmune response triggers a phase of immunoparalysis that results in the patient's inability to resist and clear infections, causing the delayed mortality observed in some septic patients.
- The inflammatory and coagulation cascades are closely linked such that a significant aspect of the disease process is attributed to the activation of the coagulation cascade by circulating inflammatory mediators.
- Therapeutic approaches to sepsis have targeted the hyper-inflammatory response, inhibition of the subsequent coagulation cascade, and immunostimulation during the immunoparalysis phase.
- Proven beneficial therapies for sepsis are limited to the mechanical eradication of the source of infection, antibiotics to clear the organism, the judicious use of fluids to support organ perfusion, and oxygen supplementation. Studies evaluating immunotherapeutics for the treatment of severe sepsis have failed to show efficacy in clinical trials.
- Further research may demonstrate effectiveness using a strategy of targeting therapies based on an improved identification of the patient's phase of sepsis, use of combination therapies, a better understanding and strategy aimed at specific host-organism interactions, and/or better specified therapies in relation to identified biomarkers.

Introduction

Severe sepsis is a hyperimmune response to an infectious stimulus resulting in a surge of cytokines and other mediators of inflammation. High circulating levels of pro-inflammatory cytokines, especially TNFα, lead to shock, multiple organ failure, and death in septic patients [1]. More recently, it has been recognized that patients with sepsis enter into a state of immune paralysis as their disease worsens and organ failures emerge. This subsequent anti-inflammatory response is characterized by apoptosis of immune cells and high levels of anti-inflammatory cytokines (IL-10, IL-13 and TGF-ß) inhibiting the function of macrophages as well as T and B lymphocytes [1,2]. These anti-inflammatory cytokines also suppress production of pro-inflammatory cytokines and inhibit the ability of monocytes to present antigens to other immune cells. This immune paralysis likely leads to the patient's inability to resist and clear infections resulting in the delayed mortality observed in some septic patients [1].

The proven beneficial therapies for sepsis are limited to the mechanical eradication of the source of infection, antibiotics to clear the organism, the judicious use of fluids to support organ perfusion, and oxygen supplementation during the initial hyperinflammatory phase of illness [3]. Outside of these effective therapies, strategies to counteract the hyper- and hypo-immune phases of sepsis have been tried thus far with only minimal success.

Antagonism of microbes and microbial products

The use of antibodies to target different components of the endotoxin molecule has been a strategy in sepsis therapy for many decades. The therapies tested have included both monoclonal immunoglobulin preparations targeting a specific antigen as well as polyclonal immunoglobulin preparations. Cellular mechanisms for recognizing and reacting to endotoxin have also been therapeutic targets [4].

Antagonism of endotoxin or cell activation through interference with endotoxin receptor/transduction apparatus

The activity of endotoxin is primarily due to the lipopolysaccharide (LPS) component of the Gram-negative bacterial cell wall. LPS has three components including the Lipid A moiety, core polysaccharide, and O-specific side chains. LPS activates the immune response when the Lipid A moiety binds to the TLR-4 receptor on monocytes and macrophages via the LPS-binding protein. Studies designed to block this interaction using antibodies to LPS have been conducted [5].

The first trial using anti-endotoxin human immunoglobulins in severe sepsis patients was performed by Ziegler et al. in 1982 [6]. This study showed improved survival when bacteraemic patients as well as those with septic shock were treated with human antibodies against the LPS core component of endotoxin. This small trial showed very promising results but its findings have never been replicated.

Further anti-LPS monoclonal antibody studies have utilized HA-1A, a monoclonal IgM LPS anticore antibody, and E5,

a monoclonal antibody directed against the lipid A moiety of LPS [5]. In 1991, Ziegler et al. compared HA-1A to placebo in a randomized, controlled trial [5]. This study of 543 septic patients showed no effect on the overall patient population, although a subset of 200 patients with culture-proven, Gram-negative bacteraemia showed improved survival in patients treated with HA-1A. In 1994, a follow-up randomized, placebo-controlled trial of 621 patients with Gram-negative bacteraemia and shock failed to confirm the positive results of the previous subset analysis. An additional trial in 1999 evaluating HA-1A in 269 children with meningococcal septic shock also failed to show improvement [4].

Greenman et al. published the first large trial evaluating therapy with E5 in 1991. This study of 316 patients with confirmed Gram-negative sepsis showed no survival difference at 30 days. However, a subgroup of 137 patients who were not in shock at the time of study entry showed improved mortality, decreasing from 43% in the placebo group to 30% in those given E5 ($p = 0.01$). In an attempt to confirm the positive results of this subset analysis, Bone et al. randomized 530 patients with Gram-negative sepsis. While this study did not show an improvement in survival, in the 139 patients who presented with organ failure there was better resolution of organ failure compared to placebo. In a final attempt to prove the efficacy of E5, a large RCT enrolled 1090 patients with documented ($n = 915$) or probable Gram-negative infections ($n = 175$) and severe sepsis, but again, showed no difference in 28-day all-cause mortality [4]. Currently, no single anti-endotoxin therapeutic strategy has been shown to provide benefit in patients with sepsis.

Further investigation has been undertaken to evaluate the efficacy of pooled serum containing polyclonal immunoglobulin preparations (IVIG). The exact mechanisms of action are not known though immunoglobulins may improve phagocytosis by coating bacteria, as well as eliciting neutralization and opsonization that inactivates bacterial endotoxins and exotoxins. It is also speculated that interaction between IVIG and the complement cascade, as well as its effects on the release of cytokines and cytokine antagonists by endotoxin, improves the immune response [4].

Two meta-analyses published by Kreymann et al. and Turgeon et al. in 2008 concluded that polyclonal IVIG improved survival. However, both analyses caution a significant amount of heterogeneity between trials. Furthermore, when Turgeon et al. eliminated studies of poor quality, the remaining trials showed no benefit from treatment [4]. A Cochrane review published in 2010 evaluated 42 studies including 17 studies of polyclonal IVIG in adults with sepsis. It reported a significant reduction in 30-day mortality, but again, noted heterogeneity across trials. Furthermore, when this analysis was restricted to trials with a low risk of bias, no mortality reduction was shown. Studies that evaluated long-term mortality (>60 days) did not show any effect of treatment. Polyclonal immunoglobulins provide some promise as an adjuvant therapy in sepsis but large, multicenter studies are needed to confirm efficacy [4].

IVIG in the paediatric population has a theoretical greater potential for benefit due to the immaturity of B cells in patients <5 years old. A prospective case-controlled study published in 2005 of 100 paediatric patients aged 1–24 months showed a significant improvement in lengths of stay, development of complications and mortality (28% treated versus 56% placebo) [3]. Due to this study, the Surviving Sepsis Guidelines published in 2008 recommend consideration of IVIG treatment in paediatric patients with severe sepsis [3]. However, the authors note the low trial quality and weak evidence base to support this recommendation. IVIG in the neonatal population is also controversial. Although the Surviving Sepsis guidelines cite evidence that IVIG decreases mortality in neonates with septic shock, the Cochrane review could not confirm this [4].

Antagonism of pro-inflammatory cytokines

Antagonism of the effects of TNFα

TNFα is a significant pro-inflammatory cytokine that acts early in the cascade of the hyperimmune response causing downstream elevation of IL-1, IL-6, and IL-8. Injection of TNFα into animals and humans triggers signs and symptoms closely resembling severe sepsis including hypotension, activation of the clotting cascade, and organ system dysfunction. Furthermore, persistent elevation of plasma TNFα levels during sepsis was associated with high mortality [7]. However, blockade of the effects of TNFα worsened the immune system's ability to clear microbes in animal models [8].

Strategies to reduce TNFα-initiated systemic inflammation have adopted multiple approaches. Trends toward improved survival have been noted, particularly in certain subgroups of patients. For example, those patients with severe sepsis as defined by failure of more than two organ systems and early hypotension responded to administration of p55 TNF receptor fusion protein. A study performed by Pittet et al. showed more organ-failure free days, a decreased incidence of new organ dysfunctions and a trend towards reduced 28-day mortality in severe sepsis patients treated with TNF neutralizing-receptor fusion protein p55 [7]. The INTERSEPT study, reported in 1996, showed improvement in shock reversal and organ dysfunction in the treatment arm, although failed to show benefit in treatment of patients without shock or improvement of 28-day mortality. The NORASEPT trial similarly showed a non-significant trend towards improved survival in those patients with septic shock. IL-6 levels are considered to be a surrogate for overall TNFα activity because of the much longer half-life of this cytokine compared to the more rapidly cleared TNFα. The MONARCS trial enrolled patients with elevated IL-6 levels and found that treatment with an anti-TNFα antibody fragment lowered TNFα and IL-6 levels, accelerated the resolution of organ dysfunction, and improved 28 day mortality though the effect was not robust enough to result in FDA approval [7]. In conclusion, most trials attempting to antagonize the effects of TNFα show a small, non-significant increase in survival. Further studies are needed to determine the true efficacy of these pharmaceutical approaches.

Antagonism of the effects of IL-1

IL-1 is another pro-inflammatory cytokine thought to work in concert with TNFα to induce the hyperimmune response of sepsis [9]. The counter-regulatory IL-1 receptor antagonist (IL-1ra) protein occurs naturally in humans [10]. This receptor antagonist functions by competitively and reversibly occupying the IL-1 receptor. However, stimulation of as few as 5% of IL-1 receptors is sufficient to trigger an inflammatory response. It thus requires 100–10,000 fold excess of IL-1ra relative to IL-1 to inhibit the effects of IL-1 [9].

A randomized controlled trial of 893 patients with sepsis syndrome published by Fisher et al. in 1994 evaluated human recombinant IL-1ra treatment versus placebo. No significant increase was seen in overall survival, but secondary and retrospective analyses showed an increased survival time among patients with sepsis who

also had organ dysfunction and/or a predicted risk of mortality of ≥24% [10]. Based on this finding, Opal et al. pursued a follow-up trial reported in 1997, which enrolled patients with severe sepsis defined as end-organ dysfunction and/or septic shock. This study was stopped early after enrolling 696 of the planned 1300 patients due to a low likelihood of finding a significant difference in 28-day mortality. As discussed by the study authors, it seems plausible that maintenance of the 100–10,000 fold excess of rhIL-1ra relative to IL-1 is needed to inhibit the immune response and this could not be consistently maintained in an ICU population [9].

Inhibition of the coagulation cascade

Intense activation of the coagulation cascade occurs in severe sepsis. The coagulation response can be used to assist in the isolation of infected areas to prevent spread of infection to other parts of the body. Unfortunately, in severe sepsis, the systemic nature of the process makes the isolation effort somewhat futile, and possibly, counterproductive. The over-exuberant coagulation response can result in microvascular thrombosis, widespread endothelial damage, and organ failure.

Tissue factor (TF) is a cell surface receptor, which, under normal circumstances, is not exposed to plasma, blood cells, or endothelium. However, bacteria and pro-inflammatory mediators cause endothelial cells and monocytes to express TF, resulting in activation of the extrinsic coagulation pathway. TF pathway inhibitor regulates this coagulation pathway [11]. Recombinant TF pathway inhibitor was tested in the OPTIMIST trial, a phase III trial of 1754 patients with severe sepsis [11]. This trial failed to show an improvement in mortality and, unfortunately, showed a trend towards harm in those treated concurrently with heparin.

Similarly, severe infection is associated with a decreased level of the endogenous anticoagulant, antithrombin (AT). AT inactivates multiple clotting enzymes to contribute to the hypercoagulation of sepsis [11]. Multiple small studies published in the 1990s suggested promising effects of AT in patients with severe sepsis. KyberSept, a multi-national phase III trial of AT in 2,314 patients however showed no difference in 28- or 90-day mortality. Further investigation of AT as a treatment for sepsis will need to focus on identification of a target population who will have the greatest potential for benefit while having minimal risks for bleeding [11].

Activated protein C (aPC) has anti-coagulant, anti-inflammatory, and anti-apoptotic effects that led to its use in sepsis. Its anticoagulant mechanism is via inactivation of factors Va and VIIIa, preventing generation of thrombin. This, in turn, decreases inflammation by reducing mast cell degranulation, platelet activation, and neutrophil recruitment. The results of the PROWESS trial generated great excitement as treatment with recombinant aPC reduced absolute 28 day mortality by 6.1% (p = 0.005). It was subsequently approved for use in the most severely septic patients with APACHE II scores ≥25 due to observations by the FDA that this subgroup derived the most benefit [12]. However, a subsequent trial, PROWESS-SHOCK, failed to replicate the positive results of the PROWESS trial causing aPC to be withdrawn from the market [13]. Activated protein C is also not recommended for use in children based on a study reported by Nadel et al. in 2007 [14]. This study evaluated 477 children with sepsis and failed to show improvement in mortality.

Corticosteroids

Steroids inhibit production of pro-inflammatory cytokines (e.g. TNFα, IL-1, IL-2, IL-6, IFN-gamma), chemokines, bradykinins, and eicosanoids while increasing the release of anti-inflammatory mediators (e.g. IL-10, IL-1ra, and TNF receptor antagonists). They also inhibit inducible nitric oxide synthase (iNOS) and decrease the function of inflammatory cells and their migration to sites of inflammation [1].

Smaller studies published by Bollaert et al. and Briegel et al. in the late 1990s showed trends to resolution of hypotension and improved mortality in patients treated with replacement dose glucocorticoids. However, these studies were underpowered to detect a significant mortality benefit [1]. In 2002, further studies of replacement dose glucocorticoids were published by Annane et al. who reported improved resolution of refractory hypotension and a decrease in absolute mortality in patients with relative adrenal insufficiency treated with hydrocortisone and fludrocortisone. In contrast, those who responded to ACTH, and thus deemed to be without adrenal insufficiency, gained no benefit and trended towards harm from glucocorticoids [2,3]. Subsequently, the CORTICUS trial compared treatment of patients with 11 days of hydrocortisone versus placebo. This trial failed to show any mortality benefit in patients treated with steroids, regardless of ACTH response, though reversal of shock was accelerated [2].

Currently, consensus is lacking with regard to steroid therapy in septic shock. The Surviving Sepsis Guidelines recommend steroids only in vasopressor-refractory shock [3]. ACTH stimulation tests are not recommended. The enthusiasm for steroid use is further dampened by concern over secondary infections, as reported by CORTICUS, and myopathy [3]. Minimal paediatric data exist regarding sepsis and steroid therapy. Currently, hydrocortisone is recommended only for children with catecholamine-resistant shock and suspected or proven adrenal insufficiency [3].

Prostaglandins

NSAIDs inhibit synthesis of prostaglandins, thus decreasing plasma levels of arachidonic acid-derived eicosanoids, particularly thromboxane A2 and prostacyclin. Thromboxane A2 is associated with bronchoconstriction, platelet aggregation, and vasoconstriction. Prostacyclin acts as a vasodilator and antagonist of thrombosis. Eicosanoids have been associated with abnormalities of airway mechanics particularly bronchoconstriction, pulmonary hypertension, hypoxaemia, cardiovascular collapse, and multiple organ failure in patients with sepsis syndrome. Additionally, the NF- κB cellular signalling pathway is inhibited by NSAIDs [15].

In 1997 Bernard et al. published a trial designed to evaluate treatment with ibuprofen versus placebo in 455 patients with severe sepsis. Despite finding a rapid decline in urinary levels of prostacyclin and thromboxane, temperature, heart rate, oxygen consumption and lactic acidosis, there was no improvement in either the incidence or duration of shock, nor development of the respiratory distress syndrome, and no significant effect on all-cause mortality [15]. The subset of patients entering the ibuprofen trial in a state of hypothermia were evaluated separately and reported in 1999. There were 44 (10%) such patients and they had significantly greater elevations in urinary thromboxane A2, urinary prostacyclin, serum TNFα, and serum IL-6 concentrations compared to the

febrile cohort. The hypothermic patients also had a worse mortality (70% versus 35%). In this subset, those treated with ibuprofen showed a beneficial effect as evidenced by an improvement in organ failure-free days, ICU-free days, ventilator-free days, and mortality. The study authors suggested that ibuprofen therapy may show benefit in high-risk patients with hypothermic sepsis [15].

Statins

Statins inhibit the HMGCoA reductase enzyme that, in turn, inhibits its synthesis of isoprenoid units necessary for the activity of multiple proteins, such as the GTP binding protein, Rho. This action subsequently affects transcription factors such as NFκB and AP-1 leading to decreased levels of inflammatory cytokines such as IL-6 and IL-1. HMGCoA-reductase also induces caspase-dependent apoptosis in smooth muscle cells that could lead to less inflammation during severe sepsis by avoiding the necrotic cell death pathway. In addition, statins inhibit the reduction of HMGCoA to mevalonate. This process is involved in synthesis of bile acids, some steroid hormones and Vitamin D. Statins also inhibit production of the cyclooxygenase (COX)-2 protein, the biosynthesis of ubiquinone (mitochondrial respiration) and haeme-A (oxygen transport), and prenalation of small G proteins. These are considered to be far-reaching effects with regard to inflammation and acute infection. Thus, though there are many potential mechanisms by which statins could alter the inflammatory response in sepsis, the precise mechanism remains to be elucidated [16].

A cohort study published by Christensen et al. in 2010 showed that patients on statin therapy immediately prior to ICU admission had a reduced risk of death within 30 days and at 1 year after ICU admission. The cohort design of this study limits the ability to infer causation but suggests positive effects of statin therapy [16]. A large meta-analysis published in 2010 by Bjorkhem-Bergman et al evaluated the potential therapeutic effects of statins in bacterial infections, reporting that statins were associated with improved survival (odds ratio 0.52, p <0.0001). However, the 15 studies analysed were of observational design and further analysis suggested significant publication bias [17]. Another meta-analysis by Janda et al. evaluated 20 studies including mostly cohort studies and one RCT. A protective effect for 30-day mortality, in-hospital mortality, pneumonia-related mortality, bacteraemia-related mortality, sepsis-related mortality, and mixed infection-related mortality were associated with statin use. This study was again limited by inclusion of mostly observational cohorts with significant heterogeneity between studies. The randomized controlled trial included in this review was done by Tseng et al. [18]. It included 80 patients with aneurysmal subarachnoid haemorrhage who were randomized to treatment with pravastatin or placebo and showed reduced mortality from sepsis as a secondary outcome. Phase II and III studies are currently in progress to evaluate the role of statins in the treatment of sepsis.

Immunostimulation

G-CSF/GM-CSF

The immunological effects of G-CSF and GM-CSF are thought to counteract the immunoparalysis state of sepsis. G-CSF use in non-neutropenic patients may act via improving the host defence response through enhancing chemotaxis and neutrophil adhesion, increasing superoxide production, and improving bacterial killing activity. It also improves the production of pro-inflammatory cytokines and increases intracellular uptake of antibiotics [19]. A trial performed by Root et al. evaluated 701 adult patients with severe sepsis due to bacterial pneumonia. While treatment with G-CSF increased white blood cell count, it did not show an improvement in mortality, occurrence of organ dysfunction, nor ICU length of stay [20]. Further studies are in progress to better identify the subset of patients with immunoparalysis with plans to evaluate the effect of immune stimulating therapies in this population.

Conclusion

Studies evaluating the use of immunotherapeutics for severe sepsis are plagued with multiple confounding factors including the predominant phase of sepsis (hyperimmune versus hypoimmune), differing offending organisms, differing host-organism interactions, heterogeneity in the patient populations, and underpowered study designs. Perhaps the correct immunotherapy will need to be tailored in order to decrease the immune response in the hyperimmune phase and increase it during the hypoimmune phase. In order to do so, better markers of these phases of sepsis are needed. Further studies may also find more efficacy in using multiple therapies simultaneously to obtain best results. Finally, there exists a close interaction between the immune and coagulation systems. Further study of this link and therapies to temper the coagulation cascade may prove to be a successful modality of therapy in order to halt the body's progression to multiple organ failure.

References

1. Rice TW and Bernard GR. (2005). Therapeutic intervention and targets for sepsis. *Annual Review of Medicine*, **56**, 225–48.
2. Skrupky LP, Kerby PW, and Hotchkiss RS. (2011). Advances in the management of sepsis and the understanding of key immunologic defects. *Anesthesiology*, **115**, 1349–62.
3. Dellinger RP, Levy MM, Carlet JM, et al. (2008). Surviving Sepsis campaign: international guidelines for management of severe sepsis and septic shock. *Critical Care Medicine*, **36**, 296–327.
4. Alejandria MM, Lansang MAD, Dans LF, and Mantaring JB. (2002). Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. *Cochrane Database of Systematic Reviews*, **1**, CD001090.
5. Fink MP. (1993). Adoptive immunotherapy of Gram-negative sepsis: use of monoclonal antibodies to lipopolysaccharide. *Critical Care Medicine*, **21**, S32–9.
6. Ziegler EJ, McCutchan JA, Fierer J, et al. (1982). Treatment of Gram-negative bacteremia and human anti-serum to a mutant *Escherichia coli*. *New England Journal of Medicine*, **307**, 1225–30.
7. Reinhart K and Karzai W. (2001). Anti-tumor necrosis factor therapy in sepsis: update on trials and lessons learned. *Critical Care Medicine*, **29**, S121–5.
8. Qui P, Cui X, Barochia A, Li Y, Natanson C, and Eichacker PQ. (2011). The evolving experience with therapeutic TNF inhibition in sepsis: considering the potential influence of risk of death. *Expert Opinion on Investigational Drugs*, **201**, 1555–64.
9. Opal S, Fisher CJ, Dhainaut JF, et al. (1997). Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The interleukin-1 receptor antagonist sepsis investigator group. *Critical Care Medicine*, **25**, 1115–24.
10. Fisher CJ, Dhainaut JF, Opal SM, et al. (1994). Recombinant human interleukin 1 receptor antagonist in the treatment of patients

with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra sepsis syndrome study group. *Journal of the American Medical Association*, **271**, 1836–43.
11. LaRosa SP and Opal SM. (2005). Tissue factor pathway inhibitor and antithrombin trial results. *Critical Care Clinics*, **21**, 433–48.
12. Bernard GR, Vincent J-L, Laterre PF, et al. (2001). Efficacy and safety of recombinant human activated protein C for severe sepsis. *New England Journal of Medicine*, **344**, 699–709.
13. Ranieri VM, Thompson BT, Barie PS, et al. (2012). Drotecogin alfa (activated) in adults with septic shock. *New England Journal of Medicine*, **366**, 2055–64.
14. Nadel S, Goldstein B, Williams MD, et al. (2007). Drotrecogin alfa (activated) in children with severe sepsis: a multicenter phase III randomized controlled trial. *Lancet*, **369**, 836–43.
15. Eisen DP. (2012). Manifold beneficial effects of acetyl salicylic acid and nonsteroidal anti-inflammatory drugs on sepsis. *Intensive Care Medicine*, **38**, 1249–57.
16. Bernard GR. (2010). Statins for acutely hospitalized patients: randomized controlled trials are long overdue. *Critical Care*, **14**, 141–2.
17. Bjorkhem-Bergman L, Bergman P, Andersson J, and Lindh JD. (2010). Statin treatment and mortality in bacterial infections—a systematic review and meta-analysis. *PLoS One*, **5**, e10702.
18. Janda S, Young A, Fitzgerald JM, Etminan M, and Swiston J. (2010). The effect of statins on mortality from severe infections and sepsis: a systematic review and meta-analysis. *Journal of Critical Care*, **25**, 656.e7–22.
19. Meisel C, Schefold JC, Pschowski R, et al. (2009). Granulocyte-macrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: a double-blind, randomized, placebo-controlled multicenter trial. *American Journal of Respiratory and Critical Care Medicine*, **180**, 640–8.
20. Root RK, Lodato RF, Patrick W, et al. (2003). Multicenter, double-blind, placebo-controlled study of the use of filgastrim in patients hospitalized with pneumonia and severe sepsis. *Critical Care Medicine*, **31**, 367–73.

CHAPTER 313

Immunoparesis in the critically ill

Fabienne Venet and Alain Lepape

Key points

- Critically-ill patients develop immune dysfunction that affects both innate and adaptive immune responses.
- Two main outcomes are potentially associated with immunoparesis, all-cause mortality, and secondary infections.
- Therapeutics aiming at restoring immunological functions are currently being tested in patients.
- Colony-stimulating factors (G-CSF and GM-CSF) have been used in a limited number of randomized clinical trials.
- Further studies are urgently needed.

Introduction

Severe injuries induce immune alterations that have, for a long time, been solely considered as an overwhelming pro-inflammatory syndrome. Enormous efforts have been expended over the last 20 years to find new therapies (mostly anti-inflammatory) that decrease the mortality from sepsis [1,2]. However, with the recent withdrawal of activated protein C (drotrecogin alfa) due to the lack of beneficial effect on 28-day mortality, severe sepsis, and septic shock represent one of the most costly therapeutic failure areas in medicine.

This repeated failure has led to the re-evaluation of our understanding of septic shock pathophysiology and, more generally, of the post-injury immune response. It is now well accepted that, in parallel with an exaggerated pro-inflammatory response, critically-ill patients develop an immunosuppressive phase, termed immunoparesis/immunoparalysis or immune reprogramming, that is associated with significant immune dysfunction [3,4]. The goal of this chapter is to provide a comprehensive overview of injury-induced immune dysfunction, and of potential immunostimulatory therapies.

Immunoparesis

The place of immunoparesis in the post-insult immune response

Severe injuries induce a major pro-inflammatory response through interaction between Toll-like (and other) receptors on immune cells and danger- or pathogen-associated molecular patterns (DAMPs, PAMPs). Due to numerous, incompletely understood mechanisms, this response may not be contained after severe injury at the local level but becomes systemic, leading to shock and organ dysfunction [1]. To maintain immune homeostasis, anti-inflammatory mechanisms controlling the initial pro-inflammatory response also develop. This compensatory phase rapidly becomes predominant at the systemic level and is associated with injury-induced immune dysfunction in intensive care unit (ICU) patients (Fig. 313.1) [3,4].

Immunosuppression in ICU patients is evidenced by the frequent occurrence of infections with relatively avirulent germs (i.e. *Candida* or cytomegalovirus) that normally occur solely in immunosuppressed hosts [3]. Importantly, in septic patients, immune dysfunction is not only observed at the systemic level, but also in organs distant from the site of infection [5]. The intensity and duration of this injury-induced immune dysfunction have been associated with an increased risk of death and of secondary nosocomial infections after admission [6].

Injury-induced innate immune dysfunctions

The innate immune response represents the first line of defence after an infection and thus is rapidly mobilized after release of DAMPs or PAMPs. Innate immune cells (i.e. neutrophils, monocytes, and dendritic cells) are affected at different levels in critical illness. In particular, neutrophil reprogramming is manifest by impaired recruitment to infection/injury sites, abnormal accumulation to remote sites, and dysregulation of effector responses [7]. An anarchic recruitment of activated neutrophils to organs distant from the injury site is thought to contribute towards organ dysfunction.

Monocyte dysfunction is a hallmark of immunoparalysis in ICU patients. In particular, decreased pro-inflammatory and increased anti-inflammatory cytokine production and a decreased antigen presentation capacity have been repeatedly described in severely-ill patients. Importantly, decreased expression of human leukocyte antigen-DR (mHLA-DR) has emerged as a reliable marker of monocyte dysfunction and immunoparalysis in ICU patients [4]. Several clinical studies have linked decreased mHLA-DR with an increased risk of death and nosocomial infection; this biomarker is now being used in clinical trials to stratify patients before initiating immunostimulation therapy [8]. Finally, the number of circulating dendritic cells is decreased and cytokine production is oriented toward production of anti-inflammatory mediators with a reduction in IL-12 secretion after injury [9].

Injury-induced adaptive immune dysfunction

Far less work has been dedicated to the study of lymphocyte alterations in ICU patients. Critically-ill patients often present with a

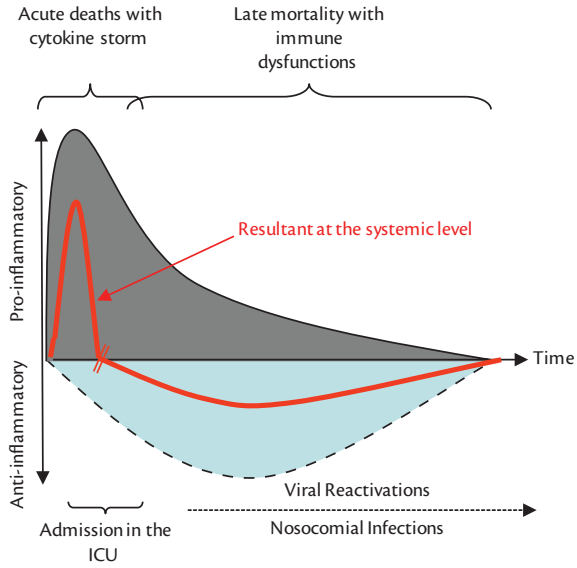


Fig. 313.1 Schematic representation of post-injury immune response.

dramatic lymphopenia that is present from admission and affects every lymphocyte subpopulation [10]. This is associated with a major induction of apoptosis [1]. Remaining lymphocytes present with functional alterations, such as decreased proliferation and cytokine production in response to stimulation. Phenotypic alterations such as increased co-inhibitory receptor expression and decreased co-stimulatory receptor and CD3 expression have also been described on circulating lymphocytes taken from septic shock patients [4]. This is associated with a decrease in T cell receptor diversity. Finally, an increased percentage of circulating $CD4^+CD25^+$ regulatory T cells has been repeatedly shown in ICU patients [11].

Is immunoparesis a target for treatment in the critically-ill patient?

The answer to this question is still unclear. Two outcomes—increased mortality and occurrence of secondary infections—are related to immune dysfunction, notwithstanding the nature of the initiating insult (trauma, surgery, infection). Studies on secondary infection in ICU patients have focused on the relationship to exposure to invasive devices, selection of resistant micro-organisms by antimicrobials and cross-transmission. There is an obvious variability in ICU-acquired infections that is not explained by the duration of ventilation nor catheterization. Immunoparesis is a probable risk factor for secondary infection; however, since this concept is more recent, and perhaps because of the numerous anti-inflammatory agent trial failures, this promising path has not been fully explored. There is a need for randomized clinical trials (RCTs) to address this question in appropriately selected patients.

Colony-stimulating factor therapy in non-neutropenic ICU patients

Two candidate drugs have been tested—granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF). Both are potent immunostimulators, inducing leukocytosis and augmenting the activity of granulocytes.

G-CSF has been used to date in eight placebo-controlled trials [12]. Overall, 2044 patients were included in these trials however the results did not favour a reduction in mortality (relative risk = 0.95, 95% confidence interval: 0.80–1.14). Although not always clearly described, G-CSF appears to have few side-effects.

Despite far fewer patients studied to date—only four randomized controlled studies (RCTs) totalizing 158 patients) (Table 313.1) [8,13–15]—GM-CSF does seem to be an interesting candidate to stimulate immune function in the context of critical illness. Besides the same immunostimulation effects as G-CSF, GM-CSF has specific actions on monocyte functions, namely stimulation of monocytes/macrophages and induction of monocytic cytokine expression (e.g. TNF-α or IFN-γ induction seen in ex vivo models after stimulation by endotoxin). GM-CSF also induces antigen presentation (increased mHLA-DR). An interesting approach used by Meisel et al is to stratify patients according to their immune dysfunction as measured by mHLA-DR and, hence, to restrict the use of GM-CSF to patients at risk [8].

Overall, despite these trials not showing any effect on 28-day or hospital mortality, a positive effect was seen on the initial infection with a higher rate of reversal (RR 1.34, 95% CI 1.11–1.62, $p = 0.002$). However, as stated by Schefold [16], this effect is globally described within a meta-analysis containing many more patients enrolled into G-CSF trials. Whereas G-CSF increases antimicrobial defences, GM-CSF has a predominant role in restoring immunocompetency, especially antigen presentation, and may play an important role in the prevention of secondary infections after the initial infectious episode.

Interferon-gamma therapy (IFN-γ) in ICU patients

The beneficial effects of IFN-γ on monocyte deactivation in septic patients were first described in 1997 by Docke et al. in a limited open-label study [17]. In 2002, Nakos et al. confirmed these results in trauma patients [18], although no RCTs have yet been conducted in ICU patients.

Anti-apoptotic therapies in ICU patients

Given the extensive apoptosis-induced depletion of immune cells, including lymphocytes, another potential strategy is to use the anti-apoptotic immunostimulatory cytokines IL-7 and IL-15. Both have shown efficacy in sepsis models [19], although no clinical experience is yet available.

Intravenous immunoglobulin therapy (IVIg) in ICU patients

The immune effects of IVIg are far too complex to be depicted here. Among its effects, improvement of bacterial clearance is clearly an important role, and this is associated with inhibitory effects upon upstream mediators of the host response plus scavenging of downstream inflammatory mediators. Several meta-analysis and systematic reviews have been published, however the heterogeneity of the RCTs and the conflicting results of the meta-analysis have been recently described [20]. The use of IVIg is still not recommended; further studies are needed before this therapeutic can be used in sepsis. Only toxin-mediated bacterial diseases, such as severe *Staphylococcus* and *Streptococcus* infections, are currently given as examples of indications for IVIg therapy in infection, even though sufficiently powered RCTs are lacking.

Table 313.1 Description of randomized clinical trials of GM-CSF versus placebo in adult human sepsis

Study	Population	Intervention	Comparison	Outcome
Presneill [15], Australia	Single centre, 18 patients within 24 hours of severe sepsis with ≥2 SIRS criteria, clinically suspected infection, and sepsis-related pulmonary dysfunction	Randomized, double-blind, placebo-controlled phase II trial of low-dose (3 μg/kg) iv GM-CSF daily for 5 days versus conventional therapy in 10 patients and 8 receiving placebo	◆ **Primary outcome**: patient survival to 30 days ◆ **Secondary outcomes**: assessed at D5 • Oxygenation (PaO_2/FiO_2) • Occurrence of ARDS. • SOFA score: number and functional status of blood and bronchoalveolar leukocytes	◆ No difference in survival, rate of ARDS or SOFA score ◆ Improvement in PaO_2/FiO_2 ◆ Increased peripheral neutrophils, decreased alveolar neutrophils
Rosenbloom[13], USA	Single centre, 40 patients with SIRS and defined focus of infection, 33 evaluable	Randomized, unblinded, placebo-controlled, prospective study; 72-hour infusion of GM-CSF (125 μg/m^2) (n = 18) or placebo (n = 15)	◆ Survival, cure of infection, leukocyte count ◆ Functional markers of inflammation on circulating neutrophils and monocytes	◆ Increase in leukocyte count and cure/improvement in initial infection ◆ No difference in survival or organ failure ◆ Upregulation of immunological markers
Orozco [14], Mexico	Single centre, 58 patients with abdominal sepsis	Daily dosage of 3 μg/kg for 4 days (group 1) or placebo (group 2)	Time to improvement, duration of antibiotic therapy, hospital stay, complications, mortality, and adverse reactions to drugs	◆ **Median time to clinical recovery and improvement**: 2 days versus 4 days (p < 0.005) ◆ **Median hospital stay**: 9 versus 13 days (p < 0.001) ◆ **Median time with antibiotic therapy**: 9 versus 13 days p < 0.001) ◆ **Episodes of infectious complications**: 1 versus 16 (p = 0.02) ◆ **Fatal outcome**: 2 versus 2 (NS)
Meisel [8], Germany	Multicentre (n = 3), 38 patients with sepsis-induced immune suppression (reduced mHLA-DR levels <8000 monoclonal antibodies (mAb) per cell in two consecutive measures)	GM-CSF 4 mg/kg/day or placebo, sc for 5 days, then GM-CSF or placebo for 3 days at either 8 mg/kg/day GM-CSF (if mHLA-DR ≤15,000 mAb per cell at Day 5), or 4 mg/kg/day (mHLA-DR >15,000 mAb per cell)	◆ **Primary outcome**: mHLA-DR expression ◆ **Secondary endpoints**: course of disease severity, cellular immunity, inflammatory markers, length of hospital/ICU stay	mHLA-DR normalized in 19/19 treated patients versus 3/19 controls (p < 0.001); shorter time of mechanical ventilation (148 ± 103 versus 207 ± 58 hours, p = 0.04); improved APACHE score (p = 0.02); shorter length of both intrahospital and ICU stay (59 ± 33 versus 69 ± 46 and 41 ± 26 versus 52 ± 39 days, respectively, both not significant)

Data from various sources (see references).

Conclusion

Critically-ill patients develop immune dysfunction, and this is collectively called immunoparesis/immunoparalysis or immune reprogramming. Both innate and adaptive immune responses are affected. The intensity and duration of injury-induced immune dysfunction is associated with an increased risk of death and secondary infections. Innovative therapeutic strategies aiming at restoring immunological functions are currently being tested. Only G-CSF and GM-CSF have been used in a limited number of RCTs while IFN-γ and IL-7 represent novel future therapeutic approaches. Importantly, there is an urgent need for further clinical trials, which should include large cohorts of ICU patients stratified by relevant markers of immune dysfunction.

References

1. Hotchkiss RS and Karl IE. (2003). The pathophysiology and treatment of sepsis. *New England Journal of Medicine*, **348**, 138–50.
2. Carlet J, Cohen J, Calandra T, Opal SM, and Masur H. (2008). Sepsis: time to reconsider the concept. *Critical Care Medicine*, **36**, 964–6.
3. Hotchkiss RS. (2010). Opal S. Immunotherapy for sepsis—a new approach against an ancient foe. *New England Journal of Medicine*, **363**, 87–9.
4. Hotchkiss RS, Monneret G, and Payen D. (2013). Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. *Lancet: Infectious Diseases*, **13**, 260–8.
5. Boomer JS, To K, Chang KC, et al. (2011). Immunosuppression in patients who die of sepsis and multiple organ failure. *Journal of the American Medical Association*, **306**, 2594–605.
6. Monneret G, Venet F, Kullberg BJ, and Netea MG. ICU-acquired immunosuppression and the risk for secondary fungal infections. *Medical Mycology*, **49**(Suppl. 1), S17–23.

7. Kovach MA and Standiford TJ. (2012). The function of neutrophils in sepsis. *Current Opinion on Infectious Diseases*, **25**, 321–7.
8. Meisel C, Schefold JC, Pschowski R, et al. (2009). Granulocyte-macrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: a double-blind randomized placebo-controlled multicenter trial. *American Journal of Respiratory and Critical Care Medicine*, **180**, 640–8.
9. Huang X, Venet F, Chung CS, Lomas-Neira J, and Ayala A. (2007). Changes in dendritic cell function in the immune response to sepsis. Cell- and tissue-based therapy. *Expert Opinion in Biological Therapy*, **7**, 929–38.
10. Venet F, Davin F, Guignant C, et al. (2010). Early assessment of leukocyte alterations at diagnosis of septic shock. *Shock*, **34**, 358–63.
11. Venet F, Chung CS, Monneret G, et al. (2008). Regulatory T cell populations in sepsis and trauma. *Journal of Leukocyte Biology*, **83**, 523–35.
12. Bo L, Wang F, Zhu J, Li J, and Deng X. (2011). Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) for sepsis: a meta-analysis. *Critical Care*, **15**, R58.
13. Rosenbloom AJ, Linden PK, Dorrance A, Penkosky N, Cohen-Melamed MH, and Pinsky MR. (2005). Effect of granulocyte-monocyte colony-stimulating factor therapy on leukocyte function and clearance of serious infection in nonneutropenic patients. *Chest*, **127**, 2139–50.
14. Orozco, H, Arch J, Medina-Franco H, et al. (2006). Molgramostim (GM-CSF) associated with antibiotic treatment in nontraumatic abdominal sepsis: a randomized, double-blind, placebo-controlled clinical trial. *Archives of Surgery*, **141**, 150–3.
15. Presneill JJ, Harris T, Stewart AG, Cade JF, and Wilson JW. (2002). A randomized phase II trial of granulocyte-macrophage colony-stimulating factor therapy in severe sepsis with respiratory dysfunction. *American Journal of Respiratory and Critical Care Medicine*, **166**, 138–43.
16. Schefold JC. (2011). Immunostimulation using granulocyte and granulocyte–macrophage colony stimulating factor in patients with severe sepsis and septic shock. *Critical Care*, **15**, 136.
17. Docke WD, Randow F, Syrbe U, et al. (1997). Monocyte deactivation in septic patients: restoration by IFN-gamma treatment. *Nature: Medicine*, **3**, 678–81.
18. Nakos G, Malamou-Mitsi VD, Lachana A, et al. (2002). Immunoparalysis in patients with severe trauma and the effect of inhaled interferon-gamma. *Critical Care Medicine*, **30**, 1488–94.
19. Opal SM. (2010). New perspectives on immunomodulatory therapy for bacteraemia and sepsis. *International Journal of Antimicrobial Agents*, **36**(Suppl. 2), S70–3.
20. Shankar-Hari M, Spencer J, Sewell WA, Rowan KM, and Singer M. (2012). Bench-to-bedside review: immunoglobulin therapy for sepsis—biological plausibility from a critical care perspective. *Critical Care*, **16**, 206.

PART 14.4

Anaphylaxis

CHAPTER 314

Pathophysiology and management of anaphylaxis in the critically ill

James Keegan and Charles D. Deakin

Key points

- Anaphylaxis is a severe life-threatening systemic hypersensitivity reaction.
- Life-threatening symptoms include airway compromise, bronchospasm, hypoxia, and cardiovascular collapse.
- Common triggers include foods, insect stings, latex, and drugs.
- Intramuscular epinephrine (adrenaline) is the primary treatment of anaphylaxis. Treatment is time critical.
- Plasma tryptase levels should be measured immediately and 1–2 hours post-onset of symptoms.

Definition

Anaphylaxis is a 'severe life-threatening, generalized or systemic hypersensitivity reaction' [1] characterized by rapidly developing airway, breathing, and/or circulation problems with associated skin and mucosal changes [2]. It most commonly results from immunologically-mediated reactions to foreign antigens.

History

Although Egyptian hieroglyphics describe the sudden death of a Pharaoh following a wasp sting in 2640BC, the first clinical record of an anaphylactic reaction was published in 1836 by the French physiologist, Magendie. In 1902, Portier and Richet used the term 'anaphylaxis' to describe the reaction of dogs to injection of sea anemone venom. Subsequently, anaphylactic reactions to many substances have been described. Early reports of histamine release following tubocurarine and thiopentone were published in 1936 and 1952 [3].

Epidemiology

Anaphylaxis occurs in approximately 10–20 per 100,000 population per annum, with 3–4 per 100,000 of these admitted to hospital. Between 2005–2009 anaphylaxis accounted for 1269 (0.3%) adult and 81 (0.1%) paediatric UK critical care admissions [2]. Ninety-two per cent of adults and 95% of children admitted to critical care survive to hospital discharge, with a mean length of critical care admission of 1.2 days in survivors.

In children, foods are the most frequent cause of anaphylaxis, while drug reactions are more common in adults. Incidence of anaphylaxis during anaesthesia is estimated at between 1 in 10,000 and 1 in 20,000 anaesthetics [4,5].

Anaphylaxis occurs more commonly in female adults (65%), but exhibits an even sex distribution in children [2]. Patients who suffer from asthma or atopy, and those on beta-blockers may have a predisposition to more severe reactions.

Pathophysiology

Hypersensitivity reactions

Hypersensitivity reactions are classified in Box 314.1. Anaphylaxis is classified as a type I hypersensitivity reaction.

Anaphylaxis

Anaphylaxis occurs due to an exaggerated reaction to foreign protein associated with release of vasoactive substances. It is characterized by release of inflammatory mediators from mast cells or basophils triggered by the interaction of an allergen with IgE bound to the Fc epsilon R1 receptor [6].

In response to IgE-mediated activation, mast cells release multiple mediators, including histamine, tryptase, arachidonic acid metabolites, leuktotrienes, prostaglandins, eosinophil, and neutrophil chemotactic factors, platelet activating factor, complement, and kinins. The roles and interactions of these agents are complex and not fully elucidated.

Anaphylactoid reactions

These are clinically identical to anaphylactic reactions, but are mediated by substances other than IgE, e.g. IgG, complement or direct stimulation of histamine release. These mechanisms again result in release of vasoactive mediators and produce a clinical picture indistinguishable from anaphylactic reactions.

The European Academy of Allergy and Clinical Immunology has proposed that the classification of anaphylactic and anaphylactoid reactions be replaced with the terms allergic anaphylaxis (IgE, IgG, complement-mediated) and non-allergic anaphylaxis [1], however this proposal has not been universally accepted [7].

Box 314.1 Classification of hypersensitivity reactions

- **Type I**: anaphylactic, with previous sensitization. Mediated via mast cells and IgE.
- **Type II**: cytotoxic; antibodies directed against the cell membrane.
- **Type III**: immune complex.
- **Type IV**: delayed-type hypersensitivity, T-cell mediated.

Reproduced from Deakin C, *Clinical Notes for the FRCA*, Copyright 2011, with permission from Churchill Livingstone. Data from Gell PGH and Coombs RRA (eds), *Clinical Aspects of Immunology*, First Edition, Oxford, England: Blackwell; 1963.

Presensitization

Predisposed individuals are exposed to many agents that may result in cross-reactivity. For example, quaternary amine groups found in neuromuscular blocking agents (NMBAs) are present in toothpastes, washing detergents, and cough medicines, e.g. pholcodine in cough syrups. IgE antibodies to pholcodine may be responsible for some NMBA anaphylaxis. Removal of pholcodine-containing products from the market in Norway was associated with a decreased number of cases of NMBA anaphylaxis [8].

Causative agents

A broad range of agents including foods, insect stings, latex, and drugs can trigger anaphylaxis. Common food allergens include nuts, shellfish, milk and eggs. Anaphylaxis to insect stings commonly occurs from hymenoptera (bees, wasps, ants) venom, and mosquito bites.

Latex allergy

Latex is a common rubber material used in health care equipment. It occurs naturally in the sap of the rubber tree *Hevea brazilensis* or can be produced synthetically. It contains protein allergens, including the natural rubber elongation factor Hev b. These act as antigens to cross-link membrane-bound IgE and cause mast cell degranulation.

Latex is associated with three clinical syndromes—irritant dermatitis, allergic contact dermatitis (type IV hypersensitivity reaction), and anaphylaxis (type I hypersensitivity). Anaphylaxis is often delayed 30–60 minutes after exposure.

Latex accounts for 20% of anaphylactic reactions during anaesthesia [5]. The increase in use of universal precautions in health care settings over recent decades has resulted in a significant rise in latex reactions in healthcare workers. Other high-risk groups include patients regularly exposed to latex, e.g. repeated bladder catheterizations & multiple surgical procedures. Male gender, non-Caucasian race, atopy (asthma, allergic rhinitis, contact dermatitis, and hay fever) and food allergies are all risk factors.

Latex fruit syndrome

Some fruits (e.g. bananas, kiwi fruit, avocados, chestnuts, tomatoes) contain proteins that cross-react with latex proteins; those allergic to these fruits are at risk of latex allergy [9].

Drugs

Neuromuscular blocking agents (NMBAs)

Approximately 50–60% of cases of anaphylaxis during anaesthesia are due to NMBAs [5,7]. Suxamethonium is the most frequently implicated in terms of total number of reactions, sharing a similar incidence per drug use as rocuronium. Data on the relative frequency of anaphylaxis to the non-depolarizing muscle relaxants are inconclusive, although cis-atracurium demonstrates consistently low rates of reaction. The benzolisoquinoliniums (atracurium, mivacurium) cause histamine release and are also associated with anaphylactoid reactions. Cross-reactivity can occur between individual drugs and also across the aminosteroid and benzolisquinolinium groups; consequently, no agent should be considered 'safe' in a patient with a history of anaphylaxis to NMBAs without formal testing.

Anaesthetic agents

Anaphylactic reactions have been reported with all commonly used hypnotic agents (thiopentone, propofol, etomidate, midazolam, ketamine). As a group they are implicated in 1% of anaesthesia-related reactions [5]. Twenty per cent of reactions to thiopentone are anaphylactic; the remainder are anaphylactoid (90% direct histamine release, 10% complement activation). Specific IgE interaction may occur against the isopropyl groups on propofol, although most adverse reactions to propofol are non-immunological.

Antibiotics

Antibiotics cause 15–20% of anaesthesia-related reactions. Most commonly, reactions occur to penicillins, cephalosporins, and vancomycin [5]. Patients who are allergic to penicillin or amoxicillin have a higher incidence of allergic reaction to first generation cephalosporins (cephalexin, cefadroxil, cephradine), but not later generations.

Opioids

Opioids, most frequently morphine, account for 2% of perioperative reactions. Morphine, pethidine and codeine also cause non-specific histamine release, which may be associated with anaphylactoid reactions.

Colloids

Colloids are implicated in 2% of reactions. Gelatins are the most common cause, but reactions to dextrans and hydroxyethyl starches are also implicated. Reactions may be immediate or delayed.

Others

Chlorhexidine is a common topical antiseptic. Anaphylactic reactions have been reported to topical and parenteral exposure, including chlorhexidine-impregnated intravascular catheters.

Reactions to intravenous contrast media and vital dyes (e.g. patent blue) are increasing, probably due to their increased use. Reactions to dyes often occur 30–60 minutes after administration, due to the rate of absorption from subcutaneous tissue at the site of dye injection.

Clinical features

Anaphylaxis typically causes rapidly developing (within minutes) features, with airway, breathing and circulation problems. There are usually associated skin and mucosal changes [6].

- **Airway**: pharyngeal and laryngeal oedema, hoarse voice, and stridor.

- **Respiratory**: bronchospasm, hypoxaemia, pulmonary oedema and respiratory arrest.
- **Cardiovascular**:
  - *Hypotension*—systemic vascular resistance is decreased by as much as 80% due to the direct effect of histamine.
  - *Tachycardia*—due to chronotropic effects of histamine and secondary release of epinephrine and norepinephrine. Bradycardia occurs in 10% of cases.
  - *Myocardial ischaemia and ECG changes*—can occur in individuals with normal coronary circulation.
  - *Cardiac arrest*—can occur due to direct myocardial depression, vasodilation, capillary leak and relative hypovolemia.
- **Gastrointestinal**: nausea and vomiting, diarrhoea, abdominal colic.
- **Neurological**:
  - Awake patients may experience a metallic taste and a sense of impending doom.
  - Decreased conscious level.
- **Skin and mucosal changes**: present in over 80% of anaphylaxis cases, these can occur together or in isolation:
  - Erythema.
  - Urticaria.
  - *Angioedema*—eyelids, lips, mouth, or throat.

Patients may present with signs from one system in isolation, e.g. cardiovascular collapse. The time course of reactions varies with the causative agent. Fatal food reactions commonly result in respiratory arrest 30–35 minutes after ingestion; insect stings cause cardiovascular collapse after 10–15 minutes, while cardiorespiratory arrest following intravenous medication typically occurs within 5 minutes [6].

Treatment

Treatment of anaphylaxis should follow European Resuscitation Council guidelines [6] (or similar) using an ABC approach (Airway, Breathing, Circulation) (Fig. 314.1).

Patient positioning

Awake patients should be positioned carefully. Sitting or standing may precipitate cardiovascular collapse, although those with breathing problems may find sitting more comfortable. Elevate the patient's legs if there is hypotension.

Remove trigger

The trigger agent may be unclear so removal of all potential causative agents should be targeted. If anaesthetized, maintain anaesthesia with an inhalational anaesthetic agent.

Airway

Maintain the airway and administer high flow oxygen. Anaphylaxis can cause airway swelling and obstruction—if necessary intubate the trachea and provide controlled ventilation.

Cardiopulmonary resuscitation

In the event of cardiac arrest perform cardiopulmonary resuscitation according to Advanced Life Support Guidelines.

Epinephrine (adrenaline): intramuscular

Epinephrine is the primary treatment for anaphylaxis. It is an agonist at both alpha and beta-adrenoreceptors. The alpha-receptor action reverses peripheral vasodilation and oedema, while the beta-receptor action causes bronchodilation, increases myocardial contractility and suppresses histamine and leukotriene release. Beta-2 adrenoreceptors on mast cells attenuate mast cell degranulation [6].

The European Resuscitation Council guidelines recommend that epinephrine be given to all patients with life-threatening features. The intramuscular (im) route is recommended as the default due to a greater margin of safety, and ease of administration. The anterolateral aspect of the middle third of the thigh is the best site for im administration.

The recommended doses for im epinephrine (equivalent volume of 1:000 epinephrine) are [6]:

- **>12 years/adult**: 500 μg im (0.5 mL).
- **6–12 years**: 300 μg im (0.3 mL).
- **6 months–6 years**: 150 μg im (0.15 mL).
- **<6 months**: 150 μg im (0.15 mL).

Epinephrine: intravenous

The intravenous route has a lower margin of safety and is prone to significant side effects due to dosage or misdiagnosis errors. Side effects include severe hypertension, myocardial ischaemia, tachycardia, and arrhythmias. However, intravenous epinephrine may be used in monitored patients (electrocardiogram (ECG), oxygen saturation, and blood pressure) by those expert in its use. Indeed, intravenous (iv) epinephrine may be needed in those patients that require repeated im doses. The critical care unit is often best placed to provide this expertise.

In adults, epinephrine should be titrated in 50 μg boluses. An infusion may be used if repeated doses are required. Use of iv epinephrine in children requires careful titration in a specialist setting. A dose as low as 1 μg/kg may be effective [6].

Fluids

Patients may exhibit profound hypovolaemia due to capillary leak and vasodilation. Give a fluid challenge of 500–1000 mL (20 mL/kg in children). There is no evidence to suggest superiority of crystalloid or colloid in this setting, but colloid administration should be considered a possible trigger in patients receiving it at the time of onset of anaphylaxis.

Antihistamines

H_1-receptor antagonists, e.g. chlorphenamine maleate, are useful to alleviate histamine-induced vasodilation and bronchoconstriction. H_2 receptor antagonists are not recommended for the initial treatment of anaphylaxis [6].

Steroids

Corticosteroid administration may be useful to shorten anaphylactic reactions, but evidence of efficacy and optimum dose is limited.

Others

Bronchodilators

Bronchodilator therapy is useful in those patients with respiratory symptoms. Inhaled salbutamol and ipratropium, alongside

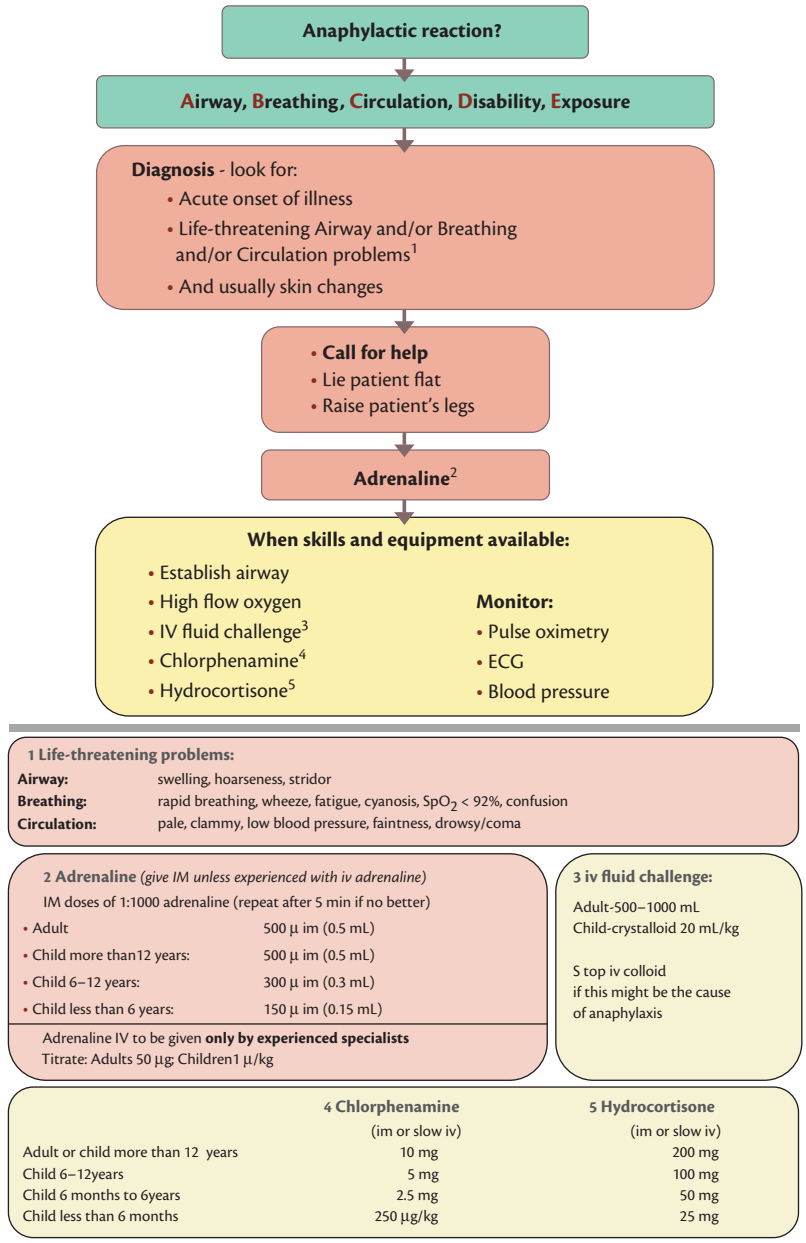


Fig. 314.1 Anaphylaxis treatment algorithm.
Reproduced with the kind permission of the Resuscitation Council (UK).

iv therapy (salbutamol, aminophylline, magnesium) may be considered.

Vasopressors

Use of second-line vasopressors and inotropes including vasopressin, norepinephrine, terlipressin, metaraminol, methoxamine and glucagon have been described [6]. Their use may be considered in the critical care unit by those experienced in their use. Glucagon may be particularly useful in anaphylaxis to beta-blockers [6]. In severe cases, cardiopulmonary bypass may be beneficial.

Rocuronium and sugammadex

The modified gamma-cyclodextrin sugammadex acts to encapsulate rocuronium and other aminosteroid NMBAs. Case reports are described of its use to treat aminosteroid-induced anaphylaxis [10–12].

Investigations

Standard investigations for all medical emergencies should include 12-lead ECG, chest X-ray, urea, and electrolytes, and arterial blood gases. Some specific tests are also applicable.

Tryptase

Mast cell tryptase is the major protein component of mast cell secretory granules. Together with histamine and other amines, tryptase is released in anaphylactic and anaphylactoid reactions. The normal basal plasma tryptase is <1 ng/mL. Peak concentrations >20 ng/mL

occur 1–2 hours after onset of anaphylaxis. Mast cell tryptase has a half-life of approximately 2 hours; therefore, levels may return to normal within 8 hours.

Measurement of mast cell tryptase is essential to diagnose anaphylaxis. These should be taken:

- As soon as possible after resuscitation.
- 1–2 hours post-onset of symptoms.
- At 24 hours (or in follow-up clinic) to define basal levels.

Skin prick testing

In patients who have suffered from IgE-mediated anaphylaxis, efforts should be made to identify the trigger. Sensitization to potential trigger agents can be detected through skin prick tests, which demonstrate the presence of specific IgE antibodies. These should be performed 4–6 weeks after the reaction.

Methylhistamine

Histamine is principally metabolized to methylhistamine, which is then excreted in the urine. Raised urinary concentrations can be detected following reactions that involve systemic release of histamine.

RAST/CAP

In vitro testing systems can be used to measure specific IgE, e.g. radio-allergosorbent test (RAST). The CAP system has replaced RAST testing in some laboratories. This fluoroimmunoassay measures antigen-specific antibodies and is often more sensitive than RAST.

Follow-up and prophylaxis

Following successful treatment of suspected anaphylaxis, patients should be observed in an appropriate clinical area with facilities for treatment of acute medical emergencies.

Up to 20% of patients may suffer from a biphasic reaction. Consequently, all patients should be reviewed by a senior clinician, educated on the signs and symptoms, and advised to return if they recur. The European Resuscitation Council recommends consideration of discharge with 3 days of antihistamine and steroid treatment to minimize the risk of recurrence [6]. An epinephrine auto-injector should also be considered for those at risk of idiopathic anaphylaxis, or in whom the trigger is difficult to avoid, e.g. insect stings, food reactions. Education on the appropriate use of an auto-injector is vital.

Follow-up

The patient's general practitioner should be informed and follow-up in an allergy clinic is required. The aim of follow-up is to identify the cause, reduce the risk of further reactions, and educate the patient on diagnosing and initiating management themselves if appropriate.

References

1. Johansson SG, Hourihane JO, Bousquet J, et al. (2001). A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy*, **56**, 813–24.
2. Gibbison B, Sheikh A, McShane P, Haddow C, and Soar J. (2012). Anaphylaxis admissions to UK critical care units between 2005 and 2009. *Anaesthesia*, **67**, 833–9.
3. McKinnon RP and Wildsmith JA. (1995). Histaminoid reactions in anaesthesia. *British Journal of Anaesthesia*, **74**, 217–28.
4. Mertes PM and Laxenaire MC. (2004). Allergy and anaphylaxis in anaesthesia. *Minerva Anestesiologica*, **70**, 285–91.
5. Dong SW, Mertes PM, Petitpain N, Hasdenteufel F, and Malinovsky JM. (2012). Hypersensitivity reactions during anesthesia. Results from the ninth French survey (2005–2007). *Minerva Anestesiologica*, **78**, 868–78.
6. Soar J, Perkins GD, Abbas G, et al. (2010). European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: Electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. *Resuscitation*, **81**, 1400–33.
7. Membership of the Working Party, Harper NJN, Dixon T, et al. (2009). Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia*, **64**, 199–211.
8. Florvaag E, Johansson SGO, Irgens Å, and de Pater GH. (2011). IgE-sensitization to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market. *Allergy*, **66**, 955–60.
9. Hepner DL and Castells MC. (2003). Latex allergy: an update. *Anesthesia and Analgesia*, **96**, 1219–29.
10. Baldo B. (2012). Sugammadex and rocuronium-induced anaphylaxis. *Anaesthesia*, **67**, 1174–5.
11. Barbosa FT and da Cunha RM. (2012). Case of anaphylaxis induced by rocuronium treated with sugammadex. *Revista Brasileira de Anestesiologia*, **62**, 538–42.
12. Kawano T, Tamura T, Hamaguchi M, Yatabe T, Yamashita K, and Yokoyama M. (2012). Successful management of rocuronium-induced anaphylactic reactions with sugammadex: a case report. *Journal of Clinical Anesthesia*, **24**, 62–4.

SECTION 15

Poisoning

PART 15.1

Principles of management

CHAPTER 315

Role of toxicology assessment in poisoning

Albert Jaeger

Key points

- Diagnosis of acute poisoning is based on history, symptoms, biomedical investigations, toxicological analyses, and sometimes therapeutic tests.
- An accurate and useful toxicological analysis needs good collaboration between the physician and the analytical toxicologist.
- Toxidromes, electrocardiographic disturbances, and biomedical abnormalities may provide diagnostic clues for specific poisons.
- Indications for toxicological analysis include assessment of diagnosis, evaluation of severity and prognosis, indication and evaluation of treatments, and medicolegal implications.
- Interpretation must take into account kinetic and toxicodynamic variation, type of poisoning, and factors such as age and underlying diseases.

Introduction

Diagnosis of acute poisoning is based on history, symptoms, biomedical investigations, toxicological analyses, and sometimes therapeutic tests [1]. Toxicological analytical methods are now widely available, but extensive and specific quantitative analyses are expensive. Therefore, the indications should be carefully considered by the physician according to assessment of diagnosis, evaluation of severity and prognosis, indication and evaluation of treatments, and medicolegal implications. The interpretation needs to take several factors into account depending on the poison and the patient.

Methods

Before a toxicological analysis is performed, the physician and the analytical toxicologist should discuss the following points [2]:

- Which substance (the parent compound and/or the metabolite(s)) should be analysed and in what biological sample(s)?
- What type of analytical method (qualitative or quantitative) and what specificity are needed?
- Is the analysis useful for the management of the patient?
- Within what time limit should the results be available for the physician?

A qualitative or semiquantitative analysis of the parent compound (or the active or non-active metabolites) may be adequate for diagnostic assessment. A quantitative analysis of the parent compound is mandatory for kinetic studies. Analysis of the parent compound and the active metabolite(s) is needed for toxicodynamic assessment (symptom–concentration relationship) [2,3]. For instance, in ethylene glycol poisoning, analysis of ethylene glycol concentrations is useful for the diagnosis, but glycolate concentrations are more relevant for the evaluation of the severity and prognosis. Therefore, the analytical toxicologist should be precisely informed about the indications and the objective of the analysis.

Indications

Assessment of diagnosis

The usefulness of systematic toxicological screening in poisoned patients has not been established. In several reports, the concordance between the drug(s) suspected clinically and the drugs detected by toxicological screens ranged from 26 to 96%, and were dependent on the physician, the age of the patient, and the drug ingested [2]. The results rarely contributed to the management of the patient. Toxicology screens give qualitative or semiquantitative results for drugs that are frequently involved in poisonings, but they do not usually include toxins that induce severe poisoning, and for which analysis is essential for the prognosis or the treatment (e.g. theophylline, digoxin, lithium, carbon monoxide, methanol, ethylene glycol, etc.) [2,3].

In practice, four different situations may be observed:

- **Poisoning is definite, the toxin(s) is known according to the history, and the symptoms are related to the toxin(s) and dose**: a toxicological analysis is not absolutely necessary if it has no prognostic, therapeutic, or medicolegal implications.
- **Poisoning is definite and the toxin(s) is known, but the symptoms are not related to the suspected toxin(s) or to the dose**: a toxicological analysis is indicated in order to detect other toxins that may have been ingested.
- **Poisoning is suspected because of symptomatology (toxic symptoms or syndromes), but the toxin(s) is unknown**: only a toxicological analysis can confirm or refute poisoning.
- **Poisoning must be excluded by toxicological analysis**: in patients presenting with disturbances of the central nervous

system (trauma, brain death, in elderly patients), cardiovascular symptoms, or convulsions.

According to the history, the symptoms and biomedical abnormalities, the analysis should be directed towards specific drugs or groups of drugs.

Groups of symptoms (or toxidromes), such as those involving the autonomic nervous system, electrocardiogram (ECG) disturbances, and biomedical abnormalities may provide diagnostic clues for toxins that are not usually included in routine screens. They reflect directly the toxic effects and are often more useful than the measurement of plasma drug concentrations in the management of the patient [1,2]. Some examples of toxidromes, ECG disturbances, and biomedical abnormalities in specific poisonings are given in Tables 315.1, 315.2, and 315.3.

Therapeutic tests, such as naloxone in opiate and flumazenil in benzodiazepine poisoning, may also confirm the diagnosis [1].

Evaluation of severity and prognosis

In order to establish the relationship between the severity and the blood/plasma concentrations, the analysis must be specific and quantitative and sometimes include the active metabolites. The relationship is dependent on the mechanism of toxicity [3].

Functional toxins (e.g. barbiturates, benzodiazepines, meprobamate, cardiotropic drugs, lithium, theophylline, etc.) impair the function of one or more organs. Patients recover without sequelae if no complications occur during the poisoning. Their toxicity is directly related to the concentration at the target organ or receptor, Symptoms appear when the plasma concentration exceeds a threshold level, and the severity increases with the concentration (Fig. 315.1). The duration of the toxicity is dependent on the plasma half-life and the decrease of the concentration at the target organ. For instance, in barbiturate, meprobamate, or ethanol poisoning, the severity of disturbances of the central nervous system and coma is closely related to the plasma concentration. In acute theophylline poisoning, toxicity is minor at concentrations between 20 and 40 mg/L, moderate at concentrations between 40 and 100 mg/L, and severe at concentrations above 100 mg/L. If the parent compound is metabolized into active metabolites that have not been analysed, there is not usually a relationship between plasma parent drug concentrations and symptoms [3].

Lesional toxins (paraquat, paracetamol (acetaminophen), colchicine, amatoxins, heavy metals, etc.) induce cellular or organ damage. The severity depends on the maximum concentration that has been (or will be) reached at the target organ. If cellular damage has occurred, symptoms may not improve even though the toxin has been eliminated from the target organ. The interpretation has to

Table 315.1 Toxidromes involving the autonomic nervous system

Syndrome	Mechanism	Symptoms	Toxins
Cholinergic Muscarinic	Stimulation of cholinergic receptors ↑ acetylcholine production or ↓ acetylcholine degradation	Sweating, hypersalivation, bronchorrhea, diarrhoea, vomiting, miosis, bradycardia	Acetylcholine, pilocarpine, mushrooms (Clitocybe), organophosphate and carbamate insecticides
Nicotinic		Tachycardia, hypertension, fasciculation, paralysis	Nicotine, nicotinic, and organophosphate insecticides
Anticholinergic (or atropinic)	Cholinergic receptors blockade	Dry skin, hyperthermia, mydriasis, tachycardia, confusion, hallucinations, hyperventilation, agitation	Atropine, *Atropa belladonna*, Datura, mushrooms (*Amanita muscaria*, *A. pantherina*), TCA, antihistamines, antiparkinson-drugs
Sympathomimetic (or adrenergic)	Stimulation of α and β-adrenergic receptors	Agitation, convulsion, hypertension, tachycardia, hyperglycaemia, hypokalaemia, leucocytosis, hyperlactataemia	Caffeine, xanthines, theophylline, amphetamines, cocaine, LSD, phencyclidine
Narcotic (or opioid)	Opiate receptors agonist effect	CNS depression, hypoventilation, hypotension, miosis	Heroin, morphine, codeine, dextropropoxyphene
Withdrawal	Adrenergic stimulation	Insomnia, hallucinations, agitation (convulsion), diarrhoea, mydriasis, sweating, tachycardia, cramps	Withdrawal of alcohol, benzodiazepines, opiates
Antabuse	Acetaldehyde accumulation	Cutaneous flush, tachycardia, headache, hypotension, hyperventilation	Disulfiram, dithiocarbamates, mushrooms (Coprinus), dimethylformamide
Serotoninergic	↑ Serotoninergic brain activity, increased activity of 5-HT1A réceptors	Hyperthermia, dysautonomia, tachycardia, consciouness disturbances, hypertonia, hyperreflexia, myoclonia	Serotonin reuptake inhibitors, serotonin receptor agonists
Neuroleptic malignant	Dopaminergic receptors antagonism, acute depletion of dopamine	Hyperthermia, dysautonomia, tachycardia, consciousness disturbances, hypertonia, rhabdomyolysis, hyperleucocytosis	Piperazine-type neuroleptics
Ecstasy (MDMA)	Disturbances of dopaminergic and serotoninergic neurones, ↑ production of serotonin	Hyperthermia, dysautonomia, tachycardia, consciousness disturbances, hypertonia, disseminated intravascular coagulation, rhabdomyolysis, renal failure	MDMA

LSD, lysergic acid diethylamide; CNS, central nervous system; MDMA, 3-4-methylene dioxymethamphetamine.

Table 315.2 ECG disturbances induced by poisons

Disturbances	Effects	Toxins
Tachycardia	Anticholinergic	Atropine, *A. belladona*, Datura, anti-H1 histaminines, TCA, quinidine, disopyramide
	Betamimetic	Salbutamol, theophylline, xanthines, caffeine
	Alphamimetic	Amphetamines, cocaine, ephedrine
Bradycardia	Cholinergic	Acetylcholine, some opiates, organophosphates
	Beta-blockade	Beta-blockers
	Na-K-ATPase inhibition	Digoxin, digitoxin
	Ca channel blockade	Class IV AAR
	Na channel blockade	Class I AAR, chloroquine, TCA, some beta-blockers
	Alphalytic	Clonidine, methyldopa
Ventricular dysrhythmias (VES, VT, VF, torsades de pointes)	Betamimetic	Salbutamol, theophylline
	Alphamimetic	Amphetaminines, cocaine, ephedrine, trichloroethylene
	Na-K-ATPase inhibition	Digoxin, digitoxin
	Na channel blockade	Class I AAR, chloroquine, TCA, some beta-blockers
Atrioventricular block	Na-K-ATPase inhibition	Digoxin, digitoxin
	Na channel blockade	Class I AAR, chloroquine, TCA, some beta-blockers, ciguatoxin, tetrodotoxin
Intraventricular block (QRS > 0,10 s)	Na channel blockade	Class I AAR, chloroquine, TCA, some beta-blockers, thioridazine
Increased QT interval	K channel blockade	Amiodarone
	Na channel blockade	Class I AAR, chloroquine, TCA, some beta-blockers

TCA, tri-tetracyclic antidepressants; AAR, anti-arrhythmics; VES, ventricular extrasystoles; VT, ventricular tachycardia; VF, ventricular fibrillation.

Table 315.3 Biomedical disturbances in specific poisonings

Disturbances	Toxin
◆ Anion gap	◆ Methanol, ethylene glycols, acetone
◆ Osmolal gap	◆ Ethanol, methanol, ethylene glycols, acetone
◆ Hypoglycaemia	◆ Insulin, oral antidiabetics
◆ Hypokalaemia	◆ Chloroquine, theophylline
◆ Hyperkalaemia	◆ Digoxin, digitoxin
◆ Hypocalcaemia	◆ Fluoride
◆ Pseudohyperchloraemia	◆ Bromine and bromide
◆ Decreased prothombin level	◆ Oral anticoagulants, rodenticides, snake venoms
◆ Methaemoglobinaemia	◆ Methaemoglobin-forming agents
◆ Decreased plasma or erythocyte cholinesterase level	◆ Organophosphate and carbamet insecticides
◆ Oxalate crystals in urine	◆ Ethylene glycol
◆ Gastric opacities on radiographs	◆ Metals, halogenated hydrocarbons

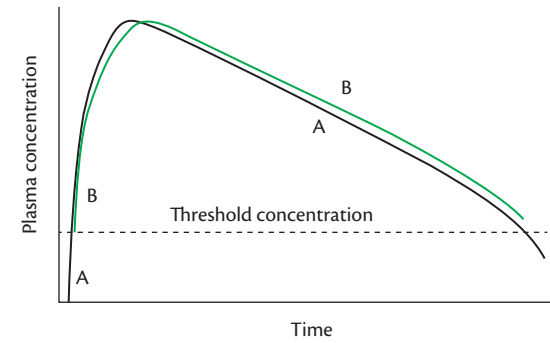


Fig. 315.1. Toxicokinetic–toxicodynamic relationship for a functional poison (monocompartment kinetics).
Curve A, concentration; curve B, toxic effect.

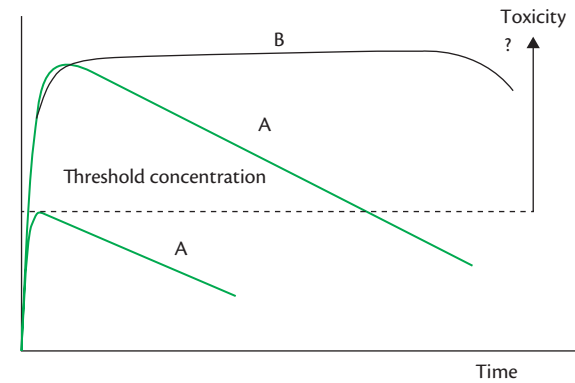


Fig. 315.2. Toxicokinetic–toxicodynamic relationship for a lesional poison.
Curve A, concentration; curve B, toxic effect.

take into account the plasma concentration and the time at which this concentration has been measured. Depending on the delay following ingestion, the same plasma concentration may be non-toxic, toxic, or lethal (Fig. 315.2). In these poisonings, plasma concentrations have a prognostic value: risk of lethal outcome in paraquat poisoning [4], and risk of hepatitis in acetaminophen poisoning [5].

Some toxins act by both mechanisms: the parent compound is a functional toxin, but after a delay cellular damage due to prolonged cellular hypoxia (carbon monoxide, cyanide) or to the accumulation of cytotoxic metabolites (methanol, ethylene glycol) may occur. The interpretation is based on the kinetic data (plasma concentrations of

the parent compound and metabolites) and on the time after ingestion or the duration of the exposure [3]. In acute short exposure to carbon monoxide, the symptoms correlate well with carboxyhaemoglobinaemia levels. In prolonged exposure, the severity depends not only on the carboxyhaemoglobin level, but also on the duration of the cerebral hypoxia. The potential toxicity of methanol is related to the methanol concentration measured in the early phase of the poisoning. The real toxicity depends on the concentrations of the toxic metabolites. If the patient is seen in a later phase, severe symptoms may be present despite low methanol concentrations.

Indication and evaluation of treatments

The management of the poisoned patient is mostly supportive and based on anamnestic, clinical, and biological data. Toxicological quantitative analyses are mandatory for some treatments [3]. Depending on the analytical results and clinical data, the physician will estimate the indication of the following:

- Alkaline diuresis in salicylate poisoning.
- Repeated dose of oral activated charcoal in phenobarbital or theophylline poisoning.
- Haemodialysis in lithium, methanol, ethylene glycol, and salicylate poisoning, and haemoperfusion in carbamate or theophylline poisoning.
- Ethanol or 4-methylpyrazole in ethylene glycol or methanol poisoning, *N*-acetyl cysteine in acetaminophen poisoning.
- Chelating agents in metal poisoning or deferoxamine (desferrioxamine) in iron poisoning.

In digitalis poisoning, the indication for Fab fragments is essentially based on clinical and biochemical (hyperkalaemia) criteria, but previous confirmation of the diagnosis by measurement of digitalis plasma concentration is recommended.

Evaluation of the methods used for decontamination or enhancing elimination must be based not only on clinical improvement but also on precise kinetic data which vary depending on the technique used.

Medicolegal implications

Quantitative and specific analyses are indicated if the poisoning may have medicolegal consequences (e.g. occupational or criminal poisoning).

Interpretation

Apart from the mechanism of toxicity, other factors must be taken into account in the interpretation of analytical and kinetic data [2,3].

Type of poisoning

Similar plasma concentrations may be associated with different severity, depending on the type of poisoning: acute, acute on chronic, or chronic. Toxic symptoms appear at lower plasma concentrations in chronic theophylline poisoning than in acute poisoning; convulsions and severe dysrhythmias may appear at concentrations between 40 and 70 mg/L, and the probability of developing convulsions is 50% when the peak concentration exceeds 40 mg/L whereas in acute poisoning the same probability is only observed if the peak concentration is above 120 mg/L. In chronic lithium poisoning, severe disturbances of the central nervous system may appear at supratherapeutic plasma concentrations (>1.2 mmol/L), whereas in acute poisoning no toxicity has been reported at concentrations ranging up to 8 mmol/L [3]. Similar severity of digoxin poisoning is observed at lower plasma digoxin concentrations in chronic overdose than in acute poisoning.

With some toxins (barbiturates, ethanol), a tolerance may be observed in patients treated or poisoned chronically. In acute ethanol poisoning with similar blood ethanol levels, symptoms are less severe in chronic alcoholics than in non-tolerant individuals. Patients treated chronically with barbiturates are more tolerant to acute barbiturate toxicity and the duration of coma is often shorter because of an increase in hepatic elimination by enzyme induction.

Age

In chronic theophylline overdoses with the same plasma concentrations, symptoms and prognosis are more severe in elderly patients than in young adults. For a given plasma concentration, the cardiotoxic effects of digoxin are more severe in adults than in children.

Underlying diseases and toxic symptoms

An underlying disease or toxic symptoms, such as hypoxaemia and shock, may strongly modify the toxicodynamics [3]. In theophylline poisoning, the risk of toxicity and the plasma half-life are increased in patients with congestive heart failure because of impaired elimination by hepatic metabolism. Patients with epilepsy are at higher risk of developing convulsions in poisoning with drugs that may induce convulsions. In poisoning with cardiotropic drugs, the toxicity is increased in patients with chronic heart diseases. In acute meprobamate overdoses, the plasma half-life is increased in patients with shock.

Concurrent ingestion of other drugs

The ingestion of drugs with anticholinergic effects may prolong the gastrointestinal absorption of other drugs. In poisoning with several cardiotoxic drugs with synergistic effects severe symptoms may appear even if the plasma concentration of each drug individually is at a therapeutic level.

Dose ingested

Dose-dependent kinetics, with a change from first-order to zero-order kinetics, have been reported in massive theophylline and salicylate poisoning.

Acknowledgements

The editors were saddened to hear of the death of Dr Albert Jaeger since writing this chapter of the book.

References

1. Jaeger A, Kopferschmitt J, Sauder Ph, Flesch F, and Tournoud, C. (1991). Diagnosis in clinical toxicology. *Archives of Toxicology*, **15**(Suppl.), 29–39.
2. Lheureux P, Askenasi R, and Maes V. (1995). Du bon usage du laboratoire en toxicologie. 2e partie: utilité clinique et interprétation des résultats. *Réanimation Urgences*, **5**, 341–52.
3. Jaeger A, Berton C, and Kempf J. (1994). Basis of kinetics in clinical toxicology. In: Vincent JL (ed.) *Yearbook of Intensive Care and Emergency Medicine*, pp. 707–15. Berlin: Springer-Verlag.
4. Proudfoot AT, Stewart SM, Levitt T, and Widdop B. (1979). Paraquat poisoning: significance of plasma paraquat concentrations. *Lancet*, **ii**(8138), 330–2.
5. Rumack BH, Peterson RC, Koch GG, and Amara IA. (1981). Acetaminophen overdose: 662 cases with evaluation of oral acetylcysteine treatment. *Archives of Internal Medicine*, **141**, 380–5.

CHAPTER 316

Decontamination and enhanced elimination of poisons

Darren M. Roberts

Key points

- Decontamination or enhanced elimination should not be used routinely for the treatment of acute poisoning. They are initiated on a case-by-case basis after consideration of the type of poison, amount and time since exposure, anticipated clinical benefit, and other factors.
- Decontamination aims to decrease the severity and, potentially, duration of poisoning. Activated charcoal is the most common form used and, in most cases, should be administered within 1–2 hours of poison ingestion.
- Enhanced elimination aims to decrease the duration and other consequences of poisoning. It is most commonly used in severe poisoning with an agent that has a long elimination half-life.
- Elimination of a poison can be enhanced with extracorporeal therapies, multiple doses of activated charcoal, sodium polystyrene sulphonate and urinary alkalinization. Data support their use in selected cases.
- To maximize poison clearance by haemodialysis or haemofiltration, the prescribed regimen may differ to that used for renal replacement therapy.

Introduction

Assessing the need for and implementation of urgent resuscitation is the first priority in the management of the poisoned patient. This is followed by the simultaneous consideration of decontamination, enhanced elimination, antidotes, and ongoing monitoring and disposition.

The term poison is used to describe any medicine, drug, chemical, natural toxin, or other xenobiotic capable of inducing poisoning. Decontamination and enhanced elimination have the principle roles of decreasing the body burden of the poison, thereby reducing the severity and/or duration of poisoning. Such treatments are administered on a case-by-case basis after consideration of clinical, physicochemical, and pharmacokinetic factors. As with any intervention, the potential risks and benefits must be considered.

Concepts in kinetics

Kinetics refers to the absorption, distribution, metabolism and excretion of a poison following an exposure [1].

The rate and extent of absorption depends on the physicochemical properties of the poison and the biological membrane. Intravenous administration bypasses absorption processes. Absorption is largely complete within 2 hours following oral exposure, although absorption may be prolonged or erratic in the following cases:

- Ingestion of modified release formulations.
- Co-ingestants that retard intestinal motility, e.g. opioids or anticholinergics.
- If the poison is poorly soluble in the intestinal fluid, including the case of massive ingestions.
- Conditions that impair intestinal function, including hypotension, hypothermia, hypoxaemia, or autonomic neuropathy.

Distribution refers to the physiological process where a poison crosses from the central compartment (plasma) into peripheral (extravascular) compartments, including adipose tissue, the intracellular fluid, or the cerebrospinal fluid. The rate and extent of this depends on the poison and time since the exposure. A poison may distribute into a compartment where it does not have a clinical effect (a 'sink') or a compartment where it can mediate a clinical effect (a 'toxic compartment').

Elimination is the sum effect of metabolism and excretion. Excretion may occur via the kidney, gastrointestinal system (e.g. biliary system) or, less commonly, via respiration.

Decontamination

General comments

The decision to perform decontamination is based on the history of exposure. Decontamination must be commenced prior to completion of absorption, which is usually within 1–2 hours of ingestion, with the exceptions outlined previously. This opportunity is uncommon in clinical practice.

Fig. 316.1 shows the effect of gastrointestinal decontamination on the concentration–time curve. Effective decontamination decreases the amount of poison absorbed into the systemic circulation. This has the effect of decreasing the severity of poisoning due to a decrease in the maximum concentration (C_{max}) and also the area under the concentration–time curve (AUC). Decontamination may also decrease the duration of poisoning, particularly when there is extensive distribution of the poison to the extravascular space.

A number of different interventions may be used for decontamination following oral exposure, including activated charcoal, whole

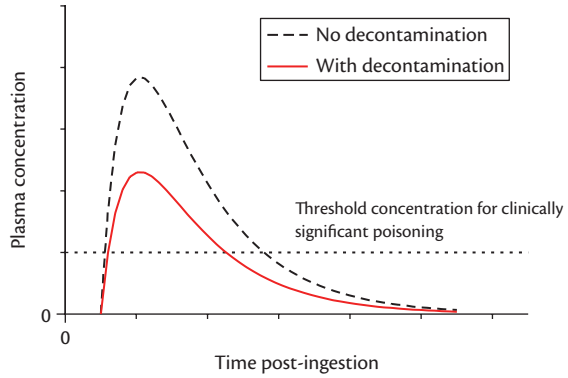


Fig. 316.1 The effect of gastrointestinal decontamination on the concentration–time curve. Gastrointestinal decontamination decreases the bioavailability of a toxic exposure. This shows how a 40% decrease in bioavailability decreases the C_{max} and the duration of poisoning. This simulation is likely to exaggerate the actual effect of gastrointestinal decontamination in clinical practise because patients rarely present to hospital within 1 hour when the maximal effect of decontamination is expected.

bowel irrigation, gastric lavage, and Fuller's earth. The usual indications and contraindications for these treatments are summarized in Table 316.1. Forced emesis is unlikely to be useful for patients admitted to hospital.

In other exposures, decontamination involves washing/irrigating the skin with dermal or ocular exposures, and moving the patient to fresh air with respiratory exposures.

Activated charcoal

Enteral activated charcoal is the most common method of decontamination. It reversibly adsorbs poisons via hydrostatic bonds so its use is limited to organic poisons, while alcohols, acids, and metal ions are not adsorbed. The dose is 50–100 g (or 1–2 g/kg in children) mixed with water, and ingested by the patient or instilled into a gastric tube. Activated charcoal is usually given as a single dose, although multiple doses may be given for ingestion of modified release formulations or for enhanced elimination.

Randomized controlled trials have not demonstrated a clinical benefit from the routine administration of activated charcoal in predominantly pharmaceutical [2] or pesticide poisoning [3]. However, in early presentation of highly toxic exposures it may be beneficial. Other studies have suggested benefits for clinically relevant measures when activated charcoal is administered early to patients with a significant exposure, including paracetamol (acetaminophen) [4], and psychotropic agents including citalopram [5], venlafaxine [6], promethazine [7], and quetiapine [8]. Although activated charcoal appears to have a favourable effect on the kinetics on *Thevetia peruviana* cardenolides [9], two randomized controlled trials reported conflicting results in terms of clinical benefits from multiple doses [3,10].

The risk of activated charcoal appears to be low. It is prudent to give it only to patients with a protected airway (including patients who are alert and willing to self-administer it) to minimize aspiration.

Enhanced elimination

General principles

Enhanced elimination is used for the purpose of increasing removal of the poison from the body. The decision to perform it is usually based on confirmed exposure, e.g. an elevated blood concentration or clinical features of poisoning, and does not depend on the

Table 316.1 Choices for decontamination following ingestion of a potentially toxic dose of a poison

	Activated charcoal	Whole bowel irrigation	Gastric lavage	Fuller's earth
Poisons to consider	Organic poisons (not acids, alkalis, metals or alcohols)	Modified release formulations; poisons not absorbed by activated charcoal, 'body packers'	Highly toxic liquids	Paraquat, any confirmed exposure
Indications	Ingestion within 1–2 hours; potentially up to 4 hours if impaired gastric emptying	Up to 24 hours post-exposure depending on the poison	Ingestion within 1 hour	Ingestion within 1–2 hours
Risks	Aspiration (uncommon if airway protected) or bowel obstruction (rare)	Aspiration (uncommon if airway protected)	Aspiration (airway must be protected); oesophageal trauma, particularly with caustic ingestions	Aspiration due to emesis (uncommon)
Dose	50–100 g in adults; 1–2 g/kg in children	1–2 L/hour of polyethylene glycol until the rectal effluent is clear	Not specified	150 g in adults
Evidence supporting intervention	In vitro studies support binding. Volunteer studies show effect if administered within 1 hour. Clinical studies support a benefit with selected, but not routine use; mortality benefit not reported	Observational studies, largely case reports	Observational studies, largely case reports. A quasi-randomized controlled trial suggested no benefit with routine use in predominantly pharmaceutical poisoning [12]	In vitro studies support binding
Other comments	Admix with water according to manufacturer guidelines. See discussion in text	Admix with water according to manufacturer guidelines	Wide-bore orogastric tubes may remove tablet fragments, but this is usually a small proportion of the dose	Admix with water according to manufacturer instructions. Infrequently available, use activated charcoal instead

route of administration. Candidate poisons have the following characteristics [1]:

- **Small volume of distribution (generally <1 L/kg) with single compartment kinetics**: for poisons with a larger volume of distribution, enhanced elimination may still be beneficial, but should be commenced prior to significant distribution from the vascular compartment (i.e. as soon as possible post-exposure) and a prolonged course may be necessary.
- **Low endogenous clearance, including renal impairment for poisons that are renally cleared**: this is reflected in a prolonged elimination half-life (although this may also occur with large volumes of distribution).
- **Binds minimally to plasma proteins**: in overdose there may be saturation of protein binding which increases the effect of enhanced elimination, e.g. valproate, salicylate, chlorophenoxy herbicides.
- **The clinical effect is reversible**: if irreversible then treatment should be commenced before they occur to a significant extent

Enhanced elimination decreases the duration of poisoning due to a shortening in the apparent elimination half-life (Fig. 316.2). If performed prior to the C_{max}, or prior to distribution of the poison from the central compartment to a toxic compartment, then it may decrease both the severity and duration of poisoning, similar to the representation shown in Fig. 316.1. Enhanced elimination may also decrease the severity of poisoning by removing the poison from the central compartment prior to distribution to a toxic compartment, for example minimizing salicylate-induced uncoupling of oxidative phosphorylation.

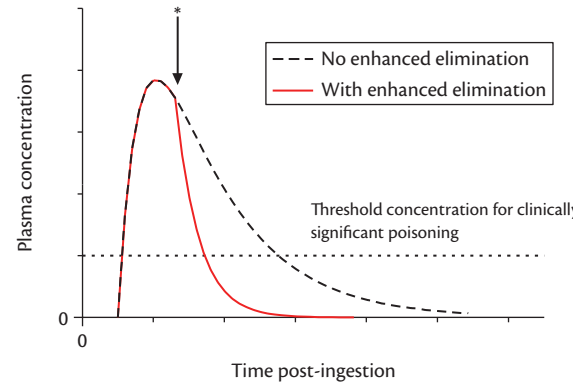


Fig. 316.2 The effect of enhanced elimination on the concentration-time curve. An enhanced elimination technique that increases clearance by 40% is initiated as indicated by the arrow and asterisk (*). This has the effect of decreasing the apparent elimination half-life and the duration of poisoning.

A number of interventions may enhance the elimination of a poison, including multiple dose activated charcoal, sodium polystyrene sulphonate, extracorporeal treatments (in particular haemodialysis, haemofiltration, or haemoperfusion), urinary alkalinization, antidotes, and high flow oxygen. The usual indications and contraindications for these treatments are listed in Table 316.2. Clinical studies confirm a kinetics benefit for most of these treatments, but clinical benefits are less clearly reported. Examples of antidotes include antivenom (various snakes and spiders), antidigoxin Fab antitoxin (digoxin, oleander, other cardioactive steroids) and chelators such as desferrioxamine, hydroxocobalamin,

Table 316.2 Choices for enhanced elimination following exposure to a potentially toxic dose of a poison

	Multiple doses of activated charcoal	Haemodialysis or haemofiltration	Haemoperfusion	Urinary alkalinization	Sodium polystyrene sulphate	High flow oxygen
Mechanisms of action	Gastrointestinal dialysis, interruption of enterohepatic recirculation	Direct extraction from the vascular compartment	Direct extraction from the vascular compartment	Decrease reabsorption in the distal tubule	Cation exchange resin promoting gastrointestinal dialysis	Promotes dissociation of carbon monoxide from haemoglobin
Poisons to consider	Carbamazepine, aspirin, theophylline, phenobarbital, digoxin, dapsone, colchicine, modified release tablets, valproate, *Amanita phalloides*	Toxic alcohols, aspirin, lithium, valproate, potassium, phenobarbital. Also if renally cleared in the context of kidney impairment (e.g. metformin)	Theophylline, paraquat (within 2 hours), phenobarbital	Aspirin, chlorophenoxy herbicides, methotrexate	Lithium and potassium	Carbon monoxide
Risks	Aspiration (uncommon if airway protected) or bowel obstruction (rare)	Procedural complications, electrolyte abnormalities	Procedural complications, electrolyte abnormalities, thrombocytopaenia	Electrolyte abnormalities, blood alkalinization	Aspiration (uncommon)	
Dose	12.5 g hourly, or 25 g every 2 hours	Maximize blood flow rate, dialysate flow rate, filter surface area, duration	Maximize blood flow rate and change the column every 2–3 hours	Intravenous sodium bicarbonate to achieve urine pH >7.5	30 g every 4–6 hours depending on severity	15 L/min via a non-rebreathing mask until recovery
Other comments	Admix with water as per manufacturer guidelines		Clearance decreases with time due to column saturation	Ensure normokalaemia	Mix with diluent as per manufacturer guidelines	

succimer, and ethylenediaminetraacetic acid (EDTA). Acid diuresis and forced diuresis are not performed.

Lithium

Lithium fulfils many of these characteristics so enhanced elimination is commonly considered in the treatment of poisoned patients. However, because of other kinetic characteristics of lithium the indications and benefits of such treatments are poorly defined at present [13].

Neurotoxicity is the most important clinical manifestation of severe lithium poisoning and it is uncommonly observed following acute poisoning. This is because of slow distribution of lithium from the plasma compartment to the brain (the 'toxic' compartment), relative to the rate of distribution to non-toxic compartments and elimination. So, despite potentially high plasma concentrations of lithium initially, the resultant concentration in the brain is lower (Fig. 316.3). However, the risk of neurotoxicity is increased with renal impairment or ingestion of a sustained release formulation, in which case enhanced elimination can be considered.

Acute overdose on a background of therapeutic dosing, or repeated supra-therapeutic dosing may lead to lithium accumulation in the brain and neurotoxicity. Although enhanced elimination techniques can decrease the plasma concentration of lithium, because the rate of redistribution out of the brain is slower than the rate of decrease from the plasma, neurotoxicity can persist despite normalization of the plasma concentration. Furthermore, following high efficiency haemodialysis, there is often a rebound in the lithium plasma concentration due to the slower rate of redistribution to the central compartment. Data demonstrating the effect of enhanced elimination on the duration of neurotoxicity are not currently available.

Extracorporeal therapies

To optimize clearance by an extracorporeal treatment the blood flow rate, filter surface area and pore size and effluent (dialysate and/or ultrafiltrate) production should be maximized. Special considerations include the following:

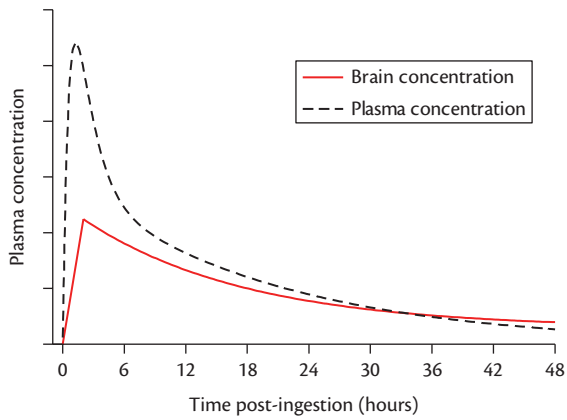


Fig. 316.3 Representation of the kinetics of lithium in the plasma and brain following an acute poisoning. The slower rate of distribution of lithium into the brain causes a lower C_{max} in the brain compared to that observed in the plasma. The rate of redistribution back to the plasma compartment is slower than the rate of systemic elimination leading to a relative accumulation in the brain. Despite this, because the concentration in the brain remains relatively low neurotoxicity is unlikely to develop.

- When a poison displays significant extravascular distribution, an increase (rebound) in the plasma concentration may be observed when the extracorporeal treatment is completed. This rebound may be accompanied by a clinical deterioration so close monitoring is required. Fig. 316.4 shows the relative effect of two extracorporeal regimens in valproate poisoning. A rebound in the plasma concentration is seen following cessation of the intermittent technique.
- In the case of haemodynamic instability a continuous extracorporeal technique may be better tolerated, although this is at the expense of poison removal.
- Charcoal haemoperfusion can achieve high clearances, including poisons that are bound to plasma proteins such as theophylline. However, supply of the cartridges is frequently limited

Determination of the endpoint of therapy or the optimal dose requires consideration of the desired effect of an enhanced elimination technique. The following factors can be considered:

- A clinical end point, such as recovery from unconsciousness or extubation.
- Confirmed removal of the poison by blood tests.
- A kinetic end point, such as the percentage change in clearance or half-life. A minimum change of 30% has been considered significant, although this value was based on therapeutic dosing. A lesser percentage increase may be clinically significant for a poison with a prolonged elimination half-life.

These assessments are complicated by variability in the time since and amount of exposure, co-ingestants, patient demographics, and endogenous organ function.

Removal of poison from the toxic compartment

It is claimed that some treatments enhance elimination from a toxic compartment. The rationale is that if a relatively small concentration

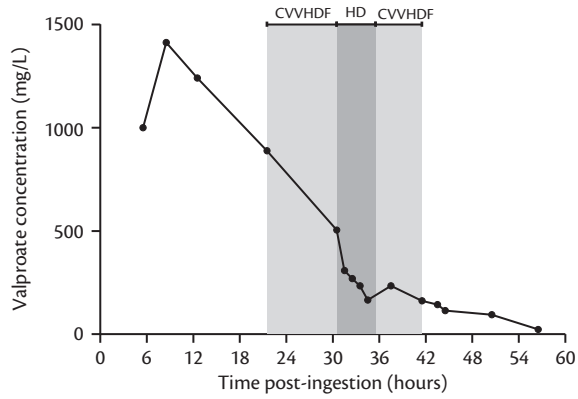


Fig. 316.4 The apparent elimination half-life of valproate is seen to be shorter during haemodialysis (HD) compared with during continuous venovenous haemodiafiltration (CVVHDF), suggesting that HD is a relatively more efficient method of enhanced elimination. Note the rebound in the plasma concentration of valproate after HD, reflecting faster elimination from the blood compartment during HD compared to the rate of redistribution from extravascular tissues. A similar phenomenon is reported with lithium and barbiturates.
Reproduced from TD Kay et al., 'Hemodialysis versus continuous veno-venous hemodiafiltration in the management of severe valproate overdose', *Clinical Nephrology*, **59**(1), pp. 56–8, copyright 2003, with permission from Dustri-Verlag.

of poison at the toxic compartment is sufficient to cause poisoning, then a treatment that decreases that concentration may be clinically useful, even if it does not significantly alter the total body burden. This had been suggested with haemoperfusion for cardiotoxic poisons with a large volume of distribution (e.g. tricyclics antidepressants). However, supporting data are lacking and this treatment is no longer recommended [14].

The intervention that has received much attention in this area is intralipid emulsion (ILE). Here, the poison is thought to be distributed from the toxic compartment into a lipid sink created by ILE (there are other proposed mechanisms of action). Animal studies are limited, case reports of life-saving effect of ILE are published, while others report a less dramatic effect; these observations are likely to reflect at least in part a publication bias. A very small randomized controlled trial reported an improvement in consciousness and decrease in blood glucose by ILE with non-local anaesthetic drug poisoning [11]. Furthermore, the complications of ILE may not be negligible.

At present, the use of ILE in the management of acute poisonings is limited to bupivacaine-induced cardiotoxicity, and life-threatening cardiotoxicity due to other poisons unresponsive to usual therapies—it is not first-line therapy. More data are required that confirm the time-course response to ILE on dynamic measures of toxicity, such as haemodynamics or the electrocardiogram.

Conclusion

Consideration of decontamination or enhanced elimination in a patient always follows acute resuscitation and the risk assessment. Decontamination and enhanced elimination aim to modify the kinetics of a poison and decrease the severity and/or duration of poisoning. The decision to perform these treatments is determined on a case-by-case basis. Poison information centres and clinical toxicologists are available in many parts of the world to provide advice.

References

1. Roberts DM and Buckley NA. (2007). Pharmacokinetic considerations in clinical toxicology: clinical applications. *Clinical Pharmacokinetics*, **46**(11), 897–939.
2. Cooper GM, Le Couteur DG, Richardson D, et al. (2005). A randomised clinical trial of activated charcoal for the routine management of oral drug overdose. *Quarterly Journal of Medicine*, **98**, 655–60.
3. Eddleston M, Juszczak E, Buckley NA, et al. (2008). Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *Lancet*, **371**, 579–87.
4. Buckley NA, Whyte IM, O'Connell DL, et al. (1999). Activated charcoal reduces the need for N-acetylcysteine treatment after acetaminophen (paracetamol) overdose. *Journal of Toxicology: Clinical Toxicology*, **37**(6), 753–7.
5. Isbister GK, Friberg LE, Stokes B, et al. (2007). Activated charcoal decreases the risk of QT prolongation after citalopram overdose. *Annals of Emergency Medicine*, **50**(5), 593–600.
6. Kumar VV, Oscarsson S, Friberg LE, et al. (2009). The effect of decontamination procedures on the pharmacokinetics of venlafaxine in overdose. *Clinical Pharmacology and Therapeutics*, **86**(4), 403–10.
7. Page CB, Duffull SB, Whyte IM, et al. (2009). Promethazine overdose: clinical effects, predicting delirium and the effect of charcoal. *Quarterly Journal of Medicine*, **102**(2), 123–31.
8. Isbister GK and Duffull SB. (2009). Quetiapine overdose: predicting intubation, duration of ventilation, cardiac monitoring and the effect of activated charcoal. *International Clinical Psychopharmacology*, **24**(4), 174–80.
9. Roberts DM, Southcott E, Potter J, et al. (2005). Pharmacokinetics of digoxin-like substances in the plasma of patients with yellow oleander (*Thevetia peruviana*) self poisoning. *Clinical Toxicology*, **43**(5), 422–3.
10. de Silva HA, Fonseka MMD, Pathmeswaran A, et al. (2003). Multiple-dose activated charcoal for treatment of yellow oleander poisoning: a single-blind, randomised, placebo-controlled trial. *Lancet*, **361**, 1935–8.
11. Taftachi F, Sanaei-Zadeh H, Sepehrian B, et al. (2012). Lipid emulsion improves Glasgow coma scale and decreases blood glucose level in the setting of acute non-local anesthetic drug poisoning—a randomized controlled trial. *European Review for Medical and Pharmacological Sciences*, **16**(Suppl. 1), 38–42.
12. Pond SM, Lewis-Driver DJ, Williams GM, et al. (1995). Gastric emptying in acute overdose: a prospective randomised controlled trial. *Medical Journal of Australia*, **163**(7), 345–9.
13. Roberts DM, Gosselin S. (2014). Variability in the management of lithium poisoning. *Seminars in Dialysis*, **27**(4), 390–4.
14. Yates C, Galvao T, Sowinski KM, et al. (2014). EXTRIP workgroup. Extracorporeal treatment for tricyclic antidepressant poisoning: recommendations from the EXTRIP Workgroup. *Seminars in Dialysis*, **27**(4), 381–9.

PART 15.2

Management of specific poisons

CHAPTER 317

Management of salicylate poisoning

Brenna M. Farmer and Neal Flomenbaum

Key points

- Salicylates are weak acids that work as neurotoxins. The goal of management is to keep salicylates out of the brain and enhance elimination.
- Acute salicylate toxicity manifests as tinnitus, nausea, vomiting, and hyperventilation in a patient who takes a single large ingestion.
- Chronic salicylate toxicity is associated with long-term use, has a more insidious onset, and symptoms tend to be less severe, resulting in delayed diagnosis. It is more commonly seen in elderly patients.
- Therapeutic interventions for toxicity include gastrointestinal decontamination, serum and urine alkalinization, and haemodialysis.
- Mechanical ventilation may lead to clinical deterioration and death in a salicylate-poisoned patient, due to worsening acidosis from respiratory failure. This results in severe acidosis, cerebral oedema, pulmonary oedema, and cardiac arrest.

Introduction

Salicylates are widely used as analgesics, antipyretics, anti-inflammatories, and antiplatelet agents for cardiovascular prophylaxis. Salicylates can cause severe poisoning and death, thus every case of ingestion must be taken seriously. Acute and chronic toxicity may occur with salicylate poisoning. Deaths occur because of misdiagnosis, lack of understanding of the complexity and severity of salicylate overdose, and lack of appropriate management. Salicylates are found in many products including aspirin (acetylsalicylic acid), methyl salicylate (oil of wintergreen; found in liniments and rubifacients), choline salicylate (found in some teething gels), and salicylic acid, which has keratolytic properties. Aspirin comes as tablets or capsules (75–500 mg). It can be in enteric-coated products and in combination products with caffeine, paracetamol, barbiturates, and opioids.

Toxicity and mechanisms

Therapeutically, salicylates are used for their inhibition of cyclo-oxygenase (COX) leading to decreased prostaglandins, prostacyclin, and thromboxane. By decreasing these substances, salicylates produce analgesia, anti-inflammatory and antipyretic effects, and reduce platelet aggregation.

Salicylates are absorbed in the stomach and small intestine. Enteric-coated products can have delayed toxicity as the coating slows absorption. Once absorbed, aspirin is rapidly converted to salicylic acid, which is further metabolized to five main metabolites—salicyluric acid, salicyl phenolic glucuronide, gentisic acid, acyl glucuronide, and gentisuric acid. The pathways for the first two metabolites involve saturable hepatic enzymes. Normally, at therapeutic doses, these liver enzymes eliminate the majority of the salicylate. However, when a large amount of salicylate is ingested, these routes quickly become saturated. This results in a change from first-order kinetics, where elimination is proportional to the plasma concentration, to zero-order kinetics, where only a certain amount is eliminated irrespective of the plasma concentration. Thus, salicylate may accumulate following mild therapeutic overdoses, particularly in children or the elderly, and prior therapeutic use of the drug may increase the toxicity of an acute overdose. In toxic doses, renal clearance becomes more important and is very sensitive to pH changes. Salicylic acid is a weak acid that is mainly ionized at serum pH of 7.4 or urine pH that is alkaline. By increasing the pH, i.e. making more alkaline, more of the ionized form of salicylic acid may be trapped in the serum and urine. The ionized form in the urine leads to increased excretion of the salicylic acid and thereby increased elimination. This is the basis of urinary alkalinization in salicylate overdose.

Patients develop hyperventilation from direct stimulation of the central nervous system (CNS) respiratory centre leading to a primary respiratory alkalosis, rarely seen in infants and young children. Aspirin uncouples oxidative phosphorylation, which interferes with oxidative adenosine triphosphate (ATP) production. In the mitochondria, anaerobic metabolism increases to produce ATP, leading to lactate production and an anion-gap metabolic acidosis. The energy normally used to create ATP in oxidative phosphorylation is shunted to heat production and causes hyperthermia. Furthermore, salicylates interfere with glucose and fatty acid metabolism leading to ketosis and further metabolic acidosis. Capillary leak eventually occurs, leading to cerebral and pulmonary oedema. Altered platelet function and coagulopathy occurs due to extension of therapeutic effects of salicylates.

Clinical features

The therapeutic serum concentration of salicylate is 15–30 mg/dL (150–300 mg/L). Toxicity can occur at doses greater than 150 mg/kg or serum concentrations greater than 30 mg/dL (300 mg/L). Acute and chronic toxicity can occur with salicylate poisoning.

Acute toxicity from salicylates occurs from a one-time exposure, usually as an intentional ingestion, resulting in early signs and symptoms of toxicity. Nausea, vomiting, hyperventilation, sweating, and tachycardia are seen. Tinnitus and hearing loss are also common. Chronic toxicity usually occurs in older patients from therapeutic misadventures in trying to treat inflammation or pain and due to increased accumulation from impaired elimination. It usually results in less severe and slower onset of symptoms that are frequently unrecognized as salicylate poisoning. It can be misdiagnosed due to a high prevalence of altered mentation with up to 25% mortality due to delayed diagnosis and treatment [1].

Common early features of salicylate overdose are irritability, tinnitus, hyperventilation, nausea, vomiting, and abdominal pain. Further symptoms include sweating, flushing, deafness, tremor, hypokalaemia, and hypernatraemia. The combination of vomiting, hyperventilation, and sweating may lead to severe volume depletion. Other findings may include hypoprothrombinaemia (due to inhibition of the vitamin K-dependent coagulation pathway), pyrexia (usually in children), confusion, drowsiness, delirium, coma, and seizures (more common in children).

Respiratory alkalosis, metabolic acidosis, ketosis, hypoglycaemia, and hyperglycaemia may all occur. The biochemical pattern of a primary respiratory alkalosis together with primary metabolic acidosis is characteristic of salicylate poisoning. The patient usually presents with a combined respiratory alkalosis and metabolic acidosis, with a blood pH in the range 7.40–7.46, low serum bicarbonate, and low PCO_2. These symptoms may be improved by correction of metabolic acidosis with sodium bicarbonate. Respiratory alkalosis is uncommon in younger children, but the likelihood of respiratory alkalosis increases with age until 12 years, when the adult picture of respiratory alkalosis, followed by metabolic acidosis occurs. The underlying mechanisms for these age-dependent differences in acid–base balance are poorly understood. Since acidosis enhances transfer of the salicylate ion across the blood–brain barrier, it is necessary to employ more active therapy at lower salicylate concentrations in children.

Confusion and depressed consciousness are serious signs, usually indicating that salicylate has entered the CNS and that the patient is at high-risk of death due to large CNS burden of salicylate. Death is usually due to cardiorespiratory arrest; attempts at resuscitation are unlikely to be successful.

Management

Assessment of the severity of salicylate intoxication involves clinical assessment, metabolic assessment (e.g. a plasma pH of 7.45 bodes well, but a pH of 7.30 indicates severe toxicity and concern for impending death), and measurement of the plasma salicylate level.

Every patient suspected of salicylate toxicity should be detained until the severity has been assessed biochemically. The plasma salicylate level should be measured on presentation and every 2–4 hours after confirmed ingestion, until levels are below detection. Absorption may continue for many hours, leading to a delay of up to 24 hours before the peak salicylate concentration is reached, especially with enteric-coated tablets. At the same time, arterial or venous blood gases, and plasma biochemistry should be checked.

Gastric decontamination should be performed. Gastric lavage may be useful if the patient presents with an acute ingestion and is expected to still have some salicylate in the stomach. However, due to enteric coating, salicylate tablets can form concretions and be difficult to remove with gastric lavage. Activated charcoal (1 g/kg) should be given and repeated doses of activated charcoal (0.5–1 g/kg every 4 hours) may be considered because salicylate may be retained in the stomach for many hours after ingestion. This treatment has been shown to shorten the plasma half-life of salicylate. Activated charcoal adsorbs salicylate but desorption may occur [2]. This regimen also appears to enhance passage of the salicylate ion from the blood back into the gut ('gastrointestinal dialysis') [3]. As this procedure is effective and non-invasive, it is recommended for mild to moderately severe salicylate toxicity. If repeated doses of activated charcoal are given, ensure that the activated charcoal does not contain a cathartic, since cathartics can cause electrolyte abnormalities.

Ensure that the patient is adequately rehydrated with intravenous fluids and remains normovolaemic. Any patient with altered mental status should have their serum glucose evaluated and hypoglycaemia corrected as it occurs.

Patients, with serum salicylate concentrations greater than 30 mg/dL (300 mg/L), should receive intravenous sodium bicarbonate for serum and urinary alkalinization to enhance elimination [4]. The aim is to produce a serum pH of 7.5–7.55 to keep the salicylate from entering the CNS and urinary pH of over 7.5. This enhances renal salicylate elimination by trapping the salicylate ion in the renal tubule. Renal elimination of salicylate is enhanced 10–20-fold when urine pH increases from 5 to 8 [5]. Urinary alkalinization is difficult to obtain in the setting of hypokalaemia. Therefore, patients should receive potassium supplementation, while undergoing serum and urine alkalinization. In the past forced alkaline diuresis (i.e. fluid plus alkali) was recommended. However, this method has led to non-cardiogenic pulmonary oedema, particularly in smokers and the elderly, with risks of hypokalaemia and/or hypernatraemia. It is no longer currently recommended [6].

Haemodialysis is recommended for severe salicylate intoxication. This includes any patient with markedly raised salicylate concentration, altered mental status or other neurological dysfunction, inability to tolerate a sodium bicarbonate infusion (such as patients with renal failure or acute lung injury (ALI)), renal failure (cannot eliminate salicylate), and those patients not responding to conservative management with sodium bicarbonate infusion. In the past, charcoal haemoperfusion was also used as an extracorporeal method of salicylate removal. However, it is usually not readily available.

Airway management is sometimes considered in patients with salicylate toxicity. However, it is a dangerous and sometimes, deadly procedure if not done with extreme caution [7]. The concern with airway management in these patients is due to the mechanical ventilator's inability to match the patient's respiratory function (both primary respiratory alkalosis and compensation from the metabolic acidosis). The likelihood of the patient developing an acidaemic serum pH, from respiratory acidosis, during the procedure can lead to increased CNS salicylate and thereby increased toxicity to the patient. If intubation and mechanical ventilation is necessary for further management such as safe placement of a haemodialysis catheter, precautions must be taken. The patient should receive a bolus of intravenous sodium bicarbonate (1–2 mmol/kg) to provide an extra buffer against respiratory

acidosis. The most experienced provider should perform the procedure on an unparalysed patient. Once intubated and connected to the mechanical ventilator, the ventilator settings should be set to maintain an increased minute ventilation (increased tidal volume and respiratory rate) to try to match the patient's previous respiratory function. Frequent blood gases should be performed to ensure an alkalaemic serum.

Conclusion

Salicylates result in both acute and chronic toxicity with death as a possible outcome. All suspected ingestions must be taken seriously. Treatment is based on the patient's clinical picture and blood analysis. It includes gastrointestinal decontamination, serum and urine alkalinization, and haemodialysis in the most severe cases. Airway management and mechanical ventilation should be performed with extreme caution with steps taken to ensure the patient maintains serum and urine alkalinization.

References

1. Anderson RJ, Potts DE, Gabow PA, Rumack BH, and Schrier RW. (1976). Unrecognized adult salicylate intoxication. *Annals of Internal Medicine*, **85**, 745–8.
2. Filippone GA, Fish SS, Lacouture PG, Scavone JM, and Lovejoy GH. (1987). Reversible adsorption (desorption) of aspirin from activated charcoal. *Archives of Internal Medicine*, **147**, 1390–2.
3. Hillman RJ and Prescott LF. (1985). Treatment of salicylate poisoning with repeated oral charcoal. *British Medical Journal*, **291**, 1472.
4. Proudfoot AT, Krenzelok EP, and Vale JA. (2004). Position paper on urine alkalinization. *Journal of Toxicology: Clinical Toxicology*, **42**, 1–26.
5. Prescott LF, Balali-Mood M, Critchley JA, Johnstone AF, and Proudfoot AT. (1982). Diuresis or urinary alkalinisation for salicylate poisoning? *British Medical Journal*, **285**, 1383–6.
6. Dargan PI, Wallace CI, and Jones AL. (2002). An evidence-based flowchart to guide the management of acute salicylate (aspirin) overdose. *Emergency Medicine Journal*, **19**, 206–9.
7. Stolbach AI, Hoffman RS, and Nelson LS. (2008). Mechanical ventilation was associated with academia in a case-series of salicylate-poisoned patients. *Academic Emergency Medicine*, **15**, 866–9.

CHAPTER 318

Management of acetaminophen (paracetamol) poisoning

Michael Levine

Key points

- Acetaminophen toxicity results from accumulation of the metabolite N-acetyl-para-benzoquinoneimine, which results in centrilobular necrosis.
- Acetaminophen toxicity is primarily characterized by liver toxicity.
- Fulminant hepatic failure from acetaminophen is frequently characterized by markedly elevated transaminases and impaired synthetic function, along with encephalopathy, renal failure, metabolic acidosis, and hypoglycaemia.
- N-acetylcysteine (NAC) is the preferred antidote.
- If NAC is started within 8 hours post-ingestion, the rate of hepatic failure is near zero.

Epidemiology

It has been nearly 120 years since acetaminophen, or paracetamol, was first marketed as an analgesic and antipyretic. Nonetheless, the first cases of hepatic toxicity were not recognized until the 1960s. Today, acetaminophen is one of the most widely used analgesic and antipyretic medications, and is often co-formulated with other medications.

Much of the increased popularity of acetaminophen can be traced back to the desire to find a safer analgesic after salicylates were linked with Reye's syndrome in the 1980s [1]. In 2011, US Poison Control Centers received more than 137,287 calls involving acetaminophen, including 260 fatal cases involving acetaminophen [2].

Furthermore, nearly half of all cases of acute liver failure in the USA are believed to be due to acetaminophen [1].

In recent years, there has been increased attention focused on the potential for hepatotoxicity following acetaminophen overdose. This concern is not, however, based on new data. An extensive review of acetaminophen toxicity was conducted in 2002. The same group rereviewed the literature in 2009 and concluded there were no new data [3].

Pharmacokinetics/Pharmacodynamics

Following ingestion, acetaminophen is absorbed rapidly from the gastrointestinal tract. The half-life of acetaminophen is approximately 1.5–2.5 hours, although it can be slightly prolonged at supratherapeutic concentrations [4].

Acetaminophen is primarily metabolized in the liver, with a small portion (approximately 4%) being excreted unchanged in the urine. In adults, glucuronidation accounts for the majority of acetaminophen's metabolism, followed by sulphation [4] Together, these two processes account for nearly 90% of acetaminophen's metabolism, when consumed in therapeutic doses. The remainder of acetaminophen is metabolized via the cytochrome P450 isoenzyme CYP2E1 to form the metabolite N-acetyl-para-benzoquinoneimine (NAPQI). Normally, the body's endogenous glutathione supplies are able to bind to NAPQI, resulting in a water-soluble, non-toxic metabolite that is subsequently excreted in the form of cysteine or mercaptopuric acid conjugates [4]. In the setting of overdose, however, glucuronyltransferases and sulfotransferases are saturated, resulting in increased production of NAPQI with subsequent glutathione depletion, and ultimately hepatotoxicity [4].

Histology of liver failure

Similar to several other toxins, acetaminophen can result in a distinctive histological pattern—centrilobular (zone III) necrosis with passive congestion and scattered leukocytes without fatty infiltration [5]. These areas of necrosis are characteristically followed by rapid disappearance of necrotic cells, resulting in reticulin collapse. Among those who survive, there is a marked histological recovery.

Risk for liver failure

Acetaminophen's toxicity results from the accumulation of NAPQI by the cytochrome P450 isoenzyme CYP2E1. Thus, any xenobiotic that induces the P450 isoenzyme CYP2E1 can theoretically increase the risk for acetaminophen-induced hepatotoxicity. Perhaps one of the best studied agents for inducing CYP2E1 is ethanol. Chronic ethanol consumption increases CYP2E1 activity, thereby theoretically increasing the risk of hepatotoxicity [6]. Conversely, the co-ingestion of ethanol with an acetaminophen overdose may result in inhibition of the microsomal oxidation thereby providing some degree of protection from acetaminophen-induced hepatotoxicity. The strongest risk factor for developing hepatotoxicity, however, is the time from a toxic ingestion until the antidote, N-acetylcysteine (NAC), is administered. The risk of hepatotoxicity if NAC is started within the first 8 hours of the overdose is exceedingly low, while the risk increases substantially with delays longer than eight hours and longer [7].

Clinical presentation

Acute acetaminophen toxicity has traditionally been divided into four stages, although the exact times of each stage are somewhat arbitrary. The first stage, which lasts up to 24 hours post-ingestion, is characterized by mild gastrointestinal symptoms shortly after the ingestion with frequent resolution of these symptoms. Patients may remain asymptomatic during the first stage. Right upper quadrant pain can begin towards the end of this stage. The second stage, which occurs from 24 to 72 hours post-ingestion, is characterized by the initial development of hepatic dysfunction. Vomiting and anorexia, if present in the first stage, have typically resolved, and right upper quadrant pain develops. Transaminitis and coagulopathy begin. The third phase, which can begin as early as 72 hours post-ingestion, is characterized by hepatic failure. Metabolic acidosis, coagulopathy, renal failure, hypogycaemia, and encephalopathy can occur [7,8]. At this stage, the patient will either improve or will continue to worsen until either death or hepatic transplantation occurs. The fourth stage is characterized by complete hepatic recovery. Unlike other causes of hepatic injury (e.g. alcohol-induced cirrhosis), acetaminophen-induced liver injury is not associated with long-term liver damage, assuming recovery occurs.

Typically, the transaminases are markedly elevated, with the aspartate aminotransferase (AAST) often exceeding 10,000 IU/L. Hypophosphataemia is relatively common and there are some data suggesting that the degree of hypophosphataemia is directly correlated with the severity of the overdose. While the degree of transaminase elevation does not predict outcome, metabolic acidosis, impaired synthetic function, renal insufficiency, and hepatic encephalopathy are independent predictors of death without transplant [9].

Uncommonly, a significant anion-gap metabolic acidosis can occur early following massive acetaminophen ingestion. It has been postulated that this early acidosis is the result of accumulation of pyroglutamic acid (5-oxoproline) [10]. This acidosis is distinct from the acidosis that can develop late as part of fulminant hepatic failure, in which accumulating lactic acid is the primary aetiology. Other uncommon features of acetaminophen poisoning are the development of pancreatitis or renal failure. Renal failure is most commonly encountered in patients with fulminant hepatic failure, but is occasionally encountered in the absence of hepatic dysfunction. In treating a patient with a metabolic acidosis following acetaminophen ingestion, it is prudent to exclude other potentially fatal causes of metabolic acidosis, such as salicylate, metformin, or toxic alcohol ingestion before attributing the acidosis to 5-oxoprolline accumulation.

Diagnosis and treatment

The diagnosis of acetaminophen toxicity relies on history and laboratory studies. Because of vague symptoms in the early stage of acetaminophen toxicity, together with patient confusion between acetaminophen, ibuprofen, and salicylates, it is recommended that all overdoses have an acetaminophen level obtained. In addition, when one encounters a new diagnosis of hepatitis without a clear aetiology, a history regarding acetaminophen use should be obtained.

The need for treatment depends on the history, physical examination, and laboratory studies. If treatment is required, the preferred antidote is NAC. An original paracetamol nomogram was developed in Scotland, in which a line on a semi logarithmic graph joined two points: 200 μg/dL at 4 hours and 30 g/dL at 15 hours [11]. In an effort to improve sensitivity in the USA, the line was reduced by 25% to a threshold of 150 μg/mL 4 hours after ingestion, and 75 μg/mL at 8 hours post-ingestion [12]. Treatment with NAC is indicated when the acetaminophen concentration is above the line on the Rumack Matthew nomogram. In 2012, the United Kingdom's Medicine and Healthcare Products Regulatory Agency (MHRA) changed their treatment recommendations, such that any acetaminophen concentration above 100 μg/mL at 4 hours warrants treatment.

As with most overdoses, the topic of gastrointestinal decontamination remains controversial. There is no role for the routine administration of syrup of ipecac or gastric lavage in the emergency department. The use of activated charcoal with oral NAC probably results in a mild decrease in NAC absorption, but this is unlikely to be of any clinical consequence [7].

N-acetylcysteine acts both as a free radical scavenger, as well as a glutathione substrate. Many different treatment durations have been proposed. One such treatment regimen involves the oral administration of 140 mg/kg, followed by 70 mg/kg every 4 hours for 17 doses. More recently, other dosing strategies have been developed, with shorter durations of therapy [13]. Because both acetaminophen poisoning and oral NAC administration can cause nausea and vomiting, the intravenous administration of NAC is appealing. The major adverse effect associated with intravenous therapy is the development of anaphylactoid reactions. One common regimen for intravenous administration of NAC involves a loading dose of 150 mg/kg intravenously over 1 hour, followed by 12.5 mg/kg/hour for 4 hours, followed by 6.25 mg/kg/hour for 16 hours. While the anaphylactoid reactions are usually mild, at least one report of death in a 'brittle asthmatic', as the authors describe, has resulted from the intravenous administration of NAC [14]. Nonetheless, most anaphylactoid reactions due to NAC are minor, and can be easily treated by temporary discontinuation of NAC, and administration of diphenhydramine. Once symptoms improve, NAC can typically be restarted, often at a somewhat slower infusion rate. The incidence of anaphylactoid reactions appears to be inversely related to the acetaminophen concentration [15]. If an intravenous preparation of NAC is not available, the oral formulation can be administered intravenously, if administered through a 0.22-μ filter.

After a patient has received at least 21–24 hours of therapy, NAC can be discontinued if the patient is asymptomatic, liver function, including the prothrombin time (PT), are normal, and a repeat acetaminophen concentration, if obtained, is not detectable.

The Rumack–Matthew nomogram was designed for a single, acute ingestion, when the time of ingestion is known to have occurred between 4 and 24 hours prior to phlebotomy. Many times patients present following multiple ingestions over several hours. In these cases, technically the nomogram cannot be utilized. However, some toxicologists will still use the nomogram by assuming plotting all pills based on the earliest and latest times of ingestion, and treat if either point exceeds the treatment line. For example, if a patient ingested 20 tablets of acetaminophen at 01.00 hours and an additional 20 tablets at 03.00 hours, an acetaminophen level should be obtained at 05.00 and 07.00 hours, and treatment should be started if either concentration is above the treatment line.

Not uncommonly, patients will present with an unknown time of ingestion. In these cases, an acetaminophen level and liver function tests, including PT should be obtained. If there is no detectable acetaminophen, and the liver functions and PT are normal, no treatment for acetaminophen ingestion is needed. If there is any detectable acetaminophen, or if there are abnormal liver function tests, treatment with NAC is indicated. Chronic ingestion, where the patients have taken supratherapeutic doses for several days should be managed the same as when the time of ingestion is not known.

Because of its low volume of distribution and minimal protein binding, acetaminophen can be removed via haemodialysis. However, because NAC is highly effective if started early, the role for extracorporeal removal is minimal. In cases of massive acetaminophen ingestion, extracorporeal elimination can be considered, especially if there is a co-existing metabolic acidosis.

Differential diagnosis

While the diagnosis of acetaminophen-induced liver failure may be obvious in a patient who presents with a suicide note and an empty bottle of acetaminophen, the clinician is frequently confronted with a patient in liver failure with no history of overdose. In these cases, the acetaminophen concentration is often negative, as it has been metabolized completely prior to the onset of severe liver dysfunction. Therefore, it is important to consider acetaminophen in the differential diagnosis of any patient with hepatic failure.

While many drugs can cause a toxin-induced hepatitis, there are fewer xenobiotics that can cause acute fulminant hepatic failure. Among these drugs are acetaminophen, amoxicillin-clavulanate, isoniazid, iron, phenytoin, valproic acid, propylthiouracil, nitrofurantoin, and herbal preparations, including pennyroyal and chaparral. Cocaine, 3,4 methylenedioxymethamphetamine (MDMA, or ecstasy), together with carbon tetrachloride, white phosphorus, arsenic, thallium, and borates can cause acute hepatic failure.

The emergency physician should always consider infectious aetiologies, vascular aetiologies (e.g. Budd–Chiari syndrome, ischaemic hepatitis, veno-occlusive disorders), and miscellaneous aetiologies such as Wilson's disease, autoimmune hepatitis, fatty liver of pregnancy, heat stroke, and haemolysis elevated liver enzymes and low platelets (HELLP) syndrome.

While the history may be helpful in distinguishing the aetiology of fulminant hepatic failure, several additional laboratory features might be helpful as well. Frequently, the AAST rises faster and peaks sooner than the alanine aminotransferase (ALAT). In addition, unlike some other aetiologies of hepatic failure there is also synthetic dysfunction that results in a rise in the prothrombin time.

Liver failure

The greatest concern following acetaminophen ingestion is the potential to develop hepatotoxicity, which is characterized by the combination of transaminitis, encephalopathy, acidosis, renal failure, coagulopathy, and hypoglycaemia. The proximate cause of death in acetaminophen-induced hepatic failure is usually cerebral oedema or sepsis.

N-acetylcysteine should be continued until one of three major endpoints happens; clinical and laboratory improvement, liver transplant, or death.

Raschke and colleagues published a protocol for management of patients in fulminant liver failure. In their series of 22 patients with fulminant liver failure and a grade 3 or 4 encephalopathy, 12/22 (55%) were due to acetaminophen [16]. In addition to NAC, their protocol involved placement of an intracranial pressure monitor, aggressive management of intracranial hypertension, and vasopressor titration. This strategy was associated with good clinical outcomes among the 18 transplant candidates, including those who did not ultimately receive a liver transplant. Importantly, none of the patients died from cerebral oedema.

Special populations

Pregnancy

Acetaminophen readily crosses the placenta, which places the fetus at potential risk of hepatotoxicity [17]. However, because NAPQI does not cross the placenta, the fetus itself must metabolize the acetaminophen in order for hepatotoxicity to occur. The fetus is able to start metabolizing acetaminophen beginning at approximately 18 weeks gestational age [17]. Fortunately, NAC does cross the placenta. The indications for NAC are not different between pregnant and non-pregnant individuals. Fetal outcome appears to be worse with delays in commencing NAC [18].

Alcoholics

Chronic alcohol consumption results in depletion of hepatic glutathione, and upregulation of CYP2E1 [6], the isoenzyme that metabolizes acetaminophen to NAPQI. Consequently, chronic alcoholics might be at increased risk for acetaminophen-induced hepatotoxicity. Therapeutic dosing does not appear to increase the risk of hepatotoxicity [19], although chronic alcohol abuse may be associated with poor outcomes in acute acetaminophen poisoning.

Prognosis

In general, patients who have NAC started within 8 hours of the overdose will do well. Once hepatic injury occurs, the King's College Criteria can be used to help predict which patients may benefit from liver transplant [20]. According to these criteria, patients should be considered for liver transplant if the arterial pH is less than 7.25 after fluid resuscitation, or if there is a combination of a prothrombin time longer than 100 seconds, grade III or IV encephalopathy, and a serum creatinine higher than 3.4 mg/dL [9].

Conclusion

Acetaminophen overdose remains a common cause of hepatic failure. In order to ensure optimal care, the diagnosis must be made early, and treatment started within 8 hours. With prompt treatment with NAC, the incidence of hepatic failure can be reduced.

References

1. Lee WM. (2004). Acetaminophen and the US Acute Liver Failure Study Group: lowering the risks of hepatic failure. *Hepatology*, **40**, 6–9.
2. Bronstein AC, Spyker DA, and Cantilena LR Jr. (2012). Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th annual report. *Clinical Toxicology*, **50**, 911–1164.
3. Gosselin S, Hoffman RS, Juurlink DN, et al. (2013). Treating acetaminophen overdose: thresholds, costs, and uncertainties. *Clinical Toxicology*, **51**, 130–3.

4. Prescott LF. (1980). Kinetics and metabolism of paracetamol and phenacetin. *British Journal of Clinical Pharmacology*, **10**, 291s–8s.
5. Rowen AK, Norvell J, Elridge DL, et al. (2006). Acetaminophen poisoning. *Clinical and Laboratory Medicine*, **26**, 49–65.
6. Riordan SM and Williams R. (2002). Alcohol exposure and paracetamol-induced hepatotoxicity. *Addiction Biology*, **7**, 191–206.
7. Zed PJ and Krenzelok EP. (1999). Treatment of acetaminophen overdose. *American Journal of Health-System Pharmacy*, **56**, 1081–91.
8. Chun LJ, Tong MJ, Busuttil RW, et al. (2009). Acetaminophen hepatotoxicity and acute liver failure. *Journal of Clinical Gastroenterology*, **43**, 342–9.
9. O'Grady JG, Alexander GJ, Hayllar KM, et al. (1989). Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology*, **97**, 439–45.
10. Fenves AZ, Kirkpatrick HM 3rd, Patel VV, et al. (2006). Increased anion gap metabolic acidosis as a result of 5-oxoproline (pyroglutamic acid): a role for acetaminophen. *Clinical Journal of the American Society of Nephrology*, **1**, 441–7.
11. Prescott LF, Illingwort RN, Critchley JA, et al. (1979). Intravenous N-acetylcystine: the treatment of choice for paracetamol poisoning. *British Medical Journal*, **2**, 1097–100.
12. Rumack BH, Peterson RC, Koch GG, et al. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. *Archives of Internal Medicine*, **141**(3 Spec No), 380–5.
13. Betten DP, Cantrell FL, Thomas SC, et al. A prospective evaluation of shortened course oral N-acetylcysteine for the treatment of acute acetaminophen poisoning. *Annals of Emergency Medicine*, **50**, 272–9.
14. Appelboam AV, Dargan PI, and Knighton J. (2002). Fatal anaphylactoid reaction to N-acetylcysteine: caution in patients with asthma. *Emergency Medicine Journal*, **19**, 594–5.
15. Waring WS, Stephen AF, Robinson OD, et al. (2008). Lower incidence of anaphylactoid reactions to N-acetylcysteine in patients with high acetaminophen concentrations after overdose. *Clinical Toxicology* (*Philadelphia*), **46**, 496–500.
16. Rashke RA, Curry SC, Gerkin R, et al. (2008). Results of a protocol for the management of patients with fulminant liver failure. *Critical Care Medicine*, **36**, 2244–8.
17. Wilkes JM, Clark LE, Herrera JL. Acetaminophen overdose in pregnancy. *Southern Medical Journal*, **98**, 1118–22.
18. Riggs BS, Bronstein AC, Kulig K, et al. Acute acetaminophen overdose during pregnancy. *Obstetrics and Gynecology*, **74**, 247–53.
19. Kuffner EK, Green JL, Bogdan GM, et al. (2007). The effect of acetaminophen (four grams a day for three consecutive days) on hepatic tests in alcoholic patients—a multicenter randomized study. *BMC Medicine*, **5**, 14.
20. Anand AC, Nightingale P, and Neuberger JM. (1997). Early indicators of prognosis in fulminant hepatic failure: an assessment of the King's criteria. *Journal of Hepatology*, **26**, 62–8.

CHAPTER 319

Management of opioid poisoning

Alison L. Jones

Key points

- The physiological action of an opioid depends on the drug type, dose, and degree of prior opioid tolerance.
- Management of opioid poisoning consists of effective respiratory support and appropriate use of an antidote, usually naloxone intravenously.
- The half-life of opioids is longer than the antagonist naloxone—hence, ongoing infusions of naloxone are often required after the initial 'wake up' bolus and titrated to clinical signs with close ongoing clinical monitoring.
- Acute withdrawal syndrome may be precipitated by overzealous administration of in opioid dependent patients. Naloxone can be used, but should be titrated slowly, aiming for a Glasgow Coma Score of 13–14.
- Patients with opioid toxicity are at risk of respiratory, septic, and central nervous system complications, e.g. anoxic encephalopathy.

Opioids

Opioids are 'morphine like' substances that have pharmacological actions at specific opioid receptors in the central nervous system (CNS) and gastrointestinal tract. There are subclasses of opioid receptor including μ, δ, and κ receptors [1]. Stimulation of the μ receptor is responsible for most of the clinical effects caused by opioids and the extent of pharmacological action is determined by the factors illustrated in Fig. 319.1 [2].

Opioid tolerance and acute withdrawal syndrome

Over time, chronic opioid users need increased doses to achieve the same pharmacological effect, i.e. tolerance occurs [3]. Tolerance of respiratory depression develops at a slower rate than analgesic tolerance, placing patients with a long history of opioid use at particular risk for respiratory depression [3]. Stimulation of the μ receptor is responsible in part for tolerance (due to uncoupling of the μ receptor from the G-protein) [4].

If chronic users stop taking opioids abruptly, due to lack of supply or illness, they develop an acute withdrawal syndrome (AWS) which lasts 24–48 hours [5]. This is characterized by lacrimation, piloerection, rhinorrhoea, salivation, shivering and yawning, and progresses to agitation, fluctuations in blood pressure, diarrhoea, and vomiting [5]. Although AWS is not usually life threatening per se [5], there is a risk of aspiration pneumonitis if emesis occurs with an unprotected airway. Controlled detoxification programmes from opioids involve sedation with benzodiazepines, or even administration of a general anaesthetic in 'ultrarapid' techniques [6].

Epidemiology

Most opioid toxicity is the result of inadvertent overdosage during recreational use or due to opioid ingestion in self-harm. Trials are under way in the UK to send the antidote naloxone home with patients who use opioids recreationally. In other cases, opioid toxicity may be due to a variety of routes of exposure and circumstances including medication misuse and drug errors (Table 319.1).

Broadly, the number of opioid analgesic overdoses is proportional to the number of opioid prescriptions [4]. Death is more common as an outcome if benzodiazepines or cocaine are co-intoxicants. Opioids accounted for 107,000 of toxic exposures reported to Poison Control Centers in the USA and more than 27,500 admissions to health care facilities in a US population close to 260 million [7].

It is important not to miss underlying paracetamol toxicity in patients presenting with features of opioid toxicity (due to ingestion of a combined opioid-paracetamol) product [8]. Therefore, initial plasma blood paracetamol concentration should be determined in all patients who have ingested excessive opioids, and repeated at 4 hours to not miss an overdose [4]. If a patient has presented with an opioid overdose and subsequently develops abnormal liver function tests, then a paracetamol-opioid co-ingestion or shocked liver due to impaired circulation, or hepatitis due to viruses, e.g. hepatitis B or C in an intravenous (iv) drug user should be considered.

There is little point undertaking a urine drug screen for opioids, as it will not guide clinical management, unless the diagnosis of opioid poisoning is in doubt or there is a medicolegal imperative.

Assessment of degree of opioid poisoning

Opioid poisoning is characterized by three main clinical features (all may not be consistently present) [4,9]:

- Depressed respiratory rate (the *sine qua non* of opioid poisoning) and respiratory volume and consequential reduced arterial oxygen desaturation (<90% on air).
- **CNS depression**: usually described by the (unvalidated in poisoning) Glasgow Coma Scale.
- Small or pin-point pupils.

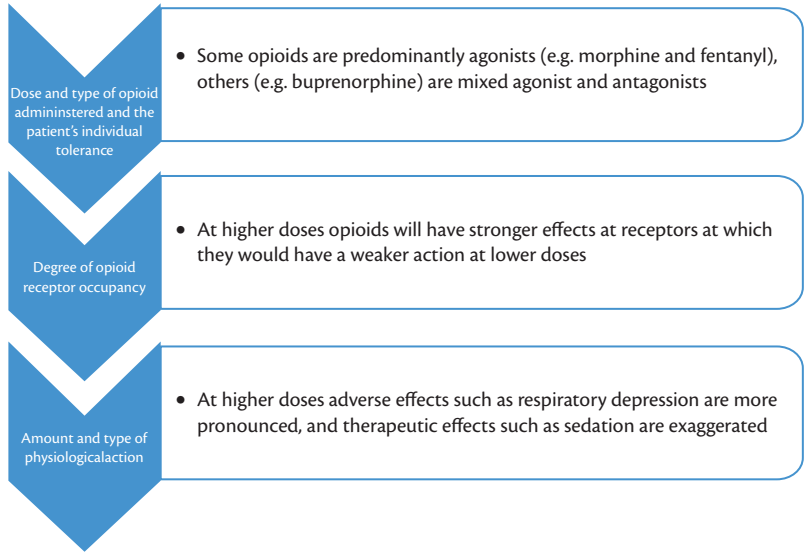


Fig. 319.1 Factors influencing amount and type of physiological action of opioids.
Data from Negus S, Bilsky E (eds) *Opioid Receptors and Antagonists: from Bench to Clinic*. Humana Press 2009. Chapter 27, pp. 511–38. DOI: 10.1007/978-1-59745-197-0.

Table 319.1 Opioid poisoning by route and circumstances of exposure

Exposure route	Circumstances	Details	References
Oral	Accidental and deliberate poisoning in children	Methadone poisoning in children is increasing paralleling its use, with 72% in one USA series requiring paediatric ICU (PICU) admission. A recent study demonstrates that patients in PICU are at increased risk of opioid adverse drug events, and a bar code-assisted opioid administration system reduced risks.	[15,16]
Oral and iv	Deliberate and accidental self-poisoning in adults	Risk profile: drug abusers or those with chronic pain. Note increasing methadone deaths with increasing methadone prescribing for pain. Note that individuals who have been incarcerated are at risk of opioid toxicity on release, due to diminished tolerance to opioids.	[7,17]
Gastrointestinal release	Body packers	Transportation of opioids within condoms or other packaging material: may leak from pack rupture and require ICU care as a prequel or sequel to abdominal surgery.	[18]
Transdermal or oral abuse of patches	Accidental in pain management or deliberate abuse	Transdermal absorption of fentanyl patches or oral abuse resulting in poisoning with is a concern.	[3]
Inhalational toxicity	Terrorism or accidental	Examples include the use of fentanyl in the Moscow theatre terrorism event. A recent case report of a pharmacy technician inhaling methadone powder in error for cocaine. The outcome was fatal with blood methadone concentration of 290 μg/L and death after 24 hours of ICU due to cerebral and pulmonary oedema.	[19]
Spinal		Spinal analgesia, mediated by opioid receptors, requires only a fraction of the opioid dose that is needed systemically. Risk is respiratory depression with long term use and recently reported, loss of opioid tolerance due to delayed pump refill may cause severe respiratory depression.	[20]

Data from Negus S, Bilsky E (eds) *Opioid Receptors and Antagonists: from Bench to Clinic*. Humana Press 2009. Chapter 27, pp. 511–38. DOI: 10.1007/978-1-59745-197-0; and various other sources (see references).

The differential diagnosis for these clinical features includes organophosphorus poisoning, or gammahydroxybutyrate (GHB) toxicity [2]. In the case of GHB, co-ingestion of opioids increases toxicity of the GHB.

The absorption, onset of action, and elimination half-life, which are known kinetic parameters for each specific opioid are often irrelevant in overdose. Opioids delay gastric emptying. Often first-order elimination kinetics changes to zero-order, as saturation occurs, leading to prolonged opioid toxicity [4].

Management of opioid poisoning

Meticulous supportive care

Opioid poisoned patients who reach hospital alive should not die, but data show death is still an outcome [10,11]. Patients require early clinical assessment, appropriate administration of naloxone and meticulous respiratory supportive care for sufficient time to allow the patient to fully metabolize and eliminate the opioid.

Most patients require temporary airway support (e.g. bag-valve mask, and chin-lift or jaw thrust) until a sufficient dose of the antagonist naloxone has reversed the opioid effect. Ongoing naloxone and close observation is then required until the opioid has been eliminated. Sometimes endotracheal intubation is required.

Rarely patients require intensive care unit (ICU) admission. This usually occurs as a result of a complication of the opioid toxicity, such as aspiration pneumonitis due to an unprotected airway, due to sepsis from iv opioid injection sites, or as a result of physical injury or trauma. In a recent retrospective chart review of a Greek intensive care unit (ICU) heroin overdose series, 19 of 42 patients (45%) were found in the field with a Glasgow Coma Scale (GCS) <8, and respiratory depression and 37 required intubation [11]. Of the patients requiring intubation 19 were extubated within the first 24 hours and 16 required assisted ventilation for 5 +/– 2 days, with a mean length of ITU stay of 8 +/– 1 days. Two patients died due to anoxic encephalopathy and brain death [11]. Complications seen across the 42 patients were acute respiratory distress syndrome in eight (19%), severe sepsis in four (9.5%), catheter-related bacteraemia in one (2.4%), iatrogenic pneumothorax in one (2.4%), and rhabdomyolysis in two (4.8%), while four (8.6%) died due to severe sepsis. The overall mortality was 14.2% [11].

Negative pressure pulmonary oedema has been reported either following reversal of opioid anaesthesia (e.g. for cardiac surgery) or with pre-existing cardiorespiratory disease [4]. Opioids can cause non-cardiogenic oedema and it is possible that use of the antidote naloxone unmasks this oedema [4]. In addition, co-administration of myocardial depressants such as propoxyphene are considered contributory. Mild cases of pulmonary oedema resolve with supportive care, but patients with more severe hypoxaemia require intubation and positive pressure ventilation [4]. Resolution of lung injury usually occurs within 24 hours, unless aspiration pneumonitis has occurred when recovery is delayed [11].

Seizures, arrhythmias, and rhabdomyolysis have also been associated with opioid overdoses, their co-ingestants or due to pre-existing disease [2].

Note, there is an emerging literature suggesting patients are not fit to drive for many days after recovering from an opioid overdose and should be advised accordingly [12].

The opioid receptor antagonist: naloxone

μ opioid receptor antagonists, such as naloxone (n-allylnoroxymorphone), competitively reverse the clinical features of toxicity by pure opioid agonists. They do not reverse opioid toxicity of partial agonist/antagonists like buprenorphine [13]. If opioid antagonists are given to regular opioid users in excess, they can precipitate acute withdrawal symptoms.

The pharmacokinetic features of naloxone include a time to clinical effect of approximately 2 minutes, if given iv, which lasts from 20 to 90 minutes [4], and an elimination half-life of approximately 60 minutes [2,4]. In clinical practice the effects may be shorter than the kinetic data suggest because its high lipid solubility creates a steep concentration gradient between brain and serum, leaching naloxone back into the serum. Because of the longer half-life of opioids than naloxone, repeated doses may be needed for long-acting opioids or large doses of shorter-acting opioids.

Optimal management of opioid poisoning consists of empirical titration of iv boluses of naloxone (0.04 mg increased to 0.5, 2, 4, 10, and a maximum dose of 15 mg each after 2 minutes to assess response to prior dose) so that patients maintain their airway and have effective ventilation [4]. In most overdose cases, an ongoing naloxone infusion is required according to the Goldfrank protocol of two-thirds of the total required 'wake up dose' given over each hour to maintain the antagonism and close clinical observation of the patient [2]. Naloxone infusions for many hours, e.g. 18–24 hours may be required. A clinical algorithm has been developed to summarize the clinical data to date.[4] Patients who had taken long-acting opioids may develop re-narcosis up to 2 hours after initial treatment and as the half-life of naloxone is 20–90 minutes it seems logical to observe patients for at least 2 hours after the last dose of naloxone has been given.

Cases have been reported where up to 20 times the recommended doses of naloxone have been needed to treat massive opioid doses, and even more with body packers with up to 50 mg used in a single patient over 24 hours (author's personal experience) [2]. Case histories reveal nearly 100-fold variation in the dose of naloxone infusions (0.125–12 mg/hour) given for prolonged overdoses [2]. Note that, in obese patients, the residence time for opioids may be increased as the opioid leaches out of fatty tissues over time and such patients may therefore require a longer duration of naloxone infusion [4]. Subcutaneous (sc) and intramuscular (im) routes for naloxone should only be used if iv access cannot be established. A recent report suggests nebulized naloxone may be effective in the prehospital environment [14].

Children often ingest a higher dose per kilogram than adults and may require larger doses of naloxone to reverse opioid toxicity than adults. Elderly patients have increased susceptibility to opioid respiratory and CNS depression effects and should be carefully monitored.

An observational study found a 0.7% complication rate within 5 minutes of naloxone administration (0.4–2.4mg), which included transient, mild fluctuations in blood pressure due to antagonism of opioid-mediated inhibition of noradrenaline release from the autonomic system [2]. An 8% complication rate occurred within 20 minutes of 2–4 mg boluses, including severe hypertension in patients with pre-existing essential hypertension [2]. Although all of the complications occurred soon after naloxone was administered, it does not mean that naloxone was the direct cause of complications [2].

Acute withdrawal symptoms can be caused by overzealous administration to chronic opioid-dependent patients. Therefore, titrating the dose of naloxone closely to the patient's respiratory rate (to maintain good arterial oxygen saturations) and coma score is recommended, aiming for a target GCS of 13–14, rather than 15.

Opioid receptor antagonists: nalmefene and naltrexone

These opioid antagonists have much longer half-lives and lower lipid solubility than naloxone and were introduced in the 1980s (half-life 10 hours for naltrexone and 8–9 hours for nalmefene) [2]. Their prolonged action means they are used for controlled, rapid detoxification of chronic opioid use, and to help former addicts abstain from further opioid use. If opioids are subsequently needed, it may be extremely difficult to achieve adequate analgesia for up to 72 hours afterwards [2].

Conclusion

Good outcomes after opioid poisoning are determined by meticulous supportive care and judicious use of appropriate doses of naloxone over time, recognizing the much shorter half-life of the antidote compared with the opioid. Even in 2012, the antidote treatment for opioid poisoning remains largely empirical and requires good observational clinical skills.

References

1. Waldhoer M, Bartlett SE, and Whistler JL. (2004). Opioid receptors. *Annual Review of Biochemistry*, **73**, 953–90.
2. Dean R, Bilsky E and Negus S. (2009). Emergency room use of opioid antagonists in drug intoxication and overdose. In: Negus S and Bilsky E. (eds) *Opioid Receptors and Antagonists: from Bench to Clinic*, Chapter 27. New York, NY: Humana Press 511–539.
3. Etches RC. (1994). Respiratory depression associated with patient-controlled anesthesia: a review of eight cases. *Canadian Journal of Anaesthesia*, **41**, 125–32.
4. Boyer E. (1990). Management of opioid analgesic overdose. *New England Journal of Medicine*, **367**, 146–55.
5. Chiang WK and Goldfrank JR. (1990). Substance withdrawal. *Emergency Medical Clinics of North America*, **8**(3), 613–31.
6. Maani CV, DeSocio PA, Jansen RK, et al. (2011). Use of ultrarapid opioid detoxification in the treatment of US military burn casualties. *Journal of Trauma*, **71**(1), S114–19.
7. American Association of Poison Control Centers (2010). *National Poisons Data System 2010 Annual Report*. Available at: http://www.aapcc.org
8. Khandewal N, James LP, Sanders C, Larson AM, and Lee WM. (2011). Unrecognised acetaminophen toxicity as a cause of indeterminate acute liver failure. *Hepatology*, **53**, 567–76.
9. Hoffman RS and Goldfrank LR. (1995). The poisoned patients with altered consciousness: controversies in the use of a 'coma cocktail'. *Journal of the American Medical Association*, **274**, 562–9.
10. Wiegand TJ, Wax PM, Schwartz T, Finkelstein Y, Gorodotsky Y, and Brent J. (2012). The Toxicology Consortium Investigators Toxicology Case Registry—the 2011 experience. Journal of Medical Toxicology, **8**(4), 360–77.
11. Grigorakos L, Sakagianni K, Tsiquo E, Apostolakos G, Nicopoulos G, and Veldekis D. (2010). Outcome of acute heroin overdose requiring acute intensive care unit admission. *Journal of Opioid Management*, **6**(3), 227–31.
12. Dassanayake T, Jones AL, Michie P, et al. (2012). Risk of road traffic accidents in patients following treatment for psychotropic drug overdose. A self-controlled case studies series in Australia. *Central Nervous System Drugs*, **26**, 269–76.
13. Megarbane B, Buisine A, Jacobs F, et al. (2010). Prospective comparative assessment of buprenorphine overdose with heroin and methadone. *Journal of Substance Abuse Treatment*, **38**(4), 403–7.
14. Weber JM, Tataris KL, Hoffman JD, Acks SE, and Myck MB. (2012). Can nebulised naloxone be used safely and effectively by emergency medical services for suspected opioid overdose? *Prehospital Emergency Care*, **16**(2), 289–92.
15. Martin TC and Roque MA. (2011). Accidental and non-accidental of methadone and buprenorphine in childhood: a single center experience 1999–2009. *Current Drug Safety*, **6**(1), 12–16.
16. Morriss FH Jr, Abramovitz PW, Nelson SP, Milavetz G, Michael SL, and Gordon SN. (2011). Risk of adverse drug events in neonates treated with opioids and the effect of a bar code assisted medication administration system. *American Journal of Health-System Pharmacy*, **68**(1), 57–62.
17. Kuehn BM. (2012). Methadone overdose deaths rise with increasing prescribing for pain. *Journal of the American Medical Association*, **308**(8), 749–50.
18. Chang CW, Lin JL, Weng CH, and Yen TH. (2011). Respiratory failure and coma in an International traveller. *International Medicine*, **50**, 2691.
19. Palmiere C, Bruel C, Sporkert F, and Auqsburger M. (2011). An unusual case of accidental poisoning: fatal methadone inhalation. *Journal of Forensic Science*, **56**(4), 1072–5.
20. Ruan X, Couch JP, Liu H, Shah RV, Wang F, and Chiravuri S. (2010). Respiratory failure following delayed intrathecal morphine pump refill: a valuable but costly lesson. *Pain Physician*, **13**(4), 337–41.

CHAPTER 320

Management of benzodiazepine poisoning

Philippe Lheureux and Marc Van Nuffelen

Key points

- Benzodiazepines are the drugs most frequently involved in acute self-poisoning.
- Benzodiazepine overdose usually has a good prognosis—most patients do well with careful observation and prevention of complications. Supportive care including oxygen, intubation, respiratory support, and fluid administration may be required in some cases.
- Care should be taken with elderly patients, or those with chronic obstructive pulmonary disease or liver disease. Fast-acting agents and ingestion of other central nervous system depressants, including alcohol, may present an additional risk.
- Early administration of activated charcoal in fully conscious patients who are able to protect their airway is only needed if there are co-ingestants.
- Flumazenil may help confirm the diagnosis, improve alertness, and prevent the need for respiratory support in some patients, especially after accidental poisoning in children. Contraindications include patients on long-term treatment and/or dependent on benzodiazepines, or those who have simultaneously ingested proconvulsant or prodysrhythmic substances, or at risk of increase intracranial pressure.

Introduction

Benzodiazepines were introduced 50 years ago. The first compound, chlordiazepoxide, was followed by multiple other agents and benzodiazepines are now among the most frequently prescribed drugs in many countries, due to their clinical efficacy and relatively good safety profile. They have replaced older sedative-hypnotics in clinical use, particularly barbiturates. They have a wide pharmacological profile including anxiolytic, muscle relaxant, amnestic, and anticonvulsant properties. Some benzodiazepines (e.g. diazepam, lorazepam) are also commonly used in clinical practice to control withdrawal symptoms, especially from alcohol. In anaesthesia, they are used as pre-anaesthetic agents and associated with other drugs for procedural sedation.

Unfortunately, due to their widespread availability, these agents are also frequently involved alone, or in combination with alcohol or other medications in drug-assisted suicide, as well as in accidental poisoning in children. Some of them, especially flunitrazepam, are known as date rape drugs.

There is also clear evidence that the prolonged use of even therapeutic doses of a benzodiazepine will lead to dependence. The risk of developing a significant withdrawal syndrome, which may be life-threatening seems related to dosage and duration of treatment.

Mechanism of action

The main action of benzodiazepines ('agonists') on the central nervous system (CNS) consists of potentiating the γ-aminobutyric acid (GABA) neurotransmission (the main inhibitory system in the CNS), and enhancing the frequency and duration of opening of the chloride channel, thereby inducing a post-synaptic hyperpolarization.

The pharmacokinetic profile of benzodiazepines is heterogeneous, because of variations of side chains around a similar basic chemical structure. Onset of action is highly variable; higher lipid solubility is associated with faster digestive absorption and distribution in the CNS through the blood–brain barrier [1,2], but peak concentrations are usually reached within 1–3 hours. Duration of action is related to redistribution to peripheral tissues, as well as to the elimination half-life of the parent compound and active metabolites. Biotransformation predominantly occurs in the liver (oxidation and/or conjugation) and may be impaired in elderly patients and those with hepatic disease. Genetic polymorphism of cytochrome P450 is also responsible for variations in the pharmacokinetics of benzodiazepines [3]. Co-ingestants, especially alcohol and drugs, enzyme induction, and acquired tolerance are other factors involved in individual variability

Assessment

Clinical evaluation

Pure benzodiazepine overdose is rarely severe, particularly in previously healthy people. It is characterized by progressive CNS depression, ranging from dizziness, drowsiness with slurred speech and blurred vision, confusion to stupor, and flaccid coma. Nystagmus may be present. Vital signs usually remain normal, although mild hypotension may be observed. Patients often remain arousable and able to provide some information when stimulated, but anterograde amnesia is common. Unresponsiveness or deep coma requiring respiratory support is infrequent, but snoring with flow limitation due to an increase in upper airway resistance and obstructive apnoea may be observed [4], even in somnolent patients. Paradoxical agitation, anxiety, disinhibition, and aggressiveness may occur. Ataxia is

a common presentation after accidental benzodiazepine ingestion in children. Alprazolam seems significantly more toxic than other benzodiazepines [5]. Benzodiazepine overdose has been anecdotally associated with atrioventricular block, perhaps mediated through an action on calcium channels [6] and bullous cutaneous eruptions [7].

A scenario of respiratory compromise due to CNS depression, hypotension, or hypothermia is more often present when a benzodiazepine is administered intravenously for procedural sedation, usually with other agents or when other central nervous system depressants (particularly alcohol) have been ingested. People with increased susceptibility include the elderly or patients with poor clinical condition, in who muscle weakness may be particularly prolonged. CNS depression may last in patients with liver disease, while the risk of respiratory depression is increased in those with chronic obstructive pulmonary disease. Other risk factors include massive ingestion, and short-acting or highly sedative compounds (midazolam, triazolam, temazepam, flunitrazepam) [1,8,9].

Despite the relative safety of benzodiazepines, morbidity and mortality of overdoses are not negligible, particularly in elderly people, but are usually related to complications, mainly respiratory problems [10]. Withdrawal syndrome may develop after acute poisoning in chronic users.

Analytical toxicology

Routine toxicological testing does not help in assessing the severity or the prognosis. It does not influence the management of benzodiazepine overdose, but may detect certain co-ingestants, especially paracetamol, when history is lacking or doubtful.

Qualitative urine testing for benzodiazepines, based on the detection of the oxazepam glycuronide, may help to confirm the presence of most 1,4-benzodiazepine derivatives. Some agents (e.g. alprazolam, clonazepam, temazepam, midazolam, lorazepam, or triazolam) and benzodiazepine-like substances are not easily detected.

Determination of benzodiazepine serum levels (parent drugs and metabolites) may occasionally help to differentiate drug-induced CNS depression from other aetiologies, although there is no strong correlation between serum concentrations and clinical presentation. In particular, very high levels with minimal impairment may be observed in tolerant people.

Other investigations

When multiple drug overdose is suspected or in coma of unknown aetiology, an electrocardiogram (ECG) should always be obtained, especially before considering flumazenil injection. Any abnormality of QRS or QTc intervals should suggest co-ingestion of cardiotoxic agents. A chest X-ray must be obtained in comatose patients or those with respiratory compromise to rule out aspiration pneumonia, which is the most frequent source of complications.

Usual chemistry values, EEG, CT scan, and analysis of cerebral spinal fluid may be helpful for excluding trauma, cerebrovascular accident, infection, or metabolic disturbances in comatose patients.

Management

General supportive care

Treatment of benzodiazepine overdose is mainly supportive. Airway, breathing, and circulation must be rapidly assessed. Repeated evaluation of neurological status and respiratory function are needed; oxygen, intubation, and ventilation support may be required to prevent hypoxaemia, hypoventilation, aspiration, and atelectasis. If present, hypotension usually responds to volume expansion alone. Usual measures must be undertaken to prevent ocular and pressure-induced complications during coma.

Prevention of digestive absorption and elimination procedures

Gastrointestinal decontamination should only be considered for patients who are at risk because they have self-harmed by ingestion of very large dose of benzodiazepines or have co-ingested dangerous drugs. If such cases are managed within the first hour after ingestion, a single dose of activated charcoal should be offered at the earliest opportunity, if the patient is conscious and able to protect the airway. Later administration of activated charcoal may still be considered if drugs in slow-release form or substances slowing gastric emptying are involved (e.g. cyclic antidepressants). If only low doses of benzodiazepine were ingested, it is unlikely that there will be any clinical benefit from the charcoal and the risk of pulmonary complications will be increased. Airway protection by endotracheal intubation must be ensured before activated charcoal is given (through a nasogastric tube) in those with significant impairment of alertness. More invasive techniques, such as induced emesis, gastric lavage, or whole bowel irrigation are never indicated in pure benzodiazepine overdose: the risks associated with these procedures outweigh their hypothetic clinical benefit, particularly in stuporous patients. In mixed overdoses, the need for gastric emptying before charcoal dosing must be carefully evaluated in each case [11].

Multiple doses of activated charcoal, enhanced diuresis, and extracorporeal techniques (e.g. haemodialysis, haemoperfusion) are never indicated for benzodiazepines, since they will not significantly improve the elimination of these agents.

Antidotes

Flumazenil is a benzodiazepine receptor competitive antagonist with no significant intrinsic effect. It rapidly antagonizes the effects of both agonist and inverse-agonist ligands. Flumazenil has proved useful in hastening reversal of benzodiazepine-induced CNS impairment after anaesthesia or procedural sedation. More debate surrounds the ability of flumazenil in reversing benzodiazepine-induced respiratory depression consistently [12].

After intentional overdose of benzodiazepine, judicious use of flumazenil may provide useful diagnostic information [13–16] and may sometimes obviate the need for invasive supportive measures or diagnostic procedures. Arousal usually occurs 30–60 seconds after intravenous administration, peaks after 5–10 minutes and may last for 1–2 hours. The rate of gradual relapse of sedation depends on the dose ingested, the substances involved, and their metabolites.

Slow injection is recommended because of the frequent side effects associated with sudden arousal, including anxiety, palpitations, nausea, and vomiting. Measures to prevent aspiration (lateral position, suction equipment) must be taken. In adults, the initial dose consists of 0.1–0.2 mg/minute intravenously over 30 seconds. It may be repeated after at least a 1-minute interval until sufficient alertness and adequate respiration are obtained or up to a maximum dose of 1–2 mg. Full recovery should not be the goal. To

prevent resedation, continuous infusion (usually 0.5–2 mg/hour) may be needed to maintain the effect [17] because flumazenil has a much shorter duration of action (0.7–1.3 hours) than most benzodiazepine agents, especially when ingested in large amounts. In children, an initial intravenous dose of 0.01 mg/kg and a maximal total dose of 0.05 mg/kg are recommended.

Although experience with flumazenil has shown good efficacy and relative safety in the management of benzodiazepine overdose [14], this antidote should not be administered to long-term benzodiazepine users, especially if they are being treated for epilepsy. They are probably benzodiazepine-dependent and flumazenil could precipitate an acute withdrawal syndrome, with associated tremor, anxiety, agitation, delirium, and seizures.

Controversy also exists regarding the use of this antidote in the setting of mixed drug overdose, particularly when substances that lower the seizure threshold are involved. Some observations, as well as animal studies suggest flumazenil precipitates cardiac arrhythmias when arrythmogenic drugs, such as cyclic antidepressants, monoamine oxidase inhibitors, isoniazide, theophylline, amfetamine, cocaine, antipsychotics, anti-arrhythmics, propoxyphene, chloral hydrate, halogenated hydrocarbons, etc., have been co-ingested. Flumazenil can unmask their toxic effects while suddenly antagonizing the protection ensured by benzodiazepines. It should not be used in patients who present with arrhythmias, or a prolonged QRS complex or QTc interval [11,17]. Moreover, flumazenil is contraindicated in patients who are suspected of increased intracranial pressure (e.g. head injury) due to its adverse effect on cerebral haemodynamics [18].

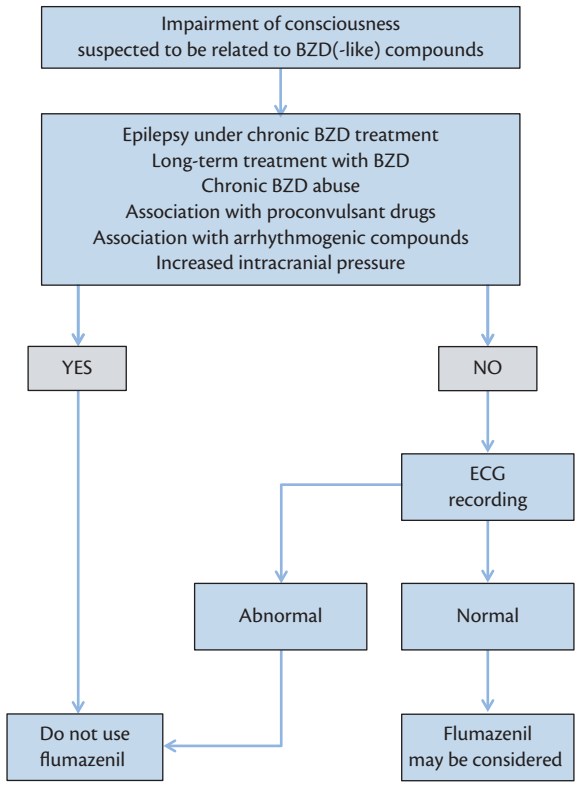


Fig. 320.1 Protocol for the rational use of flumazenil in patients suspected of benzodiazepine (BZD) intoxication.

Conclusion

Administration of flumazenil is rarely required in adult patients presenting with an overdose involving benzodiazepines or benzodiazepine-like substances and its adverse effects may unacceptably increase the risk associated with its use if contraindications are not considered [19,20]. An algorithm for its use is shown in Fig. 320.1. Flumazenil remains a very useful antidote in children presenting with accidental benzodiazepine ingestion, who are not dependent and when other drugs are commonly not involved.

References

1. Buckley NA, Dawson AH, Whyte IM, and O'Connel DL (1995). Relative toxicity of benzodiazepines in overdose. *British Medical Journal*, **310**, 219–21.
2. Greenblatt DJ, Shader RI, Divoll M, and Harmatz JS (1981). Benzodiazepines: a summary of pharmacokinetic properties. *British Journal of Pharmacology*, **11**, s111–16s.
3. Fukasawa T, Suzuki A, and Otani K (2007). Effects of genetic polymorphism of cytochrome P450 enzymes on the pharmacokinetics of benzodiazepines. *Journal of Clinical Pharmacology and Therapeutics*, **32**, 333–41.
4. Gueye PN, Lofaso F, Mellerio F, Vicaut E, Harf A, and Baud FJ (2002). Mechanism of respiratory insufficiency in pure or mixed drug-induced coma involving benzodiazepines. *Journal of Toxicology—Clinical Toxicology*, **40**, 35–47.
5. Isbister GK, O'Regan L, Sibbritt D, and Whyte IM (2004). Alprazolam is relatively more toxic than other benzodiazepines in overdose. *British Journal of Clinical Pharmacology*, **58**, 88–95.
6. Arroyo Plasencia AM, Ballentine LM, Mowry JB, and Kao LW (2012). Benzodiazepine-associated atrioventricular block. *American Journal of Therapeutics*, **19**, e48–52.
7. Verghese J and Merino J (1999). Temazepam overdose associated with bullous eruptions. *Academic Emergency Medicine*, **6**, 1071.
8. Drummer OH, Syrjanen ML, and Cordner SM (1993). Death involving the benzodiazepine flunitrazepam. *American Journal of Forensic Medical Pathology*, **14**, 238–43.
9. Serfaty M and Masterton G (1993). Fatal poisonings attributed to benzodiazepines in Britain during the 1980s. *British Journal of Psychiatry*, **163**, 386–93.
10. Höjer J, Baehrendtz S, and Gustafsson, L.L. (1989). Benzodiazepine poisoning: experience of 702 admissions to an intensive care unit during a 14-year period. *Journal of Internal Medicine*, **226**, 117–22.
11. NICE (2004). Self-harm: the short-term physical and psychological management and secondary prevention of self-harm in primary and secondary care. NICE Clinical Guideline CG16. Available at: http://publications.nice.org.uk/self-harm-cg16 (accessed 2 April 2012).
12. Howland MA. (2006). Flumazenil. In: Flomenbaum NE, Goldfrank LR, Hoffman RS et al. (eds) *Goldfrank's Toxicologic Emergencies*, 8th edn, pp. 1112–17. New York, NY: McGraw-Hill Companies Inc.
13. Sprenger H, Sharpe MD, and McLachlan RS. (1994). Flumazenil as a diagnostic tool in the differential diagnosis of coma in a critically ill patient. *Canadian Journal of Anesthesiology*, **41**, 52–5.
14. Weinbroun AA, Flaishon R, Sorkine P, Szold O, and Rudick V. (1997). A risk-benefit assessment of flumazenil in the management of benzodiazepine overdose. *Drug Safety*, **17**, 181–96.
15. Sing PK and Richell-Herren K (2000). Best evidence topic reports—flumazenil and suspected benzodiazepine overdose. *Journal of Accident & Emergency Medicine*, **17**, 214.
16. Ngo AS, Anthony CR, Samuel M, Wong E, and Ponampalam R (2007). Should a benzodiazepine antagonist be used in unconscious patients presenting to the emergency department? *Resuscitation*, **74**, 27–37.
17. Lheureux P, Vranckx M, and Askenasi R. (1991). Use and misuse of flumazenil in clinical toxicology. In: Vincent JL (ed.)

Update in Intensive Care and Emergency Medicine, pp. 482–90. Berlin: Springer-Verlag.
18. Chiolero RL, Ravussin P, Anderes JP, Lederman P, and de Tribolet N. (1988). The effects of midazolam reversal by RO 15-1788 on cerebral perfusion pressure in patients with severe head injury. *Intensive Care Medicine*, **14**, 196–200.
19. Goldfrank LR. (1997). Flumazenil: a pharmacologic antidote with limited medical toxicology utility, or an antidote in search of an overdose. *Academic Emergency Medicine*, **4**, 935.
20. Seger DL. (2004). Flumazenil: treatment or toxin. *Journal of Toxicology—Clinical Toxicology*, **42**, 209–16.

CHAPTER 321

Management of tricyclic antidepressant poisoning

Giorgio Berlot and Ariella Tomasini

Key points

- Despite the introduction of newer antidepressants, tricyclic antidepressants (TCA) are still commonly used in the treatment of depressive disorders, anxiety, and neuropathic pain with the consequent risk of accidental or voluntary intoxication.
- TCA intoxication is a potentially life-threatening condition due to multisystem involvement.
- The presence of electrocardiogram (ECG) abnormalities associated with neurological symptoms, including alterations of consciousness and/or seizures, suggests the diagnosis of possible TCA intoxication.
- If TCA intoxication is suspected, treatment should start immediately without waiting for toxicological analysis.
- The administration of sodium bicarbonate is the cornerstone of treatment, with a target blood pH of 7.45–7.55. Other drugs, including benzodiazepines, magnesium sulfate, and catecholamines should be administered if needed.

Introduction

Although a number of more recent substances with fewer side effects have become available for the treatment of depression [1], tricyclic antidepressants (TCA) are still commonly used. In addition, they are used for the treatment of neuropathic pain [2]. The common basic mechanism of action is inhibition of reuptake of different neuromediators at the presynaptic terminal in both the central nervous system (CNS) and peripheral tissues, with the subsequent prolongation of their effect on the post-synaptic membrane [3]. The earliest drug of this class was imipramine. Despite a phenothiazine-like structure it was not effective for the treatment of schizophrenia; quite unexpectedly, it improved depressive symptoms. Consequently, these substances and the derived TCAs became the first line of treatment for depression until the development of the selective serotonin reuptake inhibitors (SSRI) [3]. Although all TCAs share the same mechanisms of action, there are some differences in terms of the mediator involved. Whereas imipramine and some of its derivates, including amitriptyline and doxepin, block the reuptake of noradrenaline and serotonin at the presynaptic terminals, clomipramine has a more selective action on serotonin. After oral administration, TCAs are promptly absorbed and achieve peak blood concentrations in 2–6 hours; their absorption is reduced by antacids and drugs with anticholinergic effects. Being highly lipophilic, TCAs are rapidly taken up by the CNS. They are metabolized in the liver through oxidation and glucoronization. Although they undergo a relevant enterohepatic circulation, they are primarily eliminated through the kidney, with a half-life of 12–24 hours depending on the specific drug.

Side effects

All the molecules belonging to the TCA class share some common side effects, the effect of which whose relevance somehow varies according to the substance used (Table 321.1) and the patient's clinical conditions [4]. There are three significant side effects.

Orthostatic hypotension

This can appear well before the onset of the antidepressive effects and that can be more pronounced in hypovolaemic patients.

Anticholinergic action

Anticholinergic action may cause problems such as urinary retention, constipation, dry mouth, and in more severe forms, confusional state, tachycardia, and dryness of other mucosal surfaces. Among the various TCA, amitriptyline, and protriptyline exert the more marked anticholinergic effects. The concomitant use of drugs with cardiodepressive properties such as β-blocking agents can prevent the occurrence of tachycardia.

Cardiac conduction

Cardiac conduction disturbances may lead to the occurrence of potentially harmful arrhythmias. The most relevant features are prolongation of the PR interval, the QRS complex and of the QT corrected for the heart rate (QTc). The action of TCA on the heart conduction systems resemble that exerted by the Class Ia of antiarrhythmic agents (e.g. quinidine and procainamide). These actions and are ascribed to the altered Ca^{2+} handling in the cardiac miocytes [5]. Although these alterations are unlikely to be a problem in patients without pre-existing cardiac conduction defects and/or arrhythmias, the administration of TCA should be avoided in patients with defects of the His-Purkinje tract, such as bifascicular block, bundle branch block with prolonged PR interval, alternating bundle branch block and second and third-degree atrioventricular (AV) block; conversely, their use is safe in patients with stable first-degree AV block and right bundle branch block (RBB). All these abnormalities can be triggered and/or worsened

Table 321.1 Main side effects of TCA

Relative potencies			
Agent	**Orthostatic hypotension**	**Anticholinergic effect**	**Arrhythmogenic effect**
Doxepin	Moderate	Moderate	Present
Amitriptyline	Moderate	High	Present
Imipramine	High	Moderate	Present
Trimipramine	Moderate	Moderate	Present
Protriptyline	Low	Low	Present
Nortriptyline	Low	Low	Present
Desipramine	Low	Low	Present

by concomitant electrolyte abnormalities, especially hypokalaemia and hypomagnesaemia.

Toxic effects

Although the symptoms of TCA-associated intoxication are commonly represented by an increased severity of the symptoms listed under 'Side Effects', some can occur even in their absence. It should also be noted that the severity of symptoms is often, but by no means always dose-related.

Relevant clinical presentation of TCA intoxication

Anticholinergic syndrome

The anticholinergic syndrome is caused by TCAs and other agents including antihistamines, antipsychotics, and cyclobenzaprine. The anticholinergic syndrome refers to an array of symptoms caused by their antimuscarinic effects, which include the combination of mydriasis, dry flushed skin, hyperthermia, tachycardia, urinary retention, and reduced or absent bowel movements. At higher doses the involvement of the CNS will occur, characterized by the onset of ataxia, agitation, hallucination, delirium, and coma [6]. The occurrence of coma is considered a valuable indicator of other impeding serious complication such as arrhythmias and seizures [7].

Acute liver injury

Acute liver injury of variable severity has been associated with TCAs as well as monoamine-oxidase inhibitors (MAOI) and selective serotonin-uptake inhibitors (SSRI). The occurrence of acute liver injury is supposed to be idiopathic and thus not related to the dose or other specific risk factors. As SSRIs have largely replaced the MAOI and TCA in the treatment of depression, fewer cases of TCA-related acute liver injury have been reported in the recent years [8]. Since there is no way to predict its occurrence, a high index of suspicion is warranted in patients receiving TCA and developing signs of declining liver function.

Cardiovascular toxicity

Cardiovascular toxicity is manifested by ECG abnormalities, arrhythmias, arterial hypotension and, in most serious cases, cardiogenic shock. Among TCAs, amitriptyline has been particularly associated with these abnormalities [9]. The underlying mechanism is disturbance of Ca^{2+} handling and Na^{+} channel blockade, which enhances the duration of the action potential, as well as the refractory period of cardiac miocytes, thus increasing the AV conduction. Besides the above ECG abnormalities, more severe abnormalities include non-specific ST and T waves changes, AV blocks of varying severity, right deviation of the terminal vector of the QRS complex in the frontal plane, and a Brugada-like pattern, that include the ST elevation in V1–V3 with elevated J point and marked downslope in association with RBB (Fig. 321.1) [10]. Although the most commonly encountered arrhythmia is sinus tachycardia, related to the anticholinergic effect caused by the inhibition of the reuptake of noradrenaline, bradyarrhymias (mainly due to an AV block), and supraventricular and ventricular tachyarrhythmias, including torsade de pointes, have been reported. The combination of depressed cardiac contractility and decreased vascular resistances leads to arterial hypotension. Potentially fatal cardiac arrhythmias usually occur within 24 hours of ingestion; the cardiac toxic effects appear to be better predicted by a QRS duration >100 ms and a rightward T 40 ms axis than blood levels of TCA [9,10].

Principles of treatment

As with many other life-threatening intoxications, an early diagnosis is essential. In order to hasten the treatment, the diagnosis of TCA intoxication should be based on the clinical presentation without waiting for their detection in blood or urine; moreover, a number of factors, including the increase in the extravascular volume, reduction of drug-carrier proteins and alteration of pH influence the pharmacokinetics and pharmacodynamics of practically every drug in the critically ill patients [12].

TCA intoxication should be considered in every patient with an consciousness associated with ECG abnormalities; ECG investigation should be repeated as harmful changes that may not be evident at admission may appear later; moreover, ECG is a valuable tool to assess the efficacy of the treatment [13].

Recently, new guidelines on the treatment of TCA intoxication have been issued [14]. These recommendation are based on studies with different levels of evidence; in the absence of large, controlled double blind trials enrolling sufficient numbers of patients, the strength of each of them varies from Grade C (based upon individual level 2a or 2b papers or multiple level 3a or 3b papers) to Grade E (based to consensus guidelines or studies of expert opinion).

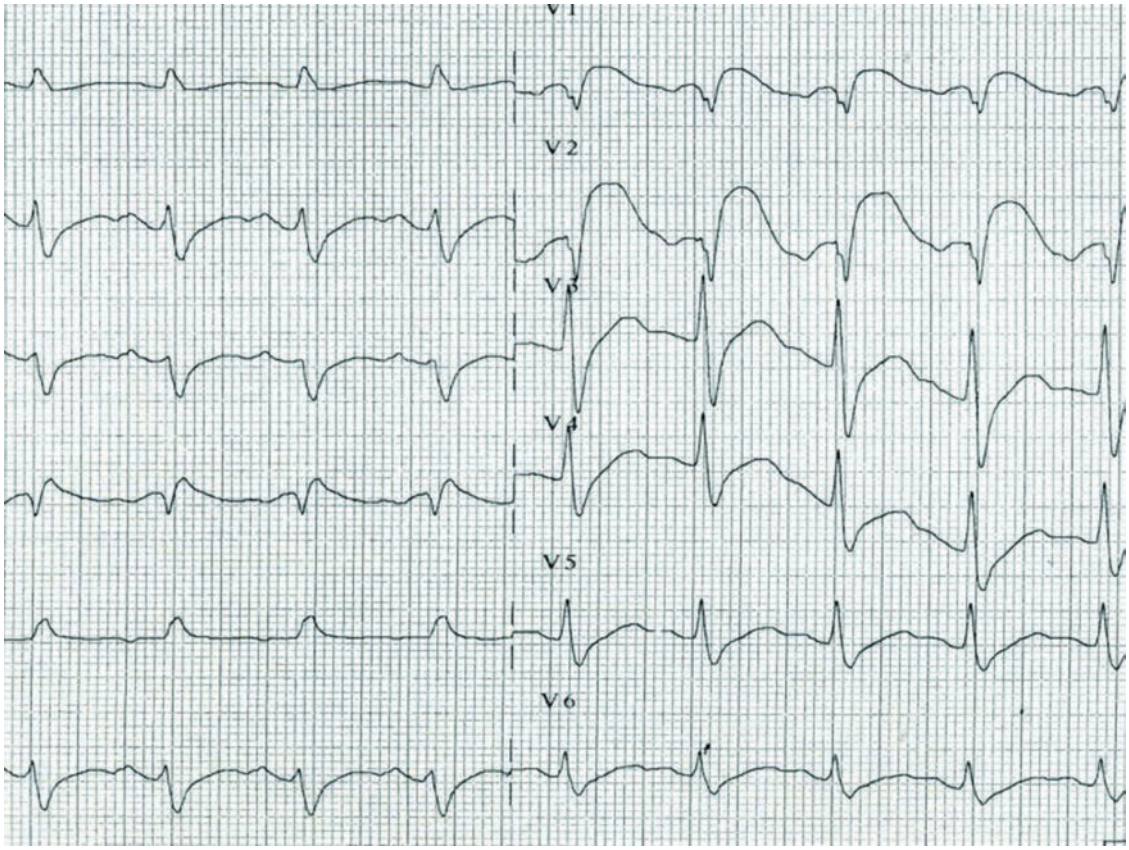


Fig. 321.1 Severe TCA intoxication, approximatively 4 hours after the ingestion of 7000 mg of amitriptyline.

Keeping these limitations in mind, the cornerstones of treatment basically consist in [14]:

- **Rapid sequence tracheal intubation** in patients with reduced levels of consciousness (Grade C), associated with volume resuscitation in the presence of arterial hypotension (Grade D); should hypotension be refractory to the administration of fluids, cautious intravenous administration of catecholamines is indicated (Grade D).
- **Prevention of (further) TCA adsorption**: in conscious patients, or after the airways have been secured, this goal can be accomplished with gastric lavage, possibly using activated charcoal; this measure appears valuable only in the early phase (within 1 hour from the ingestion) (Grade D).
- **Administration of sodium bicarbonate** to achieve a serum pH of 7.45–7.55 (Grade E); blood alkalization appears particularly valuable in the resolution of QRS widening, recovery of hypotension and the treatment of arrhythmias (Grade E), although its efficacy varies among different TCAs [15]. The underlying mechanism of action includes the reduction of cardiac toxicity and increased binding of TCA to serum proteins, which in turn decreases their free fraction.
- The **administration of magnesium sulfate** if arrhythmias persist during the administration of sodium bicarbonate and/or when the target pH value has been achieved, (Grade D).
- The **administration of benzodiazepine** to control seizures (Grade E); the use of phenytoin in this setting is contraindicated (Grade D) because its class Ia-anti-arrhythmic action could potentiate the similar effect exerted by TCA.
- The **administration of lipid emulsions**, which are supposed to sequester TCA inside an intravascular lipid compartment, is indicated when other measure fail to control the symptoms of TCA intoxication (Grade D).

Conclusion

Despite the introduction of newer drugs for the treatment of depression, TCAs are still largely used either with this indication or for the treatment of anxiety and chronic pain. A high index of suspicion is warranted, especially in patients with altered state of consciousness associated with arterial hypotension and/or ECG abnormalities. The treatment should be initiated before the confirmation of their presence in the blood or in the urine.

References

1. Ebmeier KP, Donaghey C, and Steele JD. (2006). Recent developments and current controversies in depression. *Lancet*, **367**, 153–67.
2. Namaka M, Gramlich CR, Ruhlen D, et al. (2004). A treatment algorithm for neuropathic pain. *Clinical Therapeutics*, **26**, 951–79.
3. O'Donnel JM and Shelton RC. (2011). Drug therapy of depression and anxiety disorders. In: Brunton LL (ed.) *Goodman & Gilman's the Pharmacologic Basis of Therapeutics*, pp. 397–415. Maidenhead: McGraw-Hill Co.
4. Cassem EH, Lake CR, and Boyer WF. (1994). Psychopharmacology in the ICU. In: Chernow B (ed.) *The Pharmacologic Approach to the Critically Ill Patient*, pp. 651–65. Philadelphia, PA: Williams and Wilkins.

5. Zima AV, Qin J, Fill M, and Blatter LA. (2008). Tricyclic antidepressant amitriptyline alters sarcoplasmic reticulum calcium handling in ventricular miocytes. *American Journal of Physiology: Heart and Circulatory Physiology*, H2008–16.
6. Levine M, Brooks DE, Truitt CA, et al. (2011). Toxicology in the ICU. Part 1: overview and approach to treatment. *Chest*, **140**, 795–806.
7. Bateman DN. (2005).Tricyclic antidepressant poisoning: central nervous system effects and management. *Toxicology Review*, **24**, 181–6.
8. De Santi KP and Mabile CM. (2007). Antidepressant-induced liver injury. *Annals of Pharmacotherapy*, **41**, 1201–11.
9. Thanacoody HK and Thomas SH. (2005). Tricyclic antidepressant poisoning: cardiovascular toxicity. *Toxicology Review*, **24**, 205–14.
10. Singh N, Singh HK, and Khan IA. (2002). Serial electrocardiographic changes as a predictor of cardiovascular toxicity in acute tricyclic antidepressant overdose. *American Journal of Therapeutics*, **9**, 75–9.
11. Açikalin A, Satar C, Avc A, Topal M, Kuvandk M, and Sebe A. (2010). QTc intervals in drug poisoning patients with tricyclic antidepressants and selective serotonin reuptake inhibitors. *American Journal of Therapeutics*, **17**, 30–3.
12. Smith BS, Yogaratnam D, Levasseur-Franklin K, Forni A, and Fong J. (2012). Introduction to drug pharmacokinetics in the critically ill patients. *Chest*; **141**, 1327–36.
13. Liebelt El, Ulrich A, Franci P, and Woolf A. (1997). Serial electrocardiogram changes in acute tricyclic antidepressant overdoses. *Critical Care Medicine*, **25**, 1721–6.
14. Body R, Bartram T, Azam F, and Mackway-Jones K. (2011). Guidelines in Emergency Medicine Network (GEMNet); guideline for the management of tricyclic antidepressant overdose. *Emergency Medicine Journal*, **28**, 347–68.
15. Blackman K, Brown SG, and Wilkes GJ. (2001). Plasma alkalinization for tricyclic antidepressant toxicity: a systematic review. *Emergency Medicine* (*Fremantle*), **13**, 204–10.

CHAPTER 322

Management of poisoning by amphetamine or ecstasy

Enno Freye

Key points

- Methamphetamine is a potent central nervous system stimulant affecting neurochemical mechanisms responsible for regulating heart rate, body temperature, blood pressure, appetite, attention, mood, and responses associated with alertness or alarm conditions.
- The only two approved indications for methamphetamine are attention-deficit hyperactivity (ADHD) and the short-term management of obesity.
- It is unclear if the toxic effects of ecstasy (MDMA) can be solely attributed to the pure agent or whether these are due to impurities.
- Hyperthermia and rhabdomyolysis commonly accompany MDMA intoxication.
- Since there is no specific antidote available, therapy for amphetamine or MDMA-related toxicity is purely symptomatic

Introduction

Already being abused in the years between the two wars to increase stamina and endurance, there was a widespread use of methamphetamine in the German army and the Allied Forces in order to avoid fatigue, stay alert, and to remove inhibition when faced with dangerous missions. Methamphetamine started to be known as speed in the early 1960s. Intermittently, during Vietnam and through Desert Storm, both the Air Force and the Navy made methamphetamine available for aviators with usage ranging from 3 to 96%.

The use of ecstasy or MDMA (3,4-methylendioxymethamphetamine) has significantly increased in the past years. Causing an intensified feeling of empathy and enhancement of senses, it is an agent of growing recreational misuse in discotheques, as well as the black market sales of ecstasy pills on the street have increased considerably in all Western countries over the recent years. Often ecstasy is not MDMA at all, as it tends to be diluted with almost any kind of drug powder ranging from amphetamines, LSD, cocaine, inert substances such as chalk or flour to rat poison (strychnine). Mixing with other drugs (e.g. alcohol), and drinking too little or too much water increases the risks associated with taking a drug that is already toxic.

Pharmacology of methamphetamine and ecstasy (MDMA)

Amphetamine is a simple synthetic derivative of phenylethylamine, which differs only in possessing a methyl group (-CH3) attached to the side chain. In methamphetamine, however, a second methyl group is attached protecting methamphetamine from degradation by monoamine oxidase (Fig 322.1). As a result, methamphetamine can persist in the bloodstream exerting a variety of biological effects. Amphetamines exist in two stereo-isomers. The dextro-isomer being far more biologically active than the levo-isomer.

Methamphetamine increases dopamine levels in the central nervous system (CNS) by as much as 2600 times, primarily by stimulating pre-synaptic neurotransmitter release rather than by re-uptake blockade [1]. Such increase has the effect of stimulating regions of the brain linked with vigilance and the action of the heart [1]. For a short period, the user feels sharper, stronger, and more energetic. It is believed that a significant proportion of the dopamine-producing cells in the brain can be damaged by prolonged exposure to even low levels of methamphetamine, being responsible for reduced levels of dopamine release. This can affect memory, attention, and decision-making functions.

MDMA belongs to a group of ring-substituted amphetamine congeners, called methoxylated amphetamines (Fig. 322.1). The drug is a potent indirect monaminergic agonist, acting both by increasing the release [2] and inhibiting the reuptake of serotonin and, to a lesser extent, of dopamine [3],with affinities to serotonin subreceptors of the 5-$HT2_A$ and 5-$HT2_C$ types [2,4].

Oral dosages range from 60 to 80 mg, with a benchmark standard dose of 2 mg/kg body weight. Even taken orally the effects manifest within 30–45 minutes; snorting, smoking, or injecting the agent result in a much faster onset of action (Box 322.1). With a plateau after 1 hour, the effects lasts for about 6 hours. The psychological effects largely disappear after 3 hours with the exception of some sympathomimetic residuals that last for 5 hours. A so-called 'afterglow' may be felt for days, and tertiary psychological effects (e.g. improved outlook) may even last indefinitely.

Acute effects of methamphetamine

The acute effects of the drug closely resemble the physiological and psychological effects of an adrenaline-provoked flight-or-fight

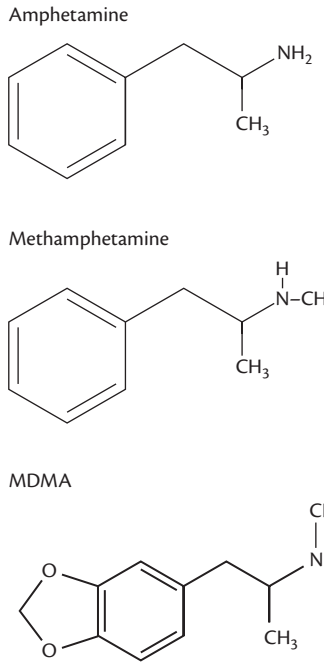


Fig. 322.1 The molecular structure of amphetamine, methamphetamine and ecstasy (MDMA, a ring substituted 3,4-methylendioxymethamphetamine).

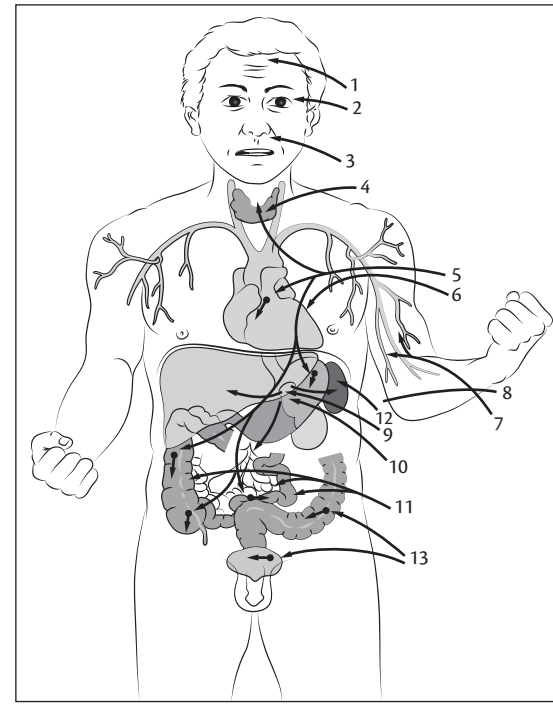


Fig 322.2 Summary of the negative effects of methamphetamine on body functions, which can be life-threatening once overactivated.
1, increase in vigilance, aggressive behaviour, insomnia, panic attacks, convulsions; 2, dilated pupils; 3, grinding of teeth; 4, release of thyreotropic hormones followed by increase of basal metabolic rate; 5, increase in heart rate, irregularity, ventricular extrasystoles; 6, increase in contractility of the heart, coronary vasoconstriction, heart attack; 7, dilatation of the vascular tree; 8, increase in muscle tension, hyperreflexia; 9, adrenal stimulation with release of epinephrine and norepinephrine; 10, glycogenolsis with raised blood sugar concentration, primary liver damage; 11, inhibition of propulsion of the gut; 12, increased lymphocyte production of the spleen; 13, urinary and bowel discharge.

Box 322.1 Summary of acute effect of MDMA

Ingestion of 50–150 mg of MDMA results in following effects:

- Perception of increased intimacy and trust with others.
- Enhanced communication.
- Increased insight into personal pattern/behaviour.
- Feeling of warmth, freshness, and love.
- Euphoria.
- Sensation of being more self-aware and at peace.

Common negative effects however can also be induced characterized by:

- Anxiety.
- Teeth grinding.
- Cheek biting.
- Anorexia.
- Sensations of being cold.
- Insomnia.
- Reduced feeling of thirst.

response, including increased heart rate and blood pressure, vasoconstriction, bronchodilation, and hyperglycaemia (Fig. 322.2). Users experience an increase in focus, increased mental alertness, and the elimination of fatigue, as well as a decrease in appetite.

Methamphetamine is a potent neurotoxin. Since dopamine and serotonin concentration, as well as dopamine and 5-HT uptake sites, together with tyrosine and tryptophan hydroxylase activities are reduced after the administration of methamphetamine [5], it has been assumed that dopamine plays a role in methamphetamine-induced neurotoxicity. This assumption is underlined by experiments, where the reduction of dopamine or the blockade for the release of dopamine decreased the toxic effects of methamphetamine. Since dopamine breakdown produces reactive oxygen species (ROS) such as hydrogen peroxide, it is probable that the oxidative stress that occurs with the intake of methamphetamine mediates its neurotoxicity [6]. In addition, recent research indicates that methamphetamine binds to a group of receptors called trace amino-associated receptors (TAARs) (7). This newly-discovered receptor system seems to be affected by a range of amphetamine-like agents, which have been shown to mediate the identification of social cues in mice, and are also present in humans and fish. To a lesser extent methamphetamine also acts as a dopaminergic and adrenergic re-uptake inhibitor and in high concentrations as a monoamine oxidase inhibitor (MAOI). Since it stimulates the mesolimbic dopaminergic reward pathway, causing euphoria and excitement, it is prone for abuse and addiction. Withdrawal is characterized with excessive sleeping, eating, and depression-like symptoms, often accompanied by anxiety and drug-craving [8].

In contrast to crack cocaine, the effects of methamphetamine are intense and persist longer than the brief 'high' of cocaine. Users

may become addicted quickly, and use it with increasing frequency and in increasing doses.

Crystal methamphetamine or 'ice' typically resembles small fragments of glass or shine-blue white 'rocks' of various sites. Unlike powdered methamphetamine, the other form of d-methamphetamine hydrochloride, which contains by-products from synthetic preparation, crystal methamphetamine has a higher purity level and produces longer-lasting and more intense euphoric effects than the powdered form of the drug.

Crystal methamphetamine is typically smoked using glass pipes similar to pipes used to smoke crack cocaine. Crystal methamphetamine may also be injected. A user who smokes or injects the drug immediately experiences an intense sensation followed by a high that may last for 12 hours or longer. Crystal methamphetamine is gaining popularity as a club drug in discotheques, but also as a stimulant in the upper and especially the middle management of big companies.

Acute effects of MDMA

Symptoms of acute intoxication with MDMA include agitation, tachycardia, hypertension, dilated pupils, trismus, and sweating, whereas more severe cases are characterized by hyperthermia, disseminated intravascular coagulation (DIC), rhabdomyolysis, and acute renal failure [9]. In such severe cases, an elevated creatinine kinase level may reach 12,200–555,000 IU/L [10].

It is important to note that serum MDMA levels do not correlate well with clinical symptoms and acute toxic reactions develop within 15 minutes to 6 hours after ingestion of MDMA.

The toxic reaction can be divided into three categories:

- Acute reaction at therapeutic doses.
- Overdose reactions.
- Residual effects.

At moderate doses (80–100 mg) the user will experience transient nausea, an increase in blood pressure, increased muscle tonicity with jaw clenching, and teeth grinding. At higher doses than 100 mg, susceptible individuals will experience numbness or tingling of extremities, luminescence of objects, increase in colour vision, and vomiting. Doses higher than 200 mg result in a classical toxic reaction with symptoms of paranoia, accompanied by auditory, as well as visual hallucinations.

Similar to cocaine and amphetamines, varying degrees of acute toxic effects may include sympathetic stimulation with arrhythmia, hypertension, tachycardia, and vasoconstriction resulting in an increase in myocardial oxygen demand. In severe cases there may be acute myocardial infarction and/or irreversible cardiomyopathy [11] accompanied by ECG changes with widespread ST-segment elevation [12]. In addition, MDMA use has been associated with intracerebral/subarachnoid haemorrhage, cerebral infarction, and venous sinus thrombosis [13], often in conjunction with an underlying malformation [11].

Chronic use of methamphetamine

Chronic methamphetamine abuse is reported to lead to significant reduction in the grey matter of the brain. Associated health risks involve social and family problems, including risky sexual behaviour. In addition, drug-induced psychosis may result. Methamphetamine effects last for days in the body, and some degree of neurological impairment may last up to 2 years or more after cessation of the drug

Continued use of high doses of methamphetamine produce anxiety reactions during which the person is fearful, tremulous, and concerned about his physical well-being, an amphetamine psychosis during which the person misinterprets others' actions, hallucinates, and becomes suspicious, sometimes resulting in a violent, aggressive behaviour. After the stimulatory phase, an exhaustion phase involves intense fatigue and the need for sleep, together with prolonged depression during which suicide is possible. Users of large amounts of methamphetamine over a long period of time develop an amphetamine-psychosis, a disorder similar to paranoid schizophrenia. Symptoms usually disappear within a few weeks after drug use stops followed by a recovery.

Tolerance of various effects develops unequally. For instance, tachycardia and enhanced alertness are diminished, but psychotoxic effects, such as hallucinations and delusions still occur. Also in contrast to cocaine, even massive doses are rarely fatal. Long-term users have reportedly injected as much as 15,000 mg of amphetamine in 24 hours without observable acute illness. One of the many prompts for repetitive abuse are the circumstances surrounding the drug taking (environmental cues) that trigger neuronal hypersensitivity, and exert a powerful influence leading to physiological arousal and increased craving at the mere sight of even the thought of the drug [5].

Addictive properties of methamphetamine

As with other psychoactive drugs, different routes of administration have different profiles of effects. For instance, oral methamphetamine ingestion tends to lack rushing, has less euphoric effects, and tends to cause far less of a feeling of wanting to do it again than other methods. Smoking or injecting methamphetamine is associated with compulsive/addictive user patterns. The most frequent route of administration among primary methamphetamine/amphetamine substance abuse treatment admissions was smoking (63%) followed by injection (19%). Thirteen per cent of primary methamphetamine/amphetamine admissions reported inhalation and only 5% reported oral consumption [14].

Withdrawal of methamphetamine

Abrupt interruption of chronic methamphetamine use results in withdrawal symptoms in almost 90% of all cases. Withdrawal of methamphetamine often causes a depression, which is even longer and deeper than the depression from cocaine withdrawal [8]. The length and the severity of the depression is related to how much and how often amphetamines had been used. Medical treatment includes the use of antidepressant agents.

Vigabatrin is a new treatment for methamphetamine. It is thought that mechanism of action is due to irreversible enzyme inhibition of γ-aminobutyric acid transaminase (GABA-T) resulting in increased levels of GABA, an inhibitory neurotransmitter [15].

Chronic use of MDMA

Synthesis of most street-sold MDMA pills (Fig. 322.3) is done in home laboratories with little chemical expertise resulting in the accumulation of by-products during the chemical reaction. Certain

Fig. 322.3 Examples of ecstasy pills with different logos, as they are being sold in the street, with unknown content of MDMA and possible adulterants.

reactions, such as hallucinations or visual distortion, are a sure sign of not ingesting pure MDMA. Taking the drug over a longer period of time, some report the desirable effect are no longer as pronounced (habituation), while others still found each MDMA session worthwhile.

It has been suggested that fluoxetine could prevent a chronic reduction in the serotonin system when taken before or even after MDMA.

Treatment of amphetamine and MDMA-related toxicity

Hyperthermia, with temperature >40°C is the most common adverse effect associated with acute MDMA toxicity. It is mostly caused by excessive heat production, due to sustained muscular hyperactivity and an increase in the metabolic rate, especially following strenuous long hours of dancing in discotheques, which may result in rigidity and seizures. Hyperthermia is considered the beginning of a cascade leading to DIC rhabdomyolysis, myoglobinuria, and renal failure [16]. This is probably the most important condition to treat immediately, since mortality has been correlated to the extent of hyperthermia and its duration. Treatment should include the following:

- Limit further heat production by cooling, using ice cubes at groin and axilla, applying cooling blankets, putting the patient in an ice bath, co-administering cold intravenous (iv) fluids, or ultimately, using peritoneal lavage with cool dialysate.
- Control agitation to prevent further heat production by sedative agents, such as diazepam, lorazepam, or midazolam.
- Administer dantrolene sodium (2.5 mg/kg repetitively) to limit muscle hyperactivity. Although being used for treatment of malignant hyperthermia it results in the inhibition of Ca^{2+}-release in the sarcoplasmic reticulum [17–19].
- Alternatively, use of non-depolarizing muscle relaxants (e.g. pancuronium bromide) is being advocated in treating the acute toxic MDMA-related reaction. This requires intubation and ventilatory support.
- Since some of the symptoms associated with acute MDMA toxicity are similar to findings in both malignant neuroleptic syndrome and the serotonin syndrome [20], additional pharmacological management is recommended (although not evaluated prospectively), such as methysergide maleate, a non-specific serotonin antagonist, the short-acting ß-blocker esmolol, a 5-$HT1_A$-antagonist such as buspirone, or the dopamine agonist bromocriptine.

Antipsychotic agents should not be used as they decrease the seizure threshold and may even affect the thermoregulatory system leading to an exacerbation of hyperthermia. In addition, SSRIs may further increase serotonergic transmission by reuptake blockade, raising the risk of a serotonin syndrome and aggravating the existing hyperthermia.

Contrary to MDMA, acute methamphetamine toxicity is characterized by a massive overstimulation of the sympathetic nervous system. Patients may be highly agitated and present a serious safety risk to themselves and prehospital personnel. If possible, one should seek additional help from police or other emergency medical services (EMS) providers before the patient

is transported. Since the cause of an altered mental status before a laboratory test is never clear, initial treatment should comprise the following:

- Ensure a patent airway, with sufficient breathing plus cardiovascular support.
- 100 mL of 50% glucose iv for reversal of a potential hypoglycaemia.
- Thiamine (vitamin B1) 100 mg intramuscularly (im) for potential alcoholic intoxication and prevention of a Korsakow syndrome.
- 2 mg of naloxone iv for reversal of a potential opioid overdose.

Box 322.2 Summary of treatment for metamphetamine intoxication

Agitation

Consider:

- Temporary physical restraint.
- Tranquillizers, such as droperidol, haloperidol, or butyrophenones, titrated iv.
- Benzodiazepines (enhance GABA neurotransmission).
- Antipsychotics (risperidone, olanzapine).
- Rapid sequence induction and muscle relaxation.

Seizures

Benzodiazepines iv:

- Diazepam 10–20 mg.
- Clonazepam 1–2 mg.
- Midazolam 5–15 mg.
- Phenobarbital 50–100 mg.

Early CT in view of intracranial haemorrhage risk.

Hypertension

Consider:

- Urapidil 25–50 mg.
- Sodium nitroprusside infusion.
- Glyeryl trinitrate infusion.
- Clonidine 0.15 mg slow iv.
- Labetalol 0.25 mg/kg.

Avoid propranolol since it is an α-stimulator.

Tachycardia

- Esmolol infusion 100 mg/kg/min.
- Metoprolol.

Myocardial ischaemia

GTN and standard acute coronary syndrome protocol.

Rhabdomyolysis

Fluid replacement, urine alkalinization.

Pre-hospital iv access is necessary for treatment of seizures and agitation using intravenous benzodiazapines. CNS overstimulation may lead to seizure-like activity and cardiovascular effects result in tachycardia with the possibility of ventricular fibrillation, systemic hypertension with intracranial/subarachnoid bleeding, and ischaemic stroke especially when three is a predisposing condition, such as an aneurysm or an ateriovenous malformation. Most cases of methamphetamine toxicity can be managed supportively. In the case of a severe overdose, immediate supportive care, including airway control, oxygenation and ventilation support, and appropriate monitoring is required. In severe overdoses, termination of methamphetamine-induced seizure activity and arrhythmias are of immediate importance. Correction of hypertension, hypotension, hyperthermia, metabolic, and electrolyte abnormalities, and control of severe psychiatric agitation are indicated. Also, consider health maintenance activities, such as testing for viral hepatitis and HIV disease and rehabilitation as a follow-up. The treatment protocol is described in Box 322.2

Conclusion

In summary, supportive care in MDMA intoxication (Table 322.1) primarily includes rehydration with iv crystalloid fluids and lowering the temperature with the aid of cooling blankets or an ice bath. Liver function should be monitored in patients with suspected MDMA intoxication with unexplained jaundice or hepatomegaly

Table 322.1 Summary of supportive management in acute MDMA intoxication

Prevent further absorption	Apply activated charcoal 50 g po if <1 hour of ingestion, apply cathartic techniques
Treat arrhythmias	Short-acting beta-blocker such as esmolol
Monitor	For at least 4 hours, heart rate, blood pressure, ECG, core temperature
Check	Electrolytes, creatinine, blood urea, creatinine phosphokinase, clotting profile, arterial blood gases
Urine drug screening (UDS)	Use specific drug screen multi sticks for methamphetamine, cocaine, opiates, etc.
Treat anxiety, agitation	Diazepam 0.1–0.3 mg/kg po or iv
Treat seizures	Diazepam 10–20 mg/70 kg iv, midazolam 5–15 mg/70 kg iv, or phenobarbital 50–100 mg/70 kg iv
Treat hyponatraemia	Fluid restriction, consider hypertonic solutions
Treat acidosis	Correct using sodium bicarbonate if QT-interval is prolonged
Treat severe hypertension with/without signs of myocardial ischaemia	Consider α/β-blocker labetalol, sodium nitroprusside, α-blocker phentolamine or, if severe, glyceryl trinitrate. Avoid propranolol because it is an α-stimulator
Treat hypotension	Volume expansion, central venous and cardiac output monitoring
Treat hyperthermia	Simple cooling methods. If temperature is >39°C give dantrolene, intubate, and ventilate
Treat renal failure	Promote diuresis with mannitol or furosemide

during supportive care. If, however, hepatic necrosis has appeared, liver transplantation would be the only option.

In methamphetamine intoxication, cardiovascular and CNS symptoms are the most prevalent signs and should be treated accordingly focusing on potential cardiac arrhythmias as they are the prodrome of detrimental ventricular fibrillation.

References

1. Garris PA, Kilpatrick M, Bunin MA, Michae ID, Walker QD, and Wightman RM. (1999). Dissociation of dopamine release in the nucleus accumbens from intracranial self-stimulation [Letter]. *Nature*, **398**, 67–9.
2. Bankson MG and Cunningham KA.(2001). 3,4-Methylenedioxymethamphetamine (MDMA) as a unique model of serotonin receptor function and serotonin-dopamine interactions. *Journal of Pharmacology and Experimental Therapeutics*, **297**, 846–52.
3. Gamma A, Buck A, Berthold T, Hell D, and Vollenweider FX. (2000). 3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [H215O]-PET in healthy human. *Neuropsychopharmacology*, **23**, 388–95.
4. Green AR, Mechan AO, Melliot JM, O´Shea E, and Colado MI. (2003). The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'). *Pharmacological Review*, **55**, 463–508.
5. Bennett B, Hollingsworth C, Martin R, and Harp J. (1998). Methamphetamine-induced alterations in dopamine transporter function. *Brain Research*, **782**, 219–27.
6. Yamamoto B and Zhu W. (1998). The Effects of Methamphetamine on the Production of Free Radicals and Oxidative Stress. *Journal of Pharmacology and Experimental Therapeutics*, **287**, 107–14.
7. Reese EA, Bunzow JR, Arttamangkul S, Sonders MS, and Grandy DK. (2007). Trace amine-associated receptor 1 displays species-dependent stereoselectivity for isomers of methamphetamine, amphetamine, and para-hydroxyamphetamine. *Journal of Pharmacology and Experimental Therapeutics*, **321**, 178–86.
8. McGregor C, Srisurapanont M, Jittiwutikarn J, Laobhripatr S, Wongtan T, and White J. (2005). The nature, time course and severity of methamphetamine withdrawal. *Addiction*, **100**, 1320–9.
9. Henry JA, Jeffrys KJ, and Dawling S. (1992). Toxicity and deaths from 3,4-methylenedioxymethamphetamine ('ecstasy'). *Lancet*, **340**, 384–7.
10. Murthy BVS, Wilkes RG, and Roberts NB. (1997). Creatine kinase isoform changes following ecstasy overdose. *Anaesthesia Intensive Care*, **25**, 156–9.
11. Ghuran A and Nolan J. (2000). Recreational drug misuse: issues for the cardiologist. *Heart*, **83**, 627–33.
12. Qasim A, Townend J, and Davies MK. (2001). Ecstasy induced acute myocardial infarction. *Heart*, **85**, E10.
13. McCann U, Slate SO, and Ricaurte GA. (1996). Adverse reactions with 3,4-methylenedioxymethamphetamine (MDMA; 'ecstasy'). *Drug Safety*, **15**, 107–15.
14. Cook CE. (1991). Pyrolitic characteristics, pharmacokinetics, and bioavailability of smoked heroin, cocaine, phencyclidine, and methamphetamine. In: Miller MA and Kozel NJ (eds) *Methamphetamine Abuse: Epidemiologic Issues and Implications*. NIDA Research Monograph Series, Number 115, pp. 6–23. DHHS Pub. No. (ADM) 91-1836. Rockville, MD: National Institute on Drug Abuse.
15. Brodie J, Figuerda E, Laska EM, and Dewy SL. (2005). Safety and efficacy of -vinyl GABA (GVG) for the treatment of methamphetamine and/or cocaine addiction. *Synapse*, **55**, 122–5.
16. Screaton GR, Cairns HS, Sarner M, Singer M, Thrasher A, and Cohes SL. (1992). Hyperyrexia and rhabdomyolysis after MDMA ('ecstasy') abuse. *Lancet*, **339**, 677–8.
17. Larner AJ. (1993). Dantrolene and 'ecstasy' overdose. *Anaesthesia*, **38**, 179–80.
18. Watson JD, Ferguson C, Hinds CJ, Skinner R, and Coakley JH. (1993). Exceptional heatstroke induced by amphetamine analogues—does dantrolene have a place. *Anaesthesia*, **48**, 542–3.
19. Singarajah C and Lavies NG. (1992). An overdose of ecstasy. A role for dantrolene. *Anaesthesia*, **47**, 686–7.
20. Demirkiran M, Jankovic J, and Dean JM. (1996). Ecstasy intoxication: an overlap between serotonin syndrome and neuroleptic malignant syndrome. *Clinical Neuropharmacology*, **19**, 157–64.

CHAPTER 323

Management of digoxin poisoning

Frédéric Lapostolle and Stephen W. Borron

Key points

- Poisoning by digitalis is primarily manifested as an exaggeration of its therapeutic effects. Cardiac effects include a wide variety of rhythm and conduction disturbances, with bradydysrhythmias predominating. They can be life-threatening.
- Non-cardiac effects include neurological and visual disturbances, generalized weakness, and gastrointestinal disturbances.
- The serum digitalis concentration is useful in assessing body burden of digitalis, but therapy for life-threatening poisoning should not be delayed while awaiting blood concentrations.
- The treatment of choice for serious poisoning is immediate administration of digitalis Fab fragments.
- Complete reversal of the digitalis body load with Fab fragments is indicated in life-threatening poisoning. Partial reversal with digitalis Fab immunotherapy is indicated in less serious poisoning.

Introduction

Indications for cardiac glycosides are restricted to heart failure, with or without associated supraventricular dysrhythmia. More appropriate maintenance regimens and widespread availability of serum digoxin concentrations have reduced morbidity in recent years. Nonetheless, digitalis toxicity remains frequent in patients chronically taking the drug (6–23% of patients, especially the elderly) [1,2]. In contrast, intentional digitalis poisoning occurs less frequently, but mortality may reach 25% in cases of acute overdose [3]. The treatment and outcomes for digitalis poisoning have been dramatically altered through use of digoxin-specific Fab fragments [4]. Antidotal treatment significantly reduces mortality rate when an anticipatory strategy is used [3,5].

Pharmacology

Two preparations of digitalis, digoxin and digitoxin, are in common use today. Digitoxin, still used in Europe but is no longer available in the United States. Both are passively absorbed from the small intestine. Digoxin has a half-life of 33–34 hours. Digitoxin is heavily protein bound and has a longer half-life (6–7 days). Drug action depends on tissue concentration, which is relatively constant in relation to serum concentration; the major depot in humans is skeletal muscle. The constant relationship of myocardial digoxin concentration to serum concentration supports measuring serum concentrations to monitor patients' compliance and toxicity. Dosage requirements and the likelihood of toxicity are better anticipated on the basis of muscle mass, rather than overall body weight. Digoxin is excreted primarily via the renal route, whereas digitoxin is metabolized in the liver. Enterohepatic circulation is important with both drugs, thus biliary production affects digitalis elimination.

Digitalis inhibits the Na^+-K^+-ATPase transport system (Fig. 323.1). The net effect is a decreased intracellular K^+ concentration and an increased Na^+ and Ca^{2+} concentration. The increased Ca^{2+} augments positive inotropic action [6]. Na^+, K^+, or Ca^{2+} fluxes across cell membranes exert significant effects on conduction. Digitalis decreases the rate of sinoatrial (SA) node depolarization, and increases the refractory period of the atrioventricular (AV) node and the bundle of His. The negative chronotropic effect of digitalis is primarily mediated through an increase in vagal tone, associated with decreased sympathetic activity. Digitalis decreases the refractory period of both atrial and ventricular cells, and improves conduction within the muscle, as reflected in a shortened QT interval. Digitalis increases myocardial automaticity (the ability of tissue to undergo spontaneous depolarization) and excitability (the ability of tissue to respond to a given stimulus).

Digitalis toxicity

Toxicity is related to exaggerated therapeutic effects and the status of the patient at the time of drug administration/overdose. Toxic effects can occur in any condition that increases the amount of digitalis in the body or modifies cardiac sensitivity to digitalis.

Drug interactions are an important consideration, because introducing or discontinuing these drugs without changing the digoxin dose may lead to digitalis toxicity. The most common interactions are listed in Table 323.1.

By far, the most important and dangerous drug interactions with digoxin are caused by the antidysrhythmics. Quinidine causes a substantial increase in serum digoxin in up to 90% of patients, beginning immediately. Other Class 1 antidysrhythmics (procainamide, disopyramide, lidocaine, mexiletine, and flecainide) do not increase serum digoxin concentrations.

Amiodarone increases digoxin concentrations by 25–70% within 24 hours of adding amiodarone. The addition more frequently results in bradydysrhythmias or heart block, rather than tachydysrhythmias.

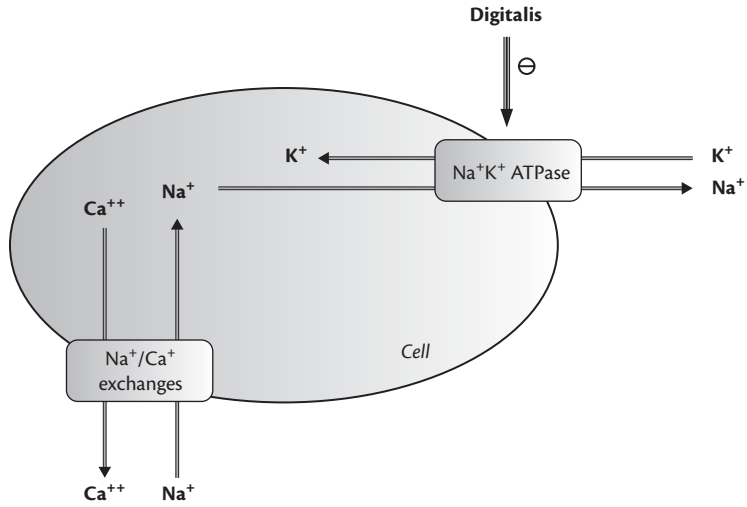


Fig. 323.1. Digitalis: mechanisms of action and toxicity.

Table 323.1 Agents affecting digitalis pharmacology

Alteration	Agents
Increased absorption (less of a problem when the capsule form is used)	Antibiotics inhibiting gut flora (erythromycin and tetracycline), anticholinergics
Decreased absorption	Antacids, antibiotics (neomycin, sulfasalazine, p-aminosalicylic acid), bran, colestyramine, cytotoxic, kaolin-pectin
Inhibited protein binding	Clofibrate, phenobarbital, phenylbutazone, prazosin, warfarin
Decreased extrarenal clearance	Diltiazem, quinidine, verapamil
Decreased volume of distribution	Quinidine
Increased renal excretion	Hydralazine, levodopa, nitroprusside
Increased serum digitalis concentration	Amiodarone, aspirin, bepridil, diltiazem, flecainide, ibuprofen, indometacin, nifedipine, nicardipine, nisoldipine, nitrendipine, propafenone

Reproduced from *Clinical Pharmacokinetics*, **15**(3), 1988, pp. 165–79, 'Digitalis. An update of clinical pharmacokinetics, therapeutic monitoring techniques and treatment recommendations', Mooradian AD, with kind permission from Springer Science and Business Media.

The interaction between calcium channel blocking drugs and digoxin varies greatly. Verapamil increases serum digoxin concentrations as much as 70%, which can lead to lethal cardiotoxicity, while the dihydropyridines (nifedipine, amlodipine, isradipine, nicardipine) and diltiazem interact minimally. Other antidysrhythmics, such as sotalol, aprindine, ajmaline, and moricizine do not affect digoxin concentrations.

Apart from drug interactions, renal dysfunction reducing excretion is the major factor leading to an increased body load of digitalis. Dialysis does not cause much body loss of digitalis.

Toxicity from digitalis may also occur in any condition that modifies the cardiac sensitivity to digitalis, such as myocardial infarction or ischaemia, myocarditis, cardiomyopathy, amyloidosis, and other trauma, including surgery. Electrolyte abnormalities, especially hypokalaemia, and hypocalcaemia are well known contributors to digitalis toxicity, but aberrations of magnesium may increase myocardial sensitivity to digitalis as well.

Acidosis, alkalosis, hypoxaemia, and hyperthermia may alter digitalis effect, but are probably not independent risk factors. Diseases of other organ systems, especially chronic lung disease and hypothyroidism, predispose patients to digitalis toxicity. Acute cerebrovascular events may lead to toxicity by large sympathetic discharge, which may lower the dysrhythmia threshold.

Clinical presentation

Cardiac manifestations are frequent and dangerous presentations of digitalis toxicity [7,8]. A healthy heart rarely demonstrates any signs of toxicity unless the ingested quantity is high. Therefore, accidental overdoses, especially in children, rarely present any cardiac findings, but may show AV conduction disturbances. On the other hand, a diseased heart is prone to lethal dysrhythmias. No dysrhythmias are pathognomonic of digitalis toxicity because similar rhythms may represent underlying disease. A change in the rhythm, especially decreased pulse rate, may be the most important clue. Toxicity should be suspected in any patient exhibiting evidence of depressed conduction, alteration of impulse formation (automaticity), or both.

Blocks of all types may be observed. SA nodal block is relatively common. The resultant bradycardia may be quite severe,

Table 323.2 Comparison of clinical features and main prognostic factors in chronic and acute digitalis poisonings

	Chronic (*n* = 722)		Acute (*n* = 116)		
	n	**%**	***n***	**%**	***p***
Male sex	247	34	34	29	NS
Age > 55 years	697	96	59	51	<0.0001
Past cardiac history	712	99	63	54	<0.0001
HR < 60 beat/min	126	17	48	41	<0.0001
HR < 40 beat/min	23	3	3	3	NS
Second or third degree atrioventricular block	81	11	17	15	NS
All degree atrioventricular block	165	23	37	32	<0.05
Ventricular fibrillation or tachycardia	11	1	5	4	<0.05
Cardiogenic shock (SBP < 100 mmHg)	52	7	10	9	NS
Serum potassium > 5.0 mmol/l	168	23	25	22	NS
Serum potassium > 4.5 mmol/l	369	51	49	42	NS

Reproduced from *Intensive Care Medicine*, **34**(8), 2008, pp. 1448–53, 'Assessment of digoxin antibody use in patients with elevated serum digoxin following chronic or acute exposure', Lapostolle F et al., with kind permission from Springer Science and Business Media and European Society of Intensive Care Medicine.

especially in the elderly and those with SA node disease. First- and second-degree AV blocks of Mobitz types I or II may be observed. The resultant heart rhythm may be complicated by accelerated junctional escape beats. Third-degree block, or complete AV dissociation, is usually associated with a narrow QRS escape focus at adequate rates, and haemodynamic alterations are rare in the absence of other cardiac abnormalities. As digitalis is usually prescribed in patients with atrial fibrillation, slow bradydysrhythmia is frequent in chronic poisoning [8].

Alterations of impulse formation may be divided into those that suppress higher pacemakers or those that excite lower pacemakers. The combination of suppression of higher pacemakers (SA node) and excitation effects (increased frequency of discharge of junctional or ventricular pacemakers) should be considered digitalis toxicity until proved otherwise. Premature ventricular contractions (PVC) and more complex ventricular dysrhythmias, including ventricular tachycardia, may be observed.

Conduction and rhythm disturbances can be seen in combination, resulting in various electrocardiographic presentations. The rhythms are usually manifested by an increased sinus rate with block or second-degree AV block with accelerated lower pacer. Examples are atrial fibrillation with slow ventricular response, resulting in irregular bradycardia or Wenckebach block with accelerated junctional escape beats. Even though non-specific, digitalis toxicity should always be considered when this type of dysrhythmia is encountered.

Gastrointestinal manifestations are seen in both acute and chronic digitalis intoxication. Anorexia, nausea, and vomiting often occur early, and may be the presenting complaint. Neurological manifestations are also frequent and range from headache, fatigue, and weakness, to depression, confusion, disorientation, aphasia, delirium, and hallucinations. Visual disturbances of blurring and alteration in colour are less common. Digitalis intoxication should always be considered in patients, particularly the elderly, who are receiving digitalis therapy and present with vague gastrointestinal complaints, malaise or altered mental status [1]. Clinical features of acute and chronic digitalis poisoning are quite similar (Table 323.2). As expected, patients under chronic digitalis treatment (and chronic overdose) are generally older with more significant past medical history [8].

Diagnostic studies

Digitalis toxicity induces hyperkalaemia, which is significantly correlated with digitalis poisoning severity and mortality. In acute poisoning, mortality was greater in patients with serum potassium >4.5 mmol/L, approaching 35% in patients with serum potassium >5 mmol/L and 100% in patients with concentrations greater than 6.4 mmol/L [9]. Renal function appears partially responsible for hyperkalaemia seen in patients with chronic digitalis poisoning. Hyperkalaemia correlates better with serum creatinine level than with digoxin concentration in chronic digitalis poisoning [10].

Digitalis concentration

Clinical correlation of therapeutic and toxic digitalis concentrations are determined at steady-state concentrations, measured 6–8 hours after administration. Measurements made before this time may give values two to three times steady-state concentration. The therapeutic range is 0.5 to 2.0 ng/mL for digoxin and 10 to 30 ng/mL for digitoxin. Serum concentrations of patients with and without clinical toxicity overlap considerably. Multiple factors predispose patients to toxicity at concentrations well below the upper limit of normal. Hypokalaemia is the most important of these. Thus, serum concentrations are not always diagnostic. False-positive elevations may occur due to chronic renal failure, caused by an endogenous circulating digoxin-like substance.

Serum concentrations should be used as a guide to appropriate therapeutic doses and as an indication of toxicity. It must be emphasized that toxicity **cannot** be diagnosed from serum concentrations alone. Physicians must maintain a high index of suspicion

for digitalis intoxication, especially in patients with predisposing factors, such as old age, renal disease, chronic lung disease, or quinidine use. In general, an increased serum digitalis concentration indicates digitalis toxicity in patients chronically-treated with digitalis who are manifesting cardiac or non-cardiac symptoms. In contrast, if a digitalis poisoning is strongly suspected, specific therapy should not be delayed on the basis of a 'therapeutic' digitalis concentration or to obtain a digitalis concentration. A blood sample should be obtained and analysed while antidotal treatment is underway. Successful treatment of digitalis intoxication depends on early recognition.

Therapy of digitalis intoxication

Supportive care

A single dose of activated charcoal should be administered within the first 2 hours following ingestion in acute poisoning. Neither repeated charcoal administration nor any extracorporeal removal technique has been demonstrated to be of value in acute or chronic digitalis poisoning.

Correction of hypokalaemia and dehydration are important in chronic toxicity. However, the pathophysiological mechanism of hypokalaemia should be kept in mind and secondary hyperkalaemia avoided. Hyperkalaemia is best treated with antidotal treatment with Fab fragments [11].

Severe bradydysrhythmias are often related to increased vagal tone. Treatment is crucial, as bradydysrhythmias increase the risk of for life-threatening ventricular dysrhythmias. Atropine is the treatment of first choice. Adrenergic agonists should be avoided because of the risk of precipitating more severe dysrhythmias.

Intravenous magnesium sulfate in digitalis-induced dysrhythmias is of theoretical benefit. Magnesium may be considered even when the magnesium concentration is normal or high if the serum potassium is elevated. Hypermagnesaemia may occur in patients with renal dysfunction, but is unlikely to result from a bolus of 10–20 mmol.

Other anti-arrhythmic drugs, such as lidocaine and phenytoin, quinidine, procainamide, disopyramide, calcium channel blockers, beta-blockers have limited efficacy, and carry a high risk of side effects.

Cardiac pacing has been used to treat bradycardia and bradydysrhythmias and to prevent ventricular dysrhythmias, but did not reduce mortality in digitalis poisoning [3,5,7]. As a rule, pacemaker use should be considered only if treatment by Fab fragments is not rapidly available.

Direct current counter shock should be performed as a last resort for life-threatening dysrhythmias, only if treatment by Fab fragments is not rapidly available. If used, the lowest effective energy level is suggested.

Antidotal therapy

High degree conduction disturbances and ventricular dysrhythmias in digitalis toxicity result in increased mortality, reaching 25% in recent studies [5,7,9,12]. The safest and most efficacious method for treating acute and chronic digitalis poisoning is the use of digoxin-specific antibody fragments (Fab). The fragments neutralize toxicity by reversing tissue binding of digitalis. Antibody-bound digitalis is eliminated by glomerular filtration and rapid excretion.

Two approaches to antidotal treatment with Fab fragments may be considered [13]. Equimolar 'curative' neutralization is used in patients with life-threatening poisoning (asystole, ventricular dysrhythmia, heart rate <40/min after intravenous atropine or serum potassium >5.0 mmol/L). Semi-equimolar 'prophylactic' neutralization is used in patients with less severe intoxication and/or poor prognostic risk factors alone (age >55, cardiac disease, heart rate <60/min after atropine, second or third degree block or serum potassium >4.5mmol/L) [7,13–15]. The aim of early Fab therapy is to prevent evolution to life-threatening complications. The use of an antidotal prophylactic strategy is associated with lower mortality.

Antidotal treatment is efficacious in both cardiac and non-cardiac poisoning. Hyperkalaemia is best treated by Fab fragments.

The dose of Fab fragments to administer may be determined empirically or, ideally, by calculating digitalis body load [7,13]. Digitalis body load may be estimated, based on supposed ingested digitalis amount (in acute poisoning) or by measured digitalis blood concentrations. Total digitalis body load calculations and empiric dosing are described in Table 323.3.

Fab fragments are given over a few minutes in the presence of life-threatening toxicity and over 1–2 hours for prophylactic

Table 323.3 Empiric dosing of Fab fragments

	DigiFab™ (BTG International)	**Digibind™ (Smith Kline Beecham)**
How supplied (mg per vial)	40 mg	38 mg
Acute ingestion of unknown amount	800 mg (20 vials)	760 mg (20 vials)
Toxicity during chronic therapy	240 mg (6 vials)	228 mg (6 vials)
Ingestion of known amount	40 mg DigiFab© digoxin immune Fab will bind approximately 0.5 mg of digoxin*	38 mg Digibind© digoxin immune Fab will bind approximately 0.5 mg of digoxin or digitoxin
Dose of Fab based on **steady state** digitalis concentration	Dose (# of vials) = serum **digoxin** concentration (ng/mL) × weight (kg)/100*	Dose (# of vials) = serum **digoxin** concentration (ng/mL) × weight (kg)/100
		Dose (# of vials) = serum **digitoxin** concentration (ng/mL) × weight (kg)/1000

For 'prophylactic' or semi-equimolar therapy, reduce calculated dose by one-half.

Brand names are included only to distinguish between the two available therapeutic antibody products and instructions for use, and do not constitute an endorsement of either product.

*DigiFab package insert does not address digitoxin, as the latter has been removed from the US market. It should effectively bind digitoxin as well.

indications. Resolution of digitalis poisoning after Fab fragments infusion is rapid. Reversal, including correction of serum potassium concentration, has been reported in 75% of the patients within 1 hour [11]. Vital signs, electrocardiogram, and serum potassium monitoring during Fab fragments infusion are methods of assessing treatment efficacy and safety.

Prior history of allergy after Fab fragment administration is the sole contraindication to administration. Allergic reactions have been reported in <1% of cases [11]. Side effects associated with Fab fragments administration are rare and minor. Hypokalaemia or withdrawal of digitalis therapeutic effects may rarely exacerbate congestive heart failure.

References

1. Borron SW, Bismuth C, and Muszynski J. (1997). Advances in the management of digoxin toxicity in the older patient. *Drugs & Aging*, **10**, 18–33.
2. Ordog GJ, Benaron S, Bhasin V, Wasserberger J, and Balasubramanium S. (1987). Serum digoxin levels and mortality in 5,100 patients. *Annals of Emergency Medicine*, **16**, 32–9.
3. Taboulet P, Baud FJ, Bismuth C, and Vicaut E. (1993). Acute digitalis intoxication—is pacing still appropriate? *Journal of Toxicology: Clinical Toxicology*, **31**, 261–73.
4. Smith TW, Haber E, Yeatman L, and Butler VPJ. (1976). Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies. *New England Journal of Medicine*, **294**, 797–800.
5. Bismuth C, Motte G, Conso F, Chauvin M, and Gaultier M. (1977). Acute digitoxin intoxication treated by intracardiac pacemaker: experience in sixty-eight patients. *Clinical Toxicology*, **10**, 443–56.
6. Smith TW. (1988). Digitalis. Mechanisms of action and clinical use. *New England Journal of Medicine*, **318**, 358–65.
7. Taboulet P, Baud FJ, and Bismuth C. (1993). Clinical features and management of digitalis poisoning—rationale for immunotherapy. *Journal of Toxicology: Clinical Toxicology*, **31**, 247–60.
8. Lapostolle F, Borron SW, Verdier C, et al. (2008). Assessment of digoxin antibody use in patients with elevated serum digoxin following chronic or acute exposure. *Intensive Care Medicine*, **34**, 1448–53.
9. Bismuth C, Gaultier M, Conso F, and Efthymiou ML. (1973). Hyperkalemia in acute digitalis poisoning: prognostic significance and therapeutic implications. *Clinical Toxicology*, **6**, 153–62.
10. Lapostolle F, Devalliere E, Alheritiere A, and Adnet F. (2012). Relation between creatinine level and kalaemia in patients with digitalis poisoning. *La Presse Médicale*, **41**, 1297–9.
11. Antman EM, Wenger TL, Butler VP, Jr, Haber E, and Smith TW. (1990). Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. *Circulation*, **81**, 1744–52.
12. Hickey AR, Wenger TL, Carpenter VP, et al. (1991). Digoxin immune Fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. *Journal of the American College of Cardiology*, **17**, 590–8.
13. Lapostolle F, Borron SW, Verdier C, et al. (2008). Digoxin-specific Fab fragments as single first-line therapy in digitalis poisoning. *Critical Care Medicine*, **36**, 3014–18.
14. Smolarz A, Roesch E, Lenz E, Neubert H, and Abshagen P. (1985). Digoxin specific antibody (Fab) fragments in 34 cases of severe digitalis intoxication. *Journal of Toxicology: Clinical Toxicology*, **23**, 327–40.
15. Woolf AD, Wenger TL, Smith TW, and Lovejoy FH, Jr. (1991). Results of multicenter studies of digoxin-specific antibody fragments in managing digitalis intoxication in the pediatric population. *American Journal of Emergency Medicine*, **9**, 16–20; discussion 33–4.

CHAPTER 324

Management of cocaine poisoning

Nicholas J. Johnson and Judd E. Hollander

Key points

- Common clinical manifestations include agitation, euphoria, tachycardia, hyperthermia, hypertension, and chest pain.
- Life-threatening sequelae include stroke, intracranial haemorrhage, seizures, myocardial infarction, dysrhythmias, and rhabdomyolysis.
- Six per cent of patients with cocaine-related chest pain will have myocardial infarction.
- Beta-blockers should not be used in cocaine intoxicated patients.
- Many manifestations of cocaine intoxication, including agitation, hypertension, and chest pain, are effectively treated with benzodiazepines.

Introduction

Cocaine (benzoylmethylecgonine) is an alkaloid compound and a powerful central nervous system (CNS) stimulant derived from the South American coca plant, *Erythroxylum coca*. It is a widely-abused illicit drug that produces a variety of clinical effects.

Epidemiology

Between 14 and 21 million people worldwide (0.3–0.5% of the population aged 15–64 years) were estimated to have used cocaine at least once in 2009 [1]. Of the estimated 4.6 million drug-related Emergency Department visits during 2009 in the USA, cocaine was involved in nearly 10% [2]. Limited data exist on cocaine-related intensive care unit admissions, but a small cohort study identified nearly 50% hospital mortality [3].

Pharmacology

Cocaine affects the body via a number of mechanisms, including blockade of fast sodium channels, increased catecholamine release, inhibition of catecholamine reuptake, and increased concentration of excitatory amino acid concentrations in the CNS. Fast sodium channel blockade produces a local anaesthetic effect, as well as a quinidine-like antiarrhythmic effect on the myocardium. Increased catecholamine levels produce a sympathomimetic effect.

Cocaine is well absorbed through the aerodigestive, respiratory, gastrointestinal, and genitourinary mucosa. The cocaine hydrochloride salt is the form most often abused transnasally or parenterally. Crack and free base cocaine are alkaloids that can be smoked, and are absorbed via the pulmonary route.

When injected intravenously or inhaled, cocaine is rapidly distributed throughout the body and CNS, with peak effects in 3–5 minutes. With nasal insufflation, absorption peaks in 20 minutes. The half-life of cocaine is approximately 1 hour. It is primarily metabolized to ecgonine methyl ester by plasma cholinesterases. Benzoylecgonine, the other major metabolite, is excreted in the urine and is the compound for which most urine toxicology screens routinely test. Cocaethylene is a long-lasting metabolite formed when cocaine is used in combination with ethanol.

The effects of cocaine are widespread and impact nearly every organ system, particularly due to the drug's ability to stimulate the sympathetic nervous system. In addition, cocaine causes direct vascular effects best described in the heart [4–6]. These include arterial vasoconstriction, thrombus formation, and inhibition of endogenous fibrinolysis. The direct local anaesthetic effect may be responsible for disturbances in cardiac conduction and dysrhythmias [7].

Clinical manifestations

Central nervous system

Common CNS effects include agitation, euphoria, and mydriasis. These effects are typically short lived and without sequelae. Less common, but more severe stimulatory effects of cocaine include seizures, ischaemic stroke, transient ischaemic attacks, focal vasospasm, intracranial haemorrhage, headache, cerebral vasculitis, spinal cord infarction, and psychiatric manifestations. Increased psychomotor activity during acute intoxication may lead to severe hyperthermia.

Cocaine-induced seizures are typically single, brief, generalized, self-limited, and not associated with permanent neurological damage [8]. These seizures may occur in the presence or absence of structural disease, such as infarction or haemorrhage. Choreaoathetosis and other repetitive movements (termed 'crack dancing') are associated with cocaine intoxication, and appear to be related to dopamine dysregulation.

Chronic heavy cocaine users can present with the 'cocaine washout syndrome', which is characterized by lethargy and depressed mental status. This self-limited syndrome typically resolves within 24 hours and is thought to result from depletion of essential neurotransmitters [9].

Cardiovascular

There are numerous cardiovascular manifestations of cocaine use. Of cocaine-related emergency department visits, chest pain is the most common presenting complaint. Although most of these patients do not have a serious underlying aetiology, 6% of patients with cocaine-related chest pain will have myocardial infarction [10,11]. Among those with cocaine-associated acute coronary syndrome, mean age is 33 years (range 18–52 years), male:female ratio is 7:1, >80% smoke cigarettes, and almost 90% are regular cocaine users. Two-thirds present within 3 hours of cocaine use, and atherosclerotic coronary artery disease was found in 31%.

Disruption in cardiac conduction (e.g. prolonged QRS and QTc) and dysrhythmias (e.g. sinus tachycardia, atrial fibrillation and flutter, supraventricular tachycardias, idioventricular rhythms, ventricular tachycardia, torsade de pointes, and ventricular fibrillation) may also occur with cocaine use. Cocaine-induced left ventricular hypertrophy can lead to a hypertrophic, and eventually a dilated cardiomyopathy and congestive heart failure.

Pulmonary

The effects of cocaine on the lungs largely depend on how the drug is abused. Smoking cocaine may induce exacerbation of asthma, alveolar haemorrhage, pulmonary hypertension, and acute respiratory failure. Forceful insufflation to maximize drug delivery may cause pneumothorax, pneumomediastinum, and non-cardiogenic pulmonary oedema.

Musculoskeletal/renal

Cocaine use may precipitate rhabdomyolysis, leading to acute renal failure in up to one-third of patients [12]. Risk factors for rhabdomyolysis include altered mental status, seizures, dysrhythmias, and haemodynamic compromise, including cardiac arrest.

Gastrointestinal

The intestinal vascular system is particularly vulnerable to the effects of cocaine due to the large numbers of α-adrenergic receptors. Acute intestinal infarction has been associated with all routes of cocaine administration.

The deadliest gastrointestinal manifestations are seen in patients who present after ingesting packets filled with cocaine, termed 'body packers' or 'body stuffers'. Body packers are patients who swallow carefully prepared latex or plastic packets filled with large quantities of highly purified cocaine to smuggle it into the country. Body stuffers are typically 'street' drug dealers who swallow poorly constructed packets of cocaine while fleeing the police. Toxicity can develop from cocaine leaking out of the ingested packets [13].

Pregnancy

Cocaine is a potent vasoconstrictor that alters placental blood flow [14]. Cocaine abuse during pregnancy increases the chance for spontaneous abortion, premature delivery, eclampsia, and placental abruption. Maternal cocaine use is associated with low birth weight, small head circumference, developmental problems, and birth defects in the neonate. Neonates exposed to cocaine in utero may experience withdrawal, which typically begins 1 or 2 days after delivery, and is characterized by irritability, jitteriness, and poor eye contact.

Diagnostic evaluation

Cocaine intoxication should be suspected based on the symptoms and signs of the sympathomimetic toxidrome—agitation, mydriasis, diaphoresis, tachycardia, tachypnoea, hypertension, and possibly hyperthermia. Further evaluation should be based on the patient's presenting complaints or symptoms.

Mildly-intoxicated patients without focal complaints or exam findings may be briefly observed. When a patient manifests severe toxicity, a laboratory evaluation may be warranted and should include a complete blood cell count, serum electrolytes, cardiac biomarkers, and creatine kinase. Patients with altered mental status, an abnormal neurological examination, or seizure should undergo computed tomography (CT) of the head. Lumbar puncture should be considered in patients with suspected subarachnoid haemorrhage. Patients who are suspected of body stuffing or packing should be evaluated by abdominal radiographs or CT and cavity searches (digital or visual examination of the oropharynx, rectum, or vagina).

If the patient has chest pain, an ECG, chest radiograph, and measurement of cardiac biomarkers should be performed. Nonspecific or non-diagnostic changes on initial ECG are common with cocaine-associated chest pain [10,15]. Cardiac troponin is the preferred method to evaluate for myocardial infarction as false elevations can be seen in the creatine kinase-MB fraction [16]. Observation for a 9–12-hour period is a useful tool with patients with cocaine-associated chest pain. Patients without new ischaemic changes on ECG, a normal troponin test, and no cardiovascular complications (e.g. dysrhythmia or recurrent symptoms) can be safely sent home with follow-up and planned outpatient work-up [17]. Patients with an abnormal electrocardiogram, concerning clinical history or elevated biomarkers will require admission and further management.

Urine drug screens to confirm cocaine use are readily available, but should be interpreted with caution. Commercial urine drug screens are sensitive to 300 ng/mL, and cocaine use within the past 24–72 hours is typically detected. In chronic users, cocaine metabolites may occasionally be detected for 2–3 weeks after last use.

Management

Initial management of patients with suspected cocaine intoxication should focus on airway, breathing, and circulation. If endotracheal intubation is required, neuromuscular blockade may be achieved with a non-depolarizing agent. In theory, suxamethonium may increase the risk of hyperkalaemia. Initial management should also focus on lowering of the core body temperature, when it is elevated. Treatments should be directed at specific signs, symptoms, or affected organs, and are summarized in Table 324.1.

Central nervous system

Patients who present with sympathetic excess and psychomotor agitation are effectively treated with benzodiazepines (1C). The role of antipsychotics is controversial, but it is generally thought that they should be avoided. Antipsychotics may lower the seizure threshold and contribute to both hyperthermia and dysrhythmias. Seizures should be treated with benzodiazepines and phenobarbital. Controversy exists about the use of phenytoin in cocaine-related seizures. Theoretically, barbiturates are preferred because they also produce sedation. If these agents are ineffective, neuromuscular blockade with a non-depolarizing agent and general anaesthesia

Table 324.1 Treatment summary for cocaine-related medical conditions. Support of airway, breathing, and circulation should precede all specific treatments

Medical condition	Treatments (level of evidence/class of recommendation)
Cardiovascular dysrhythmias	
Sinus tachycardia	◆ Observation (IIa/C) ◆ Diazepam or lorazepam (IIa/C)
Supraventricular tachycardia	◆ Diazepam or lorazepam (IIa/C) ◆ Consider diltiazem, verapamil, or adenosine (IIa/C) ◆ If haemodynamically unstable, cardioversion (IIa/C)
Ventricular dysrhythmias	◆ Diazepam or lorazepam (IIb/C) ◆ Consider sodium bicarbonate, lidocaine or amiodarone (I/C) ◆ If haemodynamically unstable, defibrillation (I/C)
Acute coronary syndrome	◆ Aspirin (I/C) ◆ Diazepam or lorazepam (I/B) ◆ Glyceryl trinitrate (I/B) ◆ Heparin (IIa/C) ◆ **For** ST elevation myocardial infarction (STEMI): • Percutaneous intervention (I/C) • Consider fibrinolytic therapy (IIb/C) • Consider morphine (IIa/C), phentolamine (IIb/C), verapamil (IIa/C), or glycoprotein IIb/IIIa inhibitors (IIa/C) • Avoid β-antagonists (III/C)
Severe hypertension	◆ Observation (IIa/C) ◆ Diazepam or lorazepam (I/C) ◆ Consider glyceryl trinitrate (I/C), phentolamine (I/C), and nitroprusside (I/C)
Pulmonary oedema	◆ Furosemide (I/C) ◆ Glyceryl trinitrate (I/C) ◆ Consider morphine sulphate (IIa/C) or phentolamine (IIb/C)
Hyperthermia	◆ Diazepam or lorazepam (I/C) ◆ Cooling methods (I/C) ◆ If agitated, consider paralysis and intubation (IIa/C)
Neuropsychiatric	
Anxiety and agitation	Diazepam or lorazepam (I/C)
Seizures	◆ Diazepam or lorazepam (I/C) ◆ Phenobarbital (IIa/C)
Intracranial haemorrhage	Neurosurgical consultation
Rhabdomyolysis	◆ Intravenous hydration (I/C) ◆ Consider sodium bicarbonate or mannitol (IIa/C) ◆ If in acute renal failure, haemodialysis (IIa/C)
Cocaine wash-out syndrome	Supportive care
Body packers	◆ Activated charcoal (IIa/C) ◆ Whole-bowel irrigation (IIa/C) ◆ Laparotomy or endoscopic retrieval (IIa/C)

are indicated. Patients with cerebrovascular complications or focal neurological findings should be managed as usual. The role of fibrinolytic therapy, however, in cocaine-associated ischaemic stroke is unknown.

Cardiovascular

Patients with suspected acute coronary syndrome should be managed with an aspirin (1C), benzodiazepine (1B), and glyceryl trinitrate (1B) as first line agents [4,15]. Antiplatelet agents (such as glycoprotein IIb/IIIa inhibitors), and unfractionated or low molecular weight heparin are reasonable to use in patients with documented ischaemia (1C). Patients who do not respond to these therapies can be treated with morphine, phentolamine (2b,C) or calcium channel-blocking agents (2b,C). β-adrenergic blockers should be avoided in the management of cocaine-associated myocardial ischaemia or infarction because unopposed stimulation of α-adrenergic receptors may worsen coronary and peripheral vasoconstriction, hypertension, and possibly ischaemia (3C). Although use of labetalol (a mixed α-adrenergic and β-adrenergic antagonist) has been proposed by some authors, labetalol increased seizures and mortality in an animal model of cocaine toxicity, and does not decrease cocaine-induced coronary vasoconstriction in humans [15]. If indicated for a STEMI, primary reperfusion therapy is best done with percutaneous interventions. The role of fibrinolytic therapy in the setting of cocaine use is controversial, and should be avoided in cases of severe hypertension, vasospasm, or suspected coronary dissection.

Supraventricular dysrhythmias should be treated initially with benzodiazepines. Calcium channel blockers may also be effective. Adenosine may be used, but its effects are often temporary. β-adrenergic blockers should be avoided. Ventricular dysrhythmias and QRS-complex prolongation may be treated with sodium bicarbonate, or lidocaine [4,15]. Benzodiazepines may also be useful.

Severe hypertension can be safely treated with benzodiazepines (1C). For patients with refractory hypertension, vasodilators such as glyceryl trinitrate, nitroprusside, or phentolamine may be used (1C). Blood pressure may be lowered if the patient is not suspected to have chronic hypertension.

Musculoskeletal/renal

Management of cocaine-associated rhabdomyolysis and renal failure should focus on decreasing agitation, lowering body temperature, intravenous hydration, and maintenance of adequate urine output. Patients whose initial serum creatine kinase level is <1000 IU/L with a normal serum creatinine level are unlikely to develop complications. Mannitol, alkalinization of the urine or haemodialysis may be considered in severe cases.

Gastrointestinal

Asymptomatic cocaine body stuffers and packers may be treated with activated charcoal and whole bowel irrigation to decrease absorption and enhance elimination. If toxicity develops, immediate surgical removal of ruptured packets may be life saving.

References

1. UN Office on Drugs and Crime. (2011). World Drug Report. Vienna: UNODC. Available at: http://www.unodc.org/documents/data-and-analysis/WDR2011/World_Drug_Report_2011_ebook.pdf (accessed 1 September 2015).
2. Substance Abuse and Mental Health Services Administration (2010). The DAWN Report: Highlights of the 2010 Drug Abuse

Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits. Rockville, MD: SAMHSA. Available at: http://www.samhsa.gov/data/sites/default/files/DAWN096/DAWN096/SR096EDHighlights2010.pdf (accesses 27 February 2012).
3. Galvin S, Campbell M, Marsh B, and O'Brien B. (2009). Cocaine-related admissions to an intensive care unit: a five-year study of incidence and outcomes. *Anaesthesia*, **65**(2), 163–6.
4. Hollander JE. (1995). The management of cocaine-associated myocardial ischemia. *New England Journal of Medicine*, **333**(19), 1267–72.
5. Lange RA and Hillis LD. (2001). Cardiovascular complications of cocaine use. *New England Journal of Medicine*, **345**(5), 351–8.
6. Pozner CN, Levine M, and Zane R. (2005). The cardiovascular effects of cocaine. *Journal of Emergency Medicine*, **29**(2), 173–8.
7. Shih RD, Hollander JE, Burstein JL, Nelson LS, Hoffman RS, and Quick AM. (1995). Clinical safety of lidocaine in patients with cocaine-associated myocardial infarction. *Annals of Emergency Medicine*, **26**(6), 702–6.
8. Holland RW, 3rd, Marx JA, Earnest MP, and Ranniger S. (1992). Grand mal seizures temporally related to cocaine use: clinical and diagnostic features. *Annals of Emergency Medicine*, **21**(7), 772–6.
9. Sporer KA and Lesser SH. (1992). Cocaine washed-out syndrome. *Annals of Emergency Medicine*, **21**(1), 112.
10. Hollander JE, Hoffman RS, Gennis P, et al. (1994). Prospective multicenter evaluation of cocaine-associated chest pain. Cocaine Associated Chest Pain (COCHPA) Study Group. *Academic Emergency Medicine*, **1**(4), 330–9.
11. Weber JE, Chudnofsky CR, Boczar M, Boyer EW, Wilkerson MD, and Hollander JE. (2000). Cocaine-associated chest pain: how common is myocardial infarction? *Academic Emergency Medicine*, **7**(8), 873–7.
12. Brody SL, Wrenn KD, Wilber MM, and Slovis CM. (1990). Predicting the severity of cocaine-associated rhabdomyolysis. *Annals of Emergency Medicine*, **19**(10), 1137–43.
13. Gill JR and Graham SM. (2002). Ten years of 'body packers' in New York City: 50 deaths. *Journal of Forensic Science*, **47**(4), 843–6.
14. Plessinger MA and Woods JR, Jr. (1998). Cocaine in pregnancy. Recent data on maternal and fetal risks. *Obstetrics and Gynecology Clinics of North America*, **25**(1), 99–118.
15. McCord J, Jneid H, Hollander JE, et al. (2008). Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation*, **117**(14), 1897–907.
16. Hollander JE, Levitt MA, Young GP, Briglia E, Wetli CV, and Gawad Y. (1998). Effect of recent cocaine use on the specificity of cardiac markers for diagnosis of acute myocardial infarction. *American Heart Journal*, **135**(2 Pt 1), 245–52.
17. Weber JE, Shofer FS, Larkin GL, Kalaria AS, and Hollander JE. (2003). Validation of a brief observation period for patients with cocaine-associated chest pain. *New England Journal of Medicine*, **348**(6), 510–7.

CHAPTER 325

Management of β-blocker and calcium channel blocker poisoning

Geoffrey Isbister and Colin Page

Key points

- β-blockers (βB) and calcium channel-blockers (CCB) can cause life-threatening toxicity due to cardiogenic shock.
- Both βBs and CCBs are heterogenous groups of drugs and particular drugs, such as propranolol, diltiazem, and verapamil are far more toxic than the others in their class.
- Like most overdoses, supportive treatment is the most important with emphasis on the primary pathophysiology, i.e. reduced cardiac output, systemic vascular resistance or both.
- Treatment of βB and CCB poisoning using absolute blood pressure as an endpoint can be misleading and measuring cardiac output can be more informative in gauging response to treatment.
- There are no specific antidotes, although β-agonists may be effective in βB overdose and calcium has been shown to be effective in CCB overdose.

Introduction

Beta blockers (βB) and calcium channel-blockers (CCB) are potentially lethal groups of drugs in overdose. Poisoning by these agents is uncommon and may only require minimal intervention and supportive care for many cases. However, large ingestions of some βB and CCB may result in life-threatening overdose requiring critical care intervention and cardiac support. The existence of slow release formulations, particularly for the CCBs, has meant that there may be delayed severe toxicity in some overdoses.

β-blockers are a heterogeneous group of drugs and can result in a range of effects in overdose. The most toxic βB are propranolol due to sodium channel effects and its ability to cross the blood–brain barrier and sotalol due to its potassium channel effects. The remaining βBs are relatively less toxic, and include atenolol, bisoprolol, carvedilol, labetalol, metoprolol, nebivolol, nadolol, and oxprenolol. The cardioselective CCB are potentially lethal and can cause cardiogenic shock refractory to treatment. The peripherally selective CCB are less likely to cause severe effects as cardiac output is often preserved. Any combination of CCB and βB, or a combination with other cardiovascular acting agents may result in severe toxicity.

Predictors of toxicity

Like all drug overdoses, dose is the most important predictor of toxicity. However, the toxic dose is poorly defined for most βBs and CCBs. One study showed that in propranolol overdose ingestion of greater than 2 g was associated with central nervous system depression, seizures, and sodium channel blockade [1]. Ingestion of greater than 10 higher-dose formulations of diltiazem or verapamil is associated with severe toxicity, although smaller amounts can be highly toxic in the elderly or in patients with underlying cardiac disease. Other predictors of toxicity are co-ingestion of another cardiotoxic drug(s) (βB, CCB, digoxin, and other vasodilators).

- **Type of β-blocker**:
  - *Propranolol*—seizures, coma, QRS widening (sodium channel blockade).
  - *Sotalol*—QT prolongation and torsades des pointes (Tdp).
- **Type of calcium channel-blocker**:
  - *Cardioselective agents*—verapamil and diltiazem.
  - *Peripherally selective agents*—nifedipine, felodipine, amlodipine, lercanidipine, and nimodipine.

Clinical effects

The clinical effects of (βB overdose and CCB overdose are compared in Table 325.1 [2,3].

Investigations

The most important investigations in (βB and CCB overdose are an electrocardiogram (ECG), blood glucose measurement and electrolytes. The ECG will identify QRS widening due to sodium channel effects with propranolol, QT prolongation with sotalol, and any arrhythmias resulting from severe toxicity. The QT nomogram should be used to determine if the QT interval is abnormal [4]. The measurement of cardiac output will often be useful in severe toxicity to determine if hypotension is due to myocardial depression, increased vasodilation or a combination of the two, and to assess the effect of inotropes and vasoconstrictors on the haemodynamics [5,6]. Serial blood glucose and potassium should be measured

Table 325.1 The clinical effects of βB overdose and CCB overdose

	β-blocker	Calcium channel-blocker
Haemodynamic effects	Hypotension due to both myocardial depression and bradycardia, progressing to cardiogenic shock	Hypotension due to both peripheral vasodilatation and myocardial depression, progressing to cardiogenic shock
Arrhythmias	Bradycardia with first degree AV block and interventricular conduction delays are the most common. Other bradydysrhythmias and asystole have been reported in fatal βB ingestions [14]. QRS prolongation with propranolol and QT prolongation and Tdp with sotalol	◆ **Verapamil/diltiazem**: sinus bradycardia, atrioventricular blocks (including complete heart block) progressing to idioventricular rhythms and asystole ◆ **Peripherally-selective CCB**: sinus rhythm and tachycardia
CNS effects	Coma and seizures can occur with lipophilic βB, e.g. propranolol	Drowsiness and confusion. Seizures are rare
Respiratory effects	Bronchospasm, pulmonary oedema	Pulmonary oedema (cardiogenic)
Gastrointestinal effects	Nil	Nausea and vomiting
Metabolic effects	Hypoglycaemia, hyperglycaemia, hyperkalaemia	Hyperglycaemia, lactic acidosis, hyperkalaemia

Data from *Toxicology and Wilderness Medicine*, Second Edition. Melbourne: Therapeutic Guidelines, 2012; and DeWitt CR and Waksman JC, 'Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity', *Toxicology Reviews*, 2004, **23**(4), pp. 223–38.

in all patients on insulin therapy and serial calcium in patients on calcium infusions.

Treatment

Treatment of βB and CCB poisoning can be complicated because of the potential combination of myocardial depression and vasodilation. There are no specific antidotes, although beta-agonists may be effective in βB overdose and calcium has been shown to be effective in CCB overdose. Calcium therapy should be considered before inotropic support. Its effect will often be short-lived unless an infusion is commenced to maintain a state of hypercalcaemia, but can provide support while other therapies are being instituted. More difficult is the choice of inotrope. This is best informed by knowledge about cardiac output to determine if an inotrope and/or a vasoconstrictor is required.

Treatment should initially follow standard advanced cardiopulmonary resuscitation guidelines with the institution of specific antidotes and inotropes as required. Hypotension should initially be treated with intravenous fluid replacement and if unresponsive inotropic support will be required. Unlike many other highly toxic medications, CNS depression may not be a major or early clinical feature so intubation and ventilation are not necessarily required for airway protection and ventilation, except for agents that enter the CNS (e.g. propranolol). In severe poisoning intubation and ventilation may facilitate monitoring and treatment of refractory circulatory collapse. Care needs to be taken with intubation, particularly in bradycardic patients with low cardiac output where atropine and/or adrenaline may be required temporarily with the institution of positive pressure ventilation.

Decontamination

Decontamination should be considered in βB and CCB poisoning because of the potential life-threatening nature of these overdoses. There is no specific evidence to guide the use and timing of decontamination, but like all overdoses a risk-assessment should be made based on the agent, dose, timing, potential for adverse effects and the willingness of the patient to cooperate with decontamination [7]. Single dose-activated charcoal should be used within 2 hours in any potentially severe poisoning with an immediate release preparation. Whole bowel irrigation should be used in large and potentially severe poisoning with slow release preparations, most importantly for slow release diltiazem and verapamil overdoses [8] However, once toxicity is evident, attempts at decontamination may be unsuccessful and will divert attention away from managing the primary toxicity.

Arrhythmias

Cardiac monitoring including serial 12-lead ECGs are essential in all βB and CCB poisoning. Bradycardia is the commonest arrhythmia and can be treated with a bolus of 0.5–1.5mg atropine if there is associated hypotension. In cases of severe bradycardia with persistent hypotension temporary transvenous pacing may be required. In CCB poisoning pacing will need to be ventricular and not atrial due to atrioventricular nodal blockade.

QRS complex widening can occur in severe propranolol toxicity. If associated with hypotension or tachyarrhythmias it can be treated with boluses of sodium bicarbonate similar to QRS complex widening associated with tricyclic antidepressant overdose.

QT prolongation and Tdp associated with sotalol toxicity (even therapeutic doses) should be managed with continuous ECG monitoring and regular 12-lead ECGs to determine if the QT is abnormal [4]. QT prolongation in isolation usually requires no specific intervention except to correct any electrolyte abnormalities. If Tdp occurs with haemodynamic instability then it should be treated as per standard advanced life support guidelines for ventricular fibrillation. In patients with QT prolongation and an episode of Tdp, magnesium sulphate or chronotropy (transvenous pacing or isoprenaline) should be considered. If isoprenaline is used then much larger doses may be required due to the β-blockade.

Inotropes

Selection of inotropes and/or vasopressors should be considered carefully and will differ for βB and CCB overdose with some similarities. Vasopressors (e.g. vasopressin) or inotropes with vasopressor properties (e.g. adrenaline, noradrenaline) are suitable for CCB overdose, but on their own are not suitable for βB blocker overdose where decreased cardiac output is the principle toxicity. High-dose insulin euglycaemia therapy (HIET), which increases cardiac output with less effect on systemic vascular resistance, is effective in

both βB and CCB overdose. If cardiac arrest occurs then prolonged cardiopulmonary resuscitation must be done (4–8 hours) because most patients are healthy prior to overdose. Cardiac assist devices and extracorporeal support should be considered, and will allow time for the drug to be eliminated.

β-blocker overdose

Glucagon has been recommended in the past with little evidence of effectiveness [9]. Glucagon is expensive and the large doses required for its inotropic effect are usually difficult to access. There are a number of potential inotropes for βB toxicity where the aim is to treat myocardial depression. These include isoprenaline, HIET, phosphodiesterase inhibitors (e.g. milrinone), and other catecholaminergic inotropes (e.g. dobutamine). The most commonly used are isoprenaline and HIET, but in resistant cases or where there is more familiarity with other inotropes the other agents can be used. All of these inotropes may initially cause hypotension when commenced and it is reasonable for small amounts of vasoconstrictors to be used to maintain blood pressure. However, recent animal studies in βB overdose suggest that the use of inotropes with vasopressor activity (adrenaline, noradrenaline) or vasopressors alone (vasopressin) may be associated with poor outcomes [10] and they should be only used in association with a pure inotrope.

HIET has become increasingly popular with both animal and anecdotal human evidence to support it as a first line agent or in combination with isoprenaline [11]. A short-acting insulin is given as an initial bolus of 1 U/kg followed by an infusion commencing at 1 U/kg/hour. Glucose needs to be administered simultaneously to prevent hypoglycaemia and can be done as either 10 or 50% infusions with boluses as required. The dose of insulin can be increased and doses of 2–10 U/kg/hour have been reported and appear to have been effective [6]. However, such high doses require large amounts of insulin, and can result in significant hypoglycaemia and hypokalaemia.

Isoprenaline can be used as an initial single agent or in combination with HIET. An initial dose of 20 μg is given, but repeat doses can be given up to 100 μg because large doses may be required to overcome the β–blockade. The bolus dose should be followed by an infusion (2–4 μg/minute), and again double, quadruple, or even higher doses may be required.

Milrinone and dobutamine have also been used to treat hypotension in βB overdose and may be used in combination with other inotropes. Low dose adrenaline, metaraminol, or vasopressin may be used in combination with an inotrope to maintain the blood pressure, but large doses or isolated use of vasopressors is not recommended in β-blocker overdose. With severe toxicity and refractory hypotension advice from a toxicologist is useful.

Calcium channel-blocker overdose

The choice of inotrope CCB overdose will be influenced by the type of CCB. A variety of different inotropes have been used with the aim to treat myocardial depression and/or peripheral vasodilatation. The commonest inotrope and most familiar is adrenaline (1 to 20 μg/min infusion), which can be used in combination with both calcium and HIET. The isolated use of vasopressors is also problematic in CCB overdose because severe toxicity with refractory hypotension (even with peripheral agents) is usually a result of myocardial depression [12].

Other inotropes or combinations of inotropes and vasopressors have been used for CCB overdose. The combination of dobutamine and noradrenaline is one such option and therapy should be guided by familiarity with various agents and toxicological advice. Similar to βB overdose, glucagon is no longer recommended.

Other pharmacological treatments

There are no specific antidotes for βB overdose although β-agonists are effectively an antagonist and inotrope. Although a specific antidote does not exist for CCB toxicity, calcium increases extracellular calcium and has been partially effective for arrhythmias and heart block in CCB overdose [8]. An initial dose of 1–3 g is recommended and if the patient is responsive, an infusion of 1–3 g/hour should be continued. However, initial doses of up to 10 g may be required in severe poisoning and for patients in cardiac arrest [13]. Serum calcium should be measured aiming for an ionized serum calcium above 2 mmol/L. Adverse effects from hypercalcaemia are uncommon.

Conclusion

Severe acidosis in CCB poisoning can be corrected with boluses of sodium bicarbonate in patients with adequate ventilation. Bicarbonate infusions are not appropriate because the body will simply buffer the changes. Seizures in propranolol overdose should be treated like any seizure in poisoning with benzodiazepines.

References

1. Reith DM, Dawson AH, Whyte IM, Buckley NA, and Sayer GP. (1996). Relative toxicity of beta blockers in overdose. *Journal of Toxicology: Clinical Toxicology*, **34**(3), 273–8.
2. Toxicology and Wilderness Medicine. 2 ed. Melbourne: Therapeutic Guidelines; 2012.
3. DeWitt CR and Waksman JC. (2004). Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. *Toxicology Review*, **23**(4), 223–38.
4. Isbister GK and Page CB. (2012). Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. *British Journal of Clinical Pharmacology*, **76**(1), 48–57.
5. Geerts BF, Aarts LP, and Jansen JR. (2011). Methods in pharmacology: measurement of cardiac output. *British Journal of Clinical Pharmacology*, **71**(3), 316–30.
6. Page C, Hacket LP, and Isbister GK. (2009). The use of high-dose insulin-glucose euglycemia in beta-blocker overdose: a case report. *Journal of Medical Toxicology*, **5**(3), 139–43.
7. Isbister GK and Kumar VV. (2011). Indications for single-dose activated charcoal administration in acute overdose. *Current Opinion in Critical Care*, **17**(4), 351–7.
8. Buckley N, Dawson AH, Howarth D, and Whyte IM. (1993). Slow-release verapamil poisoning. Use of polyethylene glycol whole-bowel lavage and high-dose calcium. *Medical Journal of Australia*, **158**(3), 202–4.
9. Bailey B. (2003). Glucagon in beta-blocker and calcium channel blocker overdoses: a systematic review. *Journal of Toxicology: Clinical Toxicology*, **41**(5), 595–602.
10. Holger JS, Engebretsen KM, Fritzlar SJ, Patten LC, Harris CR, and Flottemesch TJ. (2007). Insulin versus vasopressin and epinephrine to treat beta-blocker toxicity. *Clinical Toxicology* (*Philadelphia*), **45**(4), 396–401.
11. Engebretsen KM, Kaczmarek KM, Morgan J, and Holger JS. (2011). High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. *Clinical Toxicology* (*Philadelphia*), **49**(4), 277–83.
12. Barry JD, Durkovich D, Cantrell L, et al. (2005). Vasopressin treatment of verapamil toxicity in the porcine model. *Journal of Medical Toxicology*, **1**(1), 3–10.
13. Isbister GK. (2002). Delayed asystolic cardiac arrest after diltiazem overdose; resuscitation with high dose intravenous calcium. *Emergency Medical Journal*, **19**(4), 355–7.
14. Love JN, Enlow B, Howell JM, Klein-Schwartz W, and Litovitz TL. (2002). Electrocardiographic changes associated with beta-blocker toxicity. *Annals of Emergency Medicine*, **40**(6), 603–10.

CHAPTER 326

Management of cyanide poisoning

Stephen W. Borron

Key points

- Cyanide poisoning is characterized by cytochrome oxidase inhibition, resulting in acute central nervous system and cardiorespiratory dysfunction. Hypoxic injury may result in lasting neural deficits.
- Smoke inhalation from enclosed space structure fires is the most common source of cyanide poisoning.
- Marked elevation of plasma lactate, in conjunction with a suggestive anamnesis and clinical presentation, are sensitive indicators of cyanide poisoning.
- A 'toxidrome' exists for cyanide, but may at times be confused with those of other toxicants and sources of CNS and cardiorespiratory instability.
- Treatment relies on rapid, supportive care and, in serious cases, specific antidotes. Hydroxocobalamin and sodium thiosulfate appear to provide a greater margin of safety when the diagnosis is ambiguous.

Introduction

Our bodies have adapted to cyanide (CN) by developing CN-detoxifying enzymes (thiosulphate sulfurtransferase or rhodanase) and nitric oxide [NO] inhibition of CN binding to cytochrome oxidase [1]. Humans are generally capable of detoxification and elimination of the miniscule quantities encountered in our daily environments (foods, tobacco smoke, industrial effluents). However, in the face of massive exposure, such as fire smoke inhalation, accidental or intentional poisoning with CN gas or salts, or iatrogenic prolonged administration of nitroprusside, life-threatening toxicity may occur in minutes to hours, depending on the specific cyanide-containing substance and route of entry. Cyanide reversibly inhibits cytochrome oxidase, resulting in markedly diminished oxygen utilization and energy production. Generation of reactive oxygen species may result in necrotic or programmed cell death. Highly oxygen-dependent organs (brain and heart) suffer earliest and most. If intervention is not rapid, death or permanent brain injury may ensue. The challenge is to recognize a relatively rarely seen entity quickly, in order to permit effective intervention. Moreover, the antidotes may be rather unfamiliar.

Sources of acute cyanide poisoning

Smoke inhalation, most often from an enclosed space fire (auto, home, or other structure), is the most common source of poisoning. The importance of CN toxicity relative to carbon monoxide (CO) and other combustion gases and particulates, varies from one fire to another and remains a subject of debate [2]. The combustible material (Table 326.1), the heat of degradation, and the availability of atmospheric oxygen determine, to a large extent, how much cyanide is produced. Unfortunately, **timely** measurement of cyanide in smoke atmospheres [3] and among patients [4,5] is rare outside research settings. When blood cyanide is sampled, it is often post-mortem and sometimes long after the event [6] This leads to confusion regarding cyanide's role in smoke inhalation. Nonetheless, cyanide was suspected as early as the 1960s of contributing to fire smoke mortality and has been demonstrated to do so in prospective clinical investigations [4,5]. These studies have shown the presence of altered mental status, soot in the mouth or nose, and elevated plasma lactate should strongly suggest CN toxicity in fire victims.

Hydrogen cyanide (HCN, a gas or liquid at room temperatures), CN salts (sodium, potassium, calcium, and others), and metallocyanides (gold, silver, mercury cyanide, and others) cause CN poisoning, respectively, within minutes to hours, the delay depending on the solubility, dose, and route of exposure. HCN and its salts are used extensively in industry, mining, metal recovery, jewellery cleaning, and electroplating, and in chemistry and medical laboratories as reagents. Sudden collapse occurring in these occupational settings should always raise suspicion of exposure to CN. HCN is also produced when strong mineral acids or even water come into contact with CN salts. Thus, stomach acid may turn ingested CN salts into both a respiratory exposure to the patient and an environmental risk to rescuers.

Foods and nutritional products, such as cassava, cycad seeds, *Prunus* spp. fruit pits containing laetrile ('vitamin B17'), occasionally

Table 326.1 Household products which may release cyanide during combustion

Cyanide-containing substance	Example household product
Melamine	Countertops, cabinets
Nylon	Clothing, carpets
Polyacrylonitrile	Furniture, clothing, rugs
Polyurethane	Furniture cushions, pillows, mattresses, surface finishes
Silk	Drapes, upholstery, clothing
Urea formaldehyde	Fibreboard, plywood, laminates, glues, and adhesives
Wool	Drapes, upholstery, clothing

produce acute CN poisoning when metabolized, as do industrial nitriles (R-CN, used in plastics and pesticide production) and cyanogens (employed as fumigants). It is critical to recognize that toxicity may be delayed for hours after exposure to nitriles and cyanogens.

Finally, nitroprusside may result in CN toxicity, typically when administered in high doses over several days.

Clinical presentation

Acute cyanide poisoning follows a distinctive progression of events. A careful history may elicit early signs that have passed by the time of patient presentation. The immediate clinical response to exposure to HCN or soluble cyanide salts may include dizziness or confusion, headache, a sense of malaise, or even impending doom, chest pressure, nausea, and vomiting. Initially, the pulse becomes rapid and strong, the blood pressure increases, and tachypnoea and hyperpnoea ensue. Central nervous system depression and, sometimes, seizures intervene. Eventually, gasping and bradypnoea give way to apnoea. A sudden drop in blood pressure is observed and, if intervention is not early and correct, death follows. In the case of ingestion or skin absorption of less soluble salts or of nitriles or cyanogens, the progression may be much slower. Deaths following a spate of acetonitrile ingestion in children resulted in symptoms several hours after accidental ingestion [7].

Toxidrome

An 'asphyxiant toxidrome' may be seen after cyanide or CO poisoning. While the presentations of these two poisonings share nervous and gastrointestinal system signs and symptoms, Baud [8] has pointed out important distinctions that are unique to cyanide poisoning—severely abnormal vital signs, cardiovascular compromise, abnormal respiratory pattern (particularly bradypnoea) and severe lactic acidosis.

Impostors

CO poisoning should be high in the differential diagnosis, but typically causes less severe acidosis and cardiovascular impairment [9]. Clenbuterol, a β2-adrenergic agonist and adulterant of heroin, has caused epidemic poisoning in the USA that very closely resembled CN poisoning, with nausea, agitation, chest pain, hypotension, hyperglycaemia, and lactic acidaemia [10]. Hydrogen sulphide poisoning resembles cyanide poisoning with tachypnoea and/or apnoea, loss of consciousness, and metabolic acidosis. However, a strong sulphur smell distinguishes this exposure [11]. Sodium azide poisoning (used in automotive air bags and herbicide manufacture) may inhibit cytochrome oxidase and result in symptoms similar to cyanide poisoning.

Diagnostic studies

Definitive diagnosis of cyanide poisoning is based primarily on the blood cyanide concentration, which is not immediately available in most hospitals. A point-of-care test is undergoing development, but is not currently commercially available [12]. For late presentations, the finding of high concentrations of thiocyanate in the urine strongly suggests cyanide exposure. This test is also rarely available in a clinically-relevant timeframe.

The plasma lactate is a useful, if non-specific, marker of cyanide poisoning. Plasma lactate associated with cyanide toxicity in smoke inhalation reliably exceeds 10 mmol/L [4]. In the setting of suspected 'pure' cyanide poisoning, a plasma lactate of 8 mmol/L or above strongly supports the diagnosis [13]. The question of CO's contribution to lactate is worth mention. While CO does result in lactic acidaemia, the lactate is generally lower than that seen in smoke inhalation [9,14].

Arterial and/or venous blood gases with co-oximetry are useful. A low blood pH, elevated anion gap, and low total CO_2 can be expected in the setting of moderate to severe CN poisoning. These are, of course, less specific than lactate. Comparing arterial to mixed venous oxygen saturation permits gross assessment of tissue oxygen extraction. In CN poisoning, it is not unusual for venous oxygen saturation to approach arterial saturation. Co-oximetry allows assessment of contribution of abnormal haemoglobins, such as methaemoglobin and carboxyhaemoglobin, to the clinical condition.

Some texts and antidote package inserts [15] recommend monitoring of methaemoglobin levels after sodium nitrite administration. The idea of administering sodium nitrite to reach some arbitrary 'therapeutic' level of methaemoglobinaemia must be strongly denounced. Cyanide very rapidly binds to methaemoglobin to form cyanmethaemoglobin, which is not detected by routine co-oximetry. Thus, any **measurable** methaemoglobin in the blood is **in excess** of therapeutic levels. Suggesting a maximum methaemoglobin level of <30% implies that, in addition to non-oxygen-carrying cyanmethaemoglobin and/or carboxyhaemoglobin, an additional 30% of the circulating blood volume is incapable of carrying oxygen. If methaemoglobin is to be measured, it should be done with the understanding that **any** measured methaemoglobin represents excess capacity to bind extant cyanide.

Treatment

The *sine qua non* of the treatment of cyanide poisoning is excellent supportive care, which has been successful without specific antidotes. Antidotes appear to offer additional benefits however, including toxicokinetic support of CN elimination. The strength of evidence for antidote treatment relies heavily on case series and a handful of open-labelled prospective trials. A proposed treatment guideline for 'pure' CN poisoning is found in Fig. 326.1. In the setting of smoke inhalation, significant CN poisoning is heralded by soot in mouth, nose or secretions, altered mental status (coma, confusion, slowness of ideation), and/or cardiovascular instability not due to associated trauma.

Oxygen administration appears almost paradoxical in CN poisoning, as oxygen utilization is diminished at the cellular level due to inhibition of cytochrome oxidase, but oxygen improves outcome in CN poisoning. Most severely-poisoned patients will require intubation and mechanical ventilation, with a goal of mild respiratory alkalosis. Hyperbaric oxygen has been used in severe cases but the evidence base remains limited.

CN poisoning induces sustained and sometimes severe lactic acidaemia which persists long after correction of haemodynamics [16]. Given the pKa of 9 of HCN, acidaemia implies that more of the CN is in a non-ionized form, facilitating its movement into sensitive cells. Grave cyanide poisoning may be further complicated by respiratory acidosis. Induction of an alkaline pH in such circumstances by hyperventilation reduces cerebral distribution of CN in an animal model by some 57% [17]. Sodium bicarbonate is

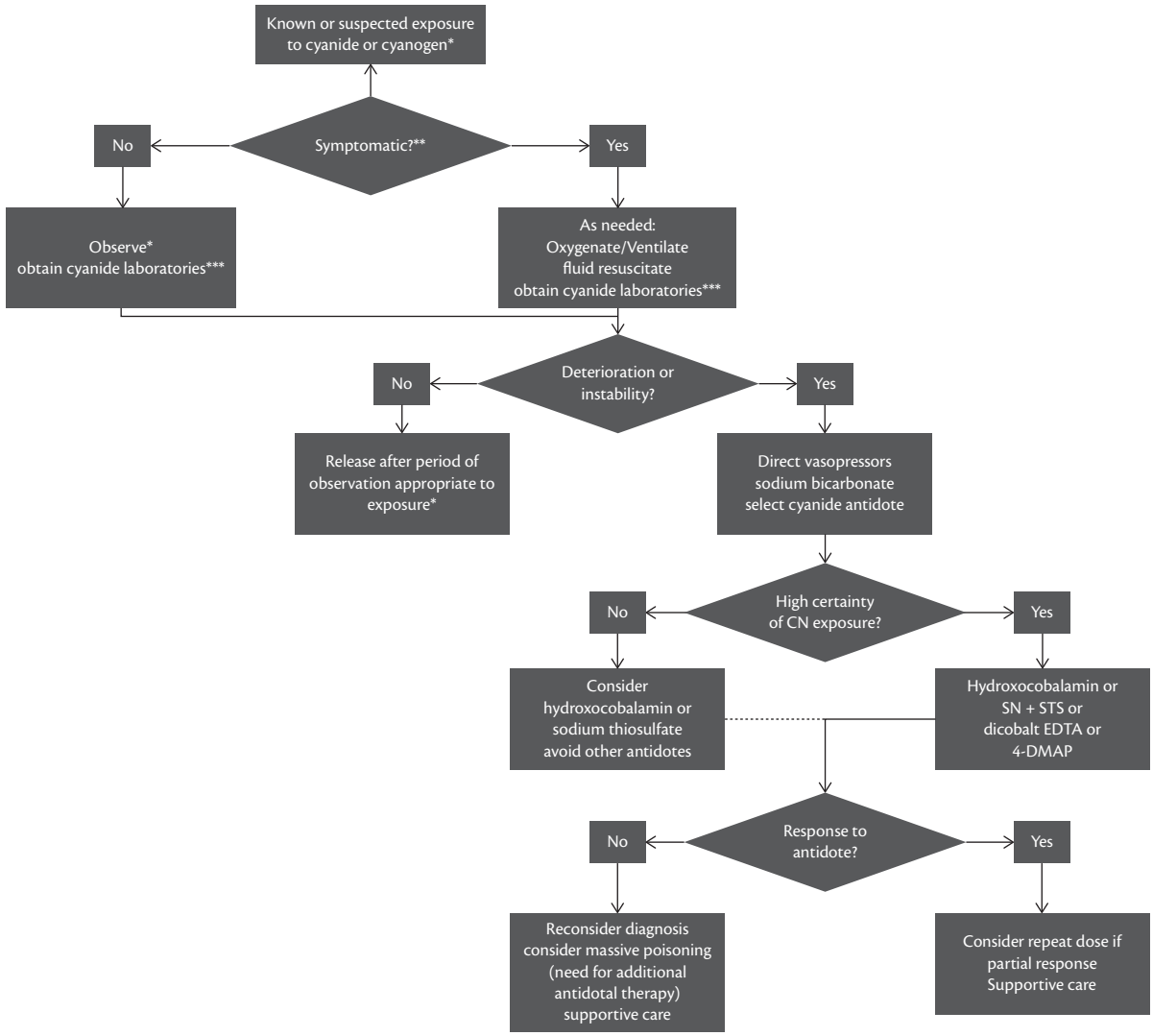


Fig. 326.1 Treatment guideline for suspected exposure to cyanide or cyanide-containing compounds.

*Cyanogens and nitriles may result in delayed toxicity. Observation for a minimum of 12–24 hours is recommended if exposure is thought to have occurred. Monitor for development of lactic acidaemia.

**Frightened non-exposed subjects may have tachypnoea, tachycardia, and hypertension. Look for evidence of mental status changes, abnormal breathing patterns (bradypnoea, hyperpnoea, apnoea) or hypotension.

*** Useful laboratories include serum electrolytes (to calculate anion gap), venous and/or arterial blood gases with co-oximetry (to assess acid-base status, presence of abnormal haemoglobins, and oxygenation/oxygen utilization), and plasma lactate (as a surrogate of significant inhibition of oxidative phosphorylation). Oxygen utilization is diminished in cyanide poisoning, giving falsely reassuring pulse oximetry values. Do not delay treatment of unstable patients while awaiting laboratory results.

CN, cyanide; dicobalt EDTA, dicobalt edetate; SN, sodium nitrite; STS, sodium thiosulphate.

frequently recommended, but appears to be supported purely on an anecdotal basis.

Vasopressors may be used as adjuncts to antidotes if fluid infusion fails to stabilize blood pressure. Bebarta and colleagues demonstrated increased survival in CN poisoned pigs treated with adrenaline versus saline alone after induction of severe hypotension (<30 mmHg) [18]. Other vasopressors were not tested. As CN poisoning results in both myocardial ischaemia and decreased systemic vascular resistance, noradrenaline or phenylephrine may be reasonable choices.

Antidotes

CN antidote availability varies by region and hospital.

Hydroxocobalamin

Hydroxocobalamin (OHCo) is vitamin B12a, which binds rapidly and irreversibly with cyanide to form cyanocobalamin (vitamin B12). Its therapeutic action likely derives from its binding of both cyanide and nitric oxide. OHCo is generally agreed to be safer than most other cyanide antidotes [19]. Adverse effects include a transient rise in blood pressure, reddish colouration of urine, plasma (leading to laboratory interference), and integument, and rare allergic reactions. It is administered via the intravenous (iv) or oral (po) route in a dose of 5 g (70 mg/kg in children). The dose may be repeated if response (haemodynamic or mental status) is incomplete. It is safe in the setting of smoke inhalation [5], as it does not form methaemoglobin or otherwise interfere with oxygenation.

Amyl nitrite, sodium nitrite, and sodium thiosulfate

Amyl nitrite, sodium nitrite, and sodium thiosulfate have been packaged in combination since the 1930s. Recently, a new antidote kit, with only the latter two drugs, has become available. The mechanism of action of the nitrites is still incompletely understood. They form methaemoglobin, which is capable of reversible binding of CN as cyanmethaemoglobin. Recent data suggest formation of nitric oxide may be important as well [1]. Unfortunately, overzealous administration of nitrites may result in hypotension or excess methaemoglobinaemia. Methaemoglobin does not carry oxygen so may aggravate hypoxaemia in smoke inhalation. Sodium thiosulfate provides a source of sulfane sulphur to the enzyme rhodanase, one of the body's innate systems of cyanide detoxification. Sodium thiosulfate appears to be quite safe, frequently causing vomiting, but there is limited experience with this drug used alone.

Amyl nitrite is generally considered a first aid measure, having little role to play in the intensive care unit. Sodium nitrite is administered iv as 300 mg over 2–4 minutes (0.2 mL/kg, not to exceed 10 mL, in children). It may be repeated once for incomplete response at one-half the original dose. Sodium thiosulfate is administered as 12.5 g (50 mL) by slow iv injection (1 mL/kg in children) and likewise may be repeated at one-half the original dose for incomplete response. The nitrite-thiosulfate combination seems most appropriate for confirmed or highly suspected pure CN poisoning. Sodium thiosulfate has been proposed for use alone in the setting of smoke inhalation, though evidence is anecdotal.

Dicobalt edetate

Dicobalt edetate, like hydroxocobalamin, is a cobalt-containing compound that chelates CN. It is recommended only for definite CN poisoning due to its adverse effect profile, which includes hypotension, anaphylactoid reactions, and ventricular arrhythmias. The iv dose is 300 mg over 1 minute in adults. Experience with children is lacking.

4-Dimethylaminophenol

4-Dimethylaminophenol is another inducer of methaemoglobinaemia. Unlike the other antidotes, it may be administered by the intramuscular route. Its use has been associated with severe toxicity, including haemolysis and multi-organ failure. The recommended iv dose is 250 mg over 1 minute in adults. Experience with children is lacking.

Cobinamide and sulfanegen

Cobinamide, a derivative of cobalamin is anticipated to soon undergo human trials in the USA. It benefits from being a smaller molecule than hydroxocobalamin and of binding two, rather than one CN anions per mole of drug, allowing smaller doses. Sulfanegen, a new sulfane sulphur donor prodrug is demonstrating promising results alone, and in combination with cobinamide in animal testing [20].

References

1. Pearce LL, Lopez Manzano E, Martinez-Bosch S, and Peterson J. (2008). Antagonism of nitric oxide toward the inhibition of cytochrome c oxidase by carbon monoxide and cyanide. *Chemical Research in Toxicology*, **21**(11), 2073–81.
2. Alarie Y. (2002). Toxicity of fire smoke. *Critical Reviews in Toxicology*, **32**(4), 259–89.
3. Bolstad-Johnson DM, Burgess JL, Crutchfield CD, Storment S, Gerkin R, and Wilson JR. (2000). Characterization of firefighter exposures during fire overhaul. *American Industrial Hygiene Association Journal*, **61**(5), 636–41.
4. Baud FJ, Barriot P, Toffis V, et al. (1991). Elevated blood cyanide concentrations in victims of smoke inhalation. *New England Journal of Medicine*, **325**(25), 1761–6.
5. Borron SW, Baud FJ, Barriot P, Imbert M, and Bismuth C. (2007). Prospective study of hydroxocobalamin for acute cyanide poisoning in smoke inhalation. *Annals of Emergency Medicine*, **49**(6), 794–801, e1–2.
6. Barillo DJ, Goode R, and Esch V. (1994). Cyanide poisoning in victims of fire: analysis of 364 cases and review of the literature. *Journal of Burn Care and Rehabilitation*, **15**(1), 46–57.
7. Caravati EM and Litovitz TL. (1988). Pediatric cyanide intoxication and death from an acetonitrile-containing cosmetic. *Journal of the American Medical Association*, **260**(23), 3470–3.
8. Baud FJ. (2007). Cyanide: critical issues in diagnosis and treatment. *Human Experimental Toxicology*, **26**(3), 191–201.
9. Benaissa ML, Megarbane B, Borron SW, and Baud FJ. (2003). Is elevated plasma lactate a useful marker in the evaluation of pure carbon monoxide poisoning? *Intensive Care Medicine*, **29**(8), 1372–5.
10. Hoffman RS, Kirrane BM, and Marcus SM. (2008). A descriptive study of an outbreak of clenbuterol-containing heroin. *Annals of Emergency Medicine*, **52**(5), 548–53.
11. Guidotti TL. (1996). Hydrogen sulphide. *Occupational Medicine* (*London*), **46**(5), 367–71.
12. Ma J, Ohira S, Mishra SK, et al. (2011). Rapid point of care analyzer for the measurement of cyanide in blood. *Analytical Chemistry*, **83**(11), 4319–24.
13. Baud FJ, Borron SW, Megarbane B, et al. (2002). Value of lactic acidosis in the assessment of the severity of acute cyanide poisoning. *Critical Care Medicine*, **30**(9), 2044–50.
14. Chou KJ, Fisher JL, and Silver EJ. (2000). Characteristics and outcome of children with carbon monoxide poisoning with and without smoke exposure referred for hyperbaric oxygen therapy. *Pediatric Emergency Care*, **16**(3), 151–5.
15. (2011). NITHIODOTE Prescribing Information. Available at: http://www.hopepharm.com/downloads/nithiodote_prescribinginfo (accessed 1 September 2015).
16. Baud FJ, Borron SW, Bavoux E, Astier A, and Hoffman JR. (1996). Relation between plasma lactate and blood cyanide concentrations in acute cyanide poisoning. *British Medical Journal*, **312**(7022), 26–7.
17. Djerad A, Monier C, Houze P, Borron SW, Lefauconnier JM, and Baud FJ. (2001). Effects of respiratory acidosis and alkalosis on the distribution of cyanide into the rat brain. *Toxicological Sciences*, **61**(2), 273–82.
18. Bebarta VS, Pitotti RL, Dixon PS, et al. (2012). Hydroxocobalamin and epinephrine both improve survival in a Swine model of cyanide-induced cardiac arrest. *Annals of Emergency Medicine*, **60**(4), 415–22.
19. Hall AH, Saiers J, and Baud F. (2009). Which cyanide antidote? *Critical Reviews of Toxicology*, **39**(7), 541–52.
20. Chan A, Crankshaw DL, Monteil A, et al. (2011). The combination of cobinamide and sulfanegen is highly effective in mouse models of cyanide poisoning. *Clinical Toxicology* (*Philadelphia*), **49**(5), 366–73.

CHAPTER 327

Management of alcohol poisoning

Knut Erik Hovda and Dag Jacobsen

Key points

- Methanol and ethylene glycol poisoning share many characteristics, often presenting with a metabolic acidosis of unknown origin.
- A common mistake is delayed diagnosis of poisoning with fatal consequences, in spite of effective treatment available.
- The long-term prognosis of cerebral (unless hypoxic damage) and kidney function in ethylene glycol poisoning is good given adequate treatment.
- Diethylene glycol is also highly toxic, but the knowledge on toxicity is limited. We recommend treatment similar to ethylene glycol poisoning.
- Poisoning with other alcohols is less severe, and will usually present without pronounced metabolic acidosis.

Ethyl alcohol

Diagnosis

The most important diagnostic procedure in the patient with a suspected alcohol poisoning is to rule out other causes for the coma such as head injuries, hypoglycaemia (children) or co-ingestion of drugs or chemicals.

Ethanol is easily determined by standard enzymatic methods or gas chromatography, and ethanol elevates serum osmolality by 24 mOsm/kgH_2O per 1 g/L (100 mg/dL).

Assessment

The lethal ethanol dose for adults is about 3–5 g/kg in adults (75 kg), corresponding to a lethal serum concentration of 5–8 g/L; or 110–180 mmol/L, lowest among the chronic alcoholics with poor nutrition. The lethal dose in children is about 2–3 g/kg (1 g = 1.2 mL). Fatalities are often related to unsecured airways and, in adults, often to alcohol-induced organ complications, such as cardiomyopathy, malnutrition, and secondary infections.

Typical features of ethanol intoxication are central nervous system (CNS) depression, hypotension, hypothermia, and respiratory problems, including aspiration into the lungs.

Ethanol intoxication in children may be complicated by hypoglycaemia. Alcoholic ketoacidosis may occur due to complex mechanisms, including hypoglycaemia (ethanol replaces the ordinary calories in ethanol abusers), dehydration (low extracellular volume gives α-adrenergic stimulus, causing inhibition of insulin-release; hence, the liver oxidizes alcohol to ketones) and lack of thiamine, which gives an increased lactate production (thiamin acts as a co-factor for pyruvate in Krebs cycle to inhibit the production of lactate).

Management

If the patient is seen within the first hour after drinking a substantial quantity of ethanol, gastric aspiration and lavage could be considered. Activated charcoal is of no value in pure ethanol intoxication, but as many patients have co-ingested other drugs, which potentiate the toxic effects of ethanol, activated charcoal should be considered in these cases.

Symptomatic and supportive treatment should be given as needed and intravenous glucose should be administered to inebriated children with regular monitoring of blood sugar.

Haemodialysis effectively removes ethanol, but is rarely indicated.

Isopropyl alcohol

Diagnosis

The clinical diagnosis of isopropyl alcohol poisoning may be suspected from CNS depression and acetone smell on the breath. The specificity of ketostix (sensitive only for acetoacetate) is far too low to be of practical value.

Both isopropyl alcohol (1 g/L = 17 mmol/L; osmolal contribution 18 mOsm/kgH_2O) and it´s metabolite acetone (1 g/L = 18 mmol/L; osmolal contribution 19 mOsm/kgH_2O) will increase the osmolal gap. The anion gap is usually normal, but may be slightly increased due to ketosis (and some lactate) in the alcoholic and lactate in the hypotensive patient.

Isopropyl alcohol is best determined by a standard gas chromatographic method where ethanol, methanol, and acetone are determined as well.

Assessment

The lethal dose 1–4 mL/kg, i.e. about twice as toxic as ethanol.

Blood isopropanol levels in the range of 2–4 g/L (34–68 mmol/L) are often seen without complications other than coma and slight respiratory depression. Others have survived with levels as high as 5.6 g/L (95 mmol/L), although haemodialysis was then performed. Elimination is mainly due to hepatic metabolism to acetone with a serum half-life of isopropanol of 6–7 hours.

The typical patient will present with CNS depression, depressed respiration, gastritis with abdominal pain and slight hypothermia. (Aspiration) pneumonia may be present. Hypoglycaemia may be present in the very young and the most severe alcoholics.

Management

If the patient is seen within 1 hour, gastric aspiration and lavage could be considered, whereas activated charcoal is of no value. The symptomatic treatment should follow the established principles of intensive care when needed. Mechanical ventilation should be used if respiratory depression is accompanied by pneumonia.

Haemodialysis will effectively remove isopropyl alcohol and should be considered at blood isopropanol levels above 4 g/L (68 mmol/L), and on clinical criteria if coma and sustained hypotension are present. In the hypotensive patient, an infusion of norepinephrine may be necessary in order to perform dialysis. The effectiveness of continuous veno-venous haemodialysis has not been confirmed, but it may be considered in the hypotensive patient.

Methanol

Diagnosis

Methanol is most often determined by gas chromatography. Measurement of serum formate by a simple enzymatic method [1] is also a sensitive and specific indirect diagnostic method for methanol poisoning. A simple bedside dip-stick version is under development showing promising results [2]. The clinical diagnosis of methanol poisoning is difficult in the absence of a history of ingestion. The objective signs of ocular toxicity of methanol include dilated pupils, which are partially or non-reactive to light and optic disc hyperaemia with blurring of the disc margins ('pseudopapilitis'). The subjective visual disturbances are only reported in 40–60% of the patients.

If a specific analytical method for methanol is not available, the anion and osmolal gaps should be calculated. The **anion gap** (AG) should be calculated using the formula:

$$AG = (Na^+ + K^+) - (Cl^- + HCO_3^-). \quad \text{[eqn 1]}$$

The anion gap normally varies between 4 and 20 mmol/L [3]. In the absence of a circulatory failure, diabetes, alcoholism, and uraemia, an increased anion gap clearly indicates poisoning with salicylate, methanol or ethylene glycol, although other rare poisonings may also be present (e.g. cyanide). There is a clear 1:1 correlation between the increased anion gap and the formate concentration.

The **osmolal gap** (OG) is the difference between the measured osmols (Om) and the calculated osmolality (Oc) in serum.

$$OG = Om - Oc \quad \text{[eqn 2]}$$

Normally, sodium (and its accompanying anions), glucose, and urea determine the osmolality of serum as expressed by the formula (SI-units):

$$OG = (1.86 \times Na + urea + glucose) / 0.93 \quad \text{[eqn 3]}$$

The reference range for the osmolal gap is 5 ± 14 (mean±2SD) or, more simply below 20 mOsm/kgH_2O [3].

The intoxicants best able to increase the osmolal gap are those which have a low molecular weight and are present in high mass units, i.e. high molar concentrations. The lower alcohols and glycols are such substances. A methanol concentration of 1 g/L (32 mmol/L) increases the osmolal gap by (32/0.93) 34 mOsm/kgH_2O; and a 1:1 linear relationship exists between the OG and the serum methanol concentration. The osmolal contribution of methanol is so significant that interference from other causes (except ethanol), will only occur at low levels of methanol (<0.5 g/L; 16 mM).

Only methanol and ethylene glycol regularly cause severe metabolic acidosis and elevation of both the anion and osmolal gaps (Fig. 327.1). However, if ethanol is co-ingested with methanol or ethylene glycol, there will be no metabolic acidosis before most of the ethanol is metabolized due to the antidotal effect of ethanol (inhibits metabolism of the other two by alcohol dehydrogenase (ALDH)). In such circumstances, calculation of the gaps must be repeated until the ethanol level is zero.

In late stages of methanol or ethylene glycol poisonings, most of the alcohol or glycol may be metabolised to its acidic metabolite. In this situation there is a pronounced metabolic acidosis with a high anion gap. Due to low alcohol/glycol levels, the osmolal gap may now be close to normal values, especially in ethylene glycol poisoning due to its higher molecular weight and thus smaller molar contribution. In this situation, a small/normal osmolal gap does not eliminate the possibility of toxic alcohol ingestion (Fig. 327.1).

Assessment

The lethal dose of methanol is about 1 g/kg (1 g = 1.2 mL). The minimum dose causing permanent visual defects is unknown.

Methanol itself is rather non-toxic and there is usually a latent period of about 12–24 hours from the ingestion of methanol to the occurrence of symptoms. This is the time it takes for sufficient amounts of methanol to be metabolized to formic acid. Since ethanol inhibits this metabolism, concomitant intake of ethanol may lengthen the latent period.

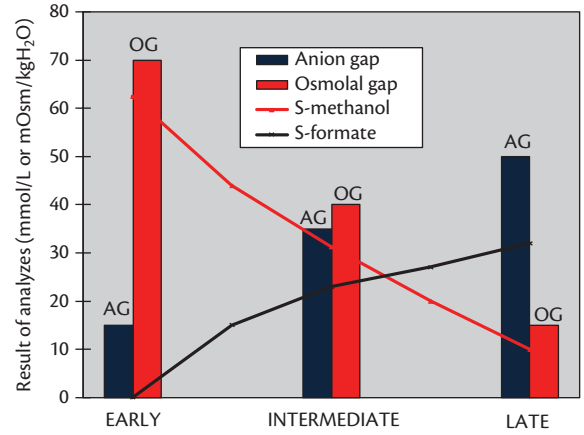


Fig. 327.1 The different stages of methanol poisoning (similar for ethylene glycol poisoning).

Reproduced from *Intensive Care Medicine*, **30**(9), 2004, pp. 1842–6, 'Anion and osmolal gaps in the diagnosis of methanol poisoning: clinical study in 28 patients', Hovda KE et al., with kind permission from Springer Science and Business Media and European Society of Intensive Care Medicine.

Clinical features are non-specific and include weakness, anorexia, headache, nausea, and chest pain, accompanied by increasing dyspnoea (hyperventilation) as the metabolic acidosis develops. Visual symptoms (blurred vision) may appear anytime during the course. A few cases may present with acute pancreatitis.

There is usually little improvement of impaired visual acuity **after** the acute stage, whereas early initiation of treatment will often reverse the symptoms. The patient should always be evaluated by an ophthalmologist as the incident may have legal and insurance implications. The most severely poisoned patients may suffer from a Parkinson-like syndrome due to methanol-induced symmetrical lesions in the putamen.

The possibility of methanol victims other than the patient treated should always be considered.

Management

The treatment should follow the established principles of intensive care when needed. If the patient is seen within 1 hour, gastric lavage should be considered. Activated charcoal is of no value.

The specific treatment of methanol poisoning includes administration of sodium bicarbonate to combat the metabolic acidosis, fomepizole [4] or ethanol to inhibit methanol metabolism to formic acid [5], and haemodialysis to remove methanol and formate, and correct the metabolic acidosis.

Aggressive bicarbonate treatment must be given to correct the metabolic acidosis and decrease the amount of undissociated formic acid and its access to the central nervous system.

Fomepizole should be given intravenously as a loading dose of 15 mg/kg, followed by bolus doses of 10 mg/kg every 12 hours (from the 5th dose and onwards; use 15 mg/kg as fomepizole induces its' own metabolism). Alternatively, give orally in equal doses. During haemodialysis dose every 4 hours. No serum monitoring of fomepizole is necessary.

If ethanol is used as the antidote, aim for a blood ethanol concentration of 22 mmol/L (1 g/L). Keeping ethanol at a constant level is difficult, especially during dialysis (double the dose as a rule of thumb), and close monitoring of the blood levels is necessary (e.g. every 1–2 hours). Start by giving a bolus dose of 0.6 mg/kg of absolute (96%) ethanol, followed by 70–150 mg/kg/hour intravenously in dextrose/saline (or orally) with the highest maintenance dose for drinkers (1 g ethanol = 1.2 mL) [4]. Ethanol solutions above 20% should preferably be given in a central line.

Haemodialysis is indicated for the critically-ill patient with a severe metabolic acidosis (base deficit >15–20 mmol/L), and/or visual disturbances. The methanol level per se is no indication for dialysis if fomepizole is the antidote used, but the treatment period will be prolonged for days without dialysis [6]. If ethanol is the antidote used, dialysis is recommended if the methanol level is above 20 mmol/L (60 mg/dL) [4].

Folinic acid (Leucovorin®) of 50mg (adult dose) should be given intravenously every 6 hours for 24 hours in order to enhance the endogenous formate metabolism.

Ethylene glycol

Diagnosis

Ethylene glycol in biological fluids can be determined by enzymatic methods or gas chromatography. If specific analysis is not available, the use of the anion and osmolal gaps may be helpful as for methanol poisoning. An ethylene glycol concentration of 1 g/L (16 mmol/L) increases the osmolality by (16/0.93) 17 mOsm/kg H_2O. Urine microscopy will often reveal needle-shaped calcium oxalate monohydrate or envelope-shaped dihydrate crystals. These findings may be absent or delayed, and a negative microscopy should therefore be repeated.

Assessment

The lethal dose of ethylene glycol is about 1–2 mL/kg. Ethylene glycol causes CNS-depression and inebriation (similar to ethanol), but its main toxicity is mediated through its metabolites from a combination of a severe metabolic acidosis caused by glycolic acid, and the precipitation of calcium oxalate monohydrate in various tissues (especially in the kidneys), with impaired end-organ function as a result.

Ethylene glycol poisoning is characterized by an initial CNS-depressant phase with inebriation progressing to coma. Following a short latent period of 4–12 hours, the signs and symptoms due to the metabolites start to appear. The increasing accumulation of glycolic acid leads to severe metabolic acidosis and an increasing hyperventilation.

Without adequate treatment, the patient will deteriorate rapidly and, in addition to CNS depression (cerebral oedema occurs), convulsions, oliguric renal failure, and respiratory problems usually develops. Pulmonary infiltrations may be observed radiologically, but these changes are thought to be non-infective in origin. In severe cases, ARDS may develop.

Management

If the patient is seen within 1 hour after ingestion, gastric aspiration and lavage should be considered. Activated charcoal is of no value.

The rapid correction of the acidosis by bicarbonate in these patients may provoke tetanic signs, especially when hypocalcaemia (result of precipitation of calcium oxalate) is already present, as discussed later. Fomepizole [7] or ethanol is given to inhibit ethylene glycol metabolism in the same dose as for methanol poisoning. Haemodialysis removes ethylene glycol and glycolate and helps in correcting the metabolic acidosis. If blood ethylene glycol values are not available, haemodialysis should be performed for 8 hours. Acute renal failure is a strong indication for haemodialysis because its origin is most probably the accumulation of calcium oxalate monohydrate in the proximal tubule cells [8], and not only prerenal failure. If treatment with fomepizole is initiated early before pronounced metabolic acidosis (BD >15 mM) and renal failure have developed, haemodialysis may not be necessary because the renal excretion of ethylene glycol is high (t/2 12–15 hours).

Tetany and seizures should be treated with calcium intravenously. However, calcium **should not be given** for hypocalcaemia per se, as this may increase precipitation of calcium oxalate crystals in the tissues. If calcium gluconate/chloride is not effective, convulsions should be treated conventionally.

It is important to acknowledge the fact that both coma (unless hypoxic brain damage), and the renal failure in ethylene glycol poisoning have a good long-term prognosis (dialysis may be necessary for weeks).

Diethylene glycol

Diethylene glycol is at least partially metabolized through ALDH and two major metabolites have been identified—2-hydroxyethoxyacetic acid (2-HEAA) and diglycolic acid (DGA). The former appears to be associated with acidosis and the latter

with cell toxicity [9]. Fomepizole may therefore be indicated, but there are no clear recommendations in the literature [10]. The clinical features include neurological and renal dysfunction, as well as a metabolic acidosis prior to multi-organ failure. Until further studies have been performed, we recommend diethylene glycol poisoning to be treated as ethylene glycol poisoning.

Higher alcohols

Higher alcohols (more CH_3-groups) are, in general, more lipid soluble than ethanol and usually have a larger CNS-depressing effect than ethanol. As their molecular weight increases dialysis becomes less effective and treatment is solely symptomatic.

References

1. Hovda KE, Urdal P, and Jacobsen D. (2005). Increased serum formate in the diagnosis of methanol poisoning. *Journal of Analytical Toxicology*, **29**, 586–8.
2. Hovda KE, Gadeholt G, Evtodienko V, and Jacobsen D. (2015). A novel bedside diagnostic test for methanol poisoning using dry chemistry for formate. *Scandinavian Journal of Clinical Laboratory Investigation*, **75**, 610–4.
3. Aabakken L, Johansen KS, Rydningen EB, Bredesen JE, Ovrebo S, and Jacobsen D. (1994). Osmolal and anion gaps in patients admitted to an emergency medical department. *Human Experimental Toxicology*, **13**, 131–4.
4. Jacobsen D and McMartin KE. (1986). Methanol and ethylene glycol poisonings. Mechanism of toxicity, clinical course, diagnosis and treatment. *Medical Toxicology*, **1**, 309–34.
5. Zakharov S, Pelclova D, Navratil T, et al. (2015). Fomepizole versus ethanol in the treatment of acute methanol poisoning: comparison of clinical effectiveness in a mass poisoning outbreak. *Clinical Toxicology* (*Philadelphia*), 1–10.
6. Hovda KE and Jacobsen D. (2008). Expert opinion: fomepizole may ameliorate the need for hemodialysis in methanol poisoning. *Human Experimental Toxicology*, **27**, 539–46.
7. Brent J. (2009). Fomepizole for ethylene glycol and methanol poisoning. *New England Journal of Medicine*, **360**, 2216–23.
8. Hovda KE, Guo C, Austin R, and McMartin KE. (2010). Renal toxicity of ethylene glycol results from internalization of calcium oxalate crystals by proximal tubule cells. *Toxicology Letters*, **192**, 365–72.
9. Besenhofer LM, McLaren MC, Latimer B, et al. (2011). Role of tissue metabolite accumulation in the renal toxicity of diethylene glycol. *Toxicology Science*, **123**, 374–83.
10. Hoyte CO and Leikin JB. (2012). Management of diethylene glycol ingestion. *Clinical Toxicology* (*Philadelphia*), **50**, 525–7.

CHAPTER 328

Management of carbon monoxide poisoning

Djillali Annane and B. Jérôme Aboab

Key points

- Carbon monoxide (CO), a colourless, odourless, and tasteless gas, is the main cause of poison-related death.
- CO causes tissue damage by oxygen deprivation and by promoting oxidative stress and systemic inflammation.
- Persistent neurological sequels and delayed neurological syndrome are the main complication of CO poisoning.
- The only specific treatment for CO poisoning is breathing 100% oxygen.
- Hyperbaric oxygen therapy should be limited to comatose patients and CO poisoning during pregnancy.

Definitions and epidemiology

Carbon monoxide (CO) poisoning could be defined as the clinical and biological consequences of increased tissue concentration as a result of acute or chronic exposure to CO. CO poisoning kills about 300 people per year in France and is the commonest cause of poison related deaths [1]. Its annual incidence is approximately 4500, and is probably underestimated. In the USA it is estimated there are about 50,000 CO victims annually, of whom about 5–7% will die [2].

Pathophysiology

CO density is very close to the density of air and it is therefore highly diffusible in the atmosphere. It has no colour, no odour, and no taste and, is thus indiscernible from air. CO is produced by incomplete combustion of carbon-containing products. Table 328.1 shows the most common sources of CO.

CO enters into the body exclusively via the lungs. It then goes rapidly into the circulation, where at least 80% of the gaseous molecules bind to haemoglobin to form carboxyhaemoglobin (COHb).Because haemoglobin affinity for CO is 210 times higher than its affinity for oxygen, oxygen is removed from haemoglobin. About 10–15% of CO binds to myoglobin, and about 5% to cytochromes and metalo-enzymes. CO is not metabolized and is cleared via the lungs. Its half-life at room air and sea-level atmosphere is about 4 hours.

There are two main mechanisms by which CO exerts its toxicity in subjects. First, CO induces profound tissue anoxia [3]. CO replaces oxygen on haemoglobin and other specific carriers blocking oxygen delivery to the tissues. CO further prevents oxygen release at the tissue level by shifting the oxygen–haemoglobin dissociation curve to the left. Moreover, CO substitutes for oxygen and binds to proteins of the mitochondrial chain preventing utilization of oxygen molecules that have already entered into the cells. Tissue anoxia with subsequent lactic acidosis is the hallmark of CO poisoning. More recently, tissues and systemic inflammatory response to CO has been recognized as a potential major cause for brain injury and organ dysfunction [4]. CO may directly activate neutrophils and, subsequently, the inflammatory cascade. More often, there is hypoxia-induced cell death, platelet aggregation, and neutrophil degranulation. The subsequent production of proteases, such as myeloperoxidase, and of radical oxygen species triggers lipid peroxydation, myelin degradation, and microglial activation.

Diagnosis

The diagnosis of CO poisoning is one of the most difficult in medicine except in very specific circumstances such as smoke inhalation, or suicide attempt by engine exhaust gas inhalation. Owing to the nature of tissue damage, i.e. anoxia and/or inflammation, the symptoms of CO poisoning are non-specific. Owing to the whole body tissue anoxia following CO intoxication, any of the body systems may be affected. As the brain is the most sensitive to hypoxia, neurological symptoms are the most frequent signs of CO intoxication and commonly include neuropsychological signs, headaches, seizures, fatigue, malaise, and altered mental status, transient loss of consciousness or coma [3,4]. Nausea, vomiting, and abdominal pain are also very common among a broad variety of clinical symptoms (Table 328.2). Rarely, CO poisoning may result in multi-organ failure syndrome. There are several aspects of the medical history that must draw the physician's attention and help him identify CO victims. First, several people may have been exposed to CO inhalation and will present together to the emergency room with similar dizziness or clinical features. Secondly, alleviation of symptoms at the time of presenting to the hospital is a clinical hallmark of CO poisoning. Indeed, when patients are extracted to the toxic atmosphere, CO is cleared via the lung with a half-life of 4 hours.

The diagnosis may be formally established by the detection of CO in room air, on the site of the accident, or by measuring exhaled CO concentrations or arterial COHb. The diagnosis of CO poisoning may be based on exhaled CO levels of 50 ppm or more, or on

Table 328.1 Circumstances of CO poisoning

Circumstances	*n*	%
All French victims during the last 3 years		
Home	3368	84.5
Public building	138	3.5
Vehicle	36	0.9
Work	303	7.6
Suicide	98	2.4
Others*	42	1.0
ICU Hospitalized Victims in Paris during the last 3 years		
Home	212	58.4
Fire smoke	106	29.2
Engine gas	45	12.4

*The 'other' category corresponds to episodes of confirmed CO poisoning without sufficient evidence to classify them in another category.

Data from the open database of the French Institute for Public Health Surveillance and from the admission directory of the intensive care unit of the Raymond Poincaré hospital (Garches – France).

Table 328.2 Clinical presentation in 3985 CO victims

Main symptoms of CO poisoning victims	%
Asthenias	4
Headache	53
Dizziness	18
Faintness	14
Nausea/vomiting	26
Transient reversible paralysis	1
Reversible loss of consciousness	12
Cardiac complication (angina, myocardial)	1
Coma	1
Stroke	0.5
Other	6
None	13

Data from the open database of the French Institute for Public Health Surveillance.

arterial carboxyhaemoglobin levels of >10% or >5%, in smokers and non-smokers, respectively [5]. Carboxyhaemoglobin levels do not correlate with clinical symptoms [6]. Routine laboratory tests may show lactic acidosis, increased levels of creatine kinase, liver, or pancreas enzymes, and increased circulating neutrophils.

Prognosis

There are two main neurological complications to CO poisoning, i.e. persistent neurological sequels and delayed neurological syndrome [4]. Patients with persistent neurological sequels are CO victims that presented initially with neurological symptoms (as described previously), which will only partly regress. The delayed neurological syndrome consists of the onset of neurological symptoms (from neuropsychological signs to permanent vegetative state) after a symptom-free period, which may last from 2 weeks to 3–4 months. It is estimated that about half of CO victims may continue to present with neurological signs—mainly neuropsychological disorders—up to 1 year after CO exposure [4].

Risk factors for persistent or delayed neurological syndromes may include long exposure to CO, engine exhaust gas inhalation, dizziness before admission, headaches, or coma at time of admission, and arterial lactate levels [7]. However, COHb levels have no prognostic value [7].

Risk factors for death from CO poisoning include pre-existing cardiac diseases and CO related myocardial injury [2], need for mechanical ventilation and high lactate levels [8].

Treatment

Basis of therapy

Tissue oxygen deprivation being the hallmark of CO related damages, oxygen supplementation is the only specific treatment for CO victims. Fig. 328.1 provides a standard decision tree for patients' management. Immediate therapeutic measures should include removal of the patient from CO exposure and oxygen supplementation [3,4]. In spontaneously breathing patients with normal lungs, inhalation of 100% oxygen reduces the COHb half-life from 4 hours to about 50–60 minutes [3]. For an appropriate delivery of an inspired fraction of oxygen of 100%, a full-face mask is needed.

Supportive care may include mechanical ventilation, fluid replacement, vasopressor therapy, and more rarely renal replacement therapy depending on the number of CO-related organ failures. Although, CO poisoning may damage tissues by triggering an oxidative stress reaction and systemic inflammatory response, there is no evidence a pharmacological anti-inflammatory approach is of any benefit. There are no data to support the use of non-steroidal anti-inflammatory drugs, corticosteroids, or anti-oxidative drugs.

Role of hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBO) consists of placing the patient in a closed chamber to increase the atmospheric pressure in addition to providing 100% oxygen [3]. According to the atmospheric pressure, arterial partial oxygen pressure, arterial and tissue oxygen content will increase substantially. The increase in oxygen molecules in blood and tissues contributes to removal of CO from haemoglobin, myoglobin, and other proteins. For example, at a pressure of 2 absolute atmospheres and 100% oxygen, the half-life of COHb may decrease to about 20 minutes.

In CO-poisoned animals, HBO may [9] or may not [10] prevent brain damage.

There are nine controlled trials that have assessed the benefit of HBO in CO victims [5,11–18]. A recent systematic review and meta-analysis has included data from six of these trials; see Table 328.3) accounting for 1361 patients [19]. The main outcome for this meta-analysis was the proportion of patients presenting with neurological sequels. At 4–6 weeks, there were 202/691 (29%) and 219/644 (34%) of patients with neurological sequels in the HBO and normobaric oxygen therapy arms, respectively. The odds ratio of persistent neurological sequels was 0.78 (95% CI, 0.54–1.12). There was some heterogeneity across the trials (I^2 = 46%). There

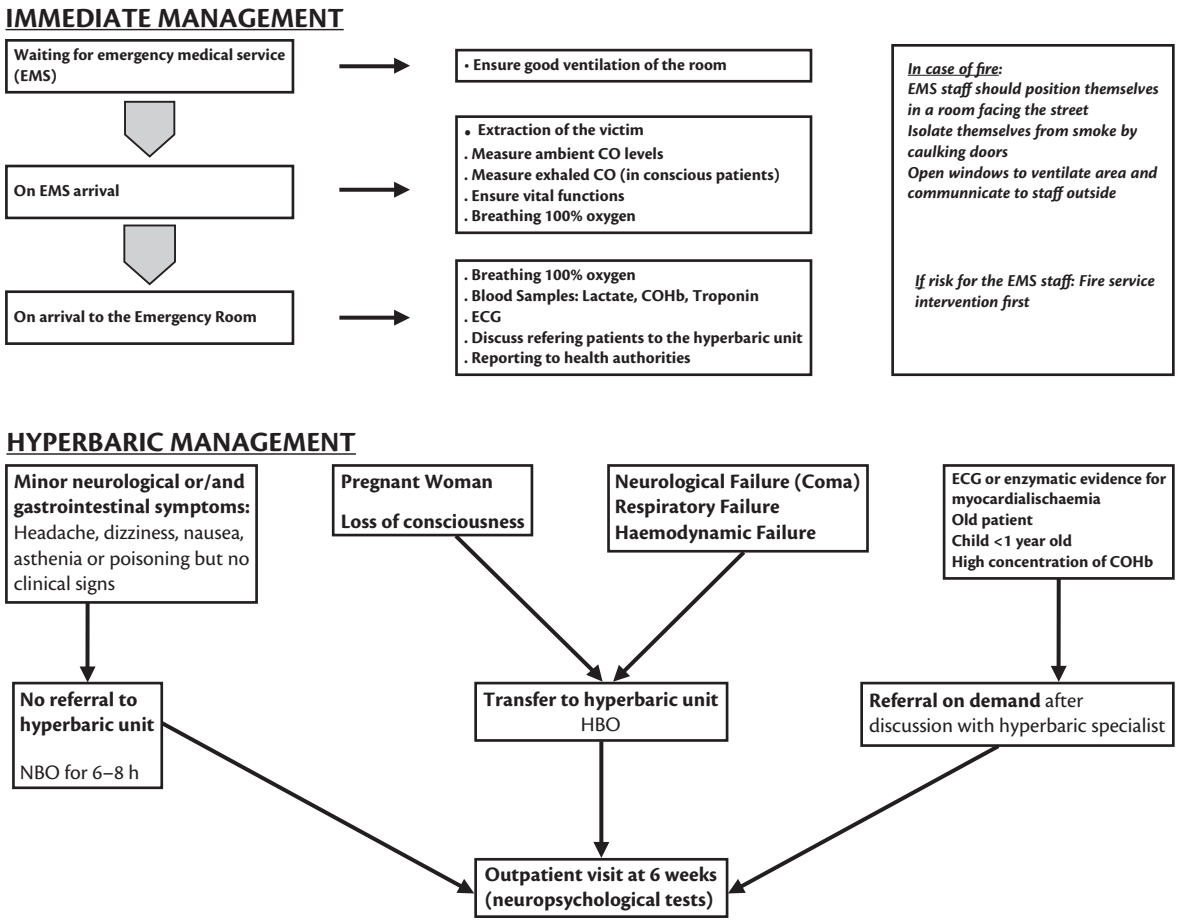


Fig. 328.1 Care and actual current indications of hyperbaric treatment for victims of CO poisoning.
CO, carbon monoxide; COHb, carboxyhaemoglobin; ECG, electrocardiogram; HBO, hyperbaric oxygen therapy; NBO, normobaric oxygen therapy.

Table 328.3 Randomized controlled trials on hyberbaric oxygen therapy (HBO) versus normobaric oxygen therapy (NBO)

Reference	Methods	*n*	Participants	Intervention	Outcomes	Effect
[5]	Randomized open label	343	◆ Adults ◆ Pure CO poisoning ◆ Who did not lose consciousness	**HBO**: 2-hour session, 1-hour plateau pressure 2.0 ATA **NBO**:100% O_2 for 6 hours	Self-assessment questionnaire and physical at 1 month	Neurological sequels 32% treated with NBO versus 32% with HBO
[17]	Randomized open label	65	Patients with no history of loss of consciousness or cardiac instability	**HBO**: 2.8 ATA for 30 minutes, then 2ATA for 90 minutes **NBO**: 100% O_2	Delayed neurological sequelae	Neurological sequels 23% treated with NBO versus 0% with HBO
[15]	Randomized open label	575	Patients with no history of loss of consciousness or cardiac instability	**HBO**: 2.5 ATA for 90 minutes. **NBO**: 100% O_2 for 12 hours	Neuropsychological testing at 1 month	Neurological sequels 26% treated with NBO versus 23% HBO
[16]	Randomized, double blind	191	All patients with CO poisoning regardless of severity	**HBO**: 2.8ATA for 60 minutes daily for 3 days. **NBO**: 100% O_2 for 3 days	Symptom after 1 month	Neurological sequels 58% treated with NBO versus 65% HBO
[18]	Randomized double blind	152	All patients with CO poisoning regardless of severity	**HBO**: 1 session 3ATA (1 hour) + 2ATA(1 hour) follow by 2 sessions 2ATA (2 hours) **NBO**: 100% O_2 for 24 hours	Neuropsychological tests at 6 weeks	Neurological sequels 46% treated with NBO versus 25% HBO

(*continued*)

Table 328.3 Continued

Reference	Methods	*n*	Participants	Intervention	Outcomes	Effect
[11]	Randomized, open label	179	◆ Adults ◆ Pure CO poisoning ◆ Transient loss of consciousness	**HBO**: 2-hour session, 1-hour plateau pressure 2.0 ATA **NBO**: 100% O_2 for 6 hours	1-month self-assessment questionnaire and a blind physical examination	Neurological sequels 59% treated with NBO versus 62% with HBO
		206	◆ Adults. ◆ Pure CO poisoning ◆ Coma	1 session of HBO 2-hour session, 1-hour plateau pressure 2.0 ATA 2 sessions of HBO		Neurological sequels 32% treated with 1 HBO session versus 53% with 2 HBO sessions

Data from various sources (see references).

were major differences between trials with regard to the investigated populations (pure CO poisoning versus mixed population), to the practical modalities of HBO (different levels of pressure, different duration, and different number of dives), and to main outcome measures (complex neuropsychological testing versus more pragmatic evaluation). In practice, we recommend against the routine use of hyperbaric oxygen therapy in patients who did not lose consciousness and to perform one session of HBO in comatose patient (Fig. 328.1). Although there are no randomized trials evaluating HBO treatment in pregnant women or in infant, current guidelines recommend the use of HBO in these populations regardless of the clinical presentation. Indeed, it is thought that the toxicity of CO for the fetus and for young babies exceeds the potential toxicity of HBO.

References

1. Verrier A, Delaunay C, Coquet S, et al. (2010). Les intoxications au monoxyde de carbone survenues en France métropolitaine en 2007. *Bulletin epidemiologique hebdomadaire*, 1–5.
2. Hampson NB and Hauff NM. (2008). Risk factors for short-term mortality from CO poisoning treated with hyperbaric oxygen. *Critical Care Medicine*, **36**, 2523–7.
3. Goulon M, Barois A, Nouailhat F, Grosbuis S, Gajdos P, and Babinet P. (1971). Intoxications oxycarbonées et anoxie aigues par inhalation de gaz de charbon et d'hydrocarbures. *Revue du Praticien*, **21**, 2290–320.
4. Weaver LK. (2009). Clinical practice. CO poisoning. *New England Journal of Medicine*, **360**, 1217–25.
5. Raphael JC, Elkharrat D, Jars-Guincestre M-C, et al. (1989). Trial of normobaric and hyperbaric oxygen for acute CO intoxication. *Lancet*, **2**, 414–19.
6. Hampson NB, Dunn SL, and UHMCS/CDC CO Poisoning Surveillance Group. (2012). Symptoms of CO poisoning do not correlate with the initial carboxyhemoglobin level. *Undersea & Hyperbaric Medicine Journal*, **39**, 657–65.
7. Annane D, Chevret S, Jars-Guincestre C, et al. (2001). Prognostic factors in unintentional mild CO poisoning. *Intensive Care Medicine*, **27**(11), 1776–81.
8. Moon JM, Shin MH, and Chun BJ. (2011). The value of initial lactate in patients with CO intoxication: in the emergency department. *Human Experimental Toxicology*, **30**, 836–43.
9. Thom SR, Bhopale VM, and Fisher D. (2006). Hyperbaric oxygen reduces delayed immune-mediated neuropathology in experimental CO toxicity. *Toxicology and Applied Pharmacology*, **213**, 152–9.
10. Bunc M, Luzar B, Finderle Z, Suput D, and Brvar M. (2006). Immediate oxygen therapy prevents brain cell injury in CO poisoned rats without loss of consciousness. *Toxicology*, **225**, 138–41.
11. Annane D, Chadda K, Gajdos P, Jars-Guincestre MC, Chevret S, and Raphael JC. (2011). Hyperbaric oxygen therapy for acute domestic CO poisoning: two randomized controlled trials. *Intensive Care Medicine*, **37**, 486–92.
12. Ducasse JL, Celsis P, and Marc-Vergnes JP. (1995). Non-comatose patients with acute CO poisoning: hyperbaric or normobaric oxygenation? *Undersea & Hyperbaric Medicine*, **22**, 9–15.
13. Gao CJ, Ge H, Zhao LM, et al. (2002). Combined therapy with hyperbaric oxygen and antiplatelet aggregation agent for the prevention of delayed encephalopathy after acute CO poisoning. *Chinese Journal of Nautical Medicine and Hyperbaric Medicine*, **9**(3), 142–4.
14. Hampson NB, Dunford RG, Ross DE, and Wreford-Brown CE. (2006). A prospective, randomized clinical trial comparing two hyperbaric treatment protocols for CO poisoning. *Undersea & Hyperbaric Medicine*, **33**(1), 27–32.
15. Mathieu D, Wattel F, Mathieu-Nolf M, et al. (1996). Randomized prospective study comparing the effect of HBO vs. 12 hours NBO in noncomatose CO-poisoned patients: results of the preliminary analysis. *Undersea & Hyperbaric Medicine*, **23**(Suppl. 7) (abstract).
16. Scheinkestel CD, Bailey M, Myles PS, et al. (1999). Hyperbaric or normobaric oxygen for acute CO poisoning: a randomized controlled clinical trial. *Medical Journal of Australia*, **170**, 203–10.
17. Thom SR, Taber RL, Mendiguren II, Clark JM, Hardy KR, and Fisher AB. (1995). Delayed neurologic sequelae after CO poisoning: prevention by treatment with hyperbaric oxygen. *Annals of Emergency Medicine*, **25**, 474–80.
18. Weaver LK, Hopkins RO, Chan KJ, et al. (2002). Hyperbaric oxygen for acute CO poisoning. *New England Journal of Medicine*, **347**(14), 1057–67.
19. Buckley NA, Juurlink DN, Isbister G, Bennett MH, and Lavonas EJ. (2011). Hyperbaric oxygen for CO poisoning. *Cochrane Database of Systematic Reviews*, **4**, CD002041.

CHAPTER 329

Management of corrosive poisoning

Ram E. Rajagopalan

Key points

- Ingestion of corrosive agents in adults has a higher potential for adverse events than accidental ingestion in children.
- Significant airway injury, and oesophageal and gastric perforation are early concerns.
- Endoscopic grading of the injury predicts the frequency of complications.
- No medical therapy reduces the rate of complications.
- Enteral nutrition can be continued in most patients, and endoscopy can guide the choice of oral or enteral routes.

Introduction

A corrosive is a substance that causes chemical damage to tissues by direct contact with them. Besides acids and alkalis, oxidizing, alkylating and dehydrating agents, phenols, halogens, and organic halides may be aetiological (Table 329.1). While some of these substances may have systemic effects as well, such effects are not a prerequisite to their toxicity on tissues. Although inhalational or cutaneous exposure to corrosives may also pose challenging clinical concerns, they will not be dealt with here.

Epidemiology

About 200,000 cases of corrosive ingestion are reported annually in the USA [1]. Caustic soda (sodium hydroxide), bleach (hypochlorite), household chemicals, including organic disinfectants (phenol) and acids are the commonest ingestants implicated. The majority of cases are accidental ingestions in children, which although declining in incidence in high-income countries, remain a significant concern in the developing world [2]. Fortunately, in most paediatric cases ingestions are of small volume, involve household chemicals that are of low concentration and seldom cause severe acute problems although long-term consequences related to strictures of the oesophagus are a serious concern in these children.

Although ingestion in adults constitutes a minority (<20%) of all corrosive ingestion, they are a greater cause for concern in the short term. These cases are invariably related to intentional consumption of large volumes of corrosive agents, which are usually of high concentration (industrial chemicals). As they are often co-ingested with alcohol or other toxins, initial management may be further complicated. It is estimated that 10% of all ingestions are severe enough to warrant medical treatment. Outcomes are best known only in patients with significant post-ingestion symptoms who require hospitalization [3]. Aspiration pneumonia (11%), respiratory failure (8%), and acute gastrointestinal haemorrhage (5%) are the three most common acute complications, with oesophageal strictures developing in nearly one-quarter of patients at around the second week after the ingestion. It is estimated that mortality in the short-term is ~10% in hospitalized adult patients in most parts of the world [4].

Mechanism of injury

The mechanism of tissue injury is dictated by the nature of the consumed corrosive. Alkali typically saponifies fat and solubilizes protein, resulting in liquefaction necrosis of affected tissue. Besides the generation of heat, collagen swelling, and thrombosis of the microvasculature, it results in a rapid progression of the injury that involves all layers of the digestive tract, especially at the sites that initially come in contact with the alkali, namely the oropharynx and oesophagus. Early oedema can significantly compromise the upper airway in these cases. The coagulative necrosis induced by acid ingestion appears more benign. Eschar formation may initially protect the underlying tissue from damage, but delayed loss of the eschar can cause significant bleeding or perforation of the gut. Although acid injuries are typically more superficial and have a tendency to spare the oesophagus, full thickness injury does occur and oesophageal lesions are seen in over one-half of all patients with acid ingestions. Ingestions of button batteries cause corrosive damage, mainly through electrolysis of tissue fluids and accumulation of hydroxide at the battery's negative pole [5]. Injury with hydrofluoric acid is initiated by the acidic (H^+) component, but after penetration of the tissues the dissociation of fluoride (F^-) ions perpetuates liquefactive necrosis and cellular dysfunction from the binding of Ca^{2+} and Mg^{2+}. The long-term sequels of corrosive ingestion are due to scar cicatrization and subsequent stricture formation in the affected segment of the alimentary tract.

In addition to the chemical properties of the ingestant, the extent of the injury can be influenced by a host of patient- and agent-specific factors [6]. Thus, solid particulate corrosive agents will cause localized deep burns in contrast to the diffuse involvement seen with liquids. The time of ingestion in relation to a meal is relevant as the food in the stomach could buffer the corrosive agent. Gastric transit times will influence the dwell time of the corrosive, and the severe gastric lesions created by acids is attributed to

Table 329.1 Common corrosive agents

Acids	Car battery fluid	Sulphuric acid
De-scalers	Hydrochloric acid	
Metal cleaners	Nitric acid	
Rust removers	Hydrofluoric acid	
Disinfectants	Phenol	
Alkali	Household cleaners	Ammonia-based
Disinfectants	Bleach (hypochlorite)	
Drain cleaners	Sodium hydroxide (caustic soda/lye)	
	Alkylating agents	Dimethyl sulphate
	Dehydrating agents	Phosphorus pentoxide, calcium oxide (quick lime), zinc chloride, elemental alkali metals
	Halogens	Elemental fluorine, chlorine, bromine, and iodine
	Organic halides	Acetyl chloride and benzyl chloroformate
	Oxidizers	Hydrogen peroxide

pyloric spasm and delayed gastric emptying caused by these agents. Although the volume of the ingestant and its concentration are obvious predictors of the extent of the damage produced by a corrosive, the importance of pH is debated. While the pH of the corrosive is relevant for strong acids and bases, it is often an inadequate correlate of the extent of tissue damage with weak agents. The titrable acid/alkali reserve (TAR; the amount of acid or alkali needed to neutralize the pH of a corrosive) has been proposed as an alternative measure, but also has been challenged in recent literature.

Clinical approach

Initial resuscitation

The initial management of the adult patient who has consumed a corrosive agent is primarily aimed at rapidly identifying life threats. Airway compromise is a significant concern, because supraglottic oedema can quickly ensue after the ingestion of corrosives. Any patient with significant injury to the oral or pharyngeal mucosa should be considered a risk. As the progression of the oedema is unpredictable, close observation and readiness for intubation of the airway is essential. In a patient with stridor, respiratory distress or depressed mentation, tracheal intubation is urgent. As oedema is likely to make the intubation difficult, the availability of fibre optic visualization can guarantee safety. The potential inability to intubate an oedematous airway after neuromuscular blockade should be considered when medications are chosen for induction of sedation and paralysis. Preparedness for the placement of a surgical airway can be lifesaving in difficult cases. Attempts at 'awake' nasotracheal intubations are very likely to be unsuccessful and have the potential to worsen the airway injury. In the patient without airway compromise, but with significant upper airway symptoms (drooling, dysphonia, hoarseness, and stridor) progression is unpredictable and close observation is essential. Most therapies attempting to minimize the oedema are extrapolated from the care of other forms of upper airway compromise (e.g. epiglottitis). Thus, the use of intravenous or aerosolized adrenaline, or of parenteral steroids has not been proven to reduce the rates of endotracheal intubation specifically in corrosive ingestion. Hypotension during the initial phases is usually related to hypovolaemia from haemorrhage, vomiting or third-space sequestration of fluids, and requires appropriate resuscitation with crystalloids.

Decontamination and dilution

Attempts to empty gastric contents by the induction of emesis or the placement of Ewald or nasogastric tubes are contraindicated in corrosive ingestion. Dilution or neutralization of the corrosive may generate heat and have no proven efficacy. Small volume dilution may be considered selectively very early (<30 minutes) after the ingestion of particulate corrosive agents. The risk of aspiration and gastrointestinal perforation must be considered in balance when attempting any of these procedures of unproven efficacy.

Primary clinical evaluation

After the initial stabilization, clinical, radiographic and endoscopic evaluations are performed mainly to identify the acute complications of corrosive ingestion (perforation and haemorrhage in the upper gastrointestinal tract), and to stratify patients by their risk of acute and long-term complications.

During the initial clinical examination, a complaint of chest or abdominal pain should raise suspicions of oesophageal and gastric perforation and ensuing mediastinitis and peritonitis. Haematemesis or malena may be seen with haemorrhage, which may be the initial presentation or occur at about 3 days after the ingestion after a disruption of eschar formed most typically after acid-induced injury. Subcutaneous emphysema and the Hamman's sign are characteristic of mediastinal air, while abdominal rigidity and rebound tenderness are seen with peritonitis. Radiographic confirmation of mediastinal leaks may be subtle ('continuous diaphragm sign') and small leaks from gastric perforation need not consistently manifest with subdiaphragmatic gas shadows. The use of water-soluble radiographic contrast may allow better identification of leaks. Immediate surgical intervention is warranted when a leak is identified.

Laboratory tests

Laboratory tests may not contribute significantly to identification or risk stratification. Though one small retrospective series [7] demonstrated a lower pH and larger base-deficit on the arterial blood gases of patients who developed surgical complications or who died, their value as independent markers is questionable. However, a WBC count >20,000 has been identified as an independent predictor of mortality after corrosive ingestion [8]. The existence of an anion gap or an osmolar gap could point in towards the existence of a co-ingestion. Hypocalcaemia is often profound in hydrofluoric acid ingestion.

Upper gastrointestinal endoscopy

The risk of early (perforation and haemorrhage) and late (cicatrization and obstruction) complications are logically proportional to the extent and depth of tissue damage. Direct evaluation of the magnitude of upper gastrointestinal injury by endoscopy is useful

in grading the severity and in triaging the patient with corrosive ingestion, besides facilitating appropriate decisions on nutritional support and in planning long-term care of the corrosive damage.

Patient selection

Patient selection for the performance of endoscopy is fairly logical. Asymptomatic patients who have no evidence of oral or airway damage do not need endoscopy. Likewise, on the other end of the spectrum, patients with identified perforation, mediastinitis or peritonitis will have no incremental value from an endoscopic evaluation as they are candidates for surgical management. Patients in whom symptoms may be inconsistent (children <6 years of age) or masked (unconscious patients) require endoscopy to grade the lesions. Endoscopy is also indicated for all symptomatic adult patients, those who have consumed large volumes of corrosives or who have ingested agents of high concentration.

Timing of the endoscopic study

There is some controversy about the timing of the endoscopic study. Very early evaluations, <6 hours after the ingestion, may not reveal the full extent of the corrosive injury. In the landmark study that developed the current grading of corrosive lesions [9], endoscopy was performed within 96 hours after the ingestion. As there are concerns that eschar destabilization, causing GI bleeding could occur by around the third day, the commonest practice is to perform the evaluation on day 1 or 2. Though it has been asserted that a relook endoscopy on day 5 allows better assessment of the extent of damage, no formal supportive evidence is available.

Grading

Corrosive lesions in the gastrointestinal tract are typically graded using the Zargar score [9]. Using this scoring system (Table 329.2) the authors demonstrated that both the mortality and complication rates were tightly correlated with the depth and extent of oesophageal and gastric injury. Patients with lesions classified as Grades 0, 1, and 2a had no long-term complications, while cicatrization occurred in 71% of higher grades. All deaths occurred with grade 3a/3b injury. A recent retrospective series of 273 adult corrosive ingestions, confirms the prognostic validity of the Zargar score [3]. In one model predicting mortality after corrosive ingestion, age, a white blood cell count of >20,000, ingestion of strong acid, the existence of an endoscopic 2b or 3a/3b lesions were independent predictors of death [8].

Table 329.2 Zargar Endoscopic Classification Scheme for corrosive mucosal injury

Grade	Definition
0	Normal mucosa
1	Hyperaemia of the mucosa
2A	Superficial ulcers, exudates, membranes, blisters, erosions, haemorrhages, and friability
2B	Grade 2A plus deep discrete or circumferential ulceration
3A	Small, scattered areas of necrosis
3B	Extensive necrosis

Reprinted from *Gastrointestinal Endoscopy*, **37**(2), Zargar SA et al., 'The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns', pp. 165–9. Copyright 1991, with permission from Elsevier.

Medications

There are no treatments of proven efficacy in reducing the progression or minimizing the complications of corrosive ingestion.

Corticosteroids

The use of corticosteroids to minimize complications is not supported by high quality evidence. In the only randomized control trial of systemic corticosteroids in this setting [10], no differences were noted in the development of oesophageal strictures or their progression in children with documented oesophageal injury who were initially given prednisolone parenterally (2 mg/kg), followed by oral prednisone for 3 weeks. Claims for the superiority of intralesional steroid injection are also not evidence-based.

Acid suppression

Though H2 blockers and proton pump inhibitors are traditionally used to attenuate the propagation of mucosal injury, only anecdotal support exists for their use in corrosive injuries.

Antibiotics

Antibiotics are indicated for established mediastinitis and peritonitis, but their use for prophylaxis is not based on reliable evidence.

Nutrition

Patients with grade 1 and 2a lesions on endoscopy can be initiated on oral feeds as soon as tolerated. The localized nature of grade 2b and 3a lesions can also permit nutrition via the enteral route, most often by the appropriate placement of a naso-enteral feeding tube. Nutritional support in grade 3b lesions can also be achieved enterally, but will require surgical placement of a feeding jejunostomy. Parenteral nutritional support is seldom required.

Referral for long-term nutritional support and management of oesophageal and gastric strictures should be appropriately handled at the time of discharge from the intensive care unit.

References

1. Bronstein AC, Spyker DA, Cantilena JR, et al. (2008). Annual Report of the American Association of Poison Control Centers National Poison Data System (NPDS): 25th Annual Report'. *Clinical Toxicology*, **46**, 927–1057.
2. Contini S, Swarray-Deen A, and Scarpignato C. (2009). Oesophageal corrosive injuries in children: a forgotten social and health challenge in developing countries. Bulletin of the World Health Organization **87**, 950–4.
3. Cheng HT, Cheng CL, Lin CH, et al. (2008). Caustic ingestion in adults: the role of endoscopic classification in predicting outcome. *BMC Gastroenterology*, **8**, 31.
4. Eddleston M. (2000). Patterns and problems of deliberate self-poisoning in the developing world. *Quarterly Journal of Medicine*, **93**, 715–31.
5. Litovitz T, Whitaker N, Clark L, White NC, and Marsolek M. Emerging battery-ingestion hazard: clinical implications. *Pediatrics*, **125**(6), 1168–77.
6. Osman M and Granger DN. (2008). Pathophysiology of caustic ingestion. In: Vincent J-L (ed.) *Yearbook of Intensive Care and Emergency Medicine*, pp. 171–8. Berlin: Springer-Verlag.
7. Cheng YJ and Kao EL. (2003). Arterial blood gas analysis in acute caustic ingestion injuries. *Surgery Today*, **33**, 483–5.

8. Rigo GP, Camellini L, Azzolini F, et al. (2002). What is the utility of selected clinical and endoscopic parameters in predicting the risk of death after caustic ingestion? *Endoscopy*, **34**, 304–10.
9. Zargar SA, Kochhar R, Mehta S, and Mehta SK. (1991). The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. *Gastrointestinal Endoscopy*, **37**, 165–9.
10. Anderson KD, Rouse TM, and Randolph JG. (1990). A controlled trial of corticosteroids in children with corrosive injury of the esophagus. New England Journal of Medicine, **323**, 637–40.

CHAPTER 330

Management of pesticide and agricultural chemical poisoning

Elspeth J. Hulse and Michael Eddleston

Key points

- Resuscitation, supportive care, and use of specific antidotes must precede decontamination.
- Aspiration of any pesticide and its solvents/surfactants can be lethal. Avoid through judicious management of the airway.
- Rapid use of atropine in patients with cholinergic features typical of organophosphorus (OP) or carbamate insecticide poisoning can be life-saving. Beware delayed recurrence of cholinergic features in patients in the intensive care unit.
- Airway obstruction and respiratory failure can occur on admission or after several days through paralysis caused by OP insecticides. Consider early intubation and ventilation for such patients.
- Supportive care is the mainstay of treatment for pesticide and agricultural chemical poisoning. In addition to atropine, other antidotes, such as methylthioninium chloride (methylene blue) and pralidoxime may be indicated for some pesticides.

Introduction

Agrochemicals are an extremely diverse group of chemicals, numbering in their thousands, with differing modes of toxicity and highly variable case fatality (from 0 to 43% in one large prospective case series) [1]. Pesticides cause at least 300,000 deaths every year, the majority following self-harm in rural Asia. The World Health Organization (WHO) now recognizes pesticide self-poisoning to be one of the most important means of suicide worldwide. Organophosphorus (OP) insecticides cause the greatest morbidity and mortality globally, although the most toxic OP insecticides are slowly being withdrawn from agricultural practice.

Most severe cases of poisoning occur after ingestion of concentrated agricultural liquid formulations. Highly toxic (WHO Class I) pesticides that have been diluted for use may cause occupational poisoning by inhalation or dermal exposure. Even the least toxic liquid pesticide may cause death, since they are co-formulated with solvents and surfactants that could cause severe chemical pneumonitis after aspiration. The effects of the pesticide or alcohol on consciousness may increase the risk of aspiration.

Diagnosis

Diagnosis of pesticide poisoning is largely clinical, combined with situational clues such as the smell of pesticides on patients' clothing. The large number of pesticides used in domestic and industrial agriculture makes identifying the particular pesticide involved difficult. In addition, patients will sometimes be exposed to more than one pesticide and co-ingest other toxins, e.g. alcohol.

Formal laboratory analysis of the pesticide using mass spectroscopy or chromatography is not available in a clinically useful time frame. However, a simple laboratory assay is available for paraquat in the urine that will confirm exposure. Cholinesterase assays may indicate OP or carbamate insecticide poisoning, but generally do not predict the course or outcome of poisoning.

Fortunately, case series with retrospective identification of the pesticide suggest that the history is often correct with the most clinically important pesticides producing clearly recognizable toxidromes (Table 330.1) [2–8]. Treatment is based on identifying the relevant toxidrome.

General management

Standard ICU management and investigations should be undertaken for all poisoned patients including routine blood tests, amylase, ABG, ECG and CXR. The pharmacokinetics and pharmacodynamics of pesticides once ingested can vary markedly depending on the combination of chemicals ingested, the pesticide's lipid solubility, enzyme reactivation, co-ingested toxicants (e.g. alcohol), extent of decontamination, and organ dysfunction.

Staff protection

Where possible, staff should wear standard universal precaution attire: gloves, gown, and eye protection. There is no evidence that nosocomial poisoning is common after agrochemical poisoning [9]. Patients should be cared for in well-ventilated rooms since the solvents may be highly volatile.

Airway, oxygen, and atropine

The airway and respiratory tract may have copious secretions that need suctioning and drying with atropine. Secretions are produced with many pesticides, but can be severe after OP and carbamate poisoning.

High flow oxygen should be administered as soon as possible. However, there is no good quality evidence to indicate that atropine should be withheld if oxygen is not available. Avoid oxygen in mild to moderate paraquat poisoning to reduce the production of superoxide radicals [7].

Swelling of the airway can be caused by aluminium phosphide and methyl bromide fumes. Some pesticides, particularly paraquat,

Table 330.1 Toxidromes for pesticide poisoning with management and complications

Toxidrome	Features	Pesticides	Pathophysiology	Antidotes and treatment	Complications
Cholinergic	**Muscarinic**: miosis, salivation, diarrhoea, vomiting, urination, bronchospasm, bronchorrhoea, bradycardia, hypotension **Nicotinic**: sweating, muscle weakness, fasiculations, flaccid paralysis (sometimes mydriasis, tachycardia, hypertension) **CNS**: coma, respiratory failure	◆ OP insecticides, e.g. dimethoate, parathion ◆ Carbamates, e.g. aldicarb	◆ Inhibition of AChE in blood, CNS, and NMJ causes excess cholinergic stimulation, pulmonary oedema, respiratory failure, and distributive shock ◆ Many patients need intubation and mechanical ventilation (40% in one study [2]); of these many will die (>50% in two studies [2,3])	◆ iv Atropine (or glycopyrrolate) and oximes (see general management) ◆ iv Benzodiazepenes	◆ NMJ dysfunction that necessitates mechanical ventilation, often for several weeks. May occur after the acute cholinergic syndrome settles, also called intermediate syndrome [4] ◆ OP-induced polyneuropathy
Seizures	Single or recurrent seizures in absence of other features	**Organochlorines**: e.g. endosulphan, lindane **Phenylpyrazoles**: e.g. fipronil **Methyl bromide**	Organochlorines and phenylpyrazoles inhibit GABA-A receptors resulting in neuronal hyperactivity	◆ Diazepam 10–20 mg iv, repeated as necessary. Do not use phenytoin as a second line agent, but if seizures persist use a barbiturate infusion [5] ◆ Check glucose levels and consider thiamine if appropriate	Hyperthermia, metabolic acidosis, rhabdomyolysis, hepatic toxicity
Methaemoglobinaemia	◆ Cyanosis ◆ Blood appears brown on inspection after phlebotomy	**Aromatic amines/nitros**: e.g. chloroaniline **Metals**: e.g. copper sulphate **Herbicides**: e.g. propanil, hydrazines **Oxadiazines**: e.g. indoxacarb	◆ Primary toxic effect is creation of metHb by compounds oxidizing iron in haemoglobin to metHb ◆ Secondary toxic effect is metHb causing systemic hypoxia due to reduced oxygen delivery	◆ Methylene blue 1% 1–2 mg/kg iv if symptomatic with metHb >20% or metHb >30% without symptoms ◆ Copper chelation therapy may be of some (unproven) benefit	◆ Intravascular haemolysis ◆ High metHb concentrations (>70-80%) may be fatal from cellular hypoxia, coma, and seizures ◆ Copper is corrosive and may cause GI haemorrhage
Nicotinic	Respiratory failure and coma in moderate-severe poisoning	**Neonicotinoid**: e.g. imidacloprid **Nicotine**	◆ Relatively selective nicotine agonist ◆ Neonicotinoids have high selectivity for insect receptors producing low human toxicity ◆ Nicotine is highly toxic to humans	◆ Supportive care ◆ Atropine for any muscarinic symptoms that occur	

(*continued*)

Table 330.1 Continued

Toxidrome	Features	Pesticides	Pathophysiology	Antidotes and treatment	Complications
Metabolic acidosis		**Acaricides**: e.g. fenpyroximate. **Triazenes**: e.g. atrazine.	Inhibition of the electron transport chain and/or oxidative phosphorylation results in poor oxygen utilization and lactic acidosis	◆ 8.4% sodium bicarbonate iv 50 mL or haemodialysis may improve acidosis. ◆ Acetylcysteine (antioxidant).	Coma, convulsions, dysrhythmias, hypotension
Coma (non-cholinergic)		**Avermectin acaricides**: e.g. abamectin. **Chloralose** (rodenticide) **Chlorophenoxy herbicides**: e.g. MCPA.	◆ Inhibitory and excitatory CNS effects via GABA receptors ◆ Chlorophenoxy poisoning may involve uncoupling of oxidative phosphorylation	◆ Supportive care for coma and hypotension. ◆ Chlorophenoxy poisoning may benefit from urinary alkalinization and haemodialysis [6]	◆ Respiratory failure, hypotension. ◆ Hyperthermia, rhabdomyolysis, hyperventilation.
Multi-organ failure		**Quaternary ammonium herbicides**: e.g. paraquat **Aluminium phosphide** (fumigant) **Glyphosphate surfactant**: e.g. Agri-dex	◆ Paraquat produces free radicals, which induce cellular toxicity and multi-organ failure ◆ Aluminium phosphide produces phosphine gas on contact with water in the stomach. Phosphine inhibits mitochondrial oxidative phosphorylation. ◆ Glyphosphate has an unknown mechanism.	◆ Avoid unnecessary oxygen therapy. Early charcoal haemoperfusion may benefit paraquat poisoning [7]. ◆ No proven efficacious therapy for aluminium phosphide poisoning—consider gastric lavage with 1:10,000 potassium permanganate and sodium bicarbonate 8.4%. Magnesium for cardiotoxicity [8]. ◆ Haemodialysis for glyphosphate poisoning.	◆ If patients survive early toxicity, death may occur from pulmonary alveolitis and fibrosis (from 1–2 weeks). ◆ Cardiotoxicity and shock in aluminiium phosphide poisoning ◆ Respiratory failure, cardiotoxicity, acidosis, hyperkalaemia in glyphosphate poisoning
Aspiration		All chemicals, plus hydrocarbon solvents, food particles, gastric contents	Chemical pneumonitis, which may progress to pneumonia and/or ARDS	◆ Avoidance of aspiration. ◆ Careful, timely airway management.	ARDS, pneumonia

CNS, central nervous system; NMJ, neuromuscular junction; AChE, acetylcholinesterase; metHb, methaemoglobinaemia; ARDS, acute respiratory distress syndrome.

Data from various sources (see references).

will injure the oropharynx and oesophagus, causing absolute dysphagia. Reflux of pesticide and solvent into the oropharynx around the endotracheal tube during long-term ventilation has caused strictures.

Atropine

- Early administration of atropine will reverse the muscarinic features of OP or carbamate poisoning. Characteristic features of cholinergic poisoning that should trigger atropine administration include pinpoint pupils and excess salivation and sweating [10]. Severely-poisoned patients will exhibit bradypnoea and gasping.
- After noting the pulse rate, blood pressure (BP), pupil size, and presence of pulmonary crackles, administer atropine 0.6 mg (for mild poisoning) or 3 mg (for severe poisoning) by rapid intravenous (iv) bolus. If there has been no improvement in observations after 5 minutes, administer double the previous dose of atropine.
- Continue to double the dose until the observations begin to show a clear improvement. Aim for adequate cardiorespiratory function: pulse rate >80 beats/min, systolic BP >80mmHg, and dry chest. Once nearly achieved, smaller doses of atropine can be used. Pupil dilatation may be delayed and should not be used to titrate atropine.
- Once the patient is stable ('atropinized'), set up an atropine infusion giving 10–20% of the dose used to stabilise the patient [10]. Titrate against signs of inadequate atropinization (reversal of cholinergic features) versus over-atropinization–tachycardia, agitation, confusion, hyperthermia, absent bowel sounds, and urinary retention. If the patient becomes atropine toxic, stop the infusion for 30–60 minutes, then restart at a lower rate.
- In one study, an average of 23 mg atropine (range 1–75 mg) was required to atropinize patients with moderate–severe OP poisoning [11]. A recent RCT showed that this approach to giving atropine benefitted patients [12].

Intubation and ventilation

Many poisoned patients will require non-invasive airway support. Severely-poisoned patients, in particular those with OP/carbamate poisoning, will often require mechanical ventilation (Table 330.1), sometimes for several weeks due to neuromuscular junction (NMJ) dysfunction. Intermittent mandatory ventilation (IMV) with continuous positive airways pressure (CPAP) maintains the patient's own respiratory pattern which can improve ventilator weaning and patient compliance [13]. Indications for intubation and ventilation are listed in Box 330.1.

Close observation of recently extubated and non-intubated patients is vitally important to detect:

- The onset of a repeat cholinergic crisis that requires further atropine.
- The onset of proximal muscle weakness (or intermediate syndrome) that may require intubation (or re-intubation) and ventilation.

Assessing whether a patient can lift their head off the bed against minimal force will pick up early signs. Tidal or minute volume should then be checked at least every 4 hours to determine whether respiratory paralysis is imminent [10].

Box 330.1 Indications for intubation and ventilation for pesticide poisonings

- Excessive secretions not controlled with atropine.
- Depressed consciousness GCS ≤ 13 [19].
- Vomiting with altered GCS.
- Uncontrolled seizures.
- Apnoea/hypoventilation:
  - Tidal volume < 5 mL/kg.
- Respiratory acidosis pH < 7.35.
- $PaCO_2$ > 50–55 mmHg (6.5 kPa).
- PaO_2 < 60 mmHg (8 kPa) on FiO_2 0.6.
- Exhaustion and cyanosis due to respiratory muscle paralysis.

GCS, Glasgow coma score.

Data from Eddleston M et al., 'Management of acute organophosphorus pesticide poisoning', *The Lancet*, 2008, **371**(9612), pp. 597–607.

Circulation

Severe pesticide poisoning can cause distributive and cardiogenic shock requiring invasive monitoring, iv fluids, vasopressors, and inotropes. Aim for an adequate blood pressure >80 mmHg with urine output >0.5 mL/kg/hour.

Drugs and antidotes for OP poisoning

- Oximes are drugs that reactivate inhibited acetylcholinesterase, reducing OP toxicity. However, a recent Cochrane review found no clear benefit from their use [14]. Administer pralidoxime 1–2 g (or obidoxime 250 mg) iv into a separate cannulae over 30 minutes to patients who require atropine in an ICU environment [15]. If there is improvement, administer further doses of pralidoxime every 6–8 hours, or obidoxime 750 mg/24 hours, for up to 48 hours.
- OP poisoned patients may have increased sensitivity to both non-depolarizing muscle relaxants (NDMRs) and depolarizing muscle relaxants (suxamethonium), and in these cases reduced doses of NDMRs for intubation should be used if required [16].

Decontamination

Topical decontamination of the patient involves removing and bagging their clothing in a well-ventilated area, and washing their body with soap and water.

Administration of multiple dose-activated charcoal (50 g every 4 hours for six doses) by the oral/nasogastric route has marginal proven benefit [17]. Patients who present early to hospital can have gastric lavage within 60 minutes of poisoning via an NG tube, except for corrosives such as paraquat [7] or copper sulphate, which increase the risk of oesophageal perforation.

Criteria for ICU admission

Many grading systems to determine the severity of OP poisoning and ICU requirement exist, but none have been prospectively validated in an independent cohort. In essence, if a patient

has consumed a large amount of pesticide, and has early respiratory signs and altered consciousness, they should be admitted to ICU [18]. In one large prospective study of mixed OP pesticide poisoning, a GCS≤ 13 gave a 37% case fatality rate for OP poisoning with an area under the receiver operator curve of 0.84 [19].

References

1. Dawson AH, Eddleston M, Senarathna L, et al. (2010). Acute human lethal toxicity of agricultural pesticides: a prospective cohort study. *PLoS Medicine*, **7**(10), e1000357.
2. Tsao TCY, Juang YC, Lan RS, Shieh WB, and Lee CH. (1990). Respiratory failure of acute organophosphate and carbamate poisoning. *Chest*, **98**(3), 631–6.
3. Eddleston M, Mohamed F, Davies JOJ, et al. (2006). Respiratory failure in acute organophosphorus pesticide self-poisoning. *Quarterly Journal of Medicine*, **99**(8), 513–22.
4. Senanayake N and Karalliedde L. (1987). Neurotoxic effects of organophosphorus insecticides—an intermediate syndrome. *New England Journal of Medicine*, **316**(13), 761–3.
5. Shah ASV and Eddleston M. (2010). Should phenytoin or barbiturates be used as second-line anticonvulsant therapy for toxicological seizures? *Clinical Toxicology*, **48**(8), 800–5.
6. Bradberry SM, Proudfoot AT, and Vale JA. (2004). Poisoning due to chlorophenoxy herbicides. *Toxicological Reviews*, **23**(2), 65–73.
7. Gawarammana IB and Buckley NA. (2011). Medical management of paraquat ingestion. *British Journal of Clinical Pharmacology*, **72**(5), 745–57.
8. Bumbrah GS, Krishan K, Kanchan T, Sharma M, and Sodhi GS. (2012). Phosphide poisoning: a review of literature. *Forensic Science International*, **214**(1–3), 1–6.
9. Little M, Murray L, Poison Information Centres of New South Wales WA, Queensland NZ, and the Australian Capital T. (2004). Consensus statement: risk of nosocomial organophosphate poisoning in emergency departments. *Emergency Medicine Australasia*, **16**(5–6), 456–8.
10. Eddleston M, Dawson A, Karalliedde L, et al. (2004). Early management after self-poisoning with an organophosphorus or carbamate pesticide—a treatment protocol for junior doctors. *Critical Care*, **8**(6), R391–R7.
11. Eddleston M, Buckley NA, Checketts H, et al. (2004). Speed of initial atropinisation in significant organophosphorus pesticide poisoning—a systematic comparison of recommended regimens. *Journal of Toxicology: Clinical Toxicology*, **42**(6), 865–75.
12. Abedin MJ, Sayeed AA, Basher A, Maude RJ, Hoque G, and Faiz MA. (2012). Open-label randomized clinical trial of atropine bolus injection versus incremental boluses plus infusion for organophosphate poisoning in Bangladesh. *Journal of Medical Toxicology*, **8**(2), 108–17.
13. Dutoit PW, Muller FO, Vantonder WM, and Ungerer MJ. (1981). Experience with the Intensive-care management of organophosphate insecticide poisoning. *South African Medical Journal*, **60**(6), 227–9.
14. Buckley NA, Eddleston M, Li Y, Bevan M, and Robertson J. (2011). Oximes for acute organophosphate pesticide poisoning. *Cochrane Database of Systematic Reviews* (online), **2**, CD005085.
15. Eddleston M, Eyer P, Worek F, et al. (2009). Pralidoxime in acute organophosphorus insecticide poisoning: a randomised controlled trial. *PLoS Medicine*, **6**(6), e1000104.
16. Karalliedde L. (1999). Organophosphorus poisoning and anaesthesia. *Anaesthesia*, **54**(11), 1073–88.
17. Eddleston M, Juszczak E, Buckley NA, et al. (2008). Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *Lancet*, **371**(9612), 579–87.
18. Bardin PG and Vaneeden SF. (1990). Organophosphate poisoning—grading the severity and comparing treatment between atropine and glycopyrolate. *Critical Care Medicine*, **18**(9), 956–60.
19. Davies JOJ, Eddleston M, and Buckley NA. (2008). Predicting outcome in acute organophosphorus poisoning with a poison severity score or the Glasgow coma scale. *Quarterly Journal of Medicine*, **101**(5), 371–9.

CHAPTER 331

Management of radiation poisoning

Francis Chin Kuok Choon and Phua Dong Haur

Key points

- Decontamination by removing clothes, washing of skin, and removal of debris can remove up to 90% of external contaminated radiation.
- Treatment of acute life-threatening injuries takes priority over treatment of radiation poisoning.
- Triage of severely-exposed patients can give an indication of dose and severity of radiation dose absorbed. Survival is related to dose absorbed.
- Early gastric lavage and specific antidotes for ingested radiation poisoning should be used with caution.
- Death is mainly due to infections and haemorrhage. Treatment of ARS is supportive with use of antibiotics, colony stimulating factors, blood products and stem cell transplants.

Definitions and principles in radiation poisoning

Exposure

This occurs when someone is near to a radioactive source and irradiated. Large acute doses to the whole body or to parts of the body can cause radiation injury or poisoning. There are specific acute radiation syndromes depending on the dose and body parts exposed. A person who is exposed may not be contaminated or continuously radiated after removal from the site/source of radioactivity.

Contamination

This occurs internally or externally when radioactive material is deposited on the clothes, skin, or open wound, ingested or inhaled. A person who is contaminated must be decontaminated as soon as possible, but without delaying critical care to the acute injuries. A contaminated person may continue to be irradiated by contaminants after removal from the site/source of radioactivity.

Radiation

Radiation can be detected by specialized equipment and this is the only way to confirm its presence. Physicists may be able to identify the nature of the radioactive source, if it is a pure source, from the signature of the compound. It may be alpha particles, beta sources, gamma photons, or neutrons.

Absorbed dose

This is the quantity of radiation energy absorbed. The unit of dose is Gray (Gy). An older unit is rad (radiation absorbed dose), 1Gy = 100rad. Dose rate is dose of radiation per unit time. Equivalent dose adjusts for different biological effects caused by the difference in potency of different types of radiation using a quality factor. Effective dose is quantity derived from International Commission of Radiological Protection (ICRP) and is a calculated dose after multiplying various organ weighting factors [1]. The unit of effective dose is Sievert (Sv), although an older unit (Roentgen equivalent man, rem) is still in use. So, because X-rays or gamma radiation has a quality factor = 1, absorbed dose in rads times quality factor yields rem:

$$100\,\text{rad} = 100\,\text{rem} = 100\,\text{cGy} = 1\,\text{Gy} = 1\,\text{Sv} \qquad \text{[eqn 1]}$$

Route of radiation poisoning

Sources of radiation poisoning and relevant isotopes are listed in Box 331.1. The route of poisoning can be internal poisoning by aerosol inhalation or ingestion of radioactive particulate matter, or by direct contamination on skin. Patients can also be exposed by accidental irradiation and not be continually exposed if no radioactive material is involved. Internal poisoning is particularly difficult to treat because it is difficult to detect and diagnose. Short-range acting radiation, such as alpha and beta radiation, is shielded by body and the greatest dose is absorbed by the body internally. Long-range acting gamma radiation is easier to detect using external detectors and less dose will be absorbed in the body.

Hospital response, decontamination, and protection of staff

Protection of staff relies on three principles of time, distance, and shielding. Reducing the time of exposure can be achieved with appropriate staff rostering and rotation. There is an annual legal limit for radiation workers and members of the public. For the UK and USA, the annual limit for radiation workers is 20 mSv and 50 mSv, respectively, and for both countries the limit for members of the general public is 1 mSv [2,3]. Pregnant women must avoid working in situations of potential exposure and radiation contaminated areas.

Box 331.1 Types of sources of poisoning

Radiation related to Nuclear Fuel Cycle

- **Mining and conversion**: U-235 and daughter products, Rn-222 and daughter products, and U-238 and daughter products.
- **Enrichment**: enriched U-235 and depleted U-238 waste.
- **Fuel fabrication**: U-235 and daughter products, Rn and daughter products, isotopes of plutonium.
- **Reactor cycle**: in addition radioactive gases (H, isotopes of xenon), solids (Rb, isotopes of strontium, isotopes of iodine, I, isotopes of Cs, neutron activation products Cr, Nitrogen, Co, Mg.
- **Nuclear waste**: U and daughter products, Rn and daughter products, isotopes of plutonium, fission by-products- Cs, I.

Sources related to medical diagnosis and therapy

Isotopes used in nuclear medicine diagnostic imaging and therapy (mTc, I), radiation oncology (Co-60, Cs-137, Ir-192, I-131, I-125, Ra-116, P-32, isotopes in biomedical research (I-125, P-32, H-3, S-35, C-14).

Sources of radiation in industry

Naturally-occurring radioisotopes H-3, C-14, Cl-36, Pb-210. Engineering, soil, pipe analysis, food irradiation, smoke detectors (Co-57,Fe57, Co-60, Kr-85, Br-82, Sr-90, Ce-144, Cs-137, Am-241).

Sources of radiation in the military

Components in various military equipment (H-3, Ni-63, Cs-137, Ra-226, Am-241, depleted U-235).

Radiation Sources in Nature

Rn-220 and daughter products, K-40, C-14, isotopes of uranium and daughter products. U-235,U-238, Th-232.

Decontamination should take place in an appropriate area of the emergency department and, ideally, only maximally-decontaminated patients should be transferred to the clean critical care or treatment area. Physicists with specialized detectors can advise if there is risk of exposure for the staff. Radioactive biological waste and effluent must be appropriately handled according to national regulatory guidelines. Patients with inhaled or ingested radioactive material usually do not pose a threat to staff because the radioactive source may have a short half-life or short effective radiation distance. Patients may need to be nursed and managed in specialized wards with radiation protection in place, especially if patients have been poisoned with a long-acting γ source and radiation can be detected outside the patient.

Increasing the distance reduces the radiation intensity significantly because of the inverse square law, which means that the radiation exposure is decreased four-fold when the distance from the source is doubled. Avoid handling radioactive sources directly with finger tips, especially during wound debridement. Use forceps or tongs and dispose of radioactive debris into appropriately shielded containers.

Depending on the radioactive sources (and on the recommendation of physicists), lead shielding may or may not be appropriate. Ingested beta sources require only simple paper gown and gloves to stop the short-acting beta radiation, even if it is excreted into blood, urine, sweat, and faeces. Generally, for ease of nursing or if lead gowns are in short supply, it may be more effective to tend to the needs of the patients quickly, and rely on reducing the time and increasing the distance, than to be encumbered by a lead gown.

Hospitals should activate their contingency radiation management protocols and alert the necessary national and international regulatory authorities, especially in mass casualty situations, seek appropriate advice from expert physicists and request the specialized equipment necessary to monitor and detect all the different types of radiation sources. Staff should be issued with personal radiation dose monitors if they are working in a designated radiation environment [4].

Psychological management of the patients, staff and members of public, including the worried well, is important. Counsellors and psychologists should be available to patients and the staff. Dissemination of appropriate information about the often inconsequential effects of minor exposure to radiation will allay fears and prevent mass panic, which may swamp the hospital system. It is important to differentiate true symptoms from psychogenic symptoms such as nausea, headaches, and episodic vomiting.

Triage

After decontamination down to a dose of twice background level, plus securing the airway, breathing, and circulation, the patient can be triaged. A full history of where and how long patients have been exposed in a particular place, a history of recurrent vomiting, or skin erythema may suggest a significant dose. Recognition of acute radiation syndrome (ARS) and differentiation from thermal injuries is important. Whole body dose monitoring with an appropriate monitoring device is helpful with contaminated patients, and doses around the nose and mouth may suggest ingestion or inhalation of a radioactive source [5]. Severity and type of symptoms is determined by the dose absorbed. Dose determination should be estimated with the Andrews lymphocyte nomogram (Fig. 331.1) for high risk patients.

Patients with psychogenic symptoms or <1 Gy whole body doses can be managed safely as outpatients with serial monitoring and will eventually recover. Those with 1–10 Gy whole body doses should be admitted for intensive treatment in a tertiary hospital environment equipped to handle bone marrow transplants.

Acute radiation syndrome

The severity of symptoms depends on the dose absorbed, and body area or system irradiated. Most common clinical situations involve radiation burns or an accidental exposure situation. If there is whole body irradiation, the symptoms and signs depend on the dose. ARS usually start with a prodromal stage of mild symptoms of nausea, vomiting, and skin erythema, followed by a delayed latent

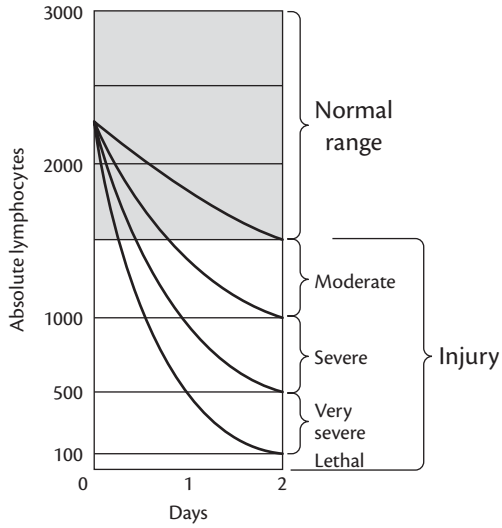


Fig. 331.1 Andrews lymphocyte nomogram.
Andrews GA et al., 'The Importance of Dosimetry to Medical Management of Persons Exposed to High Levels of Radiation'. In: *Personal Dosimetry for Radiation Accidents*. IAEA Vienna 1965. Reproduced courtesy of the IAEA.

stage, before manifesting as the full ARS symptoms [6]. Classically, ARS is a constellation of haemopoetic, gastrointestinal, and cardiovascular/central nervous system plus cutaneous radiation injury depending on the dose received. Those receiving whole body doses of 1–5 Gy may recover easily with appropriate medical management. Those with whole body doses of 6–10 Gy may survive with intensive management. Those patients with whole body doses of >10 Gy seldom survive [7].

Treatment of specific syndromes

Bone marrow

Haematopoietic syndrome occurs from exposure above 0.7–1.0 Gy and the prodromal stage is manifest by anorexia, nausea, and vomiting within a few hours up to 2 days after exposure. Stem cells in the bone marrow are acutely sensitive to radiation and start to die, although the patient can be manifestly well in the latent phase, which can last 1–2 weeks. The white cells fall first, followed by platelets and haemoglobin count. Patients will exhibit a manifest illness stage in 4–6 weeks with anorexia, fever, lethargy, and serial blood using Andrews Lymphocyte Nomogram (Fig. 331.1) can track the dose received and gauge the severity of the haematopoietic syndrome and subsequent improvement and recovery [8]. Blood in EDTA tubes for lymphocyte chromosome analysis can be sent to specialist laboratories for more precise dose absorbed estimation.

Management by haematologists experienced in stem cell transplants will increase survival. Death is primarily due to infection and haemorrhage. Consider appropriate GCSF/GMCSF and blood products infusion (Table 331.1), as well as antibiotic cover for symptomatic supportive care and barrier nursing to prevent infection [9]. Survival decreases with increasing dose and death may follow in a few weeks to months after exposure. Lethal whole body dose for an average individual is about 4 Sv. The lethal dose necessary to kill 50% of an exposed population in 60 days is about 2.5–5 Sv (250–500 rads).

Gastrointestinal

Symptoms are similar in the prodromal stage, with nausea, vomiting, and anorexia, in addition to abdominal pain, mild cramps, and diarrhoea, which may occur within a few hours up to 2 days after exposure. Doses causing gastrointestinal symptoms start from an acute dose of 6 Gy and above. Stem cells in the intestinal crypt base lining the gastrointestinal tract will die if the irradiated dose is more than 10 Gy in a single session. The patient may be well after the prodromal stage because mature gut cells are still alive and functioning. Manifest symptoms do not occur until 1–2 weeks after the death of the mature gut cells, which are not replaced by new cells generated by the stem cells. Patient will have severe cramps, watery diarrhoea with bloody mucous discharge, fever, dehydration, electrolyte imbalance, and death occurs within 2 weeks unless the patient is supported with total parenteral nutrition. Psychological counselling with a psychiatrist may be necessary for those with acutely toxic dose irradiation (>10 Gy) to the gut, while the patient is still in the acute to latent phase, because there is no curative treatment for symptoms that follow.

Cardiovascular/central nervous system

This syndrome occurs in patients with very high doses of exposure of 20–50 Gy and is characterized by nausea, vomiting, acute confusion, encephalopathy, cardiac arrhythmia, watery diarrhoea, abdominal cramps, and loss of consciousness [10]. Onset is rapid within minutes of exposure for these high doses and death occurs rapidly within a week of exposure. Typically, these high doses have only been seen in nuclear accidents, Chernobyl firefighters, and rescue workers in nuclear cleaning operations who are unwittingly

Table 331.1 Blood products and white cell stimulation

Agent	Dosage adults	Precautions
Epoetin alpha or pack red cells	150 U/kg/dose	◆ Sickle cell disease, ARDS ◆ Bone pain may result ◆ Discontinue if pulmonary infiltrates develop
GCSF or filgrastim	5 μg/kg/day till absolute neutrophil count >1000	
PEGylated G-CSF or pegfilgrastim	6 mg/day	
GM-CSF or sargamostin (leukine)	250 μg/m^2/day until absolute neutrophil count >1000	
Apheresis-derived platelets	Replacement of platelets	Maintain platelet at normal range

Table 331.2 Antidotes for internal contamination

Radionuclide	Medication	Mechanism
Iodine	KI (potassium iodide), Lugol's solution	Blocks thyroid deposition
Rare earths: plutonium(Pu), americium (Am), curium (Cu)	Zn-DTPA Ca-DTPA	Chelation and analogue blocking
Iron (Fe)	Deferasirox	
	Desferrioxamine	
Uranium	Bicarbonates	Alkalinization of urine, reducing chance of acute tubular necrosis
Caesium, thallium	Prussian Blue, (ferrihexacyano-ferrate (II))	Blocks absorption from GI tract and ion exchange resin
Tritium	Water	Isotopic dilution
Other fission isotopes without specific antidotes	Antacids	Minimize absorption
	Cathartic	Waste removal from body
	Gastric lavage/irrigation	Waste removal from body

exposed at such high doses. Fatality is inevitable and no effective cure is available.

Skin

Cutaneous radiation injury is acute injury to the skin. Skin damage can manifest within hours, days, or weeks after radiation exposure. Transient itching, tingling, erythema, and oedema may be seen within hours or days after exposure, and are usually followed by a latent period. The most common cause is accidental/overdose or skin after high dose concurrent chemoradiation. The skin may breakdown to blistering and desquamation up to 2 weeks to a few months after exposure. Occasionally, radiation recall syndrome when administering certain chemotherapy may trigger erythema in a previously irradiated site. Skin lesions may evolve and delayed occurrence of lesions is a differentiating factor from thermal burns. Cellulitis and severe wound breakdown may necessitate debridement and skin grafting. Minor injury may just be treated expectantly with wound care, emollient creams, and analgesia. Long-term sequelae of telangiectasia, chronic lymphoedema and fibrosis, and late ulcers may result [11].

Treatment of internal contamination

Internal contamination is by ingestion or inhalation, and is particularly suggested if the nose and mouth is contaminated, and there is a persistently high radiation survey reading, despite adequate repeated decontamination. Usually patients are well, unless a large amount of radioactive material has been inhaled or ingested. Consider the appropriate early administration of radionuclide-specific decorporation agents such as Prussian Blue, diethylenetriamine pentaacetate (DTPA) or bicarbonate shown in Table 331.2. If biological effluent such as blood, urine, and faecal samples are radioactive, consider getting whole body counts to assess dose and consult radiation experts [12].

Gastric lavage, antacids and cathartics may assist in clearing ingested contamination and usually only is effective if done within a few hours of ingestion.

References

1. Recommendations of the International Commission on Radiological Protection (2007). ICRP Publication 103. *Annals of the International Commission on Radiological Protection*, **37**(2–4), 1–332.
2. UK Legislation. (1999). UK Ionising Radiation Regulations 1999 (IRR1999). Available at: www.legislation.gov.uk/uksi/1999/3232 (accessed 23 June 2015).
3. US Nuclear Regulatory Commission Regulations. (2015). Part 20–Standards for Protection Against Radiation. Available at: www.nrc.gov/reading-rm/doc-collections/cfr/part020 (accessed 23 June 2015).
4. Chin FK. (2007). Scenario of a dirty bomb in an urban environment and acute management of radiation poisoning and injuries. *Singapore Medical Journal*, **48**, 950–7.
5. Berger ME, Leonard RB, Ricks RC, et al. Hospital Triage in first 24 hours after nuclear or radiological disaster, REAC/TS (Radiation Emergency Assistance Center/Training Site). Available at: www.orise.orau.gov/files/reacts/triage.pdf (accessed 23 June 2015).
6. Centers for Disease Control and Prevention. (2014). Acute Radiation Syndrome: A Fact Sheet for Physicians. Atlanta: GA: Center of Disease Control and Prevention (CDC), Radiation Emergency Assistance Center/Training Center. Available at: http://www.bt.cdc.gov/radiation/arsphysicianfactsheet.asp (accessed 23 June 2015).
7. Donnelly EH, Nemhauser JB, Smith JM, et al. (2010). Acute radiation syndrome: assessment and management. *Southern Medical Journal*, **103**, 541–6.
8. Andrews GA, Auxier JA, and Lushbaugh CC. (1965). The importance of dosimetry to medical management of persons exposed to high levels of radiation. In: *Personal Dosimetry for Radiation Accidents*, 3–16. Vienna: IAEA.

9. Waselenko JK, MacVittie TJ, Blakely WF, et al. (2004). Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. *Annals of Internal Medicine*, **140**, 1037–51.
10. Hall EJ. (2000). *Acute Effects of Total-body Irradiation. Radiobiology for the Radiologist*, 5th edn, pp.124–35. Philadelphia, PA: Lippincott Williams & Wilkins.
11. Center of Disease Control and Prevention (2014). Cutaneous Radiation Injury: Physicians' Fact Sheet. Atlanta, GA: Center of Disease Control and Prevention (CDC), Radiation Emergency Assistance Center/ Training Center. Available at: http://www.bt.cdc.gov/radiation/criphysicianfactsheet.asp (accessed 23 June 2015).
12. National Council on Radiation Protection and Measurements (NCRP) (2008). Report 161- Management of Persons Contaminated with Radionuclides. Bethesda: NRCP.

SECTION 16

Trauma

PART 16.1

Multiple trauma

CHAPTER 332

A systematic approach to the injured patient

Clay Cothren Burlew and Ernest E. Moore

Key points

- Systematic management of the seriously-injured patient consists of the primary survey with concurrent resuscitation, the secondary survey, diagnostic evaluation, and definitive care.
- The primary survey is concerned with the identification and simultaneous treatment of life-threatening injuries using a traditional airway, breathing, circulation approach with treatment prioritized to injuries that pose an immediate threat to life.
- As early decisions are time critical and affect survival, the initial resuscitation of seriously-injured patients should be carried out by a trained and practiced trauma team.
- Once life-threatening injuries have been treated and the patient stabilized, the secondary survey, a head-to-toe examination to identify all other injuries, should occur.
- The secondary survey is followed by diagnostic evaluation and definitive care.

Introduction

The initial management of the seriously-injured patient consists of the primary survey with concurrent resuscitation, the secondary survey, diagnostic evaluation, and definitive care; this approach is based upon the advanced trauma life support (ATLS) course of the American College of Surgeons [1]. The first step in management, the primary survey is to identify and treat conditions that constitute an immediate threat to life. The life-threatening injuries that must be identified and treated promptly include airway obstruction/injury, tension pneumothorax, open pneumothorax, flail chest with underlying pulmonary contusion, massive haemothorax, cardiac tamponade, bronchovenous air embolism, massive haemoperitoneum, unstable pelvic fractures, cervical spine injury resulting in neurogenic shock, and intracranial haemorrhage. The secondary survey entails a systematic evaluation for more occult, yet potentially limb- or life-threatening injuries. Data suggest that outcomes of multiply-injured patients can be improved if their initial management is performed by an efficiently functioning trauma team. While membership of the team may vary from hospital to hospital, each member of the team should have defined roles, so that all important tasks are accomplished in a simultaneous and coordinated manner. The team leader has overall responsibility and ensures each member attends to their tasks with the goal of identifying and treating life-threatening injuries as early as possible.

Primary survey

Airway

The primary survey encompasses the 'ABCDs' (airway, breathing, circulation, and disability) of resuscitation. Ensuring a patent airway, while immobilizing the cervical spine, is the first priority to avoid hypoxaemia or hypercarbia. Patients who are conscious, without tachypnoea, and have a normal voice are unlikely to need active airway intervention. Patients with penetrating injuries to the neck or complex maxillofacial trauma, however, may initially have a satisfactory airway that can become obstructed due to progression of soft-tissue swelling or expanding haematomas. Provision of a definitive airway (i.e. endotracheal intubation) is indicated in patients with apnoea, and/or an inability to protect their airway, impending airway compromise, and inability to maintain oxygenation. Orotracheal intubation is the preferred technique, even in the patient at risk for cervical spine injury, because it provides a large airway. Correct positioning of the tube should be verified with direct laryngoscopy, capnography, auscultation of bilateral breath sounds, and ultimately chest radiography. Failed intubation should be treated with a surgical airway (cricothyroidotomy) if bag and mask ventilation cannot maintain oxygenation.

Breathing

Once the airway is secured, adequate oxygenation and ventilation must be assured. All injured patients should receive supplemental oxygen and be monitored by pulse oximetry.

If there is a clinical diagnosis of a tension pneumothorax (hypotension with respiratory distress, tracheal deviation away from the affected side, or decreased breath sounds on the affected side), immediate decompression is warranted. While needle decompression with a 14-gauge venous catheter in the second intercostal space in the midclavicular line may be indicated in the field, tube thoracostomy should be performed in the emergency department (ED). An open pneumothorax (full-thickness loss of the chest wall, permitting free communication between the pleural space and the atmosphere) should be covered with an occlusive dressing taped on three sides to act as a flutter valve. Definitive treatment requires closure of the chest wall defect and tube thoracostomy remote from the wound. Flail chest occurs when three or more contiguous ribs are fractured in two locations, but the associated pulmonary dysfunction is largely due to the underlying pulmonary contusion, rather than loss of chest wall integrity. The patient's initial chest radiograph may underestimate the severity of the pulmonary contusion

as these often progress during the first 12 hours. Thus, patients with flail chest may require delayed intubation and mechanical ventilation.

Circulation

In evaluating the trauma patient's cardiovascular status, any episode of hypotension (defined as a systolic blood pressure (SysBP) less than 90 mmHg) is presumed to be due to haemorrhage until proven otherwise. External haemorrhage should be controlled with manual compression. For penetrating injuries of the neck, thoracic outlet, and groin, where bleeding is arising from deep within the wound, a gloved finger should be placed through the wound to control bleeding. Bleeding from scalp lacerations can be controlled with skin staples, Rainey clips, or a full-thickness, running nylon stitch. A massive haemothorax (defined as more than 1500 mL of blood) is evident on chest radiograph, but is best quantified by tube thoracostomy output. This volume is usually an indication for an emergency thoracotomy. Ultrasound of the pericardium (FAST exam), both hemithoraces, and abdomen is an integral component of the primary survey. When acute, the accumulation of less than 100 mL of blood in the pericardial space may cause cardiac tamponade (Fig. 332.1). Pericardiocentesis is successful in decompressing tamponade in approximately 80% of cases; the majority of failures are due to clotted blood within the pericardium in which case open surgery and clot evacuation may be required. Massive haemoperitoneum is identified by ultrasound, identifying free intraperitoneal fluid in Morison's pouch, the left upper quadrant, or the pelvis. Although exquisitely sensitive, it does not reliably determine the source of haemorrhage [2]; massive haemoperitoneum in a hypotensive patient warrants immediate laparotomy. Selected patients undergoing CPR upon arrival to the ED, or those suffering cardiac arrest after arrival, should undergo resuscitative thoracotomy based upon injury and duration of CPR (see Fig. 332.2 for criteria for resuscitative thoracotomy) [3,4].

Plain radiographs should be done to identify unstable pelvic fractures. Patients with a pelvic fracture and associated haemodynamic instability should undergo prompt stabilization with 'sheeting' of the pelvis, application of a commercial pelvic compression device, or placement of an external fixator. These devices reduce pelvic volume, which promotes tamponade of venous and cancellous bleeding, and prevents secondary haemorrhage from the shifting of bony elements. Options to control ongoing pelvic haemorrhage include embolization of bleeding vessels and pre-peritoneal pelvic packing (Fig. 332.3).

Disability

Neurological examination including Glasgow coma scale (GCS) score should be determined as soon as possible for all injured patients. Patients with a GCS <8 require immediate restoration of SysBP to >100 mmHg, normalization of $PaCO_2$, maintenance of oxygenation, and early neurosurgical consultation with consideration for intracranial pressure (ICP) monitoring. The presence of lateralizing findings (e.g. a unilateral dilated pupil unreactive to light, asymmetric movement of the extremities in response to noxious stimuli, or a unilateral Babinski sign) suggests an intracranial mass lesion, which may be amenable to surgical treatment. Once stabilized, such patients should undergo an urgent cranial CT scan.

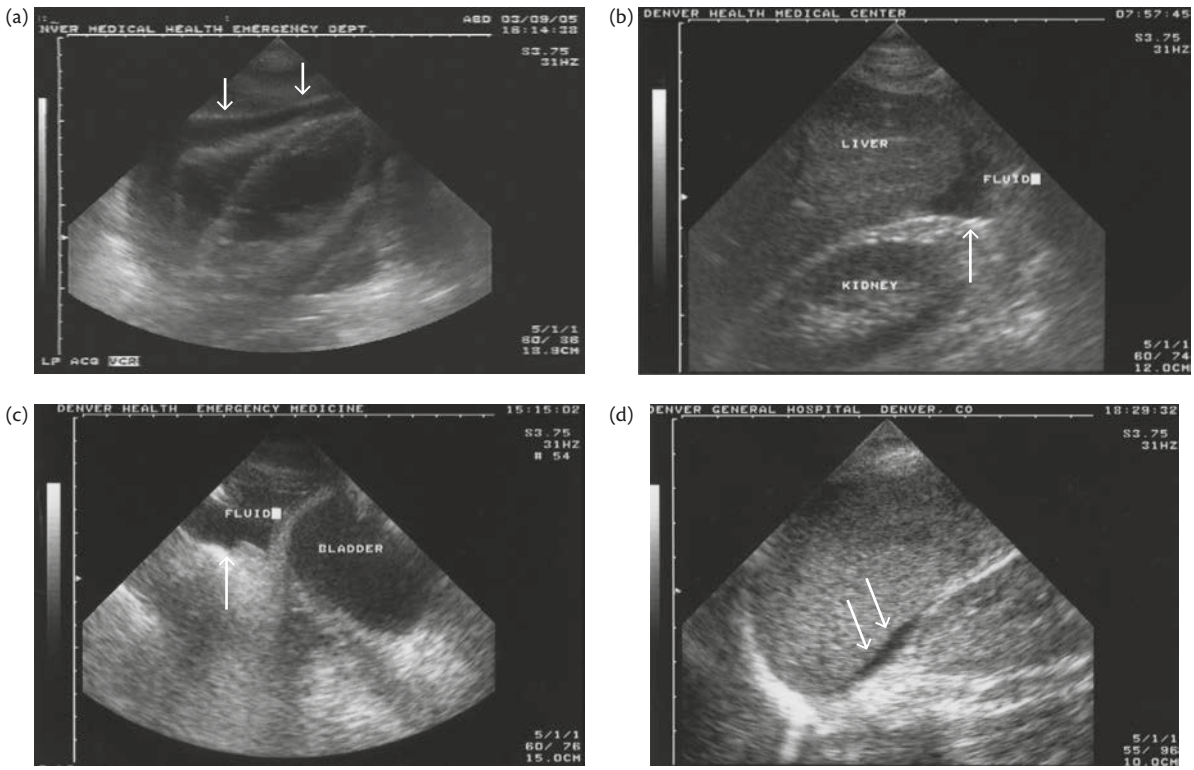


Fig. 332.1 Focused Abdominal Sonography for Trauma (FAST) examination can identify blood in (a) the pericardium, (b) right upper quadrant, (c) pelvic space, and (d) left upper quadrant.

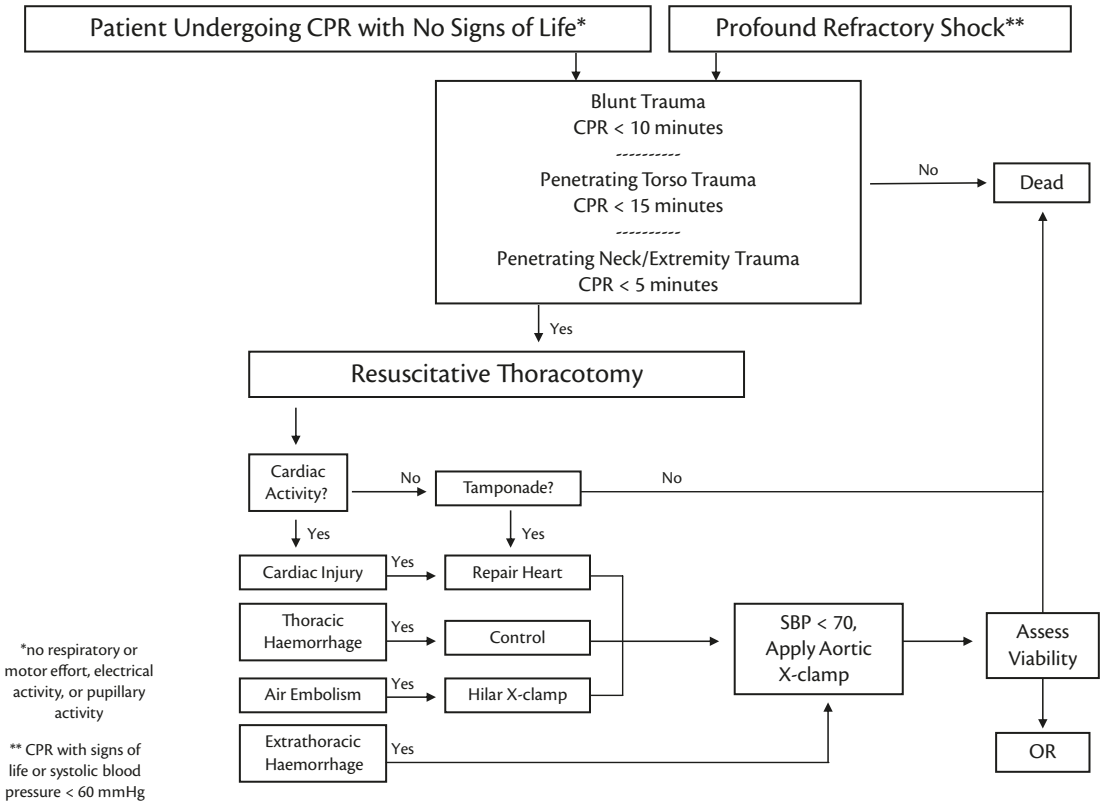


Fig. 332.2 Resuscitative thoracotomy is performed based upon injury, duration of cardiopulmonary resuscitation, and available resources.

Concurrent resuscitation

Intravenous (iv) access should be obtained with two 16-gauge peripheral catheters. If iv access is not easily obtained, an intraosseous needle should be placed. Blood should be drawn simultaneously for a bedside haemoglobin level and routine trauma laboratory tests. In the seriously-injured patient arriving in shock, an arterial blood gas, cross-matching for possible red blood cell (RBC) transfusion and coagulation tests should be obtained. In the hypotensive patient, secondary large bore cannulae should be obtained via the femoral or subclavian veins, or saphenous vein cutdown. Fluid resuscitation begins with a 2-L bolus of isotonic crystalloid in the adult. For patients with penetrating trauma, 'hypotensive resuscitation' to a SysBP of 90 mmHg should be considered to avoid increasing bleeding. In blunt injured patients with a potential head injury, however, the SysBP target should be >100 mmHg. Based on the initial response to fluid resuscitation, hypovolaemic patients can be separated into three broad categories—responders, transient responders, and non-responders. Individuals who are stable or have an appropriate response to their initial fluid therapy—'responders'—are unlikely to have significant ongoing haemorrhage and further evaluation for occult injuries can proceed. At the other end of the spectrum are patients classified as 'non-responders' who have persistent hypotension despite aggressive fluid resuscitation. A massive transfusion protocol should be activated immediately in these patients. Patients considered as 'transient responders' respond initially to volume loading, but deteriorate again.

Persistent haemodynamic instability may be due to haemorrhagic, cardiogenic, or neurogenic shock. Septic shock on presentation is extremely rare in trauma patients. Identification of haemorrhagic shock has been discussed previously. The differential diagnosis of cardiogenic shock in trauma patients is tension pneumothorax or pericardial tamponade, blunt cardiac injury, myocardial infarction, and bronchovenous air embolism. Although up to one-third of patients sustaining blunt chest trauma suffer blunt cardiac injury, this rarely results in haemodynamic embarrassment. Measurement of cardiac enzyme concentration is unhelpful as troponins lack specificity and do not predict significant arrhythmias [5]. β-Agonists may be initiated and echocardiography performed to exclude valvular or septal injuries, and evaluate wall motion abnormalities. Acute myocardial infarction may have preceded the patient's trauma; treatment for an evolving infarct, such as thrombolytic therapy or urgent coronary angioplasty, must be individualized according to the patient's injuries. Air embolism from an injured bronchus emptying into an adjacent vein can accumulate in the left ventricle and coronary arteries, impeding diastolic filling and disrupting coronary perfusion. Treatment is placement of the patient in Trendelenburg position, resuscitative thoracotomy, pulmonary hilar clamping, and aspiration of air from the apex of the left ventricle and aortic root, with coronary massage to remove air bubbles. Patients with neurogenic shock from high spinal cord injury are typified by hypotension with relative bradycardia due to physiological disruption of sympathetic outflow, and are often recognized due to paralysis, decreased rectal tone or priapism; treatment consists of volume loading and a vasopressor infusion.

Persistent hypotension during diagnostic evaluation should be treated with type O or type-specific blood transfusion. A massive transfusion protocol should be activated with empiric 1:2

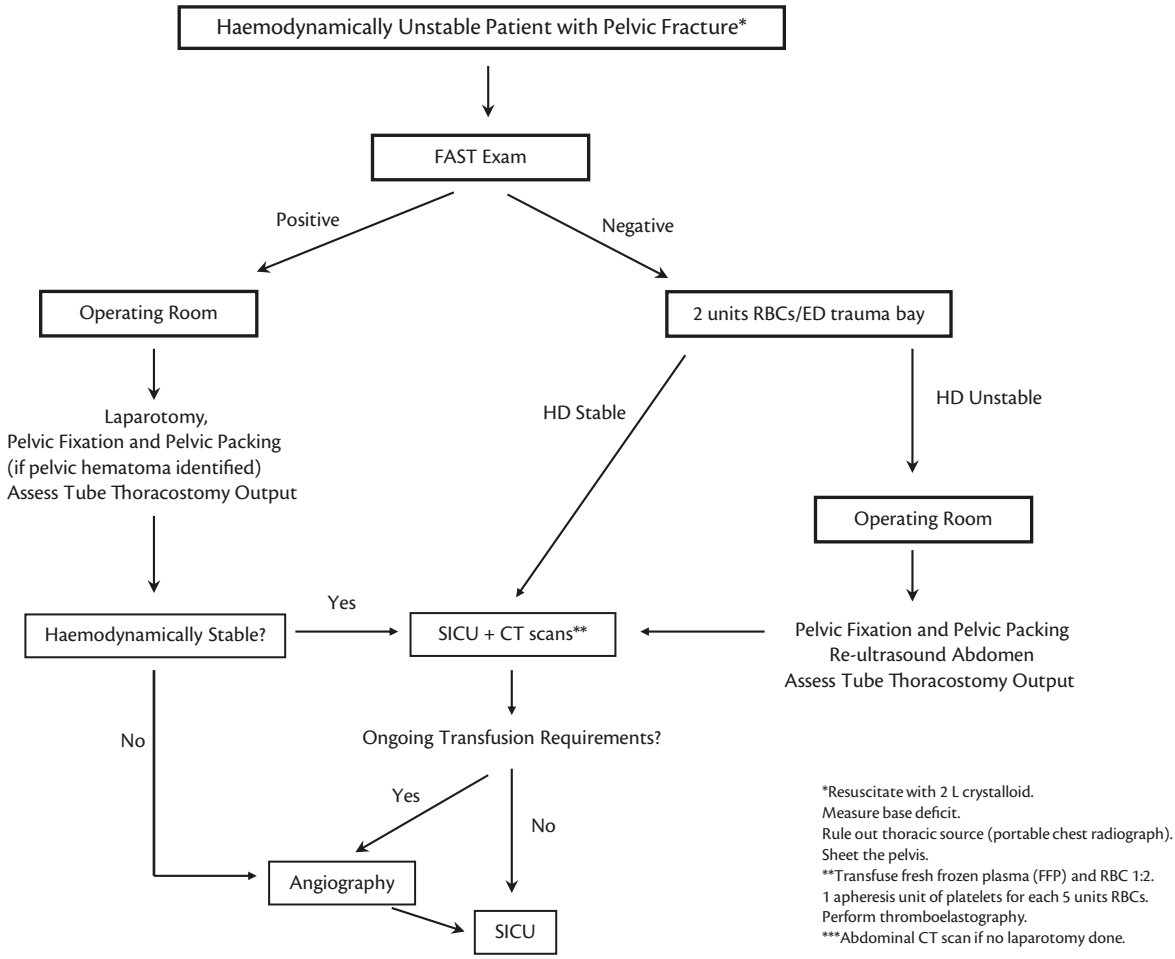


Fig. 332.3 Algorithm for the management of patients with a pelvic fracture and associated haemodynamic instability.

FFP:RBC ratio to address the acute coagulopathy of trauma. Thromboelastography (TEG) may assist in managing coagulopathy [6]. When accompanied by hypotension, the following are indications for urgent surgery:

- Penetrating chest trauma with greater than 1L chest tube output.
- Blunt chest trauma with greater than 1.5L chest tube output.
- Distended abdomen with peritoneal signs.
- Penetrating wounds entering the abdomen.

In patients without clear operative indications and persistent hypotension, one should systematically reassess the five potential sources of blood loss—scalp, chest, abdomen, pelvis, and extremities. Thoracoabdominal trauma should be evaluated with a combination of chest radiograph, FAST, and pelvic radiograph. If the FAST is negative and no other source of acute blood loss is obvious, diagnostic peritoneal aspirate (DPA) should be considered [7]. Fracture-related blood loss may be a major source of the patient's haemodynamic instability. For each rib fracture there is approximately 200 mL of blood loss, for tibial fractures 400 mL, femur fractures 800 mL, and pelvic fractures greater than 1000 mL. Although diagnostic imaging is important, transporting a hypotensive patient for CT or MRI scanning is hazardous, and should be delayed until the patient is stabilized.

Secondary survey

Once the immediate threats to life have been addressed, a thorough history is obtained and the patient is examined from head to toe in a systematic fashion. All seriously-injured patients should undergo digital rectal examination to evaluate for sphincter tone, presence of blood, and rectal perforation. Women with pelvic fractures should undergo vaginal examination to exclude an open fracture. Adjuncts to the physical exam include electrocardiogram (ECG) monitoring, nasogastric tube placement, in-dwelling urinary catheter placement, comprehensive ultrasound evaluation, laboratory measurements, and plain radiographs. A nasogastric tube (NGT) should be inserted in all intubated patients to decrease the risk of aspiration pneumonitis; the tube should be placed orally in patients with facial or base of skull fractures. NGT evaluation of stomach contents for blood may reveal occult gastroduodenal injury or the course of the NGT on chest film may indicate a diaphragm injury. Gross haematuria demands evaluation of the genitourinary system. In-dwelling urinary catheter placement should be deferred until urological evaluation in patients with signs of urethral injury; e.g. blood at the meatus, perineal, or scrotal haematomas, or a high-riding prostate.

Screening radiographs for patients with blunt trauma include chest and pelvic radiographs. Patients with gunshot wounds to the chest or abdomen, should have a chest and abdominal film, with

radiopaque markers at the wound sites, to determine trajectory of the bullet or location of retained fragments. Extremity radiographs are performed as indicated. In critically-injured patients cross-matching for transfusion, a full blood count (FBC), biochemistry, coagulation studies, lactate, and arterial blood gas (ABG) should be sent to the laboratory. Less severely-injured patients may only require an FBC and urinalysis, although the threshold for investigation should be lower in elderly patients.

Diagnostic evaluation

Depending upon mechanism, further diagnostic studies may be warranted during the initial evaluation. All patients with a significant closed-head injury (GCS <14) should have a CT scan of the head. For penetrating injuries, plain skull films may be helpful to determine the depth of injury. Patients at risk for carotid or vertebral artery injury (Fig. 332.4) should undergo multislice CT angiography because the injury may initially be asymptomatic. Similarly, a diligent evaluation for occult cervical spine injuries is mandatory to avoid the risk of subsequent spinal cord injury. In awake patients, the presence of posterior midline pain or tenderness should provoke a thorough radiological evaluation with CT scan in addition to a presumptive cervical collar. Additionally, intubated patients, patients with high energy mechanisms, distracting injuries, or another identified spine fracture should undergo imaging.

Penetrating injuries of the anterior neck that violate the platysma are potentially life-threatening because of the density of critical structures in this region. Management is structured according to level of injury (I, II, III); a selective non-operative approach is practiced in most centres [8,9]. Indications for immediate operative intervention for penetrating cervical injury include hard signs of injury, e.g. haemodynamic instability, active arterial haemorrhage, or airway distress. Most thoracic injuries can be evaluated by physical examination and chest radiograph, with a supplemental CT scan based upon initial findings and injury mechanism. Any patient that undergoes intervention—intubation, central line placement, tube thoracostomy—needs a repeat chest radiograph to document adequacy or complications of the procedure. Patients with a persistent pneumothorax or a large air leak following tube thoracostomy should undergo fibre-optic bronchoscopy to exclude a bronchial injury. Patients with haemothorax must have a chest radiograph documenting complete evacuation of the chest; a persistent haemothorax that is not drained by two chest tubes is termed a caked haemothorax and requires prompt thoracotomy.

Patients with a suspected thoracic aortic tear, suggested by widening of the mediastinum on initial AP chest radiograph, should undergo multislice CTA scan [10]. However, 7% of patients with an aortic injury will have a normal chest radiograph [11]. Thus, CT scanning is also performed based on the mechanism of injury—high-energy deceleration motor vehicle collision (MVC)

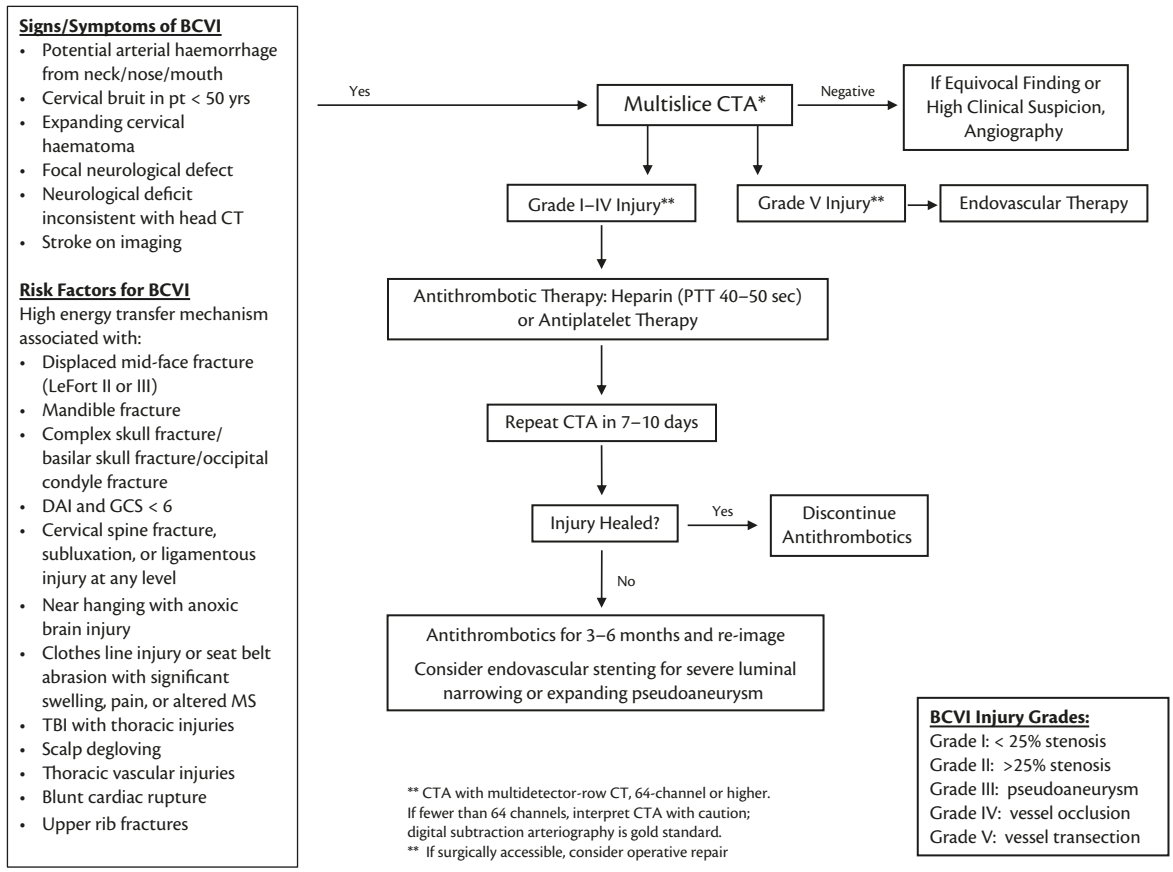


Fig. 332.4 Algorithm for blunt cerebrovascular injury screening and treatment.

BCVI Injury Grades: Reproduced from Biffl WL et al., 'Blunt carotid arterial injuries: implications of a new grading scale', *The Journal of Trauma and Acute Care Surgery*, **47**(5), pp. 845–53, copyright 1999, with permission from Wolters Kluwer.

with frontal or lateral impact, MVC with ejection, falls greater than 25 feet (7.5 m), or direct impact (horse kick to chest, collision with tree) [10]. For penetrating thoracic trauma, physical examination, plain PA, and lateral chest radiographs with metallic markings of wounds, pericardial ultrasound, and central venous pressure measurement will identify the majority of injuries. Haemodynamically-stable patients with transmediastinal gunshot wounds should undergo CT scanning to determine the path of the bullet; this identifies the vascular or visceral structures at risk for injury, and directs angiography or endoscopy as appropriate. If there is a suspicion of a subclavian artery injury, CT angiography should be performed.

Patients with anterior truncal gunshot wounds between the fourth intercostal space and the pubic symphysis, whose trajectory by radiograph or entrance/exit wound indicates peritoneal penetration should undergo operative exploration; over 90% of patients have significant internal injuries. Anterior abdominal stab wounds should be explored under local anaesthesia in the ED to determine if the fascia has been violated. If the tract does not violate the peritoneal cavity, the patient may be discharged from the ED. The optimal diagnostic approach for patients with fascial penetration, however, remains unclear. Options include serial examination, diagnostic peritoneal lavage (DPL), and CT scanning [12]. The most recent evidence supports serial examination and laboratory evaluation [13]. In haemodynamically-stable patients with penetrating trauma isolated to the right upper quadrant with trajectory confined to the liver by CT scan, non-operative observation may be considered [14–16]. Patients with penetrating trauma to the flank and back should undergo triple-contrast CT to detect retroperitoneal injuries of the colon, duodenum, and urinary tract [17]. Injury to the diaphragm should be evaluated in patients with stab wounds to the lower chest—diagnostic laparoscopy is the most accurate method to evaluate the diaphragm and allows for suture repair.

Patients with a 'positive FAST', following blunt abdominal trauma who do not have immediate indications for laparotomy, should undergo CT scan to identify and quantify their injuries [7]. The AAST injury grading scale (Table 332.1) is a useful guideline for non-operative management of solid organ injuries. Additional findings that should be noted on CT scan solid organ injury patients include contrast extravasation (i.e. a 'blush'), the amount of intra-abdominal haemorrhage, and presence of pseudo-aneurysms [18]. CT is also indicated for haemodynamically-stable patients who have an unreliable physical examination. Despite the increasing diagnostic accuracy of multislice CT scanners, CT still has limited accuracy for identification of intestinal injuries. Bowel injury is suggested by findings of thickened bowel, 'streaking' in the mesentery, free fluid without associated solid organ injury, or free intraperitoneal air [19]. Patients with free intra-abdominal fluid without solid organ injury need close monitoring for evolving signs of peritonitis; if patients have a significant TBI or cannot be examined serially, DPL should be performed to exclude bowel injury.

Plain radiographs permit early recognition of pelvic fractures, but ultimately CT scans determine the precise geometry. If the urinalysis contains RBCs, a CT cystogram is performed to rule out bladder rupture. On rare occasions, the iliofemoral arteries may be injured, and CT angiography is the preferred diagnostic tool. Hard signs of vascular injury (pulsatile haemorrhage, absent distal pulses, acute ischaemia) constitute indications for operative exploration. Extremity compartment syndromes should be suspected in patients with pain on active or passive motion of the muscles in the involved compartment. Paraesthesias with progression to paralysis can occur, but loss of pulses is a late sign. Compartment pressures can be measured with a hand-held Stryker device; fasciotomy is indicated in patients with a gradient <35 (gradient = diastolic pressure—compartment pressure).

Table 332.1 AAST Grading Scales for solid organ injuries

Liver injury grade	Subcapsular haematoma	Laceration
Grade I	<10% surface area	<1 cm in depth
Grade II	10–50% surface area	1–3 cm
Grade III	>50% or >10 cm	>3 cm
Grade IV	25–75% of a hepatic lobe	
Grade V	>75% of a hepatic lobe	
Grade VI	Hepatic avulsion	
Splenic injury grade		
Grade I	<10% surface area	<1 cm in depth
Grade II	10–50% surface area	1–3 cm
Grade III	>50% or >10 cm	>3 cm
Grade IV	>25% devascularization	Hilum
Grade V	Shattered spleen	
	Complete devascularization	

Adapted with permission from Wolters Kluwer Health: *The Journal of Trauma and Acute Care Surgery*, Moore E et al., 'Organ injury scaling: Spleen, liver, and kidney', **29**(12), pp. 1664–66, 1989.

References

1. American College of Surgeons. (2008). *Advanced Trauma Life Support*, 8th edn. Chicago, IL: American College of Surgeons.
2. Ochsner MG, Knudson MM, Pachter HL, et al. (2000). Significance of minimal or no intraperitoneal fluid visible on CT scan associated with blunt liver and splenic injuries: a multicenter analysis. *Journal of Trauma*, **49**, 505–10.
3. Moore EE, Knudson MM, Burlew CC, et al. (2011). Defining the limits of resuscitative emergency department thoracotomy: a contemporary Western Trauma Association perspective. *Journal of Trauma*, **70**(2), 334–9.
4. Burlew CC, Moore EE, Moore FA, et al. (2012). Western Trauma Association Critical Decisions in Trauma: Resuscitative Thoracotomy. *Journal of Trauma and Acute Care Surgery*, **73**(6), 1357–61.
5. Velmahos GC, Karaiskakis M, Salim A, et al. (2003). Normal electrocardiography and serum troponin I levels preclude the presence of clinically significant blunt cardiac injury. *Journal of Trauma*, **54**(1), 45–50.
6. Gonzalez E, Pieracci FM, Moore EE, and Kashuk JL. (2010). Coagulation abnormalities in the trauma patient: the role of point-of-care thromboelastography. *Seminars in Thrombosis and Hemostasis*, **36**(7), 723–37.
7. Dolich MO, McKenney MG, Varela JE, et al. (2001). 2,576 ultrasounds for blunt abdominal trauma. *Journal of Trauma*, **50**, 108.
8. Sekharan J, Dennis JW, Veldenz HC, et al. (2000). Continued experience with physical examination alone for evaluation and management of penetrating zone 2 neck injuries: results of 145 cases. *Journal of Vascular Surgery*, **32**, 483.

9. Inaba K, Branco BC, Menaker J, et al. (2012). Evaluation of multidetector computed tomography for penetrating neck injury: a prospective multicenter study. *Journal of Trauma and Acute Care Surgery*, **72**(3), 576–83.
10. Dyer DS, Moore EE, Ilke DN, et al. (2000). Thoracic aortic injury: how predictive is mechanism and is chest computed tomography a reliable screening tool? A prospective study of 1,561 patients. *Journal of Trauma*, **48**, 673.
11. Demetriades D, Velmahos GC, Scalea TM, et al. (2008). Operative repair or endovascular stent graft in blunt traumatic thoracic aortic injuries: results of an American Association for the Surgery of Trauma Multicenter study. *Journal of Trauma*, **64**(3), 561–70.
12. Biffl WL, Cothren CC, Brasel KJ, et al. (2008). A prospective observational multicenter study of the optimal management of patients with anterior abdominal stab wounds. *Journal of Trauma*, **64**, 250.
13. Biffl WL, Kaups KL, Pham TN, et al. (2011). Validating the Western Trauma Association algorithm for managing patients with anterior abdominal stab wounds: a Western Trauma Association multicenter trial. *Journal of Trauma*, **71**(6), 1494–502.
14. Renz BM and Feliciano DV. (1994). Gunshot wounds to the right thoracoabdomen: a prospective study of nonoperative management. *Journal of Trauma*, **37**, 737.
15. Demetriades D, Hadjizacharia P, Constantinou C, et al. (2006). Selective nonoperative management of penetrating abdominal solid organ injuries. *Annals of Surgery*, **244**, 620.
16. Inaba K, Branco BC, Moe D, et al. (2012). Prospective evaluation of selective nonoperative management of torso gunshot wounds: When is it safe to discharge? *Journal of Trauma*, **72**(4), 884–90.
17. Chiu WC, Shanmuganathan K, Mirvis SE, and Scalea TM. (2001). Determining the need for laparotomy in penetrating torso trauma: a prospective study using triple-contrast enhanced abdominopelvic computed tomography. *Journal of Trauma*, **51**(5), 860–8.
18. Moore EE, Shackford S, Pachter H et al. (1989). Organ injury scaling: spleen, liver, and kidney. *Journal of Trauma*, **29**(12), 1664–6.
19. Ekeh AP, Saxe J, Walusimbi M, et al. (2008). Diagnosis of blunt intestinal and mesenteric injury in the era of multidetector CT technology—are results better? *Journal of Trauma*, **65**(2), 354–9.

CHAPTER 333

Pathophysiology and management of thoracic injury

Graciela Bauzá and Ayodeji Nubi

Key points

- A high proportion of polytrauma victims suffer thoracic injury, which is associated with mortality of with 25–50%.
- Initial management is guided by ATLS principles of **a**irway, **b**reathing, and **c**irculation.
- The focused assessment with sonography for trauma (FAST) exam plays a key role in the initial evaluation of thoracic trauma.
- Tube thoracostomy is often required for pneumothorax or haemothorax; generally, this is the only intervention required for thoracic trauma. Only 10–15% of thoracic injuries require operative intervention.
- Severe blunt chest trauma is often associated with other significant injuries.

Introduction

Thoracic trauma accounts for 25–50% of trauma-related deaths [1], as well as causing significant morbidity. Thoracic injury, blunt, or penetrating, involves injury to thoracic soft tissue and bony structures, in addition to injury of the lung parenchyma, tracheobronchial apparatus, heart, and great vessels or mediastinal structures. Death at the scene of injury occurs due to exsanguination from cardiac or great vessel disruption. Patients who die within hours of thoracic trauma usually have hypoxia from airway injury, tension pneumothorax, or haemorrhage. Late deaths result from sepsis, pulmonary complications, or missed injury.

Thoracic trauma is often associated with other significant body cavity injury (abdomen, pelvis, central nervous system). The majority of thoracic injuries do not require surgery, with only 10–15% requiring operative intervention [2].

Initial assessment

The initial evaluation of the patient with thoracic trauma follows the principles for any multiply-injured patient. Immediate priority is given to performing a rapid primary survey following standard advanced trauma life support (ATLS) protocols. Immediately life-threatening thoracic injuries include airway obstruction, tension pneumothorax, massive haemothorax, open pneumothorax, flail chest, and cardiac tamponade. (Table 333.1)

Following completion of the primary survey and stabilization of the patient, a detailed secondary survey is undertaken to identify other injuries. This involves a thorough physical examination and the use of diagnostic adjuncts. Thoracic injuries that should be sought include open wounds, rib fractures, flail segments, closed pneumothorax or haemothorax, and chest wall contusions. A plain chest X-ray (CXR) should be obtained to evaluate for rib fractures, pulmonary contusion, pneumothorax, haemothorax, and mediastinal or diaphragmatic abnormalities. The use of focused assessment with sonography for trauma (FAST) for the evaluation of haemopericardium has a sensitivity and specificity exceeding 96% [3]. Extended FAST (eFAST) exam for the diagnosis of pulmonary contusions and pneumothorax has also been reported [3]. Echocardiography and CT angiography are also useful. The latter should be performed in the stable patient, as a considerable number of patients will be found to have significant thoracic injuries on CT despite a normal CXR [4].

Table 333.1 Life-threatening thoracic injuries

Immediate	Potential
Airway obstruction	Traumatic aortic rupture
Tension pneumothorax	Major tracheobronchial injury
Cardiac tamponade	Blunt cardiac injury
Open pneumothorax	Diaphragmatic injury
Massive haemothorax	Oesophageal injury
Flail chest	Pulmonary contusion, rib fractures
Commotio cordis	

The use of other more invasive, but necessary interventions, such as **resuscitative thoracotomy** deserves brief mention. Its use should be highly selective for established indications, such as relief of cardiac tamponade, for open cardiac massage, hilar control of lung haemorrhage or descending aortic cross-clamping for control of distal bleeding. Survival rates following resuscitative thoracotomy for blunt trauma is approximate 1% [5,6] and, following penetrating injury, 15–60% (Table 333.2) [7,8].

Specific injuries

Chest wall

Rib fractures

These are common following blunt chest trauma, less common following penetrating injury. As many as 50% will not be apparent on CXR. They contribute significant morbidity and mortality

Table 333.2 Operative indications for thoracic injury

Injury	Intervention
Airway obstruction or major tracheobronchial disruption	ETT-endotracheal tube, surgical airway, thoracotomy for repair of tracheobronchial injury
Haemorrhage*	Thoracotomy for initial chest tube output of >1500 mL of blood or >250 mL/hour for 3–4 consecutive hours, or large retained haemothorax despite chest tubes
Cardiac or great vessel injury	Thoracotomy, sternotomy for repair of cardiac injuries, or endovascular repair of aortic injuries as indicated
Oesophageal perforation	Thoracotomy for repair of oesophageal injury

*Patient haemodynamics is primary indication.

in all patients, particularly in patients older than 65 years of age, where mortality is twice that of their younger counterparts; the incidence of pneumonia is also higher [6,9]. The pathophysiology of this stems from poor pulmonary toileting, secondary to severe pain and splinting with inadequate cough response. Rib fractures uncommonly require surgical treatment. Prompt analgesia from oral or parenteral non- steroidal anti-inflammatory medications (NSAIDs), paravertebral nerve blocks, epidural analgesia, or opioid-based patient-controlled analgesia (PCA) is generally effective.

Sternal fractures

The sternum is comprised of the manubrium and the sternum, articulating at the manubriosternal joint—this is the most frequent site of fracture. Management of the injury is guided by findings on initial imaging, such as CXR, electrocardiogram (ECG), and chest computed tomography (CT). When the fracture fragments are significantly displaced (>1–1.5 cm) manual reduction is often needed both for pain control and to avoid long-term malunion; rarely, operative fixation is required. Expectant management with healing is the natural history of this injury. Sternal precautions with regard to upper extremity use and weight bearing are observed for weeks until fracture is considered stable.

Flail chest

Flail chest is the paradoxical movement of a section of the chest wall resulting from the presence of two or more rib fractures in multiple places, usually associated with pulmonary contusion, pneumothorax, haemothorax, or tracheobronchial injury. Disruption of chest wall continuity leads to alteration of chest wall mechanics, resulting in inadequate tidal volume. Pain from fractured ribs plays a substantial role in inadequate chest expansion, decreased tidal volume, and producing inadequate coughing. Associated lung contusions and collapse result in pulmonary shunting and hypoxaemia. Patients with flail chest should be admitted to the intensive care unit (ICU) for close monitoring and pulmonary care. Incentive spirometry with close attention to pain control and gas exchange is crucial. Patients with mild flail can be managed conservatively with frequent reassessment for worsening of function. More severe cases may need tracheal intubation with mechanical ventilation. Analgesia is paramount. Options include epidural or paravertebral analgesia, or PCA.

Diaphragm

Blunt diaphragmatic rupture

This occurs after upper abdominal trauma results in increased intra-abdominal pressure causing a tear in the diaphragm. These injuries are often missed initially. Clinical signs are non-specific. Initial CXR may reveal a gastric bubble or nasogastric tube (NGT) within the left chest in cases of a large rupture. Delayed diagnosis is common as abdominal organs progressively herniate through the diaphragmatic defect.

Penetrating diaphragmatic lacerations

This should be suspected in all penetrating thoraco-abdominal trauma. Left thoraco-abdominal or flank wounds, below the nipple line, mandate exploration of the diaphragm via laparoscopic, thoracoscopic, or open approach. Right-sided diaphragmatic injuries are not always repaired because the liver may prevent the herniation of abdominal contents into the chest.

Lung

Pneumothorax

Pneumothorax results from injury to the lung or tracheobronchial tree. Diagnosis is usually by CXR. When large enough, it is suspected when auscultation of the chest reveals decreased breath sounds on the affected side. Tube thoracostomy is the treatment of choice (Fig. 333.1), which has the following stages:

- **Identify proper indication for chest tube**: wear protective devices.
- **Identify landmarks** (as seen in Fig. 333.1): 4th and 5th intercostal space anterior to mid-axillary line or the cross between axillary tail and infra-mammary fold; stay anterior to latissimus dorsi muscle
- Prepare and drape widely exposing axilla and ipsilateral nipple.
- Use local anaesthetic for non-emergent cases to anaesthetize skin, subcutaneous tissues, periosteum, and pleura.
- Make transverse incision, ~2 cm or as needed, just inferior to desired intercostal space. Carry incision down through subcutaneous tissues. If time allows, anaesthetize periosteum and pleura at this time.
- Use a large, curved Kelly clamp to puncture pleura above the rib to avoid neurovascular bundle, which rides along the inferior border of the rib. Keep control of your clamp to avoid lung injury, spread widely.
- Place index finger into thoracic cavity and sweep circumferentially to ensure no lung adhesions to chest wall. If adhesions are present, sweep gently; if unable to create space, abort procedure.

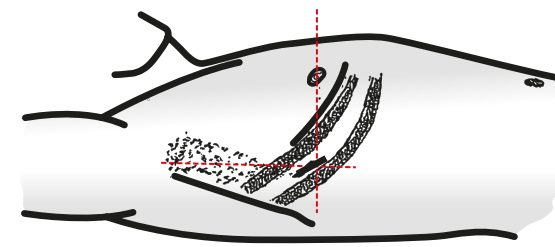


Fig. 333.1 Tube thoracostomy placement.

- **Place large bore chest tube (32 French) using clamp or finger**: guide chest tube posteriorly and apically. Stop when resistance is met. Ensure all chest tube holes are within the pleural space. (Clamp distal tube to avoid spillage prior to insertion.)
- **Confirm proper placement** by feeling tube inside thoracic cage with finger.
- **Connect tube to under water seal apparatus to 20 cm of water suction**: secure connection with tape or plastic tie.
- Secure chest tube to chest wall with heavy nylon, prolene, or silk suture.
- Obtain chest X-ray to confirm placement, resolution of pneumothorax, and evacuation of haemothorax.

Occult pneumothoraces (small pneumothorax seen on CT, but not CXR) may be observed with serial CXR regardless of the need for positive pressure ventilation [7,8,10]. Tension pneumothorax is not uncommon following trauma. Diagnosis should be clinical, not radiological; signs include absent breath sounds on the affected side, distended neck veins, hypotension, or tracheal deviation to the opposite side. Treatment is immediate needle decompression in the anterior second mid-clavicular interspace on the side with decreased breath sounds followed by chest tube insertion. Persistent air leaks from pneumothoraces should be investigated by video-assisted thoracoscopic surgery (VATS) [11,12,13,14].

Haemothorax

Haemothorax is the presence of blood in the pleural cavity, in isolation or in conjunction with a pneumothorax. When large enough, it produces similar symptoms and signs as a tension pneumothorax. Management involves the treatment of hypovolaemia and large bore tube thoracostomy (see Fig. 333.1), with the objective of complete evacuation. Initial output and ongoing drainage are carefully monitored and the need for thoracotomy (as previously discussed) is based on this. When blood is incompletely evacuated or presentation is late (>48 hours), it is defined as a retained haemothorax. For such patients, evacuation of haemothorax with early VATS, usually within 5 days of injury, is indicated to avoid infection, fibrothorax, and later need for thoracotomy. Fibrinolytic therapy for retained haemothorax may be used in patients where surgery carries high-risk.

Pleural empyema

Pleural empyema may occur due to trauma. Consequences include an adherent lung with poor mobility and compliance with or without a loculated seropurulent effusion. Causative factors include retained haemothorax or pneumonia with parapneumonic effusion. Presentation is usually that of sepsis, failure to thrive, or worsening respiratory failure. Diagnosis is best with CT. Temporizing management includes empiric antibiotics and image guided tube thoracostomy placement for drainage of collections. Decortication by open surgery or VATS is generally required [15].

Lung contusion/laceration

This is parenchymal bruising from either blunt or penetrating trauma and is the *sine qua non* of blast injury. The diagnosis is usually underappreciated on plain films and clearly delineated on CT, particularly as time progresses and following fluid resuscitation. The risk of developing ARDS (acute respiratory distress syndrome) [11], development of pneumonia are directly related to contusion size. Treatment depends on patient presentation and contusion size.

Tracheobronchial injury

The majority of blunt tracheobronchial injuries (>80%) occur within 2.5 cm of the carina [14,16,17]. Presentation depends on severity, mechanism, and location of the injury. Cervical tracheal injury is usually associated with injuries to adjacent structures—the oesophagus, vascular structures, or nerves. Symptoms include pain, swelling, stridor, subcutaneous emphysema, haemoptysis, or bleeding. When the injury is located within the thoracic cavity, the spectrum of presentation includes dyspnoea and tachypnoea, simple or tension pneumothorax, or a large air leak via chest tube with significant loss of tidal volume affecting oxygenation/ventilation. Other findings include pneumomediastinum, haemothorax, and bronchopleural fistula.

When the patient presents in respiratory distress, secure the airway by endotracheal intubation. This is optimally achieved by fibre optic bronchoscopic guidance. This method allows direct visualization of the airway, and identification of the site and extent of airway injury, avoidance of use of paralytics/sedatives in a patient with a potentially compromised airway, placement of the ETT distal to the injury, avoiding neck extension in a patient with possible cervical spine injuries. When patient presentation is more extreme, emergent cricothyroidotomy or tracheostomy may be required. Pneumothorax, if present is managed in standard fashion. When these persist or have a continuous air leak, a tracheobronchial injury with a bronchopleural fistula should be suspected.

Small disruptions of the trachea, main bronchi, and large bronchioles (<1/3rd of the circumference) can be managed conservatively. These may present late (weeks) post-injury as a persistent pneumonia secondary to scarring of the airway at the site of injury. Bronchopleural fistulas may be managed with advanced ventilator treatments such as high frequency oscillation ventilation. Prompt operative repair is usually needed for major airway disruption.

Mediastinum

Heart

Injury to the heart should be suspected with severe chest trauma marked by chest bruising, rib or sternal fractures, steering wheel deformity, or penetrating wounds in the cardiac box-from clavicles to costal margin and medial to the nipples.

Pericardial tamponade

75–100 mL of blood can produce pericardial tamponade in the acute setting, this occurs most commonly after penetrating trauma. Most patients with significant cardiac lacerations die before reaching the hospital. Those who arrive at the emergency room with cardiac tamponade often present in shock without evidence of significant blood loss or cardiac arrest after penetrating chest trauma. The signs of Beck's triad (i.e. jugular venous distention, hypotension, and muffled heart sounds) occur in only a third of patients. FAST is used to assess for fluid in the pericardial sac in both penetrating and blunt trauma [2,3]. Haemodynamically-stable patients with injury to the cardiac box or transmediastinal injury with high index of suspicion for cardiac laceration require evaluation with FAST to rule out pericardial fluid. A negative or equivocal FAST in this scenario may be confirmed by formal transthoracic echocardiography (TTE). Caution must be taken when a negative FAST exam exists

in combination with a haemothorax, as the pericardium may empty into the chest masking a cardiac injury. Finding pericardial fluid on FAST examination in a stable patient is usually treated with an operative subxiphoid pericardial window and sternotomy if blood is found in the pericardial sac. In patients in extremis, diagnosis is confirmed at emergency department thoracotomy. In the setting of trauma, needle pericardiocentesis is rarely used as an emergency manoeuvre for temporary relief of tamponade.

Blunt cardiac injury

Blunt cardiac injury after chest trauma can range from asymptomatic myocardial contusion to (rarely) acute heart failure. The right ventricle is most often affected. There is little consensus on diagnostic criteria and evaluation. Most commonly, cardiac injury presents as a dysrhythmia ranging from sinus tachycardia, premature atrial contractions, atrial fibrillation, to premature ventricular contractions. Initial assessment starts with an ECG. Patients who present as haemodynamically stable and in sinus rhythm rarely have acute complications from blunt cardiac injuries. These patients do not require further testing. Patients with known cardiac disease may be monitored for 24 hours, but risk remains low. ECG findings include arrhythmia, heart block, or ST changes. Recent evidence does not support troponin I levels as a screening tool. TTE is recommended in patients with unexplained haemodynamic instability to evaluate myocardial contractility. Invasive cardiac monitoring should be reserved for patients in whom blunt cardiac injury is suspected, those aged more than 60, haemodynamically unstable, polytrauma, have an abnormal ECG, and are undergoing a surgical procedure [18].

Commotio cordis

Commotio cordis is sudden death after a blunt chest trauma, often the result of a direct blow to the chest resulting in dysrhythmia without a structural abnormality. Management should follow guidelines for the management of cardiac arrest [19].

Great vessels

Blunt aortic injury

Blunt aortic injury results from rapid acceleration or deceleration mechanism such as motor vehicle crash or fall from a height. It is fatal in over 80% of cases. The injury itself consists of a tear in the wall of the aorta that is contained by the adventitia of the artery and the parietal pleura, most commonly at the ligamentum arteriosum, but can occur at any fixed point of the aorta. Prompt diagnosis and treatment based on high index of suspicion is paramount. Diagnosis is confirmed by spiral CT angiogram of the chest or conventional angiography. Although most patients do not have specific clinical signs, key symptoms include asymmetry in upper extremity blood pressure, wide pulse pressure, and chest or back pain. Initial CXR may reveal a widened mediastinum (>8 cm), tracheal deviation, an apical pleural cap, or left haemothorax. Transoesophageal echocardiography can make the diagnosis in patients who require immediate transport to the operating room for management of other injuries or for haemodynamically-unstable patients in the ICU who cannot be transported to CT (sensitivity 63%; specificity 84%). Although most aortic injuries are treated surgically, non-operative management is reserved for select patients in whom only intimal injury is identified. Management in those cases is similar to that of atraumatic type B aortic dissections. β-blockade and control of blood pressure to a goal systolic blood pressure of 100 mmHg may decrease risk of rupture, but should only be instituted after acute haemorrhage is controlled. Surgical repair techniques consist of endovascular aortic stent grafts; open repair is reserved for specific injuries where stenting is not a suitable option due to the location of injury or aortic size. Endovascular repair of blunt aortic injury has led to a significant decrease in overall mortality and procedure-related paraplegia.

Penetrating aortic and great vessel injury

Penetrating aortic and great vessel injury carries a high prehospital mortality rate. Those patients who present to hospital are generally *in extremis*, with pericardial tamponade or massive haemothorax, and require immediate surgical exploration.

Oesophagus

Injury to this posterior mediastinal structure is uncommon and usually occurs from penetrating trauma. Other mechanisms such as Boerhaave's injury (rupture of the oesophagus secondary to vomiting) or caustic injury affects the thoracic portion or parts of the oesophagus that are narrowed. Patients present with pain, fever, dyspnoea, or crepitus with subcutaneous emphysema. Diagnosis is often made intra-operatively at the time of thoracotomy or laparotomy for penetrating injury. Chest X-ray or CT scan may reveal mediastinal air or pleural effusion mandating further evaluation of the oesophagus and tracheobronchial tree. Combined careful upper endoscopy and oesophagography, first with gastrografin, then followed by a modified barium swallow, are adequate for evaluation of injury. Surgical management is the mainstay of therapy. Broad spectrum antibiotics, fluid resuscitation, and nutrition are essential supportive therapy.

Thoracic duct

Injury to the thoracic duct is uncommon from blunt or penetrating trauma; it is more commonly seen from iatrogenic trauma. Finding a cloudy/milky pleural effusion, which is rich in chylomicrons and triglycerides, confirms the diagnosis. The consequence is often malnutrition and immunological derangements. Treatment is initially conservative with diets high in medium chain triglycerides and an almost absolute reduction in the long and short chain versions. The use of total parenteral nutrition and octreotide may help. Surgical ligation of the thoracic duct is a last resort.

Acknowledgements

With special thanks to Andrew B. Peitzman for his input into this chapter.

References

1. McSwain NE. (1992). Blunt and penetrating chest injuries. *World Journal of Surgery*, **16**(1), 924–9.
2. Rozycki GS, Feliciano DV, and Ochsner MG. (1999). The role of ultrasound in patients with possible penetrating cardiac wounds: a prospective multi-center study. *Journal of Trauma*, **46**(4), 543–51.
3. Rocco M, Carbone I, and Morelli A. (2008). Diagnostic accuracy of bedside ultrasonography in the ICU: feasibility of detecting pulmonary effusion and lung contusion in patients on respiratory support after severe blunt thoracic trauma. *Acta Anaesthesiologica Scandinavica*, **52**(6), 776–84.
4. Exadaktylos AK, Sclabas G, and Schmid SW. (2001). Do we really need routine computed tomographic scanning in the primary evaluation of

blunt chest trauma in patients with 'normal chest radiograph'? *Journal of Trauma*, **51**(6), 1173–6.
5. Seamon MJ, Shiroff AM, and Franco M. (2009). Emergency department thoracotomy for penetrating injuries of the heart and great vessels: an appraisal of 283 consecutive cases from two urban trauma centers. *Journal of Trauma*, **67**(6), 1250–7.
6. Bulgar EM, Armeson MA, and Mock CA. (2000). Rib fractures in the elderly. *Journal of Trauma*, **48**(6), 1040–6.
7. Enderson BL and Abdalla R. (1993). Tube thoracostomy for occult pneumothorax: a prospective randomized study of its use. *Journal of Trauma*, **35**(5), 726–9.
8. Mowery, NT, Gunter OL, Collier BR, et al. Practice management guidelines for management of hemothorax and occult pneumothorax. *Journal of Trauma*, **70**(2), 510–18.
9. Bergeron E and Lavoie A. (2003). Elderly trauma patients with rib fractures are at greater risk for death and pneumonia. *Journal of Trauma*, **54**(3), 478–85.
10. Ball CG and Kirkpatrick AW. (2005). Incidence, risk factors and outcomes for occult pneumothoraces in victims of major trauma *Journal of Trauma*, **59**(4), 917–24.
11. Miller PR and Croce MA. (2001). ARDS after pulmonary contusion: accurate measurements of contusion volume identifies high risk patients. *Journal of Trauma*, **51**(2), 223–8.
12. Lee RB. (1997). Traumatic injury of cervico-thoracic trachea and major bronchi. *Chest Surgery Clinics of North America*, **285**(5), 285–304.
13. Barmada H and Gibbon JR. (1994). Tracheobronchial injury in blunt and penetrating chest trauma. *Chest*, **106**(1), 74–8.
14. Baumgartner F, Sheppard B, de Virgilio C, et al. (1990). Tracheal and main bronchial disruption after blunt chest trauma: presentation and management. *Annals of Thoracic Surgery*, **50**(4), 569–74.
15. Mandal AK, Thadepalli H, Mandal AK, and Chettipalli U. (1997). Post traumatic empyema thoracis: a 24 year experience at a major trauma center. *Journal of Trauma*, **43**(5), 764–71.
16. Karmy- Jones R and Jurkovich GJ. (2004). Blunt chest trauma. *Current Problems in Surgery*, **41**(3), 223–380.
17. Peitzman A, Rhodes M, Schwab CW, et al. (2008). *The Trauma Manual: Trauma and Acute Care Surgery*, 3rd edn. Baltimore, MD: Lippincott Williams & Wilkins.
18. Pasquale MD and Fabian MT. (1998). Practice management guidelines for screening of blunt cardiac injury. *Journal of Trauma*, **44**(6), 941–56.
19. Demetriades D, Velmahos GC, Scalea TM, et al. (2008). Diagnosis and treatment of blunt thoracic aortic injuries: changing perspectives. *Journal of Trauma*, **64**(6), 1415–19.

CHAPTER 334

Pathophysiology and management of abdominal injury

Steven B. Johnson

Key points

- Haemorrhage and sepsis are the main concerns following blunt and penetrating abdominal trauma, typically occurring early (<12 hours) and late (>5 days), respectively, following injury.
- Solid organ injuries are frequently managed non-operatively. Delayed haemorrhage may occur and angiographic embolization may be beneficial.
- Major hepatic injuries requiring operative intervention frequently require damage control surgery and haemostatic resuscitation.
- Damage control surgery requires close integration of operative and critical care management to aggressively correct physiological derangement characterized by metabolic acidosis, coagulopathy, and hypothermia.
- Abdominal compartment syndrome should be considered in patients manifesting remote organ dysfunction. Bladder pressure monitoring should be considered in patients following abdominal trauma especially in patients requiring large-volume fluid resuscitation.

Abdominal injury: pathophysiology and management

Abdominal organs are injured in approximately 25% of trauma patients. Susceptible to both penetrating and blunt trauma, these injuries present a spectrum from benign to the immediately life-threatening. Haemorrhage and sepsis are the main considerations following acute abdominal trauma, typically occurring early (<12 hours) and late (>5 days), respectively, after injury. Together with the thoracic cavity, retroperitoneum and pelvis, proximal lower extremities, and externally, the abdominal cavity is one of the five locations that can harbour sufficient acute blood loss following trauma to result in hypotension. Sepsis can result from missed or delayed diagnosis of bowel injury, ischaemic bowel injury, bowel perforation or anastomotic leak, abdominal abscess, or infected necrotic tissue.

The optimal critical care management of patients with abdominal trauma is dependent on the early and accurate identification and management of injuries, aggressive resuscitation and correction of physiological derangements, and early recognition and management of complications. Advances in damage control surgery, derived initially for management of abdominal injuries, but recently extended to other types of injuries, necessitates close alignment of operative and intensive care efforts to achieve optimal results.

Solid organ injury

Trauma to the solid organs of the abdomen include injuries to the spleen, liver, pancreas, and kidneys. Management of these injuries in major trauma centres is now more often non-operative, with or without angiographic embolization [1,2]. Non-operative management will be unsuccessful and necessitate operative intervention to control haemorrhage in 8% of hepatic and 7–19% of splenic injuries. The decision to perform non-operative management requires appropriate patient selection (Box 334.1), determination whether embolization would be beneficial, and close monitoring for haemorrhage. An abdominal and pelvic CT scan with intravenous contrast is essential in non-operative management, allowing the assessment of the extent of injury, presence of active contrast extravasation or pseudoaneurysms, extent of haemoperitoneum, and presence of associated injuries that may themselves require operative intervention. Embolization is helpful if active contrast extravasation or pseudoaneurysms are identified on abdominal CT scan [3]. Patients with significant solid organ injury, especially American Association for the Surgery of Trauma grade III–V hepatic injuries, may benefit from embolization. There is little role for embolization in injuries to the pancreas or for renal injuries with urinary contrast extravasation. Similarly, non-operative management of splenic injuries should be avoided in patients with significant portal hypertension or splenic pathology due to the increased risk of delayed haemorrhage.

Following the initial decision to perform operative or non-operative management of a solid organ injury, unique aspects are encountered for each organ. For splenic injuries, the predominant concern is delayed haemorrhage. The risk of delayed haemorrhage following non-operative management is related to the extent of injury, and presence of extravasation or pseudoaneurysms on CT scan. Prolonged bed rest, although commonly employed, does not alter the risk of delayed haemorrhage and patients can be ambulated on post-injury day 1 if other injuries do not preclude ambulation. Routine repeat CT scan to evaluate a splenic injury is not necessary and only indicated for evaluation of an unexplained decrease in haematocrit or increasing leukocytosis.

Box 334.1 Indications for non-operative management of solid organ injury

- **Haemodynamic stability**:
  - Absence of hypotension.
  - One episode of hypotension responsive to less than 2 L of fluid.
- **Minimal transfusions**: two or fewer units of packed red blood cells in first 12 hours.
- **Absence of other indications for laparotomy**:
  - Peritonitis.
  - Other organ injury requiring laparotomy.
- Non-operative management experience of personnel.
- Ability to perform close acute monitoring.
- Ability to provide close post-discharge follow-up.

Typical post-splenectomy related vaccinations are not necessary for patients managed non-operatively. The performance of partial splenic resections has become rare due to the increased use of embolization. Post-operative management of partial splenic resection patients is similar to non-operative management.

The critical care management of hepatic injuries is more complex [4]. For blunt hepatic trauma, the decision to perform operative intervention is based on significant haemodynamic instability and shock. This is typically associated with large blood loss and damage control surgery with perihepatic packing is frequently employed. The management frequently requires implementation of intensive care unit (ICU) damage control principles described later. The aggressive correction of the metabolic acidosis, coagulopathy, and hypothermia, while monitoring for ongoing blood loss are essential. These patients will require additional procedures to manage their injuries and expeditious physiological optimization is the goal. If they have not already undergone embolization prior to surgery, then consideration should be given to performing embolization prior to subsequent procedures. Major hepatic resections may be required, although this is discouraged during the initial procedure, as it may reduce hepatic function especially when associated with a marked hypoperfusion insult or portal triad in-flow occlusion clamping. Due to the associated hypoperfusion, the severity of acute hepatic dysfunction is typically more severe than observed with a similar resection performed on an elective basis. On rare occasions, total hepatectomy may be required, in which case hepatic support with an extracorporeal hepatic assist device for management of the anhepatic condition will be required, while awaiting emergent liver transplantation. In such patients, consideration should be given to intracranial pressure monitoring due to the risk of severe hepatic encephalopathy.

Penetrating hepatic trauma is more likely to require operative intervention because of concern for associated injuries. When compared with blunt trauma, these patients are more likely to undergo operative intervention without having haemodynamic instability and blood loss may be significantly less. Often, only simple hepatorrhaphy or omental packing of the hepatic injury is required and in the absence of hypoperfusion related to associated injuries or portal triad clamping, such injuries may cause minimal hepatic compromise. Alternatively, major penetrating hepatic trauma, especially those associated with high energy projectiles, can result in profound damage. The operative and critical care management is similar to those described for major operative blunt hepatic injuries.

The majority of hepatic injuries managed non-operatively are the result of blunt trauma, and therefore associated injuries, outside of the abdomen are common and may require priority. Early after injury, whether managed with or without embolization, the main risk of non-operative management of hepatic injuries is delayed haemorrhage. Hepatic injuries may also result in significant bile leakage that can result in a marked systematic inflammatory response in the early post-injury period. This response may be difficult to differentiate from that seen with a missed bowel injury. Repeat abdominal and pelvic CT scanning with intravenous contrast is warranted to assess for pneumoperitoneum suggestive of a bowel injury. Hepatobiliary scintigraphy scan can be helpful in determining if a bile leak is present [5]. If a large amount of fluid is observed on repeat CT scan, then paracentesis may be considered with evaluation for bile and microbial culture. Alternatively, patients with blunt hepatic trauma and a persistent marked systemic inflammatory response, and a large haemoperitoneum may undergo laparoscopic evacuation and perihepatic drain placement, typically between post-injury days 5 and 14. Traumatic bilomas that are contained can be treated with percutaneous drainage, but patients with persistent or uncontained bile leaks should undergo endoscopic retrograde cholangiography with common bile duct stent placement or transhepatic cholangiocatheter placement to minimize the bile leak.

Among hepatic trauma patients undergoing embolization, there is a risk of hepatic necrosis. This risk is increased with non-selective hepatic artery embolization or prolonged hypoperfusion. Major hepatic necrosis can be asymptomatic or cause a significant systemic hyperinflammatory response. Abdominal CT scan with intravenous contrast provides valuable information about the extent of hepatic necrosis and proximity to major intrahepatic structures. The most significant complication of major hepatic necrosis is secondary infection, which is not prevented by prophylactic antibiotics. Operative intervention should be considered for symptomatic or infected hepatic necrosis.

Pancreatic injuries can result from blunt or penetrating trauma. Nearly all penetrating pancreatic injuries are diagnosed at laparotomy. Failure to fully evaluate the lesser sac may result in delayed diagnosis of penetrating pancreatic injuries with subsequent marked hyperinflammatory response. Morbidity and mortality of penetrating pancreatic injuries is predominantly related to associated vascular injuries and delays in diagnosis. Blunt pancreatic injuries are more difficult to diagnosis and abdominal CT scan has a sensitivity of only 68% for detecting injury. Missed or delayed diagnosis of blunt pancreatic injuries can result in significant morbidity and mortality and serum amylase and lipase levels should be evaluated following blunt trauma especially in the presence of an unexplained hyperinflammatory condition. Pancreatic injuries are typically managed with peripancreatic drains, which may drain large amounts of fluid rich in pancreatic enzymes. These drains are a cornerstone of pancreatic injury management and should be left in place when draining significant amounts. Patients with persistent drainage may benefit from endoscopic retrograde pancreatography and pancreatic duct stent placement [6].

Hollow viscus injuries

Hollow viscus injuries are more common following penetrating, rather than blunt trauma. They may not be obvious in the first 24 hours, resulting in a delay in diagnosis, and increased morbidity and mortality [7]. Therefore, any patient with a penetrating abdominal injury that does not undergo a complete operative (open or laparscopic) evaluation must be considered at risk for a hollow viscus injury. Unless associated with a mesenteric injury, isolated hollow viscus injuries rarely cause exsanguination. More commonly, they result in abdominal sepsis, either because of delayed or missed bowel perforating injuries or leaks at enteric re-anastomosis sites. Major mesenteric vascular injuries or injuries associated with terminal mesenteric vessels can result in bowel ischaemia without perforation. Delay in return of bowel function, intolerance of enteral nutrition, new onset peritonitis, unexplained leukocytosis, or fever are indications for further evaluation. Abdomen and pelvis CT scan with intravenous and oral contrast are recommended in the absence of obvious surgical indications [8]. The addition of rectal contrast may be valuable to detect colonic perforations.

Damage control

The concept of damage control surgery recognizes that the time and procedures required to perform definitive operative repair may be detrimental when physiological derangements are excessive [9]. These physiological derangements are frequently referred to as the 'vicious bloody cycle of trauma' [10]. The criteria for initiation of damage control are listed in Box 334.2. When these conditions develop, continued operative efforts are detrimental and should be discouraged. Damage control encompasses three phases, each with specific goals and objectives. The initial phase is identification and temporarization. This occurs during the index procedure when damage control criteria are identified or anticipated to develop. During this phase, the procedure is truncated to only control haemorrhage and enteric contamination. This may include performing bowel resections without re-anastomosis, placement of temporary arterial shunts, and packing of major organ injuries. During this phase, haemostatic resuscitation should be initiated with transfusion of equal units of packed red blood cells, fresh plasma, and platelets, also known as 1:1:1 resuscitation [11]. Frequently, such patients are managed with an open abdomen and temporary non-fascial abdominal closure. Planned reoperation for definitive repairs will be required but only after physiological improvements. By definition, severe physiological derangements are present when these patients arrive in the intensive care unit.

Box 334.2 Intra-operative damage control criteria

- pH < 7.20.
- Non-mechanical bleeding related to coagulopathy (INR > 1.8, APTT > 50 seconds).
- Hypothermia (T < 34°C).
- Massive transfusion >10 units of packed red blood cells.

Data from Shapiro MB, et al., 'Damage Control: Collective Review', *Journal of Trauma*, 2000, **49**, pp. 969–78.

The second phase begins on arrival to the intensive care unit where continued aggressive resuscitation to stabilize and correct the physiological derangements are the goal. The continuation of haemostatic resuscitation should occur until correction of the coagulopathy as identified by standard laboratory parameters of coagulation or by thromboelastography (TEG). Not infrequently, these patients have hypofibrinogenaemia and benefit from administration of cryoprecipitate. Active rewarming is often necessary including the use of blood and fluid warming devices to minimize the adverse effects of hypothermia. Shock and the associated metabolic acidosis should be corrected with fluid administration. The administration of sodium bicarbonate or other alkalinizing agents should not occur unless the pH is less than 7.15. Rapid correction of shock induced lactic acidosis, even in the presence of a normal blood pressure, is associated with improved outcomes [12,13]. The goal of this phase is to aggressively restore physiological homeostasis in a timely manner in preparation for the patient returning to the operating room in 24–48 hours for definitive surgery.

The final phase occurs when the patient returns to the operating room for definitive management of their abdominal injuries. During this phase, bowel continuity is re-established or enterostomies performed, arterial reconstructions are completed, and packs removed. The physiological condition of the patient should be significantly improved as a result of ICU care in the second phase. This allows more extensive surgery to be performed without further compromise. On occasion the extent of injuries may result in recurrence of damage control criteria in which case phase 1 and 2 management, and goals should be reinstituted.

Abdominal compartment syndrome

Patients undergoing a trauma laparotomy with closure of the skin or fascia are at risk of developing increased intra-abdominal pressure due to resuscitation related oedema formation [14]. This increased pressure can be significant and result in compromise of remote organ function which is referred to as abdominal compartment syndrome. The presence of abdominal hypertension alone is not abdominal compartment syndrome, there must be associated organ dysfunction, most commonly oliguria, elevated peak and plateau airway pressures, and decreased cardiac output associated with bi-ventricular hypovolemia despite increased preload pressures. Increased intracranial pressures may also occur related to increased abdominal pressure. Patients undergoing large volume (>6 L in 24 hours) fluid resuscitation are at risk to develop abdominal compartment syndrome. Measurement of bladder pressures through an indwelling urinary catheter can be used as a surrogate measurement of intra-abdominal pressures [15]. Bladder pressures over 20 mmHg are suggestive of intra-abdominal hypertension. The management is emergency decompressive laparotomy which may be required at the bedside in the ICU. Successful decompression should rapidly reverse the physiological compromise that resulted from the abdominal hypertension. Absence of improvement is due to insufficient decompression or alternative causes of organ dysfunction. Reductions in intracranial pressure have been observed following decompressive laparotomy.

Open abdomen

In most patients undergoing damage control surgery or decompressive laparotomy, the abdominal wall fascia is left open and

a temporary abdominal closure dressing is applied. This allows preservation of the fascia and minimizes abdominal pressures by providing free expansion of oedematous abdominal contents. The open abdomen technique may be required for a prolonged period, but most trauma surgeons prefer to achieve abdominal closure within the first 7 days. Active fluid removal without causing hypovolaemia, either by diuresis or ultrafiltration, is beneficial in achieving abdominal wall closure. If the abdomen is not closed early then increased morbidity is observed especially the formation of enterocutaneous fistula and prolonged hypermetabolism [16].

Tertiary survey

All patients with blunt abdominal trauma admitted to the intensive care unit should undergo a tertiary survey to detect or exclude occult injuries that were not identified initially. This should occur within 24–48 hours of admission and involves a head to toe examination, and review of all radiological and laboratory studies. By doing a comprehensive tertiary survey, missed injuries can be reduced by 36% [17].

References

1. Como JJ, Bokhari F, Chiu WC, et al. (2010). Practice management guidelines for selective nonoperative management of penetrating abdominal trauma. *Journal of Trauma*, **68**, 721–33.
2. Richardson JD. (2005). Changes in the management of injuries to the liver and spleen. *Journal of the American College of Surgery*, **200**, 648–69.
3. Shanmuganathan K, Mirvis SE, Boyd-Kranis R, et al. (2000). Nonsurgical management of blunt splenic injury: use of CT criteria to select patients for splenic arteriography and potential endovascular therapy. *Radiology*, **217**, 75–82.
4. Kozar RA, Feliciano DV, Moore EE, et al. (2011). Western Trauma Association/critical decisions in trauma: operative management of adult blunt hepatic trauma. *Journal of Trauma*, **71**, 1–5.
5. Mittal BR, Sunil HV, Bhattacharya A, et al. (2008). Hepatobiliary scintigraphy in management of bile leaks in patients with blunt abdominal trauma. *Australia and New Zealand Journal of Surgery*, **78**, 597–600.
6. Subramanian A, Dente CJ, and Feliciano DV. (2007). The management of pancreatic trauma in the modern era. *Surgical Clinics of North America*, **87**, 1515–32.
7. Fakhry SM, Broenstein M, Watts DD, et al. (2000). Relatively short diagnostic delays (<8 h) produce morbidity and mortality in blunt small bowel injury: an analysis of time to operative intervention in 198 patients from a multicenter experience. *Journal of Trauma*, **48**, 408–15.
8. Petrosoniak A, Engels PT, Hamilton P, et al. (2013). Detection of significant bowel and mesenteric injuries in blunt abdominal trauma with 64-slice computed tomography. *Journal of Trauma and Acute Care Surgery*, **74**, 1081.
9. Rotondo MF, Schwab CW, McGonigal MD, et al. (1993). 'Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. *Journal of Trauma*, **35**, 375–82.
10. Cotton BA, Guy JS, Morris JA, et al. (2006). The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. *Shock*, **26**, 115–21.
11. Holcomb JB, Wade CE, Michalek JE, et al. (2008). Increased plasma and platelet to red blood cell ratios improves outcome in 334 massively transfused civilian trauma patients. *Annals of Surgery*, **248**, 447–58.
12. Claridge JA, Crabtree TD, Pelletier SJ, et al. (2000). Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. *Journal of Trauma*, **48**, 8–15.
13. Abramson D, Scalea T, Hitchcock R, et al. (1999). Lactate clearance and survival following injury. *Journal of Trauma*, **35**, 584–8.
14. Rizoli S, Mamtani A, Scarpelini S, et al. (2010). Abdominal compartment syndrome in trauma resuscitation. *Current Opinion in Anaesthesiology*, **23**, 251–7.
15. Zengerink I, McBeth PB, Zygun DA, et al. (2008). Validation and experience with a simple continuous intra-abdominal pressure measurement technique in a multidisciplinary medical/surgical critical care unit. *Journal of Trauma*, **64**, 1159–64.
16. DuBose JJ, Scalea TM, Holcomb JB, et al. (2013). Open abdominal management after damage-control laparotomy for trauma: a prospective observational American Association for the Surgery of Trauma multicenter study. *Journal of Trauma and Acute Care Surgery*, **74**, 113–22.
17. Biffl WL, Harrington DT, and Cioffi WG. (2003). implementation of a tertiary trauma survey decreases missed injuries. *Journal of Trauma*, **54**, 38–44.

CHAPTER 335

Management of vascular injuries

Ramyar Gilani and Kenneth L. Mattox

Key points

- Prioritizing injuries and controlling the resulting sequelae are the predominant guiding principles in managing vascular injuries; the highest priority is saving the patient's life.
- Control of haemorrhage is life-saving and usually rapid, vascular reconstruction is often neither; definitive repair may need to be delayed while the patient is stabilized.
- Vascular trauma is almost invariably associated with injuries to other organ systems and many patients with vascular trauma are critically ill with limited physiological reserve.
- Endovascular repair may allow safe and efficacious intervention with less overall impact on the patient than open surgery.
- Vascular trauma may have a profound effect on the coagulation system; transfusion using a 1:1:1 ratio of packed red blood cells, fresh frozen plasma, and platelets is currently considered the best strategy.

Introduction

Despite significant advances in modern trauma care, management of vascular injuries continues to present a unique set of challenges involving all phases of patient care. Prioritizing injuries and controlling the resulting sequelae are the predominant guiding principles; paramount priority is given to saving a patient's life. Vascular trauma is almost invariably associated with injuries to other organ systems and with marked physiological derangements, and as a result many patients with vascular trauma are critically ill and while control of haemorrhage is life saving and usually rapid, vascular reconstruction is often neither. Complex vascular reconstructions in critically-wounded patients are often not practical.

Categorization of injuries can be made based on resulting life-threatening haemorrhage or distal ischaemia. Success with both entities is time dependent and, as a result, all that is technically feasible is not often in the patient's best interest. Vascular repairs for trauma should always adhere to principles derived from experience through elective and emergent procedures with continued evaluation of patient physiological envelope. When appropriate, imaging via computed tomographic angiography (CTA) or digital subtraction angiography (DSA), assists in expeditious diagnosis of vascular injuries, which then must undergo appropriate prioritization taking into account the patients overall clinical condition and the urgency of treating other injuries.

Recent advances in technology have expanded the application of intraluminal vascular solutions to vascular injuries. Endovascular techniques allow safe and efficacious interventions to occur with decreased overall impact to patients [1,2]. Finally, much recent focus has been placed upon vascular trauma and its profound impact on coagulation. Insults to this delicate framework due to various forms of traumatic injury severely disrupt the dynamic homeostatic environment of the vascular and haematological systems resulting in severe physiological derangements.

General principles

Injury assessment

Patient presentation with vascular injury can be quite variable even with similar injury patterns and this mandates flexibility in treatment algorithms. However, patterns of injury remain relatively finite in number and pattern recognition can assist with the categorization of injury severity. Penetrating trauma results in simple laceration, partial wall disruption or complete vessel transection. In addition, cavitation from high-velocity missiles can result in further injury that is not appreciable at initial inspection. Injury from blunt trauma leads to intimal flap, partial wall disruption, avulsion of branches, or complete vessel transection. Resulting haemorrhage indicates disruption of vessel wall architecture, whereas distal ischaemia indicates loss of lumen integrity.

Severity of haemorrhage and ischaemia must be noted early and their impact continuously and repeatedly assessed. A patient who is nearly exsanguinated from a stab wound to the brachial artery and arrives in the hospital unresponsive with a barely palpable pulse and a pH of 6.9 is clearly not a candidate for any type of vascular exploration. A patient with gunshot injuries to the liver, duodenum, colon, inferior vena cava, and right renal artery, even though appearing stable after initial control of haemorrhage and blood replacement, has in fact sustained a major insult. After an hour of surgery, transfusion of 10 units of blood, and a resulting temperature of 32°C, any attempt at renal revascularization may be lethal to this patient.

Exposure and vessel control

Initial control of haemorrhage is usually performed by applying direct manual pressure over the site of bleeding. Alternatively, tourniquets can be used for life-threatening extremity haemorrhage that cannot be controlled with manual pressure. Tourniquets should be removed as soon as possible. Adjunctive haemorrhage control techniques include the use of balloon catheters into a bleeding cavity providing external compression and tamponade [3]. Attempts at blind clamping without proper visualization should be avoided as they are often ineffective and result in injury to adjacent structures.

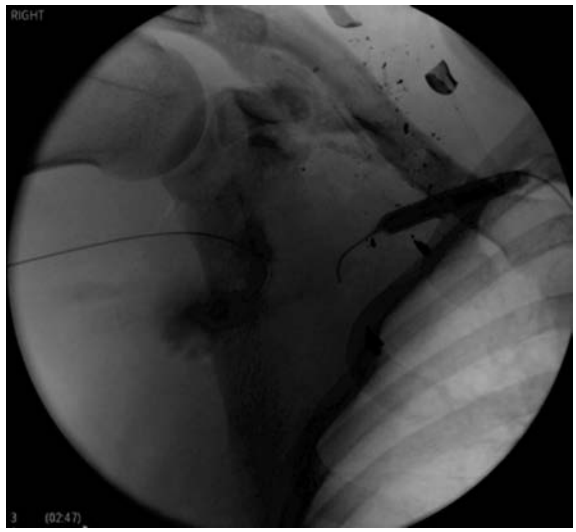


Fig. 335.1 Proximal balloon control of the subclavian artery, while performing endovascular repair.

Surgical haemorrhage control begins with proper exposure often beginning outside the zone of injury. For example, haemorrhage from a carotid artery may begin with a sternotomy and an injured common femoral artery may be approached first through a laparotomy. Injuries of the extremity and neck are exposed via axial incisions beginning beyond the injury. Within the chest, proper selection of incision provides access away from injury. Vessels within the abdomen are exposed via mobilization manoeuvres beyond zones of haematoma.

Although very effective, traditional surgical techniques can be suboptimal in situations such as transition zones, re-operative fields or for patients in extremis. Newer paradigms emphasize the principles of expeditious vessel control, while overcoming such challenges by shifting focus from the immediate area of injury towards a more familiar environment and utilizing the structural continuity of vessels to obtain access into proximity location and ultimately establishing flow control. Angiographic balloon control can be achieved expeditiously and without much technical difficulty (Fig. 335.1) [4]. Using standard over-the-wire techniques, a balloon catheter is guided into proper position proximal to the site of extravasation and inflated (Box 335.1). Once control is established, repair can be pursued either through a continued endovascular approach or in combination with open surgery.

Damage control

'Damage control resuscitation' refers to a surgical strategy intended to guide the management of a multiply-injured patient requiring collective interventions that would be exhaustive to physiology if performed without pause. With this approach, the traditional single definitive operation for trauma is replaced by staged operations, whereby a rapid operation is followed by a delayed more complex reconstruction after the patient's physiology has been stabilized [5,6]. The underlying premise is that prolonged operation in the severely-injured patient is further harmful to already deranged physiology. Prolonged operations and massive blood replacement result in a triad of hypothermia, acidosis, and coagulopathy that can be self-propagating and fatal [7].

Box 335.1 Approximate vessel sizes for balloon selection

- **Innominate**: 10–14 mm.
- **Carotid/subclavian/axillary**: 8–12 mm.
- **Common iliac**: 8–10 mm.
- **External iliac**: 6–8 mm.
- **Aortic bifurcation**: bilateral common iliac balloons, Fogarty balloons or aortic occlusion balloon (32, 40 mm; 46 mm).
- **Aorta**: 32, 40 mm; 46 mm.

Therefore, it is vital to distinguish between simple and complex vascular repair techniques. Simple repairs are rapid and include simple lateral repair, ligation, and temporary shunt insertion. The last two can also be viewed as vascular 'damage control' techniques. Complex repairs are more time-consuming and include patch angioplasty, end-to end anastomosis, and graft interposition [8]. Although simple repairs are feasible even under adverse physiological circumstances, complex repairs may not be. However, the decision not to restore vessel continuity may force the surgeon to accept tissue loss in order to save the patient's life. These are some of the most difficult decisions in trauma vascular surgery.

Repair techniques

Thrombectomy

Disruption to the vessel wall or lumen integrity leads to alterations in flow and resulting thrombosis. As a result, prior to re-establishment of flow, surgical thrombectomy is a necessary adjunct to remove any potential luminal thrombus. Once control is established, balloon catheters appropriate in size are passed proximally and distally until no further thrombus is yielded and preferably flow is appreciated.

Lateral repair

Technical keys to accomplishing a direct lateral repair of an injured vessel include debridement of the damaged wall and tension-free suture repair of the vessel wall preferably in a transverse fashion to avoid stenosis of the vessel lumen. Most would consider a mural defect of more than half the vessel circumference to be the upper limit of damage amenable to direct repair; but, in fact, as long as some of the posterior wall is present and the transverse orientation of the repair can be maintained, it is possible to re-approximate even large defects without tension. Additional dissection along the axis of the vessel may provide additional length for tension-free repair. In larger vessels such as the inferior vena cava (IVC) or aorta, simple lateral repair with some luminal narrowing is acceptable.

Ligation

Ligation is a valid technical option when the injured vessel is inaccessible, reconstruction is difficult, or more commonly the patient is too unstable to allow for other approaches. Ligation is quite well tolerated for arteries of distribution, such as the external carotid or internal iliac arteries. For arteries of conduction, such as the external iliac or superficial femoral arteries, ligation is often not

plausible and other forms of 'damage-control', such as shunting should be considered. Many injured veins can be ligated with the only resulting consequence being distal oedema to varying degrees [9]. However, ligation of certain veins such as the portal vein, superior mesenteric vein, suprarenal IVC, right renal vein and popliteal veins carries increased risk of end-organ damage that is not well defined.

Temporary shunting

The use of temporary vascular shunts is a simple and expeditious 'damage-control' option that has been extensively described by civilian and military surgeons [10,11]. It should be considered as a distal organ-preserving manoeuvre when more complex repair is not possible, this may be due to the patient's general condition or to surgeon capability. A commercially available carotid shunt, endotracheal suction catheter, or a piece of sterile nasogastric tube trimmed to the appropriate length can be inserted into both ends of a disrupted vessel and cinched in place with ties or Rummel tourniquets (Fig. 335.2). It is helpful to secure the shunt beyond side branches to avoid migration of the cinching apparatus. Also, appropriate thrombectomy should be performed prior to re-establishing flow. When the patient's condition allows and appropriate surgical expertise is available the patient can return to the operating room for shunt removal and definitive reconstruction.

Short-term (3–6 hours) shunt patency is very good when placed proximal to the elbow or knee and is maintained without systemic anticoagulation. Shunt dislodgement is an infrequent occurrence [12]. Indications for shunt placement are the following:

- Peripheral vascular injury requiring transfer from a remote facility to a trauma centre, where vascular reconstruction will be undertaken.
- Maintain perfusion, while addressing other life-threatening injuries.
- Perform skeletal alignment before vascular reconstruction.
- For 'damage control' in severely-injured patients who have exhausted their physiological reserves.

Primary end-to-end anastamosis

Primary end-to-end repairs of injured arteries are often performed in the setting of low energy penetrating wounds causing laceration to the vessel wall. Injuries from high-energy projectiles are often very difficult to approximate together in a tension-free anastomosis after adequate vessel debridement. The technical principles of vascular anastomosis apply equally well to direct end-to-end anastomosis and to graft interposition: arterial ends smaller than 1 cm in diameter should be bevelled, balloon thrombectomy should be performed distally and proximally, and both segments should be flushed with heparinized saline.

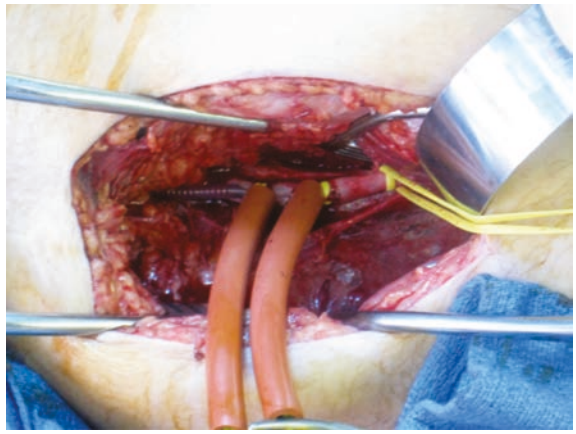


Fig. 335.2 Temporary shunt placed in the popliteal artery.

Interposition grafts

An interposition conduit is used for extensive vessel injury when simpler reconstructive options are inappropriate. Considerable discussion, debate, and research have focused on the use of synthetic versus autogenous grafts. Currently, for vessels of 5 mm or less in diameter, the use of a saphenous vein graft is the only practical option [13]. The use of prosthetic material in a contaminated field is also a subject of considerable debate. One option is to ligate the injured vessel and perform an extra-anatomic bypass around the contaminated area. The classic example is ligation of the iliac artery in an abdomen with gross faecal spillage and performance of a femoro-femoral bypass graft. In some instances, such as reconstruction of an injured abdominal aorta, it is virtually impossible to avoid reconstruction in an area of contamination.

A major advantage in the use of synthetic grafts is not requiring time for conduit harvest and preparation. A technical pitfall in graft selection for arterial trauma is inappropriate size selection. The arteries of young trauma victims are often surprisingly small, especially in the patient who is hypotensive and vasoconstricted. A conscious effort should therefore be made to select a slightly larger graft size than that thought to be appropriate.

Endovascular repair

Rather than clamp, sew, and tie, endovascular interventions can be thought of in terms of balloon, stent, and coil. The ability to obtain intraluminal vascular control especially in areas difficult to expose, such as subclavian arteries [14], or re-operative fields cannot be overestimated. Furthermore, once control has been established, intervention can continue with endovascular techniques or can be converted to an open procedure.

In contrast to balloons, stents are almost always intended for therapeutic intervention. They are designed as balloon-expandable or self-expanding and constructed as bare-metal or covered with graft material, and are available in any combination of those characteristics depending on intended use. Furthermore, stents are available in a wide array of sizes allowing for interventions in arteries ranging from coronary arteries to the aorta. Covered stents are intended to seal an area of injury or an arteriovenous fistula whereas bare-metal stents are designed to achieve luminal gain for intimal flap or dissection.

Surgical wisdom advices against 'cavalier' surgical methods for haemorrhage from arteries of distribution, such as hypogastric and profunda femoris arteries. Uncontrolled bleeding from these vessels can create a difficult dilemma requiring directed haemorrhage control without causing additional collateral damage. A solution lies in the use of angiographic coils. These coils are constructed with various materials all of which are designed to stagnate blood flow and result in thrombosis. They can be directly delivered to the site of injury, while minimizing damage and further thrombosis to adjacent structures and vessels.

Haemorrhage and coagulopathy

Trauma to the vascular system can cause significant disruption in the flow of blood leading to haemorrhage and thrombosis. Disruption of the vessel wall can lead to active haemorrhage, shock and a systemic inflammatory response. Damage to the layers of the vessel wall may cause cessation of blood flow, thrombosis, and impaired distal perfusion. Ongoing haemorrhage produces signs of haemorrhagic shock once 15% of blood volume is lost and loss beyond 40% is immediately life-threatening [15]. Haemorrhage control is paramount in vascular trauma not only because uncontrolled bleeding is eventually lethal, but it also places severe stress on physiological reserves and corrective manoeuvres such as surgery and anaesthesia can have additional negative effects.

Ongoing haemorrhage is accompanied by consumption of coagulation components, which can lead to a consumptive coagulopathy. Targeted blood component therapy should be initiated once large volume blood loss is anticipated. Use of thromboelastogram (TEG) has a role in trauma as results can be generated and acted upon rapidly [16]. However, waiting for laboratory evaluation of coagulation status should not delay blood component therapy. Transfusion using a 1:1:1 ratio of packed red blood cells (pRBCs), fresh frozen plasma (FFP) and platelets (PLTs) is currently considered the best strategy and is adjusted based on need [17].

With active ongoing haemorrhage and fluid resuscitation, hypothermia is almost inevitable, and exposure of large areas of skin may make correction of hypothermia quite difficult. The surrounding environment should facilitate maintenance of core body temperature. Active warming should be initiated early to prevent hypothermia from occurring. Keeping operative times to a minimum will also help to reduce heat loss and its consequences.

Ischaemia and the resulting acidosis from shock, thrombosis, and even vascular control have a definite impact on coagulation. Therefore, attempts should be made to minimize the impact of ischaemia and acidosis on coagulation. Haemodynamic status needs constant attention to optimize end organ perfusion through intravascular volume expansion or inotropic support. In the setting of thrombosis, rapid restoration of blood flow helps decrease ischaemic time and subsequent acidosis whereas cross-clamping for vascular control may worsen acidosis. Furthermore, in addition to causing ischaemia of other vital abdominal organs, supra-coeliac clamping causes hepatic ischaemia and may further worsen coagulopathy; consequently, clamp times must be kept to a minimum.

References

1. White R, Krajcer Z, Johnson M, Williams D, Bacharach M, and O'Malley E. (2006). Results of a multicenter trial for the treatment of traumatic vascular injury with a covered stent. *Journal of Trauma*, **60**, 1189–96.
2. Demetriades D, Velmahos G, Scalea T, et al. (2008). Operative repair or endovascular stent graft in blunt traumatic thoracic aortic injuries: results of an American Association for the Surgery of Trauma Multicenter Study. *Journal of Trauma*, **64**, 561–70.
3. Feliciano DV, Burch JM, Mattox KL, Bitondo CG, and Fields G. (1990). Balloon catheter tamponade in cardiovascular wounds. *American Journal of Surgery*, **160**, 583.
4. Gilani R, Tsai PI, Wall MJ Jr, and Mattox KL. (2012). Overcoming challenges of endovascular treatment of complex subclavian and axillary artery injuries in hypotensive patients. *Journal of Trauma and Acute Care Surgery*, **73**(3), 771–3.
5. Burch JM, Ortiz VB, Richardson RJ, Martin RR, Mattox KL, and Jordan GL Jr. (1992). Abbreviated laparotomy and planned reoperation for critically injured patients. *Annals of Surgery*, **215**, 476.
6. Morris JA Jr, Eddy VA, Blinman TA, Rutherford EJ, and Sharp KW. (1993). The staged celiotomy for trauma: issues in unpacking and reconstruction. *Annals of Surgery*, **217**, 576.
7. Ferrara A, MacArthur JD, and Sright HK. (1990). Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *American Journal of Surgery*, **160**, 515.
8. Schickler WJ and Baker RJ. (1992). Types of vessel injuries and repairs. In: Flanigan DP (ed.) *Civilian Vascular Trauma*, p. 36. Philadelphia, PA: Lea & Febiger.
9. Bermudez KM, Knudson MM, Nelken NA, et al. (1997). Long-term results of lower-extremity venous injuries. *Archives of Surgery*, **132**, 963–8.
10. Johansen K, Bandyk D, Thiele B, Hansen ST Jr. (1982). Temporary intraluminal shunts: resolution of a management dilemma in complex vascular injuries. *Journal of Trauma*, **22**, 395.
11. Gifford SM, Aidinian G, Clouse WD, et al. (2009). Effect of temporary shunting on extremity vascular injury: an outcome analysis from the Global War on Terror vascular injury initiative. *Journal of Vascular Surgery*, **50**, 549–55.
12. Rasmussen TE, Clouse WD, Jenkins DH, Peck MA, Eliason JL, and Smith DL. (2006). The use of temporary vascular shunts as a damage control adjunct in the management of wartime vascular injury. *Journal of Trauma*, **61**, 8–12.
13. Feliciano DV, Mattox KL, Graham JM, and Bitondo CG. (1985). Five year experience with PTFE grafts in vascular wounds. *Journal of Trauma*, **25**, 71–82.
14. DuBose JJ, Rajani R, Gilani R, et al. (2012). Endovascular management of axillo-subclavian arterial injury: a review of published experience. *Injury*, **43**(11), 1785–92.
15. American College of Surgeons. (1997). *American College of Surgeons Committee on Trauma: Advanced Trauma Life Support Coarse Manual*. Chicago, IL: American College of Surgeons.
16. Tapia NM, Chang A, Norman M, et al. (2013). TEG-guided resuscitation is superior to standardized MTP resuscitation in massively transfused penetrating trauma patients. *Journal of Trauma and Acute Care Surgery*, **74**(2), 378–85.
17. Holcomb JB, del Junco DJ, Fox EE, et al. (2013). The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *Journal of American Medical Association: Surgery*, **148**(2), 127–36.

CHAPTER 336

Management of limb and pelvic injuries

Omar Sabri and Martin Bircher

Key points

- Pelvic injuries with disruption occur mainly due to motor vehicle accidents or falls from height.
- Less than 10% of pelvic injuries cause haemodynamic instability due to haemorrhage, where this occurs stabilization with a pelvic binder and correction of acidosis, coagulopathy, and hypothermia should be prioritized.
- Mechanical disturbance of the primary clot by log-rolling the patient or springing of the pelvis are strongly discouraged.
- Pelvic ring injuries are associated with significant concomitant injuries, including urinary, gastrointestinal, neurological, and reproductive organ injury.
- Limb trauma can be life or limb threatening; early identification, splinting, and resuscitation follow the same guidelines as for pelvic ring injuries.

Pelvic trauma

Anatomical considerations

The bony pelvis is made up of the two innominate bones and the sacrum. The two innominate bones are joined anteriorly at the symphysis pubis, while both innominate bones articulate with the sacrum posteriorly at the sacroiliac joints. The pelvis behaves as a ring with ligamentous structures joining the bony elements. The posterior ligamentous structures (sacroiliac ligaments) are some of the strongest in the body (Fig. 336.1).

The main functions of the pelvic ring are to transfer load between the spine and the lower limbs, protect internal organs and allow for muscle and vital organ attachment in order to facilitate their function. The ring has to therefore remain a stable structure to continue performing its functions.

Incidence and demographics

Pelvic fractures account for approximately 3% of all skeletal injury after blunt trauma [1], most result from motor vehicle crashes and falls from a height.

Significant disruption needs a deceleration force of at least 30 mph, which explains the high incidence of concomitant injuries in patients presenting with pelvic injuries [1].

The average age is 40 years old with a male predominance [2]. Pelvic fractures in the elderly are usually low energy and rarely result in instability. Less than 10% of pelvic fractures will result in haemodynamically instability from haemorrhage.

Pathophysiology

There are several classification systems available to describe the anatomical and biomechanical aspects of pelvic ring injuries. The most widely used and accepted is that of Young & Burgess [3] that relies on the description of the direction and magnitude of the energy sustained by the pelvis. Its categories are lateral compression, anteroposterior compression, vertical shear, and combined mechanical instability (Fig. 336.2). Each category is further subdivided into 1, 2, and 3 depending on pattern and the degree of displacement. In injuries where a mild amount of energy is absorbed, the pelvic ring tends to fail anteriorly first; symphysis pubis diastasis or pubic rami fractures of different configurations occur at the front. This is usually accompanied by some degree of strain to the sacrospinous and sacrotuberous ligaments.

With the continued application of force, the pelvic ring then fails posteriorly. This can occur at the sacroiliac joint, through a sacral fracture or through the posterior aspect of the iliac wing (crescent fracture). Sacral fractures can be difficult to identify on plain radiographs and the exact configuration is better appreciated on CT scans. The Denis Classification of vertical sacral fractures associated with a pelvic ring injury is widely used and accepted, and is a good predictor of neurological injury. It relies on the position of the vertical fracture line in relation to neural foramina:

- **Type I**: the fracture line runs lateral to the neural foramina. Nervous structures are generally are not affected.
- **Type II**: this type incorporates transforaminal fractures of the sacrum, frequently associated with lesions of sacral nerve roots (25% incidence).
- **Type III**: central fractures of the sacrum involve the sacral spinal canal and are therefore associated with 50% concomitant neurological injuries (Fig. 336.3).

Bleeding following a pelvic ring injury can be life threatening. The mechanism of injury has been directly linked to the amount of blood loss [4]. The majority of pelvic bleeding is venous arising mainly from the posterior presacral and paravesical venous plexus, and from bleeding cancellous surfaces. Such bleeding will quickly fill retroperitoneal space and the formation of a clot in that space is essential to stop further bleeding. In approximately 10% of cases with significant pelvic bleeding, an arterial injury will be the cause.

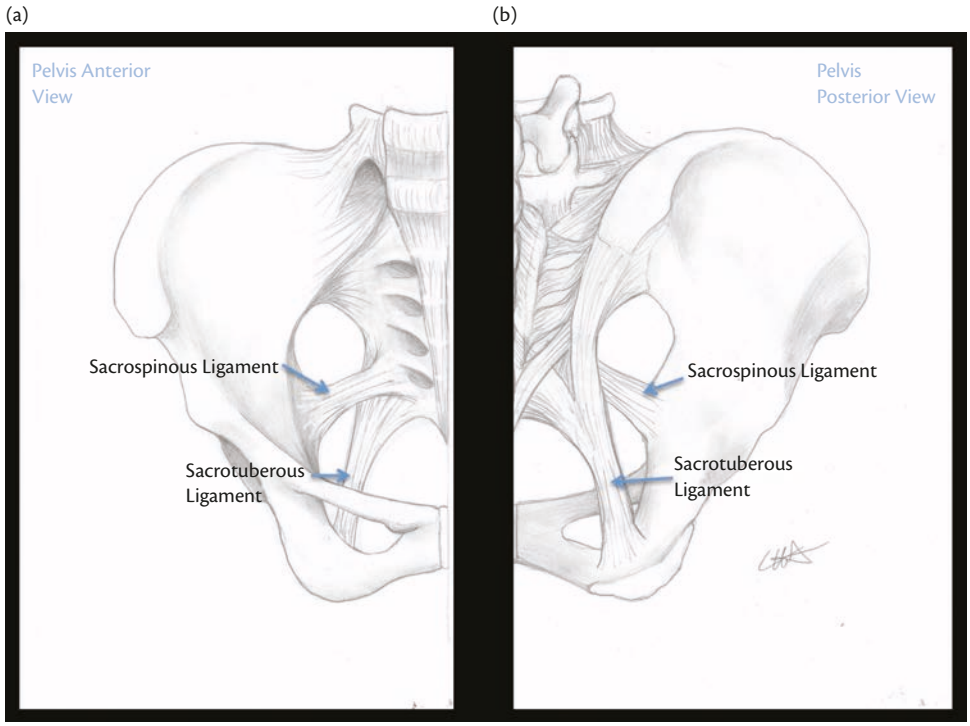


Fig. 336.1 (a) Anterior and (b) posterior views of the pelvis.
Reproduced with permission from Miss Laura Hamilton.

The bony pelvis also provides protection and soft tissue attachments for intrapelvic organs. The integrity of the pelvic floor is an important consideration and the direction of displacement can give an indication of associated soft tissue injury. Urogenital injuries are most common with anteroposterior compression and lateral compression injuries, while neurovascular injuries are more common in vertical sheer type injuries. More than 80% of patients with unstable pelvic fractures have additional musculoskeletal injuries.

Open fractures

Although a rare occurrence, open pelvic fractures are very serious injuries and carry a mortality of up to 50% [5]. The open nature of the fracture can be due to penetration of rectum or vagina, as well as through external wounds. Open injuries are frequently missed and often only discovered at time of surgery.

Management

Pre-hospital care

Having established that pelvic ring injuries are potentially life threatening and that a significant amount of energy is needed to create such injuries, the management of pelvic fractures begins at the scene. The mechanism of injury should be the first indicator of a possibility of a pelvic ring injury. Motor vehicle accidents and falls of greater than 2 m are the most common modes of injury. A pelvic binder should be applied at the scene in any major trauma patient especially if hypotensive. There is good evidence that the binder is effective in pelvic stabilization and can be life-saving irrespective of the injury pattern [6]. The binder needs to be applied correctly over the greater trochanters and inspected regularly for pressure necrosis should it be left on for more than 24 hours.

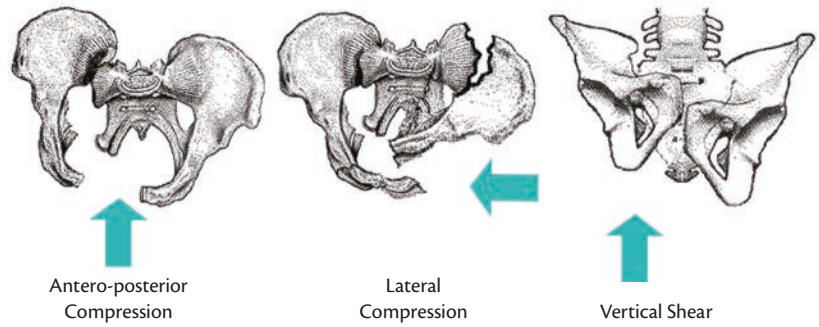


Fig. 336.2 Young & Burgess Classification of Pelvic ring injuries. Arrows denote the direction of force striking the pelvis.
Data from Burgess AR et al. 'Pelvic ring disruptions: effective classification system and treatment protocols', *Journal of Trauma*, 1990, **30**, pp. 848–56.

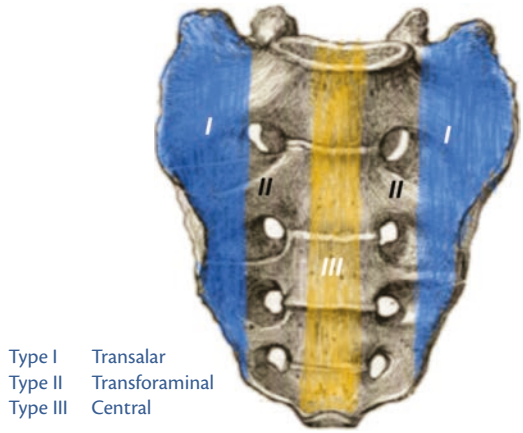


Fig. 336.3 Denis Classification of vertical fractures of the sacrum associated with a pelvic ring injury.
Data from Denis F et al., 'Sacral fractures: An important problem. Retrospective analysis of 236 cases', *Clinical Orthopaedics and Related Research*, 1988, **227**, pp. 67–81.

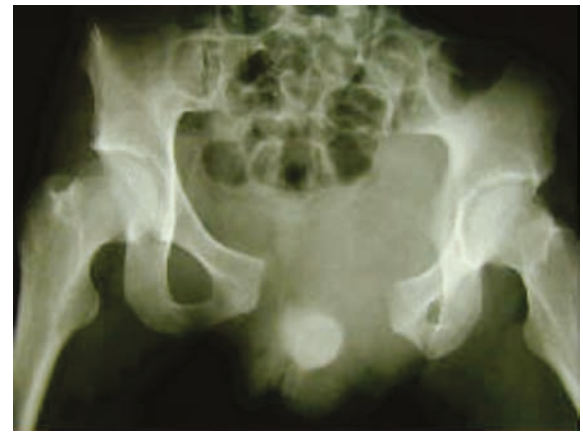


Fig. 336.4 Pelvic ring injury with significant displacement raising the suspicion of haemodynamic instability.
BCVI Injury Grades: Reproduced from Biffl WL et al., 'Blunt carotid arterial injuries: implications of a new grading scale', *The Journal of Trauma and Acute Care Surgery*, 47(5), pp. 845–853, copyright 1999, with permission from Wolters Kluwer.

Haemorrhage control

The pelvis is next evaluated in the emergency department. Following Advance Trauma Life Support (ATLS) guidelines, pelvic injuries are addressed during the 'Circulation with Haemorrhage Control' part of the primary survey [7] . Springing or stressing the pelvis is now discouraged if an injury is suspected. It's both unreliable and risks disturbing the retroperitoneal clot. A pelvic X-ray used as an adjunct to the primary survey should be obtained early (Fig. 336.4).

If a pelvic ring injury is identified, resuscitation should continue with the pelvic binder *in situ*. Log rolling the patient is contraindicated if a pelvic ring injury is identified as this also risks disturbing a retroperitoneal clot. The best clot is the first clot and every effort should be made to preserve it. The retroperitoneal space can easily accommodate 2–2.5 L of blood.

Damage control resuscitation

The concept of damage control resuscitation (DCR), which started in the military, is now well accepted and is being adopted in civilian trauma centres. Initial resuscitation for severely-injured patients is based on a strategy of permissive hypotension and blood product resuscitation guided by patient's physiological response. In severely-injured trauma patient with ongoing major haemorrhage, there is improved outcome from early haemostatic resuscitation compared to large volume clear fluid resuscitation [8]. In the UK, NICE (National Institute for Care Excellence) recommends that crystalloid fluid therapy should only be administered to a trauma patient if there is an absent radial pulse. Boluses of 250 mL of crystalloid should be given, while the patient is transported to hospital without delay and the radial pulse intermittently checked. Haemostatic transfusion (also referred to as massive transfusion protocols) should be initiated early. Most transfusion protocols will contain plasma and platelets, as well as packed cells in an attempt to replenish clotting factors. Tranexamic acid has also been shown to be effective in reducing mortality as a result of significant bleeding [9]. It is most effective when administered as a 1 g bolus within the first 3 hours following the injury.

In approximately 90% of haemodynamically unstable patients with pelvic ring injuries, the previously outlined measures should be sufficient to control haemorrhage and stabilize the patient. In the remaining 10% of patients who continue to exsanguinate, more aggressive intervention is needed.

In a major trauma centre, a combination of surgical stabilization, pelvic packing and angiographic embolization can be used if general resuscitative measures do not control the bleeding. The management algorithm is dependent on available local resources. The use of cell-savers and other auto-transfusion devices has become standard practice during pelvic and acetabular surgery.

The lethal triad

The 'bloody vicious cycle' of coagulopathy, hypothermia, and acidosis should be corrected simultaneously to give the patient the best chance of survival. Surgical intervention to stabilize the pelvis has been shown to help control haemorrhage and avoid late complications. The timing of surgery is based on the patient's physiological state. A traffic light system of monitoring venous lactate, in conjunction with correcting acidosis, hypothermia and coagulopathy, has been shown to be effective in guiding management [10]. A venous lactate greater than 2.5 mmol/L is a STOP sign for surgical intervention, as the surgery will provide another physiological insult that a compromised patient may not tolerate. A venous lactate of less than 2 mmol/L is GO for surgical stabilization. If the venous lactate is between 2 and 2.5 mmol/L, then the trend is observed with descending pattern being favourable for surgery.

Dynamic assessment and observing of trends during resuscitation with regular communication between the decision-making clinicians has been demonstrated to improve overall safety and team effectiveness.

Urinary and bowel injury

The incidence of urethral lacerations and bladder ruptures in complex pelvic injuries appears to be 5–10%. The perineum should be inspected for any external signs of a urological injury. Blood at the external meatus is a sign of potential urethral or bladder injury. One catheterization attempt by an experienced practitioner should be performed along with a retrograde urethrogram. Early urological consultation should be sought if an injury is suspected

or catheterization fails. A suprapubic catheter or complete urinary diversion may have to be undertaken in severe cases.

Open injuries

In addition to inspection of the perineum, an open pelvic ring injury is not excluded until rectal and vaginal examinations have been performed. If this is not possible in the emergency department, it should be documented as 'outstanding' and eventually performed once the patient is stabilized or prior to surgery. Early administration of intravenous antibiotics with Gram-positive and -negative cover is now considered life saving in these injuries. If a rectal or bowel injury is suspected, a diverting colostomy with placement in the upper abdomen is advised.

Surgical stabilization and reconstruction

The aim of sophisticated reconstruction of the pelvis is the prevention of deformity. Deformity can occur as a result of fracture displacement at the time of injury or develop over time because of loading through unstable fractures or disrupted ligaments. Unequal leg length, rotational inequality of the legs and asymmetry of the ischial tuberosities resulting in a sitting deformity, are sequelae of malunited fractures of the pelvis.

Anterior ring

Injuries of the anterior part of the pelvic ring are best treated by open reduction and internal fixation. The type of fixation used will be determined by the pattern of injury the options available include plate fixation and column screws.

Anterior plating (Fig. 336.5) for a symphyseal diastasis normally only requires a Pfannenstiel-type incision and it is common to discover that the insertion of the rectus abdominis muscles has been avulsed from the anterior aspect of the pubis, making dissection relatively straightforward.

Where injury to the anterior part of the pelvic ring is complex and involves the pubic rami, additional access for longer plates may be required. Image-guided and/or navigated column screws (Fig. 336.6) may be used if the fracture is minimally displaced after closed reduction.

Pelvic external fixation is a good method of surgical pelvic stabilization. It can be used in the emergency setting or as definitive fixation. Several pin and bar configurations can be utilized, but the authors' preferred method is the use of two supra-acetabular pins and two iliac crest pins with either a low or a high bar configuration (Fig. 336.7a, b). If severe pelvic displacement is present, skeletal traction through a distal femoral pin can also be utilized in combination with the external fixator.

Posterior ring

Stabilization of the posterior structures of the pelvic ring can be achieved by a combination of closed or open reduction, percutaneous screw fixation or plate fixation.

Complications

Venous thromboembolism

Pelvic fractures are a risk factor for venous thromboembolism. Currently, the natural history of pelvic vein thrombosis is not known, but evidence suggests that more proximal clots are more likely to embolize. Pulmonary embolism is a potentially lethal complication in patients with pelvic and acetabular fractures, and has been reported as the most common fatal complication after operation or trauma to the lower extremities.

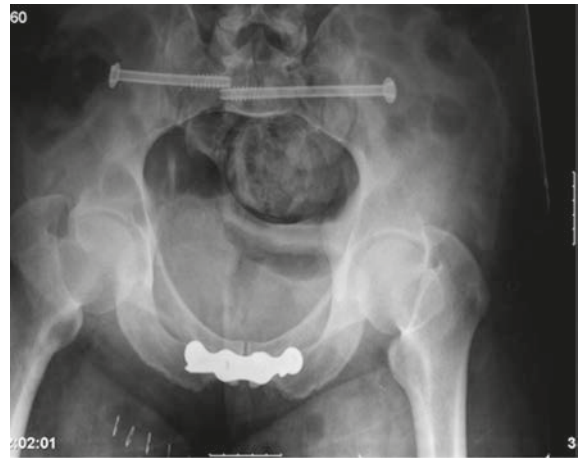


Fig. 336.5 Anterior plating + sacroiliac screw fixation.

Patients should commence low-molecular-weight-heparin (LMWH) without delay. This strategy reduced the incidence of proximal deep vein thrombosis (DVT) to 10% in a cohort of 103 consecutive patients who were screened for this condition at 10–14 days after surgery [11]. The incidence of DVT was only 3% when LWMH was started within 24 hours of injury [11].

Authors current practice is to use LMWH, and compression stockings pre- and post-operatively until oral anticoagulation with warfarin reaches therapeutic levels. Patients are prescribed warfarin for 3 months.

An alternative is to place a vena cava filter, which is recommended in patients with a contraindication to anticoagulation (e.g. traumatic brain injury, patients managed non-operatively for splenic or liver laceration) or in patients with pelvic or acetabular fractures that warrant surgical management and are considered high risk for a thromboembolic event [12].

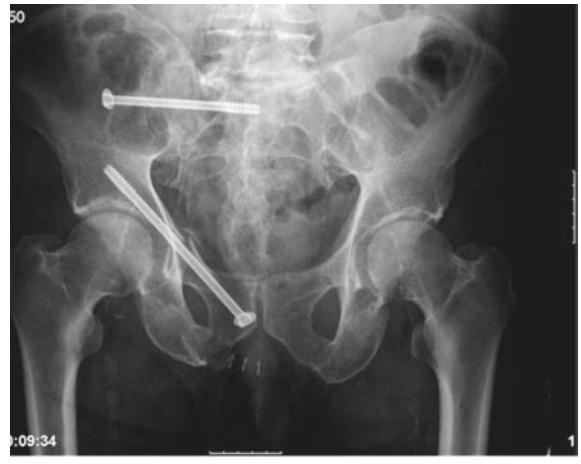
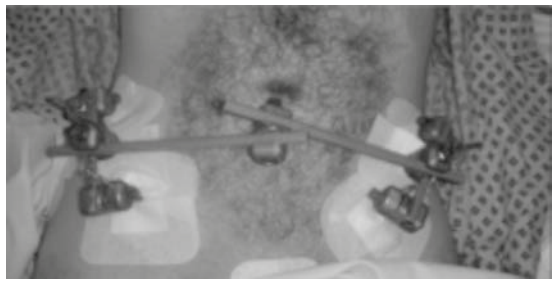


Fig. 336.6 Column screw fixation to anterior ring.

(a)



(b)

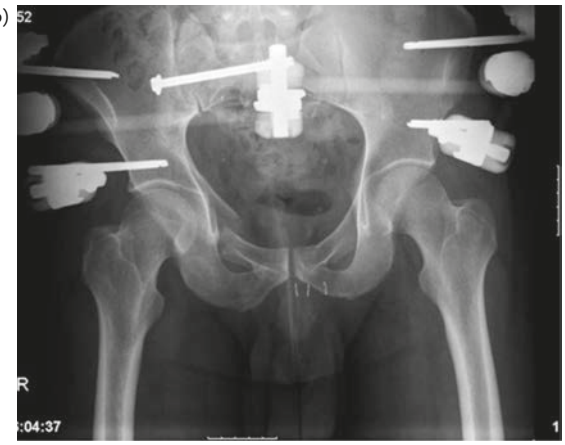


Fig 336.7 (a,b) Pelvic external fixator.

Functional outcome

There is a significant discrepancy in the reporting of functional outcomes after fractures of the pelvis. Different authors have reported many factors associated with worse functional outcome including open fracture [13], urological injury [14], neurological injury [15], fractures requiring open reduction and internal fixation [15,16], residual posterior displacement [16], injury pattern, and psychological problems [17].

Suzuki et al. [14] found that the Majeed score [18] Iowa pelvic score and Medical Outcomes Study Short Form 36-item Health Survey (SF-36) [19] are each altered after fracture of the pelvis and correlate closely with the presence of a neurological injury.

What is well recognized is that these are serious injuries and this group of patients will require prolonged physical, psychological and nutritional rehabilitation, as well as vocational support until return to the pre-injury level of function.

Limb trauma

Limb trauma can result in significant morbidity and mortality. Expeditious identification and treatment of limb injuries can avert potential complications, and improve outcome.

With any fracture of an extremity in a trauma patient, there must be an awareness of the possibility of a compartment syndrome or vascular injury that may result in limb ischaemia. Open fractures are also serious injuries that demand urgent attention.

Limb stabilization usually results in improvement in the patient's overall pulmonary status, hospital course, length of stay, and rehabilitation. Whether limb trauma is isolated or patient component of multitrauma, initial resuscitation should occur along the same principles outlined earlier in this chapter. Simple splinting and or longitudinal traction are usually sufficient until the patient has been adequately resuscitated. Fracture reduction and definitive stabilization is now usually performed on dedicated trauma operating lists during day light hours.

Open fractures

New guidelines have resulted in a move away from the historical rule of urgent debridement within 6 hours. Antibiotic administration within 3 hours, splintage and surgery on the next available operating list are now considered best treatment, especially when dealing with the tibia. Highly contaminated injuries and those with marine contamination need urgent washout and debridement. New Guidelines (BOAST 4) recommend definitive fracture stabilization within 24 hours and definitive soft tissue cover within 72 hours [20].

The use of tourniquets has been re-introduced by the military to control catastrophic limb haemorrhage with good effect. In cases where tourniquets cannot be applied, novel haemostatic agents, such as chitosan-coated gauze dressings can be directly applied to the bleeding surface. These work independently of the clotting cascade.

Compartment syndrome

Increase in the pressure within an osteofascial compartment following an injury can be limb threatening. This condition can occur with or without a fracture and with open or closed injuries. The most commonly affected patient group are males between 18–30 years of age. The tibia is the most commonly affected bone. The diagnosis is essentially clinical with 'disproportionate pain' being the main symptom and pain with passive stretching the main sign. Compartment monitoring is of use in the unconscious patient. Once diagnosed, urgent open complete decompression is the treatment.

Acknowledgements

Text credit for Denis classification: Reproduced from Denis F et al., 'Sacral fractures: An important problem: Retrospective analysis of 236 cases', Current Orthopaedic Practice, 227, pp. 67–81, copyright 1988, Wolters Kluwer.

References

1. Gosling JA, Harris PF, Humpherson JR, Whitmore I, and Willan PLT (eds). (2009). *Human Anatomy, Color Atlas and Textbook*, 5th ed. Phila delphia: Mosby-Elsevier, 2009.
2. Odutola A, Sabri O, Halliday R, Chesser TJS, and Ward AJ. (2012). High rates of sexual and urinary dysfunction after surgically treated displaced pelvic ring injuries. *Clinical Orthopaedics*, **470**(8), 2173–84.
3. Burgess AR, Eastridge BJ, Young JW, et al. (1990). Pelvic ring disruptions: effective classification system and treatment protocols. *Journal of Trauma*, **30**, 848–56.
4. Dalal SA, Burgess AR, Siegel JH, et al. (1989). Pelvic fracture in multiple trauma. Classification by mechanism is key to pattern of organ

injury, resuscitative requirements, and outcome. *Journal of Trauma*, **29**, 981–1002.
5. Bircher M and Hargrove R. (2004). Is it possible to classify open fractures of the pelvis? *European Journal of Trauma*, **30**, 74–9.
6. Vermeulen B, Peter R, Hoffmeyer P, and Unger PF. (1999). Prehospital stabilization of pelvic dislocations: a new strap belt to provide temporary hemodynamic stabilization. *Swiss Surgery*, **5**, 43–6.
7. American College of Surgeons. (2008). *Advanced Trauma Life Support Course: Student Manual*, 8th edn. Chicago, IL: American College of Surgeons.
8. Harris T, Thomas GOR, Brohi K. (2012). Early fluid resuscitation in severe trauma. *British Medical Journal*, **345**, e5752.
9. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. (2010). Effects of Tranexamic Acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*, **376**(9734), 23–32.
10. Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, and Greenspan J. (1993). Lactate clearance and survival following injury. *Journal of Trauma*, **35**(4), 584–8; discussion 588–9.
11. Steele N, Dodenhoff RM, Ward AJ, and Morse MA. (2005). Thromboprophylaxis in pelvic and acetabular trauma surgery. *Journal of Bone and Joint Surgery (British volume)*, **87B**, 209–12.
12. Tile M. (2003). *Fractures of the Pelvis and Acetabulum*, 3rd edn. Philadelphia, PA: Lippincott, Williams and Wilkins.
13. Brenneman FD, Katyal D, Boulanger BR, Tile M, and Redelmeier DA. (1997). Long term out-comes in open pelvic fractures. *Journal of Trauma*, **42**, 773–7.
14. Bjurlin MA, Fantus RJ, Mellett MM, and Goble SM. (2009). Genitourinary injuries in pelvic fracture morbidity and mortality using the National Trauma Data Bank. *Journal of Trauma*, **67**, 1033–9.
15. Suzuki T, Shindo M, Sorna K, et al. (2007). Long-term functional outcome after unstable pelvic ring fracture. *Journal of Trauma*, **63**, 884–8.
16. Tornetta P, Dickson K, and Matta JM. (1996). Outcome of rotationally unstable pelvic ring injuries treated operatively. *Clinical Orthopedics*, **329**, 147–51.
17. Kabak S, Halici M, Tuncil M, et al. (2003). Functional outcome of open reduction and internal fixation for completely unstable pelvic ring fractures (type c): a report of 40 cases. *Journal of Orthopedic Trauma*, **17**, 555–62.
18. Majeed SA. (1989). Grading the outcome of pelvic fractures. *Journal of Bone and Joint Surgery (British volume)*, **71B**, 304–6.
19. Ware JE Jr and Sherbourne CD. (1992). The MOS 36 Item Short Form Health Survey (SF-36). I: conceptual framework and item selection. *Medical Care*, **30**, 473–83.
20. British Orthopaedic Association. (2008). *BOAST 3: Pelvic and Acetabular Fracture Management*. London: British Orthopaedic Association Standards for Trauma (BOAS).

CHAPTER 337

Assessment and management of fat embolism

Neil Soni

Key points

- Fat embolism is common, while fat embolism syndrome (FES) is rare.
- Theories as to mechanisms include the mechanistic and free fatty acids theories, but both probably require an additional inflammatory component.
- Gurds major and minor diagnostic criteria may be helpful as there is no definitive diagnostic test. Cerebral magnetic resonance imaging may be useful and increase the certainty of the diagnosis in neurological FES.
- Early fixation of long bone fractures may reduce likelihood of FES.
- There is no proven specific treatment; supportive treatment forms the mainstay of therapy.

Definition

Fat embolism is seen when fat globules enter the circulation and form potential emboli. This occurs relatively commonly, but is infrequently symptomatic. Fat embolism syndrome (FES) is when there is not only fat in the circulation, but the fat gives rise to an identifiable pattern of symptoms and signs. The syndrome is seen in a wide range of circumstances, and consists of a variable combination of respiratory failure with or without neurological disturbance and with a petechial rash.

Incidence

The incidence is difficult to define and is dependent on the diagnostic criteria used and the population studied. The incidence in clinical retrospective studies tends to be low, less than 1%, while prospective studies may report an incidence that is 10–20 times higher. In contrast post-mortem studies report a very high incidence of pulmonary fat embolism; 82% in patients dying after trauma and 63% in patients dying without trauma [1]. Cardiopulmonary resuscitation is associated with a high incidence of pulmonary fat embolism at post-mortem regardless of the underlying cause of death. The issue is, whether it is cause of death or an association.

In specific situations it is better defined. In patients with long bone fractures a rate of 0.7% has been reported. Patients with bilateral femoral fractures treated with reaming and nailing have an incidence of 4.1% with acute respiratory distress syndrome (ARDS) reported in 14.6% and death in 6.9%. Following elective orthopaedic surgery such as bilateral knee replacement, an incidence of 0.17% has been reported [2].

Pathophysiology

The mechanism underlying FES is unclear, although several theories have been advanced.

The mechanistic theory holds that fat embolism occurs when fat is forced into the circulation during trauma, or due to high pressure within the bone marrow or in fat tissues. Evidence for this is that emboli can be seen during and after various orthopaedic manoeuvres where high pressures are exerted in the marrow cavity. Interestingly, fat alone does not cause the syndrome in animal models and an inflammatory process is also important. The 'two hit concept' requires fat embolism and inflammation [3,4].

The free fatty acids theory suggests that trauma or surgery results in the release of lipases into the plasma, which destabilize circulating fats resulting in saponification and de-emulsification. This may be linked to or be an alternative to the concept that FES results from the histotoxic effects of free fatty acids, which in experimental models cause a vasculitis and inflammation with both inflammation and fibrosis developing within hours of fat embolism [5].

A key feature of the syndrome is that signs are seen on both the arterial and venous sides of the circulation, while fat is released only into the systemic venous system. Transit through a patent foramen ovale (PFO), present in up to 30% of the population, has always been suggested as important, but it is quite clear that it is not always present in those who develop the syndrome. As deformation of micelles that can traverse the pulmonary vessels has been shown in animal models it is clear there must be mechanisms or pathways, other than PFO for fat to pass from the systemic venous circulation to the systemic arterial circulation [6,7].

The haemodynamic changes associated with fat infusions have been characterized in animal studies. These include a rapid rise in pulmonary vascular resistance associated with a concomitant decrease in both cardiac output and blood pressure. This very transient effect leaves only a small incremental increase in pulmonary vascular resistance. Whether this is the same in clinical scenarios associated with FES is unknown [8].

Situations associated with FES

See Box 337.1 for situations associated with FES.

Box 337.1 FES is seen in a wide range of situations; the major ones are listed here

Bone marrow disruption

- Trauma especially long bones.
- Surgery involving marrow instrumentation. (Joint replacements, fracture fixation, scoliosis surgery.)
- Bone marrow harvest.
- Bone marrow transplantation.

Mechanical disruption of adipocytes

- Soft tissue injury: crush and blast injuries.
- Liposuction.
- Electrocautery.
- Liver failure: fatty liver.

Exogenous fat administration

- Parenteral nutrition.
- Propofol infusion.
- Lymphography.

Non-specific

- Burns.
- Extracorporeal circulation.
- Acute sickle cell crisis.
- Acute pancreatitis.
- Decompression sickness.
- Altitude sickness.

Box 337.2 Gurds modified diagnostic criteria—one major and four minor criteria needed for a positive diagnosis

Major criteria

- Petechial rash.
- Respiratory symptoms: tachypnoea, dyspnoea.
- Respiratory signs: bilateral inspiratory crepitations, haemoptysis, bilateral diffuse patchy shadowing on chest X-ray.
- Neurological signs: confusion, drowsiness, coma.

Minor criteria

- Tachycardia > 120 beat/min.
- Pyrexia > 39.4.
- Retinal changes: fat or petechiae.
- Renal changes: anuria or oliguria.
- Jaundice.

Laboratory

- Thrombocytopenia >50% decrease on admission value.
- Sudden decrease in haemoglobin level by >20% of admission value.
- High erythrocyte sedimentation rate >71 mm/h.
- Fat macroglobulaemia.

Clinical signs of FES

Fat emboli can be detected with Doppler ultrasound techniques, but the presence of fat emboli on ultrasound does not correlate well with the clinical syndrome. The clinical syndrome is a collection of signs not all of which will be necessarily present, and the severity of the syndrome can range from subclinical to catastrophic with an onset that may be slow and insidious through to fulminant. It is also a diagnosis of exclusion.

Presentation may occur intra-operatively or at time of injury, but more commonly the onset is over the 12–36 hours following injury or surgery. Increasing hypoxaemia is the most frequent sign and may be associated with neurological symptoms such as confusion, drowsiness, or coma. It may be accompanied by fever and a characteristic petechial rash, often in the axillae, but the rash may also be on the face or in the conjunctivae. These can all occur in relative isolation and post-operative confusion has been flagged as a potential sign of FES even when it occurs in isolation [9,10].

Diagnosis may be helped by using Gurds classification, or modifications thereof (Box 337.2). The classification discriminates between major signs or criteria, such as petechial rash, respiratory distress, and confusion, and a list of minor signs or criteria. Diagnosis requires one major and four minor criteria. While fat globules in the blood used to be a requirement, it is problematic because they can often be found with little or no suggestion of any clinical signs, and not just in high risk situations such as trauma or orthopaedics, but also in healthy volunteers. Therefore, they are not pathognemonic of FES [11].

Lindeque suggested an alternative approach, which is almost exclusively respiratory, and excludes the neurological and other presentations. It is unhelpful except as an indicator of a non-specific but severe respiratory presentation.

Pulmonary criteria for FES: lindeque

- A sustained PaO_2 of less than 8 kPa (FIO_2 0.21).
- A sustained $PaCO_2$ of more than 7.3 kPa or pH of less than 7.3.
- A sustained respiratory rate of more than 35 breaths/min even after adequate sedation.
- Increased work of breathing judged by dyspnoea, use of accessory muscles, tachycardia, and anxiety

Clinical features

Diagnosis of a syndrome requires an appropriate clinical context or predisposition, and the conditions listed in Box 337.1 provide those contexts. Most patients with FES (70%) have a significant respiratory component. It is important to realize that the patients in whom FES is likely, such as patients who have suffered trauma

or following orthopaedic surgery, may be expected to have some degree of hypoxaemia independent of the possible occurrence of FES. Of those with significant chest X-ray changes diagnosed as having FES, the degree of lung injury is very variable, but up to 44% may require mechanical ventilation [12].

The lung injury usually takes between 3 and 7 days to resolve, but this is highly variable as is the overall outcome.

The petechial rash, which is considered pathognemonic of FES is seen in only about 60% of cases. It is characteristic in the axilla, but may be seen elsewhere, including the forehead, the conjunctivae, and submucosa. One theory is that the distribution is due to fat droplets accumulating in the aortic arch, and showering through the carotid and subclavian vessels. The occurrence of petechiae is not directly associated with a decrease in the platelet count, which may remain over 50×10^9/L, but thrombocytopaenia may also be part of the syndrome. The mechanism of the rash is uncertain, but it may be due to vascular stasis, endothelial damage from free fatty acid or embolization.

The neurological features vary from mild confusion and disorientation to convulsions and coma, and almost anything between. The speed of onset is also highly variable with signs not necessarily present on admission to hospital following trauma or immediately post-operatively. There is no specific characteristic that is readily identified, but confusion in any patient at risk should have FES considered in the differential diagnosis. FES is particularly likely if the neurological abnormality is focal [13].

Outcome from cerebral fat embolism is often, but not always, good so accurate prognostication soon after presentation is difficult. It is increasingly likely that the improved sensitivity of cerebral MRI scanning may be helpful in showing either reversible vasogenic oedema or other evidence of damage. Cerebral MRI may assist in prognostication although that is not yet the case [14].

Investigations

FES is a syndrome so there are no definitive diagnostic tests, and it is the pattern that is important. Thrombocytopaenia (platelet count $<150 \times 10^9$/L) and anaemia are both common (37 and 67%, respectively). Hypocalcaemia and hypoalbuminaemia are non-specific features.

Fat globules may be identified in both blood and urine, but as they may be found in patients in the absence of FES, they are also not diagnostic. Serum lipase and phospholipase A2 both tend to increase in lung injury and are again non-specific. Monitoring pulmonary artery pressure with a pulmonary artery catheter was advocated for diagnosis of fat embolism, but pulmonary hypertension has many acute and chronic causes, and so this is no longer considered of benefit. Pulmonary artery fat sampling has also been reported, but its diagnostic value is not known. Bronchoalveolar lavage to find macrophages containing fat also lacks specificity.

The chest X-ray usually shows bilateral patchy oedema-like infiltrates and the term 'snow storm appearance' has been used in more severe cases. However, this is also a non-specific finding and not diagnostic.

Computed tomographic (CT) scanning of the lung is also unhelpful beyond showing non-specific markers of injury. CT of the brain is also non-specific, although an absence of correlation between the neurological picture and the cerebral CT findings should raise the possibility of FES. In severe, non-traumatic brain injury there may be cerebral oedema or high density spots, which in context may lend weight to a potential diagnosis of FES, but is not diagnostic.

Magnetic resonance imaging (MRI) is increasingly useful and is now the radiological investigation of choice with some characteristic findings, which are potentially, diagnostic. It may show a 'starfield' pattern (innumerable punctate areas of restricted diffusion). T2-weighted images are particularly useful showing small non-confluent hyperintense lesions in both white and gray matter, which are thought to indicative of micro-infarcts [15]. Vasogenic oedema is identified by areas of enhancement with gadolinium with background increases in the signal intensity of diffusion and T2-weighted images, and iso-intensity on apparent diffusion coefficient (ADC) mapping. These findings are relevant as they are reversible lesions that usually disappear by 21–30 days and often appear to correlate with clinical improvement [16].

Prevention of FES

This can be theoretically achieved by either changes in surgical management or by pharmacological intervention. With fractured long bones surgery techniques such as the use of external fixators, which reduce the risk of fat being pushed into the circulation should help. Early surgical fixation of long bone fractures compared with conservative management may reduce the risk of FES from 22% to 4.5%. There are high risk periods and evidence that fixation between days 2 and 5 should be avoided [4]. Avoidance of elective surgical techniques that generate high intramedullary pressures seems intuitively advisable, but is not definitely proven.

The role of pharmacological prophylaxis with corticosteroids remains unclear. One meta-analysis suggests that they might reduce the incidence and severity of FES following bone fractures, but these outcomes are subject to ascertainment bias and mortality, a more robust outcome, was not affected [17]. The conclusions are also limited by the poor quality of the trials included in the meta-analysis and based on current evidence corticosteroids should not be administered routinely.

Management of established FES

This is entirely supportive as there are no specific interventions proven to improve outcome. Animal studies suggest that FES may result or be exacerbated by a combination of fat emboli and then a secondary trigger by shock like states, the so called two hit hypothesis, resulting in an inflammatory reaction [3]. If this is the case, then early clinical stabilization, including early fixation of long bone fractures in patients well enough to tolerate surgery would make sense. Patients with FES may be clinically unstable so that although an MRI scan may help in diagnosis, transport to an MRI scanner may jeopardize immediate care without necessarily altering treatment. Corticosteroids are of unproven value in the treatment of established FES as are other treatments, such as dextrans and heparin, which have been used in the past.

Conclusion

First and foremost this is a clinical diagnosis based on appropriate clinical circumstances and the clinical features of the syndrome. As the clinical severity of FES is highly variable and the diagnosis is often unclear, it is difficult to define the impact of FES on clinical outcomes. Additionally, FES is rare so there are

few published series of any size with much of the data on outcome being extracted from case reports or small series. The high rate of fat embolism detected at post-mortem in patients dying within 1 hour of major trauma probably indicates an association with the severity of trauma and the poor outcome of patients who undergo CPR following trauma rather than indicating that FES is the cause of increased mortality. It is also clear that many patients with fat emboli do not develop the syndrome. However, severe pulmonary FES may be fatal and patients with severe neurological FES may be left with substantial deficits or die. MRI scanning may prove useful for prognostication but this requires further evaluation.

Acknowledgements

Text credit for Pulmonary criteria for FES - Lindeque: Adapted with permission and copyright © of the British Editorial Society of Bone and Joint Surgery, Lindeque BG et al., 'Fat embolism syndrome: A double blind therapeutic study', *Journal of Bone and Joint Surgery British Volume*, 1987, 69, pp. 128–131.

References

1. Eriksson EA, Pellegrini DC, Vanderkolk WE, Minshall CT, Fakhry SM, and Cohle SD. (2011). Incidence of pulmonary fat embolism at autopsy: an undiagnosed epidemic. *Journal of Trauma*, **71**(2), 312–15.
2. Stavlas P and Giannoudis PV. (2009). Bilateral femoral fractures: does intramedullary nailing increase systemic complications and mortality rates? *Injury*, **40**(11), 1125–8.
3. Blankstein M, Byrick RJ, et al. (2010). Amplified inflammatory response to sequential hemorrhage, resuscitation, and pulmonary fat embolism: an animal study. *Journal of Bone and Joint Surgery (American volume)*, **92**(1), 149–61.
4. Lasanianos NG, Kanakaris NK, Dimitriou R, Pape HC, and Giannoudis PV. (2011). Second hit phenomenon: existing evidence of clinical implications. *Injury*, **42**(7), 617–29.
5. Glover P and Worthley LI. (1999). Fat embolism. *Critical Care Resuscitation*, **1**(3), 276–84.
6. Nikolic S, Zivkovic V, Babić D, Djonić D, and Djurić M. (2010). 'Systemic fat embolism and the patent foramen ovale—A prospective autopsy study'. *Injury*, **43**(5), 608–12.
7. Eriksson EA, Schultz SE, Cohle SD, and Post KW. (2011). Cerebral fat embolism without intracardiac shunt: a novel presentation. *Journal of Emergencies, Trauma, and Shock* **4**(2), 309–12.
8. Eyjolfsson A, Plaza I, Brondén B, Johnsson P, Dencker M, and Bjursten H. (2009). Cardiorespiratory effects of venous lipid micro embolization in an experimental model of mediastinal shed blood reinfusion. *Journal of Cardiothoracic Surgery*, **4**, 48.
9. Johnson MJ and Lucas GL (1996). Fat embolism syndrome. *Orthopedics*, **19**(1), 41–8; discussion 48–9.
10. Cox G, Tzioupis C, Calori GM, Green J, Seligson D, and Giannoudis PV. (2011). Cerebral fat emboli: a trigger of post-operative delirium. *Injury*, **42**(Suppl. 4), S6–S10.
11. Neri M, Riezzo I, et al. (2010). CD61 and fibrinogen immunohistochemical study to improve the post-mortem diagnosis in a fat embolism syndrome clinically demonstrated by transesophageal echocardiography. *Forensic Science International*, **202**(1–3), e13–17.
12. Bulger EM, Smith DG, Maier RV, and Jurkovich GJ. (1997). Fat embolism syndrome. A 10-year review. *Archives of Surgery*, **132**(4), 435–9.
13. Weathers AL and Lewis SL. (2009). Rare and unusual . . . or are they? Less commonly diagnosed encephalopathies associated with systemic disease. *Seminars in Neurology*, **29**(2), 136–53.
14. Eguia P, Medina A, Garcia-Monco JC, Martin V, and Monton FI. (2007). The value of diffusion-weighted MRI in the diagnosis of cerebral fat embolism. *Journal of Neuroimaging*, **17**(1), 78–80.
15. Liu HK and Chen WC. (2011). Fat embolism syndrome. *New England Journal of Medicine*, **364**, 176.
16. Chen JJ, Ha JC, and Mirvis SE. (2008). MR imaging of the brain in fat embolism syndrome. *Emergency Radiology* **15**(3), 187–92.
17. Bederman SS, Bhandari M, McKee MD, and Schemitsch EH. (2009). Do corticosteroids reduce the risk of fat embolism syndrome in patients with long-bone fractures? A meta-analysis. *Canadian Journal of Surgery*, **52**(5), 386–93.

CHAPTER 338

Assessment and management of combat trauma

Sara J. Aberle and Donald H. Jenkins

Key points

- The practice of medicine in combat settings comes with additional challenges, including a potentially hostile environment, delayed patient evacuation, and limited resources.
- Data from recent combat continues to show haemorrhage as a primary cause of death, with most deaths occurring prior to hospital arrival and before injuries can be managed surgically.
- Life-saving interventions, such as tourniquet application and needle thoracostomies, decrease combat-related mortality if performed appropriately and in a timely fashion.
- The search for better outcomes is focused on improving prehospital management, including targeting remote damage control resuscitation.
- The usual order of management in civilian trauma hold true in the combat setting.

Introduction

General concepts

Combat trauma is a unique clinical entity that has important implications for those who are not well-versed in this area. Lessons learned from combat trauma can be highly relevant in both the military and civilian settings. Key areas that warrant exploration include the differences between combat casualties and civilian trauma patients, namely the environment in which they are treated, the mechanisms by which they are injured, and the methods used to provide their care. There are of course additional challenges of practicing medicine in the combat arena in what may be a hostile environment with prolonged patient evacuation times and limited resources.

Roles or levels of care

Medical care in the combat setting begins on the battlefield or at the site of injury and can extend as far back as the country of origin. The terms 'roles' or 'echelons', numbered one to five, are used to describe the capabilities and resources of various points of medical treatment along this spectrum. Once a patient is determined to need medical care that exceeds that role's capabilities, the care team works to evacuate the patient to a higher role or level of care [1].

Role 1 indicates care that is provided in the prehospital setting, to include that provided by soldiers and trained combat medics in the field. At this level, the primary goal is assess the patient, determine if a life-saving intervention is needed and either treat the patient and allow them to return to duty or evacuate the patient to a higher level of care. Role 2 teams or medical treatment facilities are generally mobile and have additional resources such as basic radiological (X-ray) and laboratory capabilities, limited in-patient facilities, and may have appropriate subspecialty expertise available. This level would also include forward surgical teams (FSTs), who are able to perform emergency surgery for life-saving stabilization. This allows the patient to be transported to a higher level of care when otherwise they would not have survived transportation.

The most extensive care patients can receive while still in the combat arena is that received at Role 3 medical treatment facilities. They may include combat support hospitals with in-patient bed capacities (usually ranging from the 80s to 200s). Examples of such medical treatment facilities include NATO alliance facilities, where the varied experiences and practice patterns of medical providers from different countries and training backgrounds come together to form a collective knowledge and skill base that can be shared and developed. Examples of this are advances in the use of tranexamic acid, tourniquets, and freeze-dried plasma, which are discussed later in the chapter.

A Role 4 facility has even greater care capacity as it is the first level at which care is provided outside the combat zone. An example of this is the facilities at Landstuhl Regional Medical Center near Landstuhl, Germany. Role 5 medical treatment facilities are located in the home countries of those injured and offer the most definitive care that the injured personnel requiring this extent of evacuation can receive. Included in these would be the Royal Centre for Defence Medicine in the United Kingdom (UK), one of the German Armed Forces Hospitals, such as those in Hamburg or Berlin, or Brooke Army Medical Center in the United States.

Medical provider functions

A health care provider deployed and serving in a combat zone or in any of the aforementioned levels of care can potentially perform a number of functions, including that of continuing their usual activities of practicing within their medical specialty, in day-to-day general practice, or ensuring soldier health and readiness. Closer to the front lines, health care personnel may serve directly as part of the trauma or forward surgical teams.

Mechanisms of combat injuries

Injuries sustained in combat can arise from a number of different mechanisms. While not exclusive to the military setting, certain

injuries are seen more commonly in those injured in combat. One such injury pattern is that seen from falling or landing after jumping or rappelling from a fixed- or rotary-winged aircraft. Landing injuries most often observed are fractures, sprains, and strains affecting primarily the lower extremities (especially the ankle), followed by the upper extremities and spine [2]. The risk of sustaining an injury is increased when jumps are made at night and in jumps made with the additional weight of protective and combat equipment used in operational jumps [2,3].

Blunt trauma is less common in combat injuries although it does occur. The causes of blunt combat trauma range from the landing injuries already discussed, to direct blows from an opposing soldier, motor vehicle accidents, or from tertiary blast injuries resulting from the explosive propulsion of the body into a hard surface. Standard spinal precautions and blunt trauma management strategies apply in these cases.

Penetrating injures are more common in combat trauma. Injuries from sharp or edged weapons, as well as small arms fire, are generally managed similarly in combat as they would be in the civilian setting. The many types of firearms can cause varying injuries and many of these wounds require operative management; this presents a key logistical consideration in combat trauma coordination. A core principle of managing gunshot wounds is the concept of 'trajectory determination equals injury identification', and establishing the trajectory of the projectile can help guide management planning. An easy and low-cost way to determine trajectory is taping paperclips near external wounds so that the entry and exit points can be pictured on radiographs or by CT imaging allowing the injuries in between to be surmised.

Some of the most significant injuries in modern combat are explosion-related blast injuries. In the recent years these have been seen primarily in injuries from improvised explosive devices (IEDs). These devices can be made in many ways, with various different substances; for instance, organic peroxides were used in the London Underground bombings in 2005. An important factor, while serving as a medical provider within a combat setting is that there is the potential to be affected by chemical, biological, or radiological warfare. As an example, an IED could be built with a propane component, as well as powdered chlorine, so that upon detonation there is both a combustive or fire element along with a chemical component. Methods like these pose a risk to the medical team, as well as the patient, and medical providers should be aware of these potential threats.

The fragmentation pieces associated with IEDs, or as a result of projectile debris that comes with a blast, serve as secondary blast injuries. The devastating effects of these flying fragments have been described as being similar to gunshot wounds [4,5], although some studies found a higher likelihood of surgical intervention from gunshot wounds compared to explosion-related injuries [4]. The biggest surprise to many combat providers is realizing just how many penetrating injuries casualties will suffer in one explosion.

There are two specific quaternary blast injuries of which medical providers in combat need to be aware, namely pulmonary embolism (PE) and traumatic brain injury (TBI). A recent study suggests the rate of PE in combat-wounded patients with extremity fractures and amputations is 4.7%, nearly twice the rate expected with civilian trauma [6]. This should raise the medical provider's concern for appropriate prophylaxis, including considering placement of a vena cava filter. Traumatic brain injury, which is now a common combat-related injury, increases the risk of affected persons developing psychiatric illness and sleep complaints, with both blast and blunt injuries having a high association with insomnia [7].

Studies from recent conflicts over a 10-year period have examined the injuries sustained in combat and reported that the majority of combat mortality (87.3%) occurs in premedical treatment facilities prior to reaching surgical intervention. Over three-quarters of the injuries were deemed to be 'non-survivable' with just under a quarter of the injuries thought to have been 'potentially survivable'. The vast majority of deaths occurring from potentially survivable injuries were due to haemorrhage; found most often to be truncal, with junctional and peripheral or extremity bleeding following thereafter. As most deaths occur in the prehospital setting, improvements in outcome will result from developing treatment strategies that target haemorrhage control, airway management, and efficient evacuation [8]. Another possible cause of preventable deaths are underperformance of life saving interventions (LSI's), the aforementioned uncontrolled major haemorrhage, and delayed evacuation before subsequent surgical intervention [9].

Management of combat injuries

The practice of Tactical Emergency Medicine Services (TEMS) and combat medicine has additional challenges. Taking these challenges into account, as well as the available data regarding the types of injuries and causes of death, many groups and individuals have worked to develop medical training specific to the combat setting and to optimize logistical systems to improve survival. Examples include battlefield advanced trauma life support (BATLS), battlefield advanced resuscitation techniques and skills (BARTS), combat lifesaver (CLS), and tactical combat casualty care (TCCC), which have been shown to be effective in decreasing mortality [10].

A major management theme taking prominence is 'damage control resuscitation'. Damage control resuscitation stresses haemorrhage control in the form of a permissive hypotension, with a goal of the return of a palpable pulse, a systolic blood pressure of greater than 80 mmHg, or a mean arterial pressure of 50 mmHg [11,12]. Haemostatic resuscitation seeks to administer blood products in a similar ratio to that of whole blood; namely by administering a 1:1:1 ratio of red blood cells (RBCs), fresh frozen plasma, and platelets [13]. Dried plasma is also being offered as a more versatile option than liquid plasma as it is easier to store and should be easier to employ in the combat environment. Studies of dried plasma are ongoing in Germany, France, and the United States [14].

The next logical step in addressing the majority of deaths occurring prior to arrival at medical treatment facilities is to extend these principles of damage control resuscitation to the pre-medical treatment facility setting [9]. This has been termed remote damage control resuscitation. Medical emergency response teams from the UK, as well as the Israeli Defence Force have reported success with similar approaches, extending use to other products like the antifibrinolytic, tranexamic acid [15]. Determining the patient's physiological trajectory in the resuscitation process will dictate plans to provide adequate transfusion of RBCs, plasma and platelets, along with pharmacological haemostatic adjuncts [16].

In addition to early transfusion, remote damage control resuscitation may also involve patient monitoring technologies or even telemedical technology to connect an on-scene pre-medical treatment facility with a medical provider capable of giving appropriate

instruction in instituting lifesaving interventions. While many soldiers are trained in BATLS, BARTS, CLS, or TCCC there are still a number of 'missed' LSIs where the delay or omission of the intervention is associated with increased mortality [9].

Actions considered as LSIs include appropriate tourniquet application, pressure dressings, or haemostatic agent application, needle or tube thoracentesis, obtaining intravenous or intraosseous access, and airway management. To execute these interventions, almost all soldiers in combat are issued with an Individual First Aid Kit, or 'IFAK'. These are now stocked with haemorrhage control methods, such as commercially-produced one-handed tourniquets that have shown to be more effective than improvised tourniquets, as well as haemostatic agents and pressure dressings such as Combat Gauze and Israeli bandages, respectively. Many IFAKs will also come with needles for chest decompression, and tools for obtaining vascular access. Medics in the premedical treatment facility setting may also have supraglottic airway devices, the training and tools to perform a surgical airway in the form of a cricothyroidotomy, and blood and procoagulant or antifibrinolytic products.

There are other changes and additions to tactical emergency medical services in the combat arena, many of which are being formally included in official tactical training. One such addition is the recommended use of ketamine for pain management prior to arrival at a medical treatment facility. The addition of tranexamic acid is also relatively new. Junctional haemorrhage causes 19.2% of lethal haemorrhage (5.7% more than peripheral haemorrhage) [8], and is not easily amenable to tourniquet application. Junctional haemorrhage in the inguinal region can be treated with tools like the combat ready clamp, in addition to haemostatic agents. Care should be taken if using the combat ready clamp, to place the clamp on the common iliac artery in the case of lower extremity junctional haemorrhage as opposed to the external iliac artery, to avoid ongoing bleeding from the collateral circulation [17]. Management of traumatic brain injury is also being initiated in the pre-medical treatment facilities setting, chiefly through efforts to limit secondary brain injury by minimizing hypotension and hypoxia with specific instructions to keep oxygen saturations above 90%.

The success of combat-related injury management has resulted in concepts being carried over to the civilian sector. An example of this is the Hartford Consensus, where leaders in the field issued a formal statement with recommendations for civilian organizations to improve survival during mass casualty shooting events. With concepts stemming from the combat zones of Iraq and Afghanistan, and TCCC training, recommendations were made in order to stress 'the importance of early and definitive hemorrhage control to maximize survival of the victims . . . '. They did so by proposing the acronym THREAT: **t**hreat suppression, **h**aemorrhage control, **r**apid **e**xtraction to safety, **a**ssessment by medical providers, and **t**ransport to definitive care [18]. Services in the UK have also taken steps towards haemorrhage control in the prehospital civilian setting by bringing blood products to the scene [19]. Additionally, various groups are working to develop competency-based training derived from military tactical medical teaching that can be applied in training those involved with tactical emergency medical services in the civilian sector.

One final principle of management for combat-related mechanisms and injuries is that 'common things are common', and best practice in the civilian setting is typically safe and effective in the combat-injured. The health care provider should recognize that the usual thought processes of civilian trauma management hold true for the management of those injured in combat. Treating patients with modern resuscitative and supportive techniques and to the same endpoints, is the hallmark of high-quality injury management regardless of the mechanism of injury or the location of the care facility [16].

References

1. Szul, AC, Davis LB, Maston, BG, Wise D, and Sparacino LR (eds) (2004). *Emergency War Surgery*, 3rd United States revision. Washington, DC: Borden Institute, Walter Reed Army Medical Center; 2004.
2. Glorioso JE Jr, Batts KB, and Ward WS. (1999). Military free fall training injuries. *Military Medicine*, **164**(7), 526–30.
3. Chu Y, Sell TC, Abt JP, et al. (2012). Air assault soldiers demonstrate more dangerous landing biomechanics when visual input is removed. *Military Medicine*, **177**(1), 41–7.
4. Navarro S. (2012). Gunshot and improvised explosive casualties: a report from the Spanish role 2 medical facility in Herat, Afghanistan. *Military Medicine*, **177**(3), 326–32.
5. Ramasamy A. (2008). Injuries from roadside improvised explosive devices. *Journal of Trauma*, **65**(4), 910–14.
6. Gillern S. (2011). Incidence of pulmonary embolus in combat casualties with extremity amputations and fractures. *Journal of Trauma*, **71**(3), 607–13.
7. Collen J. (2012). Sleep disturbances among soldiers with combat related traumatic brain injury. *Chest*, **142**(3), 622–30.
8. Eastridge BJ, Mabry RL, Seguin P, et al. (2012). Death on the battlefield (2001–2011): implications for the future of combat casualty care. *Journal of Trauma and Acute Care Surgery*, **73**(6), S431–7.
9. Gerhardt RT, Berry JA, and Blackbourne LH. (2011). Analysis of life-saving interventions performed by out-of-hospital combat medical personnel. *Journal of Trauma*, **71**(1), S109–13.
10. Kotwal RS, Montgomery HR, Kotwal BM, et al. (2011). Eliminating preventable death on the battlefield. *Archives of Surgery*, **146**, 2350–8.
11. Gerhardt RT, Mabry RL, Delorenzo RA, and Butler F. (2010). Fundamentals of combat casualty care. Combat casualty care: lessons learned from OEF & OIF. [DVD.] Los Angeles, CA: Pelagique, LLC. 2010.
12. Morrison CA, Carrick MM, Norman MA, et al. (2011). Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. *Journal of Trauma*, **70**, 652–63.
13. Borgman MA, Spinella PC, Perkins JG, et al. (2007). The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *Journal of Trauma*, **63**, 805–13.
14. Dickey NW, Jenkins DH, and Butler FK. (2011). *Use of Dried Plasma in Prehospital Battlefield Resuscitation*. Falls Church, VA: Defense Health Board Memo.
15. Gerhardt RT, Strandenes G, Cap AP, et al. (2013). Remote damage control resuscitation and the Solstrand Conference: defining the need, the language, and a way forward. *Transfusion*, **53**, 9S–16S.
16. Jenkins DH, Holcomb JB, Letourneau PA, Smoot DL, and Barnes SL. (2012). Resuscitation from shock following injury. In: Irwin RS and Rippe JM (eds). *Irwin and Rippe's Intensive Care Medicine*, 7th edn, pp. 1656–9. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins.
17. Dickey NW and Jenkins DH. (2011). *Combat Ready Clamp™ Addition to the Tactical Combat Casualty Care Guidelines*. Falls Church, VA: Defense Health Board Memo.
18. Jacobs L, McSwain N, Rotondo M, et al. (2013). Improving Survival from Active Shooter Events: The Hartford Consensus. April 2013.
19. Lockey DJ, Weaver AE, and Davies GE. (2013).Practical translation of hemorrhage control techniques to the civilian trauma scene. *Transfusion*, **53**, 17S–22S.

PART 16.2

Ballistic trauma

CHAPTER 339

Pathophysiology of ballistic trauma

Michael C. Reade and Peter D. Thomas

Key points

- Explosions in air wound by four mechanisms: pressure waves (1°), accelerating projectiles (2°), the direct and indirect effects of a mass movement of gas (3°), and miscellaneous effects such as burns and asphyxiation (4°). Most casualties surviving to hospital care will not have significant primary blast injury.
- Energy transfer and the nature of the affected tissue are the two most important factors determining the effect of projectiles. Dichotomizing causative firearms into 'low' and 'high' velocity reflects only a small part of the relevant information.
- Military bullets must (by international law) be jacketed in a hard metal to reduce 'unnecessary suffering', while hunting bullets often have soft tips that maximize energy transfer to kill quickly. Fragmentation of projectiles does not prove they were not fully jacketed.
- The extent of devitalisation caused by projectiles is difficult to determine at early inspection, so serial debridement over a number of days is usually a better approach than early extensive resection of potentially viable tissue. Not all high-energy wounds require extensive debridement.
- Ballistic wounds are usually heavily contaminated with micro-organisms. Antibiotic prophylaxis is indicated as soon as possible after wounding, ideally within 3 hours.

Introduction

'Ballistics' is the study of projectiles. Explosions wound by various mechanisms, but in common medical use 'ballistic trauma' (inaccurately) refers to both blast and projectile effects. Intentionally used, weapons cause '**wounds**' not '**injuries**', a distinction important to soldiers as the repercussions of battle versus accidental aetiology are profound. Failing to understand the pathophysiology of ballistic trauma can result in treatment, such as unnecessary extensive debridement, which is worse than the injury itself.

Blast trauma

Mechanisms

Explosions release energy as a pressure wave, gas, and heat. **High explosive** (e.g. trinitrotoluene) produces a supersonic pressure wave; **less powerful explosives** (e.g. black powder) produce a subsonic wave. The first force felt by an affected body is the static pressure wave (Fig. 339.1). There is no mass movement of gas, rather pressure increases rapidly then falls to below baseline. The pressure wave can spread around walls, and is reflected from hard surfaces, increasing the force felt by bodies in enclosed spaces. The second force felt by a body in air is the mass movement of gases liberated by the exploding substance—the 'blast wind'. **'Enhanced' blast weapons** produce a lower but more prolonged overpressure that extends further than conventional high explosive. An example is the fuel-air missile, which disperses then ignites a cloud of vaporized fuel.

Primary blast injury is a common cause of death due to blast [1], but is uncommon in survivors. If the casualty is close enough to suffer a primary blast injury, other blast effects are usually fatal. Explosions commonly wound by other mechanisms listed in Table 339.1.

Pathophysiology of primary blast injury

The immediate response to primary blast to the chest is transient vagally-mediated hypotension, bradycardia, and apnoea. More significant are shear forces caused by alternating positive and negative pressure, greatest at the interfaces of tissues of different densities—ears, lungs, and gastrointestinal tract. Low peak overpressure may cause tympanic membrane haemorrhage without rupture, while higher pressures can almost obliterate the membrane and dislocate the auditory ossicles. At least half of blast-perforated tympanic membranes heal spontaneously. Persistent high-frequency hearing loss occurs in around 30% of patients, but in one series only 5% required a hearing aid [2].

Partly due to the importance of head orientation at the time of the explosion, rupture of the tympanic membrane is not an effective screening sign for significant blast injury elsewhere. In a recent series, half the patients with significant primary blast injury to other organs had intact tympanic membranes [3].

The pathophysiology of primary blast lung injury was a matter of speculation as late as the Second World War [4]. Noting experiences from the 1914–1918 war, three possibilities were considered:

- Blast wind overdistending the alveoli.
- Negative pressure following overpressure causing alveolar collapse.
- The pressure wave on the chest wall causing pulmonary contusion.

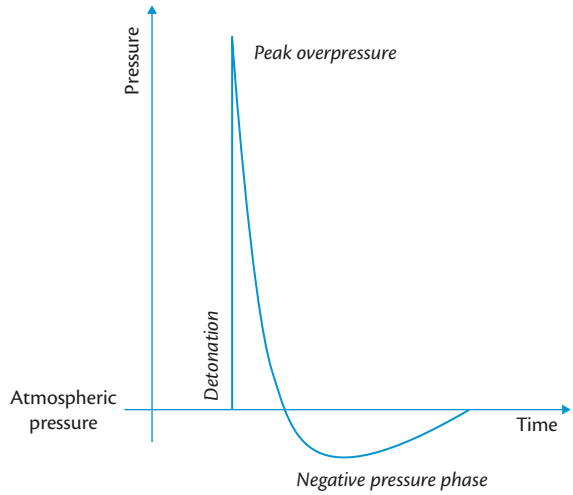


Fig. 339.1 The blast static pressure wave in air, described by the Friedlander equation.

Experiments showed the last of these was correct. The pressure wave shears the alveolar-capillary barrier, flooding alveoli with blood, fluid, and cellular debris. Hypoxaemia is usually apparent immediately, but can be delayed up to 72 hours. Arterial air emboli from alveolar-pulmonary venous communication cause most early deaths, and often result in neurological dysfunction and cardiac ischaemia in survivors. Pneumothorax, haemothorax, subcutaneous, and mediastinal emphysema are all possible (Fig. 339.2).

Table 339.1 Mechanisms of blast injury

Type of blast injury	Mechanism of injury	Wounds
Primary	Pressure wave	◆ Tympanic membrane rupture ◆ 'Blast lung' ◆ Rupture of hollow abdominal viscera ◆ Traumatic brain injury
Secondary	Penetrating trauma due to accelerated projectiles	Penetrating and blunt injury
Tertiary	Mass air movement ('blast wind'), injuring either directly or by interaction with the surroundings, e.g. collapse of buildings	◆ Blunt and penetrating injury ◆ Traumatic amputation* ◆ Traumatic brain injury ◆ Crush injury and entrapment
Quaternary	All other mechanisms, including burns, oxygen depletion, cyanide and carbon monoxide production, and inhaled dust	◆ Burns ◆ Inhalation of toxic gases ◆ Effects of ionizing radiation ◆ Asphyxiation

*Traumatic amputation is usually a combination of primary and tertiary effects. Primary blast trauma fractures long bones, the distal portion of which is then amputated by the blast wind. This explains why traumatic amputation due to blast is usually not through joints.

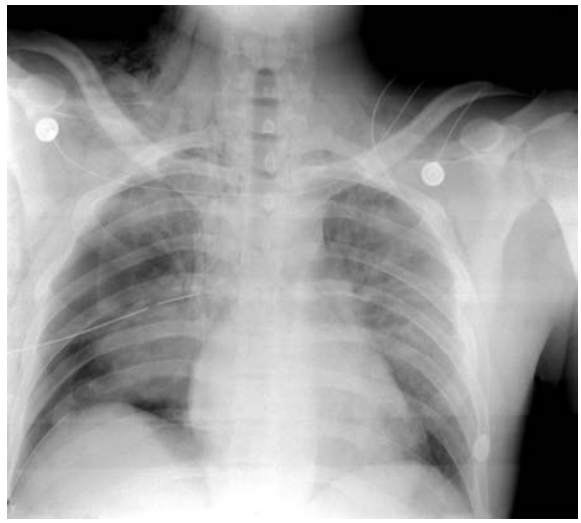


Fig. 339.2 Chest radiograph demonstrating bilateral opacity and pneumothorax due to blast injury.
Courtesy of the Australian Defence Force, Afghanistan, 2009.

Primary abdominal blast injury is uncommon, typically presenting late (after up to 14 days) with peritoneal irritation indicating visceral rupture. Multifocal bowel contusion, ischaemia, necrosis, and perforation may occur. The colon is the hollow viscus most commonly disrupted.

Blast waves can also cause traumatic brain injury (TBI). Intracranial haemorrhage or diffuse axonal injury can occur, but more common is mild traumatic brain injury, the pathological mechanism of which is unclear. Mild TBI shares many symptoms with post-traumatic stress disorder (PTSD), such as headache, insomnia, and mood changes, making diagnosis challenging [5]. Diffusion tensor MRI shows abnormalities in mild TBI, curiously poorly correlated with clinical signs [6].

Pathophysiology of secondary, tertiary, and quaternary blast injuries

Blast weapons can augment their effect by incorporating fragments. Fragments can be preformed projectiles (e.g. shrapnel and flechette), formed by casing fragmentation, or improvised using rocks, bolts, etc. Fragmentation multiplies many times the range and effect of smaller blast weapons such as grenades. Secondary blast injuries were more than three times more common than primary blast injuries during Operation Iraqi Freedom [7] and were the commonest cause of death. Survivors of blast fragmentation often have many low-velocity superficial wounds (Fig. 339.3). Around 10% will have eye injuries [8]. Urban explosions are particularly likely to cause secondary blast injury due to glass fragments energized from a bomb's surroundings.

Tertiary blast injuries mostly occur when the body is propelled against objects or crushed by structural collapse. This mechanism has the potential to kill the most victims. Quaternary injuries include respiratory compromise from inhaled pollutants (carbon monoxide, particulates, and toxic by-products of combustion such as cyanide) and airway burns, and external thermal burns from the superheated blast wind. Such effects are infrequently the major clinical problem in survivors.

(a)

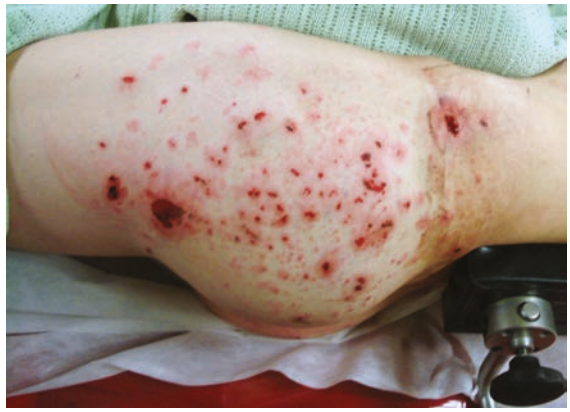


Fig. 339.3 (a) 'Peppering' or 'battle acne' caused by blast fragmentation.
Courtesy of the Australian Defence Force, Afghanistan, 2009.

Penetrating ballistic trauma

Wound ballistics

The most important considerations in wound ballistics are the amount of energy that is transferred from the projectile to the tissue, the function of that tissue, and its ability to tamponade haemorrhage. Energy transfer is determined by:

- **Kinetic energy (KE)**: mass and velocity.
- **Rotational energy**: usually negligible.
- **Projectile shape and impact angle**: determined by the distance travelled and any objects hit during flight. A bullet hitting side-on deposits more energy early than one hitting point-on.
- Projectile deformability.
- **Whether the projectile 'tumbles'** in tissue, determined by track length, shape, impact angle, and tissue density. Tumbling, a 180° rotation leaving the bullet lying base forward, occurs with all full metal jacketed bullets after a certain distance. A bullet exiting at the midpoint of this rotation will produce a large exit wound, but if rotation proceeds 180° the exit wound may be small. Exit wound size is therefore not an indicator of tissue damage.
- **Specific gravity of the tissue hit**: the higher the specific gravity (bone > muscle and liver > fat >> lung), the more energy transferred [9].

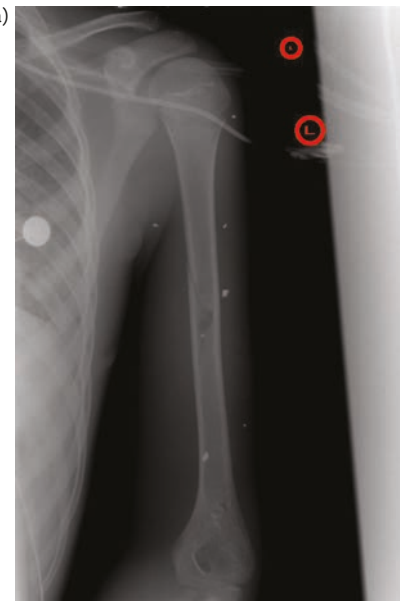
The terms 'high' and 'low' velocity firearms (demarcated at 1100–3000 ft/second) [10] are not as useful as 'power', incorporating mass, and even less useful than energy transfer. A high-powered rifle bullet will cause less tissue trauma if it misses bone and traverses a short muscle path than a 'low powered' pistol bullet that deposits all its kinetic energy after hitting bone. Notwithstanding, the kinetic energy of a rifle bullet is around 5–10 times that from a pistol. Hitting bone, a pistol bullet typically causes a simple fracture, while a rifle bullet causes extensive bone loss (Fig. 339.4).

Bullet deformability

Density preserves kinetic energy, so bullets are typically made of lead. Lead bullets melt at low velocities, necessitating 'jacketing' in a more resilient metal. Military bullets (according to Hague Convention of 1899) must have all but their base encased in hard metal (a 'full metal jacket'), which reduces bullet deformation in tissues and so causes less 'unnecessary suffering'. In contrast, hunting bullets are only partly jacketed, with a soft metal or polymer tip, increasing the chance of a quick, 'humane' kill. Police bullets can have a hollowed-out point, resulting in greater air drag and shorter range, but less probability of exiting the target and so harming bystanders.

Doctors are sometimes asked to comment on the type of bullet found in a patient. Even fully-jacketed bullets can deform and fragment. Indeed, many invariably will do so after a sufficient tissue

(a)



(b)

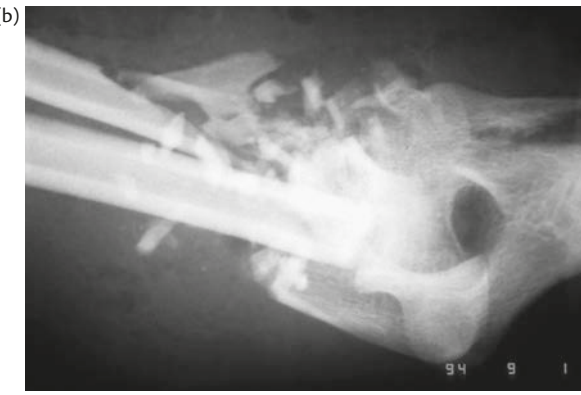


Fig. 339.4 Low and high energy transfer ballistic fractures. (a)The midshaft humeral fracture was the result of blast fragmentation, while (b) the fractures at the elbow were caused by a 7.62 mm high-energy AK47 bullet.
(a) Courtesy of the Australian Defence Force, Afghanistan, 2009. (b) Courtesy of the Australian Defence Force, Rwanda, 1995.

track. Finding no intact fully jacketed bullets does not allow this question to be answered.

Mechanisms of tissue damage

Bullets damage tissues by crushing/laceration, shock waves, and cavitation. Crushing and laceration are the principal mechanisms of injury due to 'low powered' firearms and blast fragmentation. Serious injury generally results only if vital structures are damaged. Tissue compression causes shock waves to propagate ahead of the bullet, which generally cause little damage but can rupture gas-filled organs [9] and possibly cause neurological injury. Cavitation results from tissue inertia imparted by a high-powered bullet. As tissues continue to move away from the bullet track, subatmospheric pressure sucks in debris. This 'temporary cavitation' produces an area of dead tissue around the wound track **up to** 30–40 times the bullet diameter (Fig. 339.5) [9,13]. Cavitation is dependent on the elasticity of the tissue, and damage is increased by shear forces if the cavity crosses a boundary between a mobile and immobile structure [11]. The much smaller residual permanent cavity is not a reliable indicator of the extent of devitalised tissue. Theoretical conceptualization of the size of the temporary cavity is rarely a useful guide to debridement [12]. The extent of tissue damage was traditionally identified using the 'four C's'—capillary bleeding, contractility, colour, and consistency. However, use of these criteria results in debridement of much potentially viable tissue, leading to recommendations for serial debridement only of clear necrosis [12].

While wound morphology varies with tissue type and energy deposited, the principal characteristics are shown in Fig. 339.6 [14]. Swelling of tissues affected by the temporary cavity can cause a compartment syndrome in limb wounds, particularly in the lower leg.

Retained fragments and lead poisoning

Bullets can become embedded in otherwise healthy tissue, where they do little damage. The exceptions are those that might erode vital structures such as major vessels, those that become a source of infection, and projectiles containing lead retained in joints (where they can cause arthropathy or systemic toxicity) or the subarachnoid space (potentially causing nerve damage or systemic toxicity).

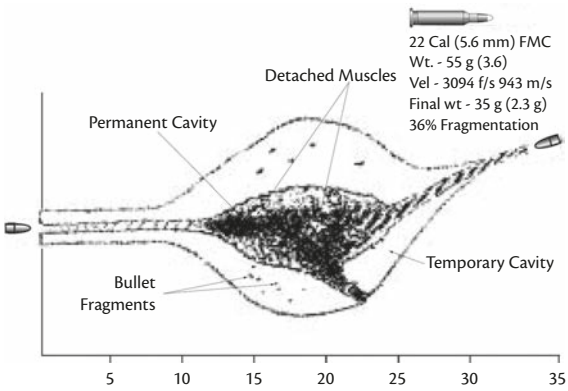


Fig. 339.5 Path of a M16 rifle bullet through tissue, showing bullet fragmentation, 180° tumbling, and permanent and temporary cavities. The exit wound may be no larger than the entrance wound.
Reproduced from *Emergency War Surgery*, Fourth United States Revision. Fort Sam Houston, Texas, USA. Borden Institute/Office of the Surgeon General; 2013.

Special cases

Landmines and improvised explosive devices

Buried or air-dropped landmines containing little metal are difficult to detect, so many omit fragmenting casings and wound mainly by blast, with penetrating injury only from local debris. Typically, such mines explode when stepped on, producing traumatic amputation through the midfoot or distal tibia. 'Bounding' landmines use two charges—one to propel a tethered canister upwards and a second, larger explosive to project fragments up to 100 m. The person stepping on them is usually killed, with bystanders suffering blast fragmentation.

Incendiaries (napalm, white phosphorous)

White phosphorus and napalm are incendiaries, and white phosphorus is also used to create smokescreens. However, both inflict severe wounds. Napalm is an adherent gel that produces full thickness burns involving muscle. A 10% burn typically causes rhabdomyolysis. White phosphorus ignites on air contact, so debridement requires keeping the wound moist. Systemically-absorbed white phosphorus causes hypocalcaemia and hyperphosphataemia.

Behind armour blunt trauma

Rifle bullets can be stopped by body armour but still kill by transmission of a force wave. The immediate effects of behind armour blunt trauma (BABT) are vagally-mediated apnoea and hypotension, accompanied by pulmonary and myocardial contusion, rib fractures, haemothorax, and pneumothorax. The commonest military bullet calibre, 5.56 mm, has negligible BABT potential, but larger calibres carry substantial risk. Body armour provides negligible protection against primary blast.

Infection in ballistic injury

Military wounds are particularly prone to infection. Typically, 3–6 different bacterial species are isolated from infected combat wounds, compared to single organisms in a civilian setting [15]. Bullets are not sterilized by firing, but this is clinically insignificant. Temporary cavitation sucks contaminated debris deep into devitalized tissue. The major infecting organisms are β-haemolytic streptococci and *Clostridia*, both effectively treated by penicillin. Contamination by soil is a particular feature of landmine wounds, and is associated with infection with other, more resistant organisms. Some modern military protocols recommend broader spectrum antibiotics, but the possible association of this strategy with invasive mould infection [16] is not yet understood.

Expected patterns of ballistic injury

Landmines caused over half the casualties in the Balkan wars, but less than 5% in the Vietnam War. IEDs have been the predominant weapon in the recent Afghanistan conflict. Mechanism affects

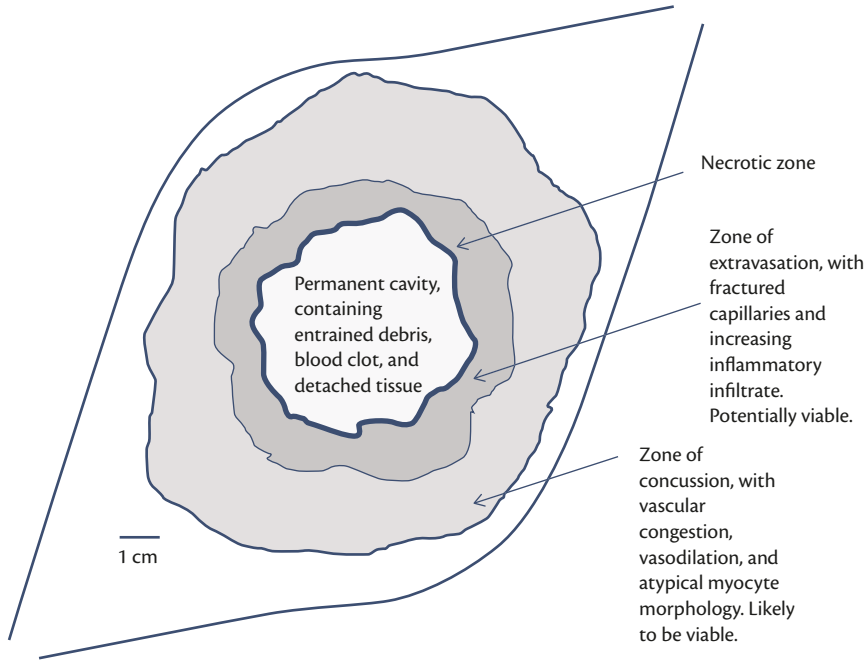


Fig. 339.6 Typical characteristics of a high-energy bullet wound cross-section in skeletal muscle.
Data from Garner J, 'Pathophysiology of ballistic wounding'. In: Smith J et al., (eds) *Oxford Desk Reference: Major Trauma*. Oxford: Oxford University Press; 2011. pp. 408–26.

case fatality rate—bullets (on average) kill 30–40%, artillery shells around 20%, and grenades around 10% of those wounded. The average lethality of combat wounds over the last century is around 25%, compared with more than 75% when weapons are used in a civilian context [17]. Civilian shootings tend to occur at close range to victims who cannot escape. Higher than expected case fatality raises the suspicion of executions, rather than battlefield deaths. Most patients killed by ballistic trauma die within 5 minutes of wounding, due to brain injury or exsanguination. Few have wounds amenable to treatment. Of potentially preventable deaths, 60% are due to limb haemorrhage, a third to tension pneumothorax, and 6% from airway obstruction [18].

Conclusion

Application of detailed epidemiological analysis to the 2001 wars in Iraq and Afghanistan has transformed military trauma care into a field based on data, with therapy guided by observational and trial evidence. Previous wars left legacies as diverse as penicillin, blood banking, and plastic surgery; the epidemiological approach to ballistic trauma will be that of early twenty-first century conflict.

Acknowledgements

Major Anthony Chambers FRACS RAAMC, Major Brett Courtenay FRACS FAOrthA RAAMC, and Commander Paul Luckin FANZCA RAN kindly provided many of the photographs.

References

1. Mellor SG and Cooper GJ. (1989). Analysis of 828 servicemen killed or injured by explosion in Northern Ireland 1970–84: the Hostile Action Casualty System. *British Journal of Surgery*, **76**(10), 1006–10.
2. Ritenour AE, Wickley A, Ritenour JS, et al. (2008). Tympanic membrane perforation and hearing loss from blast overpressure in Operation Enduring Freedom and Operation Iraqi Freedom wounded. *Journal of Trauma*, **64**(2 Suppl.), S174–8.
3. Harrison CD, Bebarta VS, and Grant GA. (2009). Tympanic membrane perforation after combat blast exposure in Iraq: a poor biomarker of primary blast injury. *Journal of Trauma*, **67**(1), 210–11.
4. Zuckerman S. (1940). Experimental study of blast injuries to the lungs. *Lancet*, **236**(6104), 219–24.
5. Bryant RA. (2008). Disentangling mild traumatic brain injury and stress reactions. *New England Journal of Medicine*, **358**(5), 525–7.
6. Mac Donald CL, Johnson AM, Cooper D, et al. (2011). Detection of blast-related traumatic brain injury in U.S. military personnel. *New England Journal of Medicine*, **364**(22), 2091–100.
7. Chambers LW, Green DJ, Gillingham BL, et al. (2006). The experience of the US Marine Corps' Surgical Shock Trauma Platoon with 417 operative combat casualties during a 12 month period of operation Iraqi Freedom. *Journal of Trauma*, **60**(6), 1155–61.
8. Mines M, Thach A, Mallonee S, Hildebrand L, and Shariat S. (2001). Ocular injuries sustained by survivors of the Oklahoma City bombing. *Ophthalmology*, **107**(5), 837–43.
9. Ordog GJ, Wasserberger J, and Balasubramanium S. (1984). Wound ballistics: theory and practice. *Annals of Emergency Medicine*, **13**(12), 1113–22.
10. Fackler ML. (1986). Ballistic injury. *Annals of Emergency Medicine*, **15**(12), 1451–5.
11. Giannou G and Baldan M. (2012). *War Surgery: Working with Limited Resources in Armed Conflict and Other Situations of Violence*. Geneva: International Committee of the Red Cross.
12. Santucci RA and Chang YJ. (2004). Ballistics for physicians: myths about wound ballistics and gunshot injuries. *Journal of Urology*, **171**(4), 1408–14.
13. Borden Institute (2013). *Emergency War Surgery*, Fourth United States Revision. Fort Sam Houston, TX: Borden Institute/Office of the Surgeon General.

14. Garner J. (2011). Pathophysiology of ballistic wounding. In: Smith J, Greaves I, Porter KM (eds) *Oxford Desk Reference: Major Trauma*, pp. 408–26. Oxford: Oxford University Press; 2011.
15. Clasper J. (2001). The interaction of projectiles with tissues and the management of ballistic fractures. *Journal of the Royal Army Medical Corps*, **147**(1), 52–61.
16. Paolino KM, Henry JA, Hospenthal DR, Wortmann GW, and Hartzell JD. (2012). Invasive fungal infections following combat-related injury. *Military Medicine*, **177**(6), 681–5.
17. Coupland RM and Meddings DR. (1999). Mortality associated with use of weapons in armed conflicts, wartime atrocities, and civilian mass shootings: literature review. *British Medical Journal*, **319**(7207), 407–10.
18. Bellamy RF. (1984). The causes of death in conventional land warfare: implications for combat casualty care research. *Military Medicine*, **149**(2), 55–62.

CHAPTER 340

Assessment and management of ballistic trauma

Timothy Hooper and David Lockey

Key points

- Prehospital care of trauma patients should include immediate life-saving interventions and rapid transfer to an appropriate hospital.
- Careful clinical assessment and CT scanning guides initial management.
- Life-saving interventions should not be delayed by unnecessary investigations.
- Treat the wound and not the weapon.
- Damage control resuscitation and surgery should be considered in unstable and critically unwell patients.

Introduction

Ballistic trauma refers to the wounds sustained from the discharge of arms or munitions, most commonly firearms, as a result of armed conflicts, crime, hunting, or attempted suicide.

Access to firearms varies substantially by country. The USA has an estimated 270 million civilian firearms (88.8 per 100 population) compared with 25 million in Germany (30.3 per 100 population), 3.4 million in England and Wales (6.2 per 100 population), and 3.05 million in Australia (15 per 100 population) [1]. Although strong associations between firearm availability and homicide rates have been demonstrated [2], other factors, particularly socioeconomic are influential. This is evident in Honduras, which has the world's highest homicide rate (68 deaths per 100,000 population) despite only having 6.2 firearms per 100 population [3].

Nearly seventy per cent of homicides in the USA result from firearm use (approximately 11000 firearm-related homicides in 2013) [4]. Of the 526 homicides in England and Wales during the year 2013/14 only 29 (6%) resulted from the use of firearms [5].

Ballistic injury severity depends on multiple factors including:

- Bullet type (mass, shape, deformation, and fragmentation tendency).
- Velocity.
- Whether it has passed through objects prior to entering the body (clothing, body armour).
- Tissue type penetrated.
- Energy transfer; dependent on the bullet's path through the body, mass, velocity, and yaw (deviation of the long axis from its line of flight).

Tissue damage is caused by two mechanisms. First, the direct crushing effect of the bullet as it passes through tissues (permanent cavity) and, secondly, the displacement of surrounding tissue by the pressure wave (temporary cavity). The type of tissue through which the bullet passes also influences the degree of damage caused. Elastic tissues, such as skeletal muscle and lung, suffer little damage from temporary cavitation whereas inelastic tissues, such as liver and spleen, can sustain significant disruption [6]. Of note, shotgun injuries result in mortality rates nearly twice that of other firearms due to the destructive nature of the shot, especially at short range.

Although knowledge of ballistic science can help medical staff understand the wounds sustained, information from the patient or bystanders about the weapon used and the situation surrounding wounding is often unreliable. Furthermore, entry and exit wound characteristics, although important, do not necessarily give insight into the degree of underlying tissue damage. Management of ballistic trauma patients therefore needs a considered, objective approach with careful assessment, appropriate imaging, and directed treatment of the wounds found, rather than those suspected—Dr Douglas Lindsey's quote from 1980 of 'treating the wound, not the weapon' [7] still holds true.

Prehospital care

Only time-critical life-saving interventions, most often related to the control of bleeding, should be carried out at the scene of the injury. Most patients with penetrating trauma should to be transported to an appropriate hospital as rapidly as possible.

Triage, treatment, and transport form the framework of effective prehospital care and this is particularly important where there are multiple casualties. Triage to prioritize the most severely-injured and treatment of individual patients using ATLS™ (Advanced Trauma Life Support) principles should be carried out prior to and during transport.

Emergency department

The emergency department (ED) may receive little warning of the arrival of a gunshot victim, particularly when the patient is conveyed to hospital by private transport. On arrival in the ED the patient should have a rapid primary survey performed using an 'airway, breathing, circulation' approach to reveal any injuries that need immediate intervention.

Clothing should be removed to fully expose the patient and evaluate wounds, while aiming to maintain body temperature.

To preserve forensic evidence bullets or fragments should be collected and wound characteristics carefully documented. Particular attention should be paid to the axilla, perineum, and scalp, as wounds can be missed in these areas. Cutting through bullet holes in clothing should be avoided. While entry wounds (Fig. 340.1a.) are normally round to oval in shape with a punched out clean appearance, exit wounds vary considerably (Fig. 340.1b.). Although generally larger and more irregular than entry wounds, due to deformation and yawing of the bullet in the body, they may be of similar size if little energy has been lost along the bullet's path. Occasionally, entry wounds may be larger if the bullet has deformed or fragmented prior to impact with the body [8]. To this end, documenting wounds as 'entry' and 'exit' should be avoided.

Emergency interventions are common to other trauma patients:

- Injuries to head and neck may need urgent intubation to protect and secure the airway.
- Insertion of one or more chest drains may be indicated to treat pneumothoraces or haemothoraces.
- Haemorrhagic shock can be associated with injuries to any body region, but particularly the abdomen and chest, and may need significant blood product transfusion to correct hypovolaemia [9].

Tetanus prophylaxis should be administered using tetanus toxoid if the patient does not have adequate protection with the addition of human tetanus immunoglobulin in patients not previously immunized or with uncertain immunization history [8].

The belief that bullets are sterilized by the heat of firing is false [10]. However, there is ongoing debate about the use of prophylactic antibiotics for ballistic injuries. Approximately 2% of minor gunshot wounds become infected and this is not necessarily reduced by prophylactic antibiotics. Prophylaxis should be considered if there are multiple injuries, gross wound contamination, significant tissue devitalization, large wounds or a delay in treatment [11].

Broad-spectrum intravenous antibiotics are indicated for penetrating abdominal, cranial, and thoracic injuries, and injuries where there is significant tissue damage (including shotgun wounds) [12,13]. Duration of antibiotic treatment varies according to injury. A single pre-operative dose may be adequate for

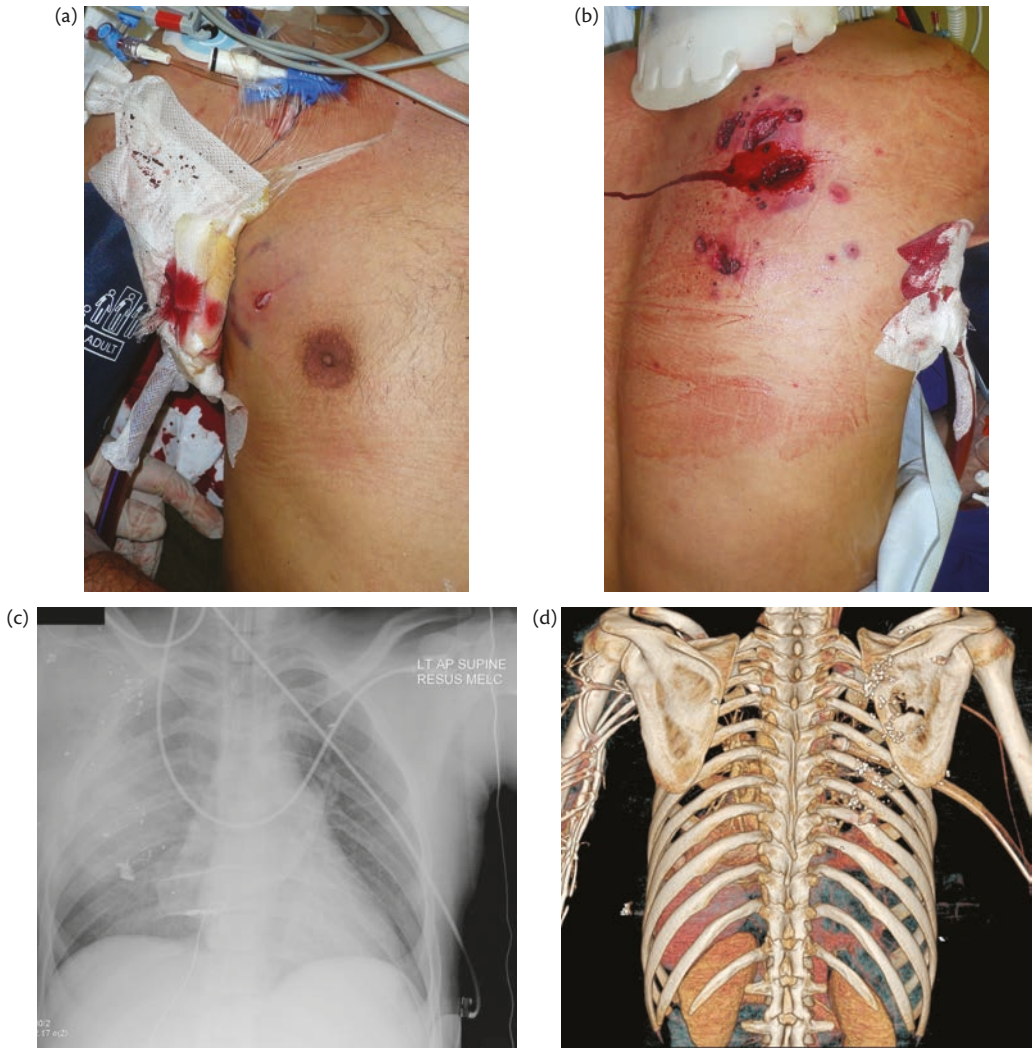


Fig. 340.1. High velocity entry (a), and exit (b) wounds. The entry wound is a neat punched out oval with surrounding bruising, while the multiple exit wounds are due to bullet fragmentation, which can be seen on the chest X-ray (c), and bony fragments from the underlying fractured scapula, as seen on the CT reconstruction (d).

penetrating abdominal injuries without hollow viscus damage. High-velocity, shotgun, and intra-articular gunshot fractures may be adequately treated by 2 days of an intravenous first generation cephalosporin, with the addition of penicillin if grossly contaminated, and gentamicin in the presence of significant tissue damage [12]. Many protocols advocate up to 2 weeks of broad spectrum antibiotics where there is gross contamination of the wound (e.g. from bowel contents or soiled clothing), although there is little evidence of benefit beyond 24 hours [13].

Investigations

Bullets and fragments may be identified with plain radiography (Fig. 340.1c.). Both anteroposterior and lateral radiographs help localize fragments and skin wound markers can be useful to estimate the trajectory of projectiles. Other injuries, such as pneumothoraces, haemothoraces, and fractures can also be identified.

Performing an extended focused assessment with sonography for trauma (eFAST) examination allows rapid, bedside evaluation of the lungs, pericardium and peritoneum. In the presence of penetrating abdominal trauma, a positive FAST is highly predictive of intraperitoneal injury (sensitivity 46% and specificity 94% in one study) [14] and occult pneumothoraces are more likely to be detected with ultrasound than with chest X-ray alone [15].

Computed tomography (CT) is considered to be the gold standard for imaging projectiles, including those that are not radio-opaque (Fig. 340.1d.). Imaging can define the bullet tract, injuries sustained, and extent of tissue damage, helping to guide further management. CT angiography can provide additional information about vascular injuries. Modern helical scanners are fast, but some unstable patients may require transfer to the operating theatre for surgery without imaging.

Surgery

The decision to operate and nature of surgery is determined by the patient's suspected injuries, physiological condition, and the surgical expertise available [8,9]. Bullet and fragment removal and debridement of wound tracts in penetrating head and spinal injuries is becoming less common. However, dural leaks should be closed to prevent secondary infections and insertion of intracranial pressure monitors can aid intensive care management. Thoracic injuries can usually be treated by the insertion of pleural drains, while thoracotomies are reserved for patients with cardiac tamponade, high output from existing pleural drains, or cardiovascular instability. Diaphragmatic injury occurs in approximately 50% of patients, and the co-existence of thoracic and abdominal injuries is reported to be between 6 and 42%. Abdominal injuries may be treated conservatively if imaging suggests there is no intra-abdominal pathology. However, an exploratory laparotomy is usually required for patients who are haemodynamically unstable, have peritonitis or have bowel evisceration. Laparoscopy is an alternative approach, although a proportion will proceed to laparotomy.

Management of soft tissue injury depends on the degree of tissue damage and contamination. Wounds with minimal tissue damage, frequently caused by low-velocity hand guns with low-energy transfer may only require superficial debridement, irrigation, and be left open to heal by secondary intention. Wounds with extensive tissue damage (from high-velocity bullets or close range shotgun wounds) need aggressive and repeated surgery, typically every 48–72 hours, to assess need for further debridement of devitalized tissue (Fig. 340.2). The degree of debridement needs careful consideration as studies have suggested that overzealous debridement of potentially healthy tissue can cause greater disability to the patient than the initial gunshot wound [16].

Fractures caused by low-energy gunshot injuries have similar characteristics to closed fractures and can often be managed in the same way. Some will be amenable to non-operative management, while others will require operative intervention, especially if unstable. By contrast, high-energy gunshot fractures are frequently severely comminuted with devitalized fragments and extensive surrounding tissue damage. Due to the risk of infection and compartment syndrome, external fixation, often with fasciotomies, is commonly required.

Damage control resuscitation

Damage control resuscitation (DCR) is a systematic approach to major trauma that aims to minimize blood loss, maximize tissue oxygenation and optimize outcome from point-of-wounding to definitive treatment. Damage control surgery is part of this and consists of an initial time-limited operation to save life, a period of haemostatic resuscitation on the intensive care unit (ICU), then further definitive surgery. Patients with ballistic injury may benefit from this approach.

During DCR, haemostatic resuscitation seeks to address the lethal triad of hypothermia, acidosis, and coagulopathy while tolerating a short period of moderate hypotension until surgical control is achieved. This approach is different to standard resuscitation methods that are suitable for the 90% of trauma patients who are not shocked or coagulopathic on admission to hospital [17].

Recent trauma transfusion strategies have developed to mimic the delivery of whole blood using packed red blood cells, and high ratios of plasma and platelets [18]. The early use of empirical blood component therapy is likely to become standard practice in shocked trauma patients although the optimal ratio of blood products is still unclear. The use of laboratory tests and point-of-care dynamic clot assessment (thromboelastometry) to target appropriate administration of blood products and other factors, especially fibrinogen, is also gaining favour.

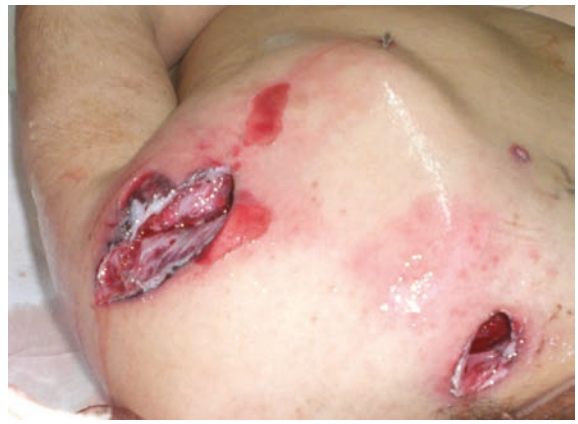


Fig. 340.2 Second-look surgery after initial debridement and washout of a high velocity gunshot wound through soft tissues of the shoulder.

Intensive care

Indications for admission to intensive care are standard and include the need for on-going organ support, cardiovascular instability and injuries that require close observation or have the potential for rapid deterioration.

The ICU management of patients with ballistic trauma is generally supportive and common to that of other trauma patients. Particular attention should be paid to cardiovascular status, coagulation, nutrition, thromboprophylaxis, infection, and the management of specific injuries.

Antibiotic therapy should be driven by wound cultures and local microbiology protocols. Infective organisms are likely to be from skin commensals, clothing, and other contaminants. Clostridial infections may occur, potentially causing severe myonecrosis (*C. perfringens*) and rarely botulism (*C. botulinum*). These have been more commonly associated with older or homemade shotgun ammunition, where animal fibres and other substances are used as wadding [8]. Botulism should be considered in at-risk patients with an unexplained bulbar palsy and descending motor weakness.

Patients often require surgery for wound inspection, further debridement, and definitive surgery on multiple occasions. Communication with the multidisciplinary team, including transfusion services, is vital for effective planning. Compartment syndrome should be considered and actively excluded in all limb injuries where there are comminuted fractures and tissue damage, even if fascitomies have been performed.

Lead and copper poisoning can occur due to retained bullet fragments. Although lead fragments in soft tissue usually become encapsulated with fibrous tissue and cause few problems, those in intra-articular, disc space and bursal locations can cause systematic effects [19]. This usually takes years to develop, but can occasionally be rapid. Treatment is based on chelating agents and fragment removal. Lead, copper, and nickel can also cause local inflammation and necrosis, leading to arthritis if joints are involved.

Rehabilitation

Gunshot wounds may require protracted hospital stays and extensive reconstructive surgery. Chronic pain, permanent disability, and post-traumatic stress disorder are common, especially where injuries affect the brain, spinal cord, or peripheral nerves. The psychological and social impact of these injuries should not be underestimated, and rehabilitation may be harder with the demographic skew of patients from lower socioeconomic groups. Timely and comprehensive rehabilitation makes successful functional recovery and social reintegration more likely [20].

References

1. Graduate Institute of International Studies. (2007). *The Small Arms Study 2007: Guns and the City*. Geneva: Cambridge University Press.
2. Hemenway D and Miller M. (2000). Firearm availability and homicide rates across 26 high-income countries. *Journal of Trauma*, **49**, 985–8.
3. United Nations. (2011). *Global Study on Homicide: Trends, Contexts and Data*. Geneva: United Nations Office on Drugs and Crime.
4. Center for Disease Control and Prevention. (2015). Assault or homicide. Available at: http://www.cdc.gov/nchs/fastats/homicide.htm (accessed 24 August 2015).
5. Available at: http://www.ons.gov.uk/ons/rel/crime-stats/crime-statistics/focus-on-violent-crime-and-sexual-offences--2013-14/rpt-chapter-2.html
6. Fackler ML. (1996). Gunshot wound review. *Annals of Emergency Medicine*, **28**, 194–203.
7. Lindsey D. (1980). The idolatry of velocity, or lies, damn lies, and ballistics. *Journal of Trauma*, **20**, 1068–9.
8. Bartlett CS. (2003). Clinical update: gunshot wound ballistics. *Clinical Orthopaedics and Related Research*, **408**, 28–57.
9. Lichte P, Oberbeck R, Binnebosel M, et al. (2010). A civilian perspective on ballistic trauma and gunshot injuries. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, **18**, 35.
10. Wolf AW, Benson DR, Shoji H, et al. (1978). Autosterilization in low-velocity bullets. *Journal of Trauma*, **18**, 63.
11. Ordog GJ, Sheppard GF, Wasserberger JS, et al. (1993). Infection in minor gunshot wounds. *Journal of Trauma*, **34**, 358–65.
12. Simpson BM, Wilson RH, and Grant RE. (2003). Antibiotic therapy in gunshot wound injuries. *Clinical Orthopaedics and Related Research*, **408**, 82–5.
13. Cornwell EE, Dougherty WR, Berne TV, et al. (1999). Duration of antibiotic prophylaxis in high-risk patients with penetrating abdominal trauma: a prospective randomized trail. *Journal of Gastrointestinal Surgery*, **3**, 648–53.
14. Udobi KF, Rodriguez A, Chiu WC, et al. (2001). Role of ultrasonography in penetrating abdominal trauma: a prospective clinical study. *Journal of Trauma*, **50**, 475–9.
15. Kirkpatrick AW, Sirois M, Laupland KB, et al. (2004). Hand-held thoracic sonography for detecting post-traumatic pneumothoraces: The extended focused assessment with sonography for trauma (EFAST). *Journal of Trauma*, **57**, 288–95.
16. Mendelson JA. (1991). The relationship between mechanisms of wounding and principles of treatment of missile wounds. *Journal of Trauma*, **31**, 1181–202.
17. Holcomb JB. (2007). Damage control resuscitation. *Journal of Trauma*, **62**, S36–7.
18. Holcomb JB, Wade CE, Michalek JE, et al. (2008). Increased plasma and platelet to red blood cell ratios improves outcomes in 466 massively transfused civilian trauma patients. *Annals of Surgery*, **248**, 447–58.
19. Hollerman JJ, Feckler ML, Coldwell DM, et al. (1990). Gunshot wounds: 2: Radiology. *American Journal of Research*, **155**, 691–702.
20. Greenspan AI and Kellerman AL. (2002). Physical and psychological outcomes 8 months after serious gunshot injury. *Journal of Trauma*, **53**, 709–16.

PART 16.3

Traumatic brain injury

CHAPTER 341

Epidemiology and pathophysiology of traumatic brain injury

Imoigele Aisiku and Claudia S. Robertson

Key points

- Traumatic brain injury (TBI) is a devastating injury that causes a huge burden of disease around the world; approximately 1.6 million people suffer a TBI in the USA each year.
- TBI is a bimodal disease that affects young adults (15–34), the elderly (>75), and males more than females.
- Mechanism of injury, age, gender, and initial severity of injury are the most significant predictors of mortality.
- Harm from TBI arises from direct damage to the brain at the time of the initial injury (primary injury), which places the brain at risk of further harm from secondary injury.
- Secondary injury may occur due to intracranial hypertension, hypotension, hypoxia, reduced cerebral perfusion, and inflammation.

Introduction

Current estimates suggest that traumatic brain injury (TBI) will surpass many diseases as the major cause of death and disability by the year 2020. The burden of disease due to TBI is evident throughout the world, and is especially prominent in low and middle income countries. Latin America and Sub Saharan Africa have a particularly high incidence of TBI—varying from 150–200 per 100,000 respectively [1,2]. Detailed data on the incidence and impact of TBI are available for the USA, where someone sustains a traumatic brain injury every 15 seconds resulting in 1,500,000 new cases of brain injury each year. Of these patients, over 260,000 (17%) will be hospitalized, of who more than 50,000 will die, and 80,000 will survive with permanent disability [3]. The risk of brain injury is highest among adolescents, young adults, and those older than 75 years, and the risk for males is twice that for females. An estimated 5.3 million persons, slightly more than 2% of the United States populations, currently live with disabilities resulting from traumatic brain injury. The immediate medical costs for these patients are estimated to be $48.3 billion annually, with hospitalization accounting for $31.7 billion, and fatal injuries costing $16.6 billion each year [4,5]. Survivors with functional disabilities, such as changes in language, thinking, emotion, and behaviour are also major contributors to the costs of TBI.

Classification of traumatic brain injury

TBI begins with high-energy acceleration or deceleration of the brain within the cranium or with a penetrating injury to the brain. Classically, TBI has been divided into two different periods, representing primary and secondary injury. The demarcation between these two periods is somewhat arbitrary as primary and secondary injury represents more a continuum of injury. TBI can also be classified by severity with the most commonly used severity grading scale being the Glasgow Coma Score (GCS) Scale. The GCS which stratifies TBI as mild, moderate or severe Scale. TBI can also be classified by type of radiographic injury as focal or diffuse (Figs 341.1 and 341.2) [6,7]. Focal injuries tend to occur at the site of impact, with focal neurological deficits referable to those areas. The orbitofrontal and anterior temporal lobes are characteristic sites of injury. Diffuse injuries are a combination of linear translational and rotational forces, which when combined produce angular acceleration or deceleration injuries resulting in straining, shearing, and compression of brain tissue. The effects of these injuries are maximal on axonal projections and small blood vessels within and around the brain stem, the parasagittal white matter of the cerebrum, the corpus callosum, and the gray–white matter junctions in the ventral and anterior frontal and temporal lobes [8]. These injuries are

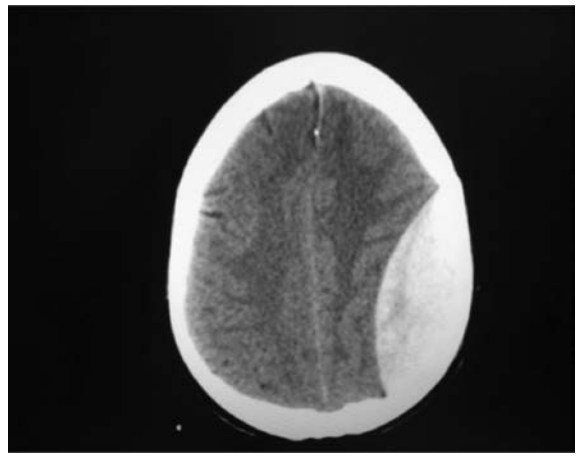


Fig. 341.1 Focal lesion (epidural haematoma).

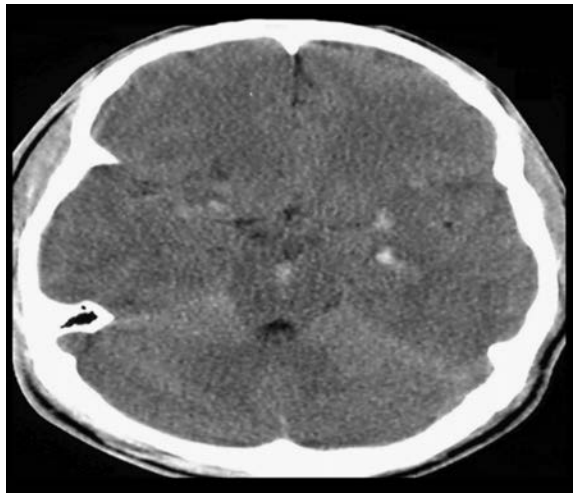


Fig. 341.2 Diffuse lesion.

often referred to as diffuse axonal injuries or multifocal injuries [9]. Diffuse axonal injury is the predominant mechanism of injury in 40–50% of traumatic brain injuries and often believed to be a component in most presentations of non-penetrating injury [9].

Risk factors for poor outcome

Various risk factors are associated with poor outcome following TBI. These include mechanism of injury (penetrating versus blunt), age, gender, genetic factors, and the occurrence of secondary insults, such as hypotension and hypoxia. Physical findings with prognostic significance include the Glasgow Coma Score (GCS) and pupillary reactions to light. Approximately 20–30% of patients who present with a GCS of 8 or less have bilaterally fixed and dilated pupils; 70–90% of these patients will have a poor outcome. The GCS has been a widely used tool for over 40 years and has been well validated for its prognostic utility (Table 341.1). The GCS, however, does not provide any information on the type of intracranial injury and the need for surgical versus medical management. CT findings provide additional information. While various grading systems have been developed, the Marshall classification is arguably the most often used or quoted [10]. (Table 341.2)

Pathophysiology

Cellular pathophysiology

Pathophysiological processes initiated by TBI are complex, and can be divided into those due to the primary and secondary injuries. The primary injury is a direct result of the original insult. Depending on the severity of the insult, the primary injury can result in immediate physical damage to neuronal and glial cells, glial endfeet, axonal and dendritic projections, and synapses, as well as to the cells making up the cerebral vasculature. This damage can result in focal or multifocal contusions, diffuse axonal injury, and/or haematoma formation [11]. Primary pathologies develop extremely rapidly and are not therefore amenable to therapeutic interventions other than prevention. In addition to causing immediate physical damage to the brain, the primary injury sets in motion molecular, cellular, genomic, and metabolic alterations that result in secondary injury. Secondary injury includes physical disruption of cell membranes and infrastructure, disturbances of ionic homeostasis secondary to increased membrane permeability and a cascade of neurotoxic events mediated by intracellular calcium. Secondary brain injury occurs minutes, hours, or days after the primary injury as a result of pathophysiological events, also called secondary insults [12]. These secondary pathological processes may be of intracranial or systemic origin. Intracranial secondary insults include intracranial hypertension or elevated intracranial pressure (ICP), cerebral oedema (fluid-mediated swelling), and cerebral ischaemia. Systemic events include systemic arterial hypotension, hypoxaemia and hyperthermia. In severe TBI, secondary events include changes in cerebral blood flow, local and systemic inflammation, alterations in oxygen delivery and metabolism, and both ischaemic and apoptotic death of neural cells [13]. Intravascular coagulation is common in severe TBI and in addition to causing local ischaemia may also lead to a systemic consumptive coagulopathy [14]. A majority of secondary insults contribute to ischaemia and are associated with poorer outcome [15,16]. Secondary insults occur frequently, despite current intensive care management [17], and their effect may be particularly detrimental when adaptive responses that normally act to maintain cerebral perfusion are impaired. Since secondary insults evolve over time they are at least potentially preventable [18]. A large percentage of patients suffering from severe TBI (GCS < 8) manifest elevated ICP and decreased cerebral blood flow (CBF) that are significantly associated with increased morbidity and mortality.

Intracranial pressure and cerebral autoregulation

Elevated ICP is a key secondary event that is associated with increased morbidity and mortality. One of the primary considerations of clinicians caring for patients with TBI is controlling elevated ICP. A sustained increase in ICP to greater than 20 mmHg has been linked to increased morbidity and mortality, whereas monitoring and treatment of elevated ICP have been associated

Table 341.1 Glasgow Coma Scale

	Score					
	1	2	3	4	5	6
Eye opening	No response	To painful stimuli	On spoken command	Spontaneous		
Motor responses	No response	Extensor posturing	Abnormal flexion	Normal flexion	Localizing response	Obeys commands
Verbal responses	No response	Incomprehensible speech	Inappropriate speech	Confused conversation	Orientated	

Reprinted from *The Lancet*, **304**, Teasdale G and Jennet B, 'Assessment of coma and impaired consciousness: a practical scale', pp. 81–4, Copyright 1974, with permission from Elsevier.

Table 341.2 Marshall classification

Category	Description
Diffuse injury I (no visible pathology)	No visible intracranial pathology seen on CT scan
Diffuse injury II	Cisterns are present with midline shift 0–5 mm and/or lesion densities present. No high- or mixed-density lesion >25 mL, may include bone fragments and foreign bodies
Diffuse injury III	Cisterns compressed or absent with mid-line shift 0–5 mm. No high- or mixed-density lesion >25 mL
Diffuse injury IV	Mid-line shift >5 mm. No high- or mixed-density lesion >25 mL
Evacuated mass lesion	Any lesion surgically evacuated
Non-evacuated mass lesion	High- or mixed-density lesion > 25 mL, not surgically evacuated

with improved outcomes [19]. Elevated ICP can lead to further brain damage by causing tissue herniation and cerebral hypoperfusion. If severe, hypoperfusion can reduce blood flow to the extent that it is insufficient to meet the tissue's metabolic needs, it will then cause ischaemia, additional brain damage, and ultimately death.

Cerebral autoregulation

Cerebral autoregulation is an adaptive mechanism that maintains a relatively constant blood flow to the brain despite changes in systemic arterial blood pressure. Therefore, cerebral autoregulation is one of the major mechanisms responsible for brain protection when cerebral perfusion pressure (CPP) is unstable. Cerebral autoregulation is impaired in up to 90% of patients following severe TBI and may be one of the mechanisms rendering the brain more vulnerable to potentially preventable secondary ischaemic injury. Autoregulation is often impaired from early following TBI and may remain impaired for 3 weeks or longer after the original injury.

Pro-inflammatory and cellular injury biomarkers

Inflammatory responses to TBI, both local and systemic, are complex. Invading cells from the blood (e.g. leukocytes, monocytes, macrophages) and/or activated resident cells (e.g. microglia) release a number of inflammatory molecules and free radicals that can contribute to brain oedema and worsen neurological outcome. Increased serum and/or CSF concentrations of pro- and anti-inflammatory cytokines, chemokines, and acute phase reactant proteins have been observed following TBI. The role of inflammation in determining the progression of TBI-associated pathologies has been the focus of numerous studies. More recently, the expressions of these factors has been appreciated as potential markers of injury, and studies are ongoing to test if their levels correlate with outcome or can serve as surrogate markers of treatment efficacy. For example, glial fibrillary acidic protein (GFAP) is a monomeric intermediate filament protein expressed by astrocytes. It is a brain-specific protein that is released after TBI. Increases in serum GFAP levels after TBI have been shown to be predictive of elevated ICP, reduced mean arterial pressure (MAP), low CPP, poor Glasgow Outcome Scores (GOS), and increased mortality.

Cerebral oxygenation

Maintaining adequate cerebral oxygenation is considered a key objective in optimizing recovery after TBI. There currently exist three methods for monitoring cerebral oxygenation. Brain tissue oxygenation ($PbtO_2$) monitoring, jugular venous saturation ($SjvO_2$) monitoring, and near infrared spectroscopy. Brain tissue oxygenation is the most widely used. $PbtO_2$ can be monitored continuously and requires the placement of an intracranial catheter. Some controversy exists as to whether placement in damaged versus undamaged regions of the brain is the optimal placement. Brain hypoxia as measured by $PbtO_2$ of less than 10 mmHg for more than 15 minutes is an independent predictor of worse outcome and mortality. Although $PbtO_2$ less10 mmHg is associated with poor outcomes, most clinical practice parameters target $PbtO_2$ 15–20 mmHg for treatment goals. A meta-analysis of four studies comparing an ICP/CPP-based algorithm to a combined $PbtO_2$/ICP/CPP algorithm suggested improved outcomes in the $PbtO_2$ treatment group. Jugular venous saturation monitoring has been in use for over 20 years and values of less than 55% suggest increased oxygen extraction relative to perfusion indicating brain ischaemia. Increased $SjvO_2$ values most likely reflect hyperaemic states. The value of $SjvO_2$ monitoring in the absence of an ICP monitor and CPP measurements is limited. Currently, there is significant controversy over the ideal patient and situation in which to use cerebral oxygenation monitors, but these tools provide insight to the mechanisms of secondary injury in TBI and additional information to aid clinical decision making.

Conclusion

TBI remains a major cause of death and disability around the world. It affects many people with significant productive years ahead of them and results in major economic burdens. The pathophysiology is complex and the varying degrees of secondary insults make the care of patients with TBI particularly challenging. Hopefully improved diagnostic and neuroprotective mechanisms will lead to improvements in mortality and neurocognitive outcomes. The principal goal of neurological critical care is to intervene in time to prevent, detect and treat secondary injury mechanisms described previously [13].

References

1. Bryan-Hancock CHJ. (2010). The global burden of traumatic brain injury: preliminary results from the global burden of disease project. *Injury Prevention*, **16**, A17.
2. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, and Kobusingye OC. (2007). The impact of traumatic brain injuries: a global perspective. *NeuroRehabilitation*, **22**(5), 341–53.
3. Thurman DJ, Alverson C, Dunn KA, Guerrero J, and Sniezek JE. (1999). Traumatic brain injury in the United States: a public health perspective. *Journal of Head Trauma Rehabilitation*, **14**(6), 602–15.
4. Langlois JA, Rutland-Brown W, and Wald MM. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. *Journal of Head Trauma Rehabilitation*, **21**(5), 375–8.

5. Lewin I. (1992). *The Cost of Disorders of the Brain*. Washington DC: The National Foundation for the Brain.
6. Andriessen TM, Jacobs B, and Vos PE. (2010). Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. *Journal of Cell and Molecular Medicine*, **14**(10), 2381–92.
7. Graham DI, Adams JH, Doyle D, et al. (1993). Quantification of primary and secondary lesions in severe head injury. *Acta Neurochirugia (Wien)*, **57**(Suppl.), 41–8.
8. Narayan RK, Michel ME, Ansell B, *et al*. (2002). Clinical trials in head injury. *Journal of Neurotrauma*, **19**(5), 503–57.
9. Meythaler JM, Peduzzi JD, Eleftheriou E, and Novack TA. (2001). Current concepts: diffuse axonal injury-associated traumatic brain injury. *Archives of Physical and Medical Rehabilitation*, **82**(10), 1461–71.
10. Marshall LF MS, Klauber MR, and Clark MV. (1991). A new classification of head injury based on computerised tomography. *Journal of Neurosurgery*, **75**(Suppl.), 14–20.
11. Adams JH, Doyle D, Ford I, Gennarelli TA, Graham DI, and McLellan DR. (1989). Diffuse axonal injury in head injury: definition, diagnosis and grading. *Histopathology*, **15**(1), 49–59.
12. Jones PA, Andrews PJ, Midgley S, et al. (1994). Measuring the burden of secondary insults in head-injured patients during intensive care. *Journal of Neurosurgical Anesthesiology*, **6**(1), 4–14.
13. Decuypere M and Klimo P, Jr. (2012). Spectrum of traumatic brain injury from mild to severe. *Surgical Clinics of North America*, **92**(4), 939–57, ix.
14. Stein SC, Chen XH, Sinson GP, and Smith DH. (2002). Intravascular coagulation: a major secondary insult in nonfatal traumatic brain injury. *Journal of Neurosurgery*, **97**(6), 1373–7.
15. Chesnut RM and Marshall LF. (1991). Management of head injury. Treatment of abnormal intracranial pressure. *Neurosurgical Clinics of North America*, **2**(2), 267–84.
16. Wald SL. (1995). Advances in the early management of patients with head injury. *Surgical Clinics of North America*, **75**(2), 225–42.
17. Cortbus F, Jones PA, Miller JD, Piper IR, and Tocher JL. (1994). Cause, distribution and significance of episodes of reduced cerebral perfusion pressure following head injury. *Acta Neurochirugia (Wien)*, **130**(1–4), 117–24.
18. Maas AI, Stocchetti N, and Bullock R. (2008). Moderate and severe traumatic brain injury in adults. *Lancet Neurology*, **7**(8), 728–41.
19. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, and Pickard JD. (1996). Monitoring of cerebral autoregulation in head-injured patients. *Stroke*, **27**(10), 1829–34.

CHAPTER 342

Assessment of traumatic brain injury

Peter J. D. Andrews and Jonathan K. J. Rhodes

Key points

- Traumatic brain injury is a common clinical problem and the resulting burden of disease is expected to increase substantially, particularly in the developing countries, in the next 10 years.
- Early assessment is based on a careful history, clinical assessment, and neurological imaging—usually a CT scan of the brain.
- An immediate CT scan of brain should be obtained in any adult patient at risk of harbouring intracranial pathology.
- In adult patients who have a Glasgow Coma Scale score below 15 and indications for a brain CT scan, the scan should include the cervical spine by scanning from the base of skull to T4.
- Establishing a reliable prognosis early after injury is notoriously difficult, but recent predictive models are readily accessible to clinicians via a web-based calculator to aid early clinical decision making and to allow better informed discussions with patients' families.

Introduction

Traumatic brain injury (TBI) is a major cause of death and disability throughout the world. The epidemiology of traumatic brain injury (TBI) is difficult to describe accurately due to inconsistencies in the definition and classification of the condition, but it is estimated that the annual incidence in the United States is been between 180 and 250 per 100,000 population per year [1]. TBI is the cause of one-third to one-half of all trauma deaths, and the leading cause of disability in people under 40, severely disabling 15–20 people per 100,000 population per year [2]. Injuries are projected to account for 20% of the worldwide burden of death and disability by 2020 [3].

Research into new therapies for TBI has been disappointing. More than 23 multicentre clinical trials have been conducted since 1985, none of which has produced an effective treatment for TBI. Clinical trials into TBI provide significant challenges; trauma is a neglected research topic worldwide, consent in unconscious patients requires careful ethical consideration, and traumatic brain injuries have very heterogeneous mechanisms and pathologies [4].

Assessment of traumatic brain injury

The heterogeneity of traumatic brain injury (TBI) is considered one of the principal barriers to finding effective treatments. Considerable international research effort has gone into outlining the steps needed to develop a reliable, efficient and convincing classification system for TBI that could be used to link specific patterns of brain and neurovascular injury with appropriate therapeutic interventions.

Currently, the Glasgow Coma Scale (GCS-Table 342.1) is the primary criterion for the clinical classification of patients with TBI. It has high inter-observer reliability and generally good clinimetric and prognostic capabilities [5]. The GCS is obtained by eliciting the best response in three domains—eye opening, verbal response, and motor response. The score ranges from 3 to 15 with lower scores indicating more severe injury or deeper coma. Mild injury is defined as GCS score 15–13, moderate by GCS score 12–9 and severe by GCS score <9. A meta-analysis found that decreased GCS was a strong predictor of intracranial injury in adults with a minor head injury (relative risk, 5.58) [6].

While the GCS is extremely useful in the clinical management and prognosis of TBI, it does not provide specific information about the pathophysiology and mechanisms that are responsible for neurological deficits, and might be targeted by available and novel interventions. Due to the limitations of the GCS the development of a new, multidimensional classification system for use in clinical trials of patients with TBI has been proposed, although no such system is yet agreed and this remains a vision for the future.

Prehospital assessment

A large number of variables have been identified as elevating risk of deterioration or adverse outcomes after TBI (Box 342.1).

Prehospital assessment includes not only the probable severity of injury assessed using the GCS score and the mechanism of injury, but also the likelihood of adverse outcome from modifiable factors, such as hypotension, hypercarbia, and hypoxaemia.

Assessment in the emergency department

A detailed review of all aspects of assessment of patients with TBI in the emergency department (ED) is not within the scope of this chapter. Evidence-based guidelines approve the principles of advanced trauma life support (ATLS), the systematic,

Table 342.1 The Glasgow Coma scale (derived by adding the score for the best response in each of the three categories eye opening, verbal response, and motor response)

Response	Best response recorded	Score
Best eye opening response	**Select one option:**	1
	◆ Does not open eyes	2
	◆ To painful stimuli	3
	◆ In response to voice	4
	◆ Spontaneously	
Best verbal response	◆ Makes no sounds	1
	◆ Incomprehensible sounds	2
	◆ Utters inappropriate words	3
	◆ Confused, disorientated	4
	◆ Orientated, converses normally	5
Best motor response	◆ Makes no movements	1
	◆ Extension to painful stimuli	2
	◆ Abnormal flexion to painful stimuli	3
	◆ Flexion/withdrawal to painful stimuli	4
	◆ Localizes painful stimuli	5
	◆ Obeys commands	6

internationally accepted approach for assessment and resuscitation of trauma patients developed by the American College of Surgeons Committee on Trauma.

On arrival in the ED a patient with a TBI should have their GCS reassessed if possible, patients who have a symptomatic TBI or who cannot be assessed clinically are likely to need a CT scan once stabilized. In the past, the approach to management of TBI was often observation and repeated examination, and only taking urgent action following the detection of neurological deterioration, this approach has been superseded by pre-emptive investigation to detect lesions before they lead to neurological deterioration. The main focus of ED assessment should be assessing the risk of clinically important brain injuries, injuries to the cervical spine, and the need for imaging. Attention should also be paid to co-existing injuries and to other concerns (for example, non-accidental injury and a possible non-traumatic aetiology, such as intracerebral haemorrhage). Early imaging, rather than admission and observation for neurological deterioration, reduces the time to detection for life-threatening complications and is associated with better outcomes.

Box 342.1 Risk factors for deterioration after TBI

- Loss of consciousness.
- Amnesia.
- Age.
- Neurological signs.
- Bleeding disorders and anticoagulant/antiplatelet use.
- Skull fracture.
- Mechanism of injury.
- Headache.
- Vomiting.
- Drugs and alcohol.
- Irritability and altered behaviour.
- Previous cranial neurosurgery.

Imaging

The current primary investigation for the detection of acute clinically important brain injuries is CT imaging of the brain. This is based on level one evidence and is considered to be a grade A recommendation in many evidence-based guidelines.

For safety, logistic and resource reasons, magnetic resonance imaging (MRI) scanning is not currently indicated as the primary investigation in patients who have sustained a traumatic brain injury, although it is recognized that additional information of importance to the patient's prognosis can often be detected by MRI. Importantly, MRI is contraindicated in both head and cervical spine investigations, unless there is absolute certainty that the patient does not have an incompatible device, implant, or foreign body, the exclusion of which often necessitates a CT scan of head/brain.

Four studies have sought to develop 'decision rules' for selecting patients for CT imaging by identifying patients at a high risk for traumatic brain injury (usually intracerebral haemorrhage or haemorrhagic contusion). The Canadian CT-rules and the 'New Orleans' criteria are considered the most clinically relevant [7,8]. Two versions of the Canadian rules are available, a 5-point version designed

Box 342.2 Risk factors that indicate CT scanning of the head be requested immediately

- GCS less than 13 on initial assessment in the ED.
- GCS less than 15 at 2 hours after the injury on assessment in the ED.
- Suspected open or depressed skull fracture.
- Any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign).
- Post-traumatic seizure.
- Focal neurological deficit.
- More than one episode of vomiting.
- Amnesia for events more than 30 minutes before impact.
- CT should also be requested immediately in patients with any of the following risk factors, provided they have experienced some loss of consciousness or amnesia since the injury:
  - Age 65 years or older.
  - Coagulopathy (history of bleeding, clotting disorder, current treatment with warfarin).
  - Dangerous mechanism of injury (a pedestrian or cyclist struck by a motor vehicle, an occupant ejected from a motor vehicle or a fall from a height of greater than 1 m or five stairs).

to detect 'need for neurological intervention', and a seven point version designed to detect 'clinically important brain injury'. The latter outcome is more clinically relevant and is therefore recommended. However, it is acknowledged that the 5-point rule has some benefit in determining the urgency with which CT imaging should be obtained.

The Canadian derivation sample was much larger than the New Orleans sample with 3121 and 520 patients, respectively, and 909 patients in the New Orleans validation phase. Marion Smits et al., have published an external validation of the Canadian CT Head Rule (CCHR) and the New Orleans Criteria (NOC) for CT scanning of patients with minor head injury [9]. The authors report that the results of adapted rules that did not consider loss of consciousness as a prognostic factor, and showed that both the NOC and the CCHR had 100% sensitivity for identifying patients who underwent neurosurgical intervention after minor head injury. This was true for both the original decision rules (when applied to the patient population that these rules were designed for) and for the adapted rules applied to Smits' entire study population. Sensitivity for traumatic lesions detected by CT scanning or for clinically important lesions, however, was not 100% for both rules. The NOC decision rule had high sensitivity for traumatic brain CT lesions, but the CCHR did not. The difference in sensitivities for traumatic brain CT findings between the two decision rules seems to be mainly due to the more strict use of the risk factor of external injury in the CCHR.

Current guidelines recommend adult patients who have sustained a traumatic brain injury and present with any one of the risk factors listed in Box 342.2 should have a CT scan of the brain without delay [9].

Radiological classification of TBI

Cranial CT scans provide information on the presence of mass lesions, such as intracranial haematomata (Fig. 342.1a, b) and contusions, diffuse brain swelling, and distortion of normal intracranial architecture, such as shift of midline structures. Cranial CT scans in patients with TBI are often classified or graded using the Marshall classification (Box 342.3).

Prognosis

Establishing a reliable prognosis early after traumatic brain injury is notoriously difficult. Prognostic models are statistical models that

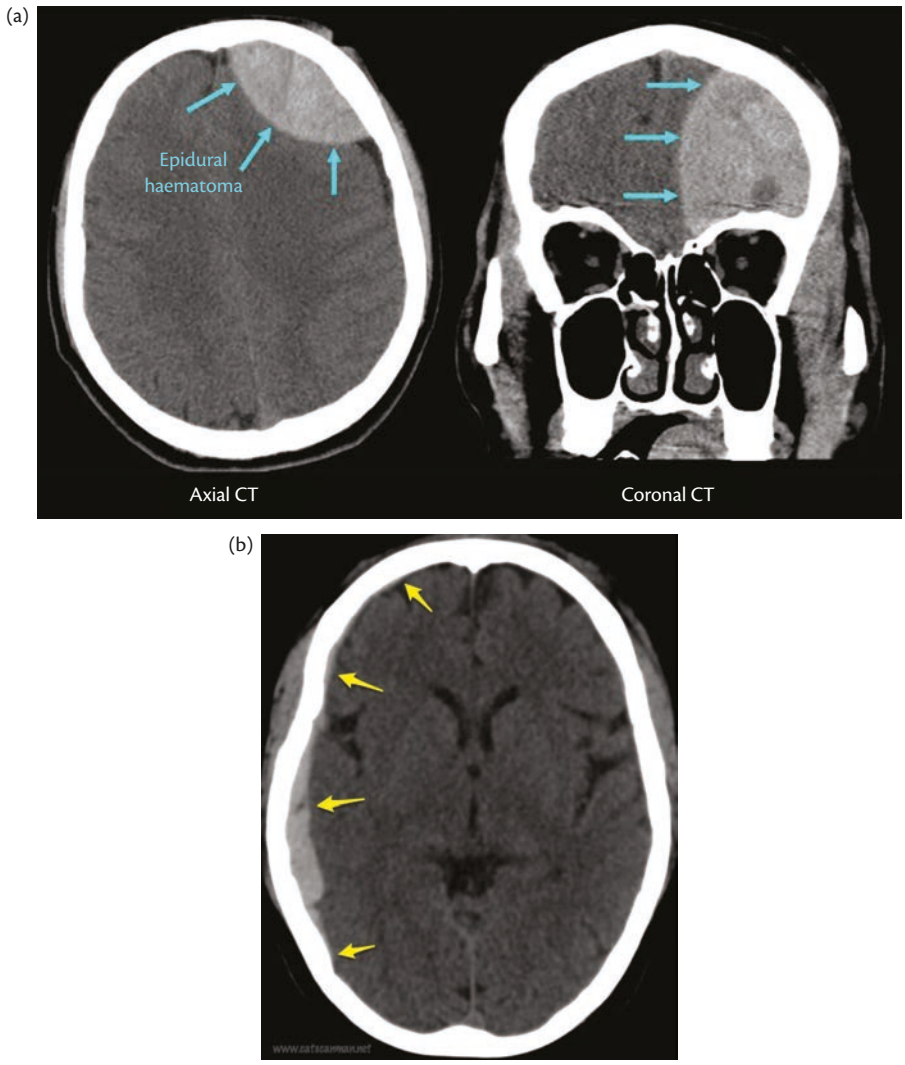


Fig. 342.1 (a) Extradural haematoma detected by CT scanning. (b) Subdural haematoma detected by CT scanning.

Box 342.3 Marshall classification

Ct abnormalities in brain trauma

- **Diffuse injury I (no visible pathology):** no visible intracranial pathology seen on CT scan.
- **Diffuse injury II:** cisterns are present with midline shift of 0–5 mm and/or lesions densities present; no high or mixed density lesion >25 cm^3 may include bone fragments and foreign bodies.
- **Diffuse injury III (swelling):** cisterns compressed or absent with midline shift of 0–5 mm; no high or mixed density lesion >25 cm^3.
- **Diffuse injury IV (shift):** midline shift >5 mm; no high or mixed density lesion >25 cm^3.

Evacuated mass lesion

Any lesion surgically evacuated.

Non-evacuated mass lesion

High or mixed density lesion >25 cm^3; not surgically evacuated.

With permission from Lippincott Williams and Wilkins/Wolters Kluwer Health, Maas AIR, Hukkelhoven CWPM, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. *Neurosurgery*, 2005 Dec.; **57**(6), 1173–82.

combine data from patients to predict clinical outcome. Such models based on data collected soon after presentation could, in theory, be used to aid early clinical decision-making and to allow better informed discussions with patients' families. They could also assist in clinical audit by allowing adjustment for case mix.

However, while many prognostic models have been developed, none are widely used. A recent systematic review of prognostic models in TBI found that they were developed from small samples of patients, had poor methodology (for example, in over half of the models loss to follow-up was not reported), were rarely externally validated, and were not clinically practical [4].

Prognostic models based on admission variables are essential to support early clinical decision-making, and to facilitate reliable comparison of outcomes between different patient series and variation in results over time. Furthermore, prognostic models have an important role in randomized controlled trials (RCTs), for stratification and statistical analyses that explicitly consider prognostic information, such as covariate adjustment.

In recent years there have been two milestones that helped forward research into TBI: the formation of the IMPACT (International Mission on Prognosis and Analysis of Clinical Trials in traumatic brain injury) database [10], and the CRASH (corticosteroid randomization after significant head injury) trial [11]. The IMPACT database combined patient data from eight randomized controlled clinical trials and three observational studies to give a patient population of over 9000. The CRASH trial was a RCT of the effect of early steroid administration on outcome after TBI. The CRASH trial enrolled 10,008 patients and is the largest clinical trial ever conducted in patients with TBI [12,13].

As well as being the largest prognostic models developed for TBI, there are other key differences from previous models—the new models were externally validated, included patient data from low and middle income countries, and are accessible to clinicians and public via a web-based calculator [14,15]. While the predictors of age, motor score, and pupillary reactivity have been included in many prognostic models for TBI, Steyerberg and colleagues' model, and the model produced by the CRASH collaborators are the largest and most robustly validated that have been developed so far [12,13].

Caution must be advised in applying population-based estimates of outcome to individual patients. While both of these prognostic

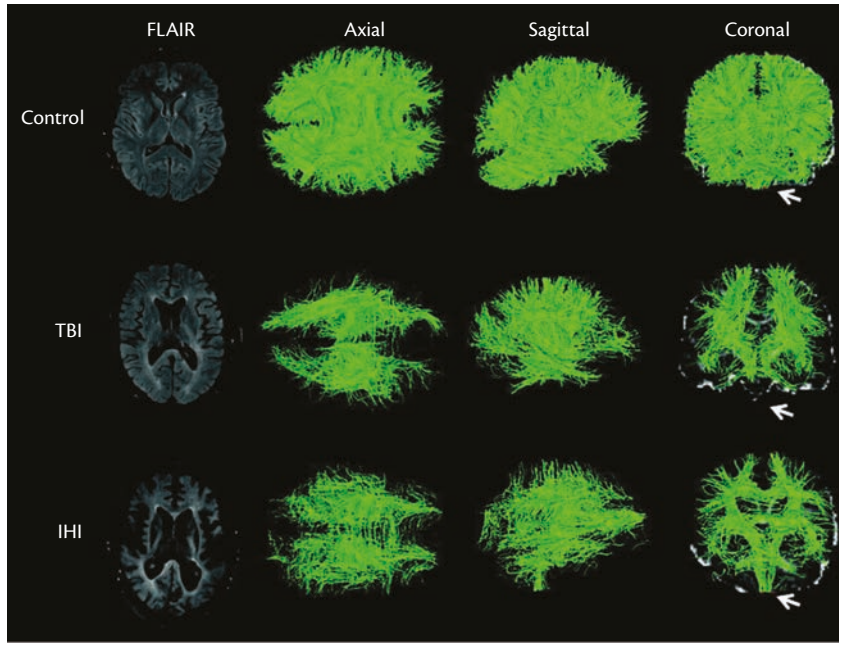


Fig. 342.2 Diffusion tensor imaging after trauma or ischaemic hypoxic injury (IHI).

models have been externally validated, they have essentially been validated against the populations of each other. All of the patients from CRASH and most of the patients from IMPACT were enrolled in clinical trials. Work is needed to establish the accuracy of these models prospectively in patients **not** enrolled in clinical trials. The CRASH data set are more heterogeneous than many of the phase III neuroprotection studies because inclusion GCS included moderate and severe injury, and included a high number of patients from low and middle income countries. Steyerberg and colleagues models seemed less accurate at predicting outcome following TBI in low and middle income countries.

These models may provide useful additional information in regard to clinical decision making and the counselling of patients' relatives, but it must be remembered that their outcomes apply to populations, and so great caution is needed if applying them to individual patients. These models are potentially of great use in clinical audit, allowing comparison between different hospitals and changes in management over time, with adjustment for case mix. The models should also allow better trial design and analysis: many patients with TBI previously included in clinical trials have expected outcomes that are so good or bad that no intervention could be expected to alter the outcome [16]. Future clinical trials could focus on those patients with a more uncertain prognosis.

Advanced imaging and prognosis

Diffuse axonal injury (DAI) is the predominant mechanism of the injury in 40–50% of patients with TBI who require hospitalization and is probably a factor in most cases that result from high-speed motor vehicle collisions. DAI is a consequence of acceleration and deceleration forces that can shear axons and produce microscopic changes in the brain. Diffusion tensor imaging (DTI, MR sequence) permits quantification of white matter integrity and TBI frequently involves white matter injury. Therefore, DTI represents an appealing method of demonstrating white matter pathology attributable to TBI (Fig. 342.2). Diffuse axonal injury is a multifocal injury that primarily affects the parasagittal white matter, corpus callosum, and brainstem. Recent studies have shown that DTI tractography-based quantification may be useful for detecting DAI and predicting outcome [17]. However, in mild TBI, this methodology has some limitations as alterations in white matter integrity are not specific to TBI, and their presence does not necessarily confirm a diagnosis of TBI.

References

1. Bruns J Jr and Hauser WA. (2003). The epidemiology of traumatic brain injury: a review. *Epilepsia*, **44**(Suppl. 10), 2–10.
2. Fleminger S and Ponsford J. (2005). Long term outcome after traumatic brain injury. *British Medical Journal*, **331**, 1419–20.
3. Finfer SR and Cohen J. (2001). Severe traumatic brain injury. *Resuscitation*, **48**, 77–90.
4. Perel P, Edwards P, Wentz R, and Roberts I (2006). Systematic review of prognostic models in traumatic brain injury. *BMC Medical Informatics and Decision Making*, **6**, 38.
5. Narayan RK1, Michel ME, Ansell B, et al. (2002). Clinical trials in head injury. *Journal of Neurotrauma*, **19**(5), 503–57.
6. Dunning J, Stratford-Smith P, Lecky F, et al. (2004). A meta-analysis of clinical correlates that predict significant intracranial injury in adults with minor head trauma. *Journal of Neurotrauma*, **21**(7), 877–85.
7. Sultan HY, Boyle A, Pereira M, Antoun N, and Maimaris C. (2004). Application of the Canadian CT head rules in managing minor head injuries in a UK emergency department: implications for the implementation of the NICE guidelines. *Emergency Medicine Journal*, **21**(4), 420–5.
8. Korley FK, Morton MJ, Hill PM, et al. Agreement between routine emergency department care and clinical decision support recommended care in patients evaluated for mild traumatic brain injury. *Academic Emergency Medicine*, **20**(5), 463–9.
9. National Institute for Health and Care Excellence. (2014). Head injury: assessment and early management. Available at: http://www.nice.org.uk/CG176 (accessed 1 Nov 2015).
10. Maas AIR, Marmarou A, Murray GD, Teasdale GM, and Steyerberg EW (2007). Prognosis and clinical trial design in traumatic brain injury: the IMPACT study. *Journal of Neurotrauma*, **24**, 232–8.
11. CRASH trial collaborators. (2004). Effect of intravenous corticosteroids on death within 14 days in 10 008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet*, **364**, 1321–8.
12. MRC CRASH trial collaborators. (2008). Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *British Medical Journal*, **336**, 425–9.
13. Steyerberg EW, Mushkudiani N, Perel P, et al. (2008). Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Medicine*, **5**(8), e165; discussion e165.
14. MRC Crash trial collaborators. Head injury prognosis. Available at: http://www.crash2.lshtm.ac.uk/Risk%20calculator/index.html (accessed 1 November 2015).
15. International Mission for Prognosis and Analysis of Clinical Trials in TBI. Available at: http://www.tbi-impact.org/ (accessed 3 July 2015).
16. Menon D and Harrison D. (2008) Prognostic modelling in prognostic brain injury can reliably estimate the probability of outcomes for groups but not for individuals. *British Medical Journal*, **336**, 397–8.
17. Wang JY, Bakhadirov K, Devous MD SR, et al. (2008). Diffusion tensor tractography of traumatic diffuse axonal injury. *Archives of Neurology*, **65**(5), 619–26.

CHAPTER 343

Management of traumatic brain injury

Alistair A. Gibson and Peter J. D. Andrews

Key points

- Traumatic brain injury is a leading cause of death and disability worldwide.
- Admission to a centre offering specialist neurological critical care and management of extracranial injuries improves outcome.
- Initial management priorities address the 'ABCs'—airway with cervical spine control, breathing, and circulation. Neurological assessment using the Glasgow Coma Score and pupillary reaction should be repeated regularly to detect deterioration.
- Intracranial haematomas causing mass effect should be surgically evacuated without delay.
- Specific TBI management focuses on avoiding secondary cerebral insults by avoiding hypotension and hypoxia, controlling ICP, and maintaining cerebral perfusion pressure.

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. It carries a significant social and economic burden and affects patients indiscriminately; young male adults are at particular risk. In the United States of America TBI kills approximately 52,000 people annually [1]. TBI is associated with a mortality rate of up to 33% [1] and up to half of those adults admitted to hospital with TBI will suffer from long-term psychological or physical disability [2].

Neurological damage occurs through two mechanisms:

- **Primary injury**: direct injury to brain tissue and neuronal cells as a result of blunt or penetrating trauma, which causes shearing and compression of surrounding structures. The extent of injury depends on the nature of the impact.
- **Secondary injury I**: as a result of raised intracranial pressure (ICP) and other 'secondary insults'; reduced brain perfusion and ischaemia result in failure of oxygen delivery to the primarily injured area of brain. This can occur within minutes, but can take days to manifest itself.
- **Secondary injury II**: the primary injury initiates many secondary process that are believed to be injurious. These include energy failure, mitochondrial dysfunction, free radical formation, inflammation, and excitotoxicity. It is believe these processes are worsened by secondary insults.

Primary injury is irreversible and as a result the management of TBI has focused on preventing or reducing the impact of the secondary injury processes [3]. Prevention and/or recognition and treatment of these secondary insults has resulted in improved outcomes including reduced mortality and improved functional capacity [4].

TBI can be classified as mild, moderate, or severe based on the Glasgow Coma Scale scores (GCSs) (13–15, 9–12, and 3–8, respectively). This chapter will focus on the management of patients with severe TBI as these patients require assessment and management in a critical care unit, and have better outcomes if managed in a specialist centre.

Prehospital management

Initial assessment of TBI patients should follow standard National guidelines and local protocols with the aim being to follow an Airway with cervical spine control, Breathing and Circulation approach. Patients with TBI are often multiply injured and those injuries that are immediately life threatening should be treated first. Assessment of the brain injury is not straightforward as the patient may be confused, combative, or intoxicated. Management priorities for first responders are prevention of hypoxaemia and hypotension both of which are associated with worse outcome [5–7] . Hypotension (systolic blood pressure (SysBP) <90 mmHg) should be treated with isotonic intravenous (iv) fluid (if iv access can be established) and hypoxia should be treated with appropriate oxygen therapy titrated to maintain SpO_2 above 90%. GCS should be monitored as it provides a standardized and reliable method for evaluating a change in a patient's neurological status and is refined by assessment of focal signs including the pupillary response to light.

Prehospital endotracheal intubation may help prevent cerebral hypoxia and control intracranial pressure by preventing hypercarbia. Tracheal intubation can prevent airway obstruction and aspiration of gastric contents when protective airway reflexes are absent. However, tracheal intubation can also be harmful. If performed in difficult settings, and by unskilled staff, failure, and resulting hypoxaemia are possible. Intubation on scene may increase the risk of early onset pneumonia and hyperventilation during the prehospital period can aggravate cerebral ischaemia and secondary brain injury with associated increased mortality. It is therefore controversial whether patients with severe TBI benefit from prehospital intubation and mechanical ventilation, and no firm guidance can be given. The benefit and harm of prehospital intubation almost certainly depend on additional factors including organization of

emergency medical services, competency of staff, risk of procedure failure, and expected transport times. If such factors are well known in a given clinical situation, they should be used to inform the decision-making at the accident scene.

Management in the emergency department

Emergency department (ED) management should aim to avoid secondary insults by avoiding hypoxia and hypotension. Ongoing assessment of neurological status, including GCS and pupillary reaction should continue.

UK National Institute for Health and Clinical Excellence (NICE) guidelines for the management of TBI state that care in the ED should concentrate on airway, breathing, and circulation before assessing other injuries. In patients with a GCS of less than 9 an appropriately-trained clinician should provide airway management and assist with resuscitation. Those patients who have not been intubated in the prehospital setting may benefit from a secure airway to avoid hypoxaemia, ensure normocarbia, and to facilitate subsequent investigation/imaging. Sedation and analgesia should be given with care, and titrated to effect with attention to maintaining cardiovascular and respiratory stability.

In patients with clinical signs of severe TBI (Box 343.1) a CT scan of brain and cervical spine should be carried out following stabilization, ideally this should occur within 1 hour of the initial CT request. Plain radiographs are no longer indicated for investigation of TBI, although they may have a role in the investigation of paediatric non-accidental injury.

Referral to tertiary centre

Transfer to a specialist neuroscience centre reduces mortality for patients suffering from TBI [8]. All patients with TBI and survivable injuries should be treated in a facility that provides 24-hour neurological intensive care.

Referral to specialist neuroscience services should take place when [2,7]:

- CT scan in a non-specialist hospital shows a recent intracranial lesion.
- A patient fulfils the criteria for CT scanning but facilities are unavailable.
- Patient has clinical features that suggest that specialist neuroscience assessment, monitoring, or management are appropriate, irrespective of the result of any CT scan.

Features suggesting that specialist neuroscience assessment, monitoring, or management are appropriate include [2,7]:

- Persisting coma after initial resuscitation.
- Confusion which persists for more than 4 hours.
- Deterioration in level of consciousness after admission.
- Focal neurological signs.
- Seizure without full recovery.
- Compound depressed skull fracture.
- Definite or suspected penetrating injury.
- Cerebrospinal (CSF) leak or other sign of a basal skull fracture.

Transfer

It is common for patients with TBI to require transfer from the admitting hospital to specialist centres. This can either be by ambulance or an aeromedical transfer depending on the distances and urgency of transfer. Critically-ill patients are at risk of marked physiological instability which in turn can result in secondary insults and consequently worsen outcomes [2,7,9]. Transfer of patients with TBI should not be undertaken prior to effective resuscitation, management of life threatening extracranial injuries and establishment of high level of critical care monitoring [9]. Transfer of patients with multiple injuries should be to a centre with the expertise to manage both the TBI and all associated injuries [9].

Organization of services for patients with TBI varies greatly around the world. In the UK, NICE recommend that all patients meeting the criteria should be intubated, and ventilated for transfer and adequate ventilation (PaO_2 > 13 kPa and $PaCO_2$ 4.5–5.0 kPa) achieved.

Box 343.1 Criteria for immediate cranial CT scan in adults

- GCS less than 13 on initial assessment in the ED.
- GCS less than 15 at 2 hours after the injury on assessment in the ED.
- Suspected open or depressed skull fracture.
- Any sign of basal skull fracture.
- Post-traumatic seizure.
- Focal neurological deficit.
- More than one episode of vomiting.
- Amnesia for events more than 30 minutes before impact.

Box 343.2 Indications for immediate intubation and ventilation

- **Coma:** GCS less than 8.
- Loss of protective laryngeal reflexes.
- Ventilatory insufficiency as judged by blood gases: hypoxaemia (PaO_2 < 13 kPa on oxygen) or hypercarbia ($PaCO_2$ > 6 kPa).
- Spontaneous hyperventilation causing $PaCO_2$ < 4 kPa.
- Irregular respirations.

Box 343.3 Indications for intubation and ventilation prior to patient transfer

- Significantly deteriorating conscious level (one or more points on the GCS motor score) even if not coma.
- Unstable fractures of the facial skeleton.
- Copious bleeding into mouth.
- Seizures.

- **Coma**: GCS less than 8.
- Loss of protective laryngeal reflexes.
- **Ventilatory insufficiency as judged by blood gases**: hypoxaemia (PaO_2 <13 kPa on oxygen) or hypercarbia ($PaCO_2$ >6 kPa).
- Spontaneous hyperventilation causing $PaCO_2$ <4 kPa.
- Irregular respirations.
- **Significantly deteriorating conscious level:** one or more points on the GCS motor score, even if not coma.
- Unstable fractures of the facial skeleton.
- Copious bleeding into mouth.
- Seizures.

During transfer of the patient, management should focus on maintaining mean arterial pressure (MAP) greater than 80 mmHg, ensuring adequate oxygenation and preventing intracranial hypertension.

Management of secondary insults

Secondary insults (Table 343.1.) are largely amenable to intervention and aggressive treatment can result in improved outcomes. The aims for the management of secondary injury are to:

- Reduce ICP.
- Maintain cerebral perfusion pressure (CPP).
- Maintain adequate oxygenation.

Management of intracranial causes of secondary injury may require neurosurgical intervention.

Neurosurgery

An intracranial haematoma is present in 25–40% of patients with severe TBI and in up to 12% patients with moderate TBI [10]. Without effective and prompt (generally <4 hours) [10] surgical intervention severe morbidity can arise that may ultimately result in death or permanent neurological injury. Decompressive craniectomy is performed in some centres as a treatment for refractory intracranial hypertension. However, a recent study reported that very early decompressive craniectomy in patients with diffuse TBI [11] may result in worse outcome at 6 months after the injury.

Table 343.1 Causes of secondary injury

Intracranial	Systemic
Cerebral oedema	Hypotension (SysBP < 90 mmHg)
Haematoma	Hypoxaemia (SpO_2 < 90%)
Hydrocephalus	Hypocapnia ($PaCO_2$ < 4 kpa)
Seizures	Hypercapnia ($PaCO_2$ > 6 kpa)
Infection	Hypertension (MAP >110 mmHg)
Metabolic disturbance	Anaemia (Hb < 10 g/dL)
	Hyperglycaemia (blood sugar >10 mmol/L)
	Hyponatraemia
	Hyperthermia (Temp > 37.5°C)
	Acid base disturbance (acidaemia or alkalaemia)

Ongoing trials will hopefully further clarify the role of later decompressive craniectomy used to treat more refractory intracranial hypertension.

General critical care

High quality critical care is fundamental to achieving the best possible outcomes as patients with TBI are at risk of multiple complications.

In common with all critical care patients' supportive care should be undertaken as outlined here:

- Turning the patient regularly.
- Providing eye care, mouth care, and skin hygiene.
- Bowel regimen to ensure nutritional goals are met (and avoid constipation).
- Physiotherapy.

Sedation, analgesia, and paralysis

Opiates are essential to provide good analgesia and to achieve synchrony with mechanical ventilation, and combined with a judicious sedation regimen will obtund airway reflexes preventing patient coughing and associated rises in ICP. Opioids are commonly provided by continuous iv infusion and combined with sedatives by infusion. Commonly used sedatives are benzodiazepines and propofol. Younger patients often require large doses of sedatives for extended periods. Patients should not be administered neuromuscular blocking drugs unless required for the management of raised ICP. The use of neuromuscular blocking drugs is associated with critical illness neuropathy and an increased risk of developing ventilator associated pneumonia (VAP).

Lung protective ventilation

In an attempt to reduce the occurrence of the acute respiratory distress syndrome (ARDS) in patients with TBI a lung protective ventilation strategy using low tidal volumes and moderate PEEP should be adopted with the goal to maintain oxygenation (PaO_2

>13 kPa) and normocapnia ($PaCO_2$ 4.5–5.0 kPa). The theoretical deleterious effects of PEEP causing increased intrathoracic pressure and impeding cerebral venous drainage, are only seen when PEEP is above 15 cmH_2O; it is therefore safe and encouraged to apply PEEP in patients with TBI.

Venous thromboembolism

Patients with TBI are at increased risk of developing venous thromboembolism [3]. Mechanical thromboprophylaxis using graduated compression stockings and sequential compression devices are recommended unless contraindicated. Unless contraindicated, low molecular weight heparin (LMWH) should be prescribed as pharmacological thromboprophylaxis within 72 hours of injury. Care should be taken when prescribing LMWH as it increases the risk of haematoma expansion in the patient with existing intracranial haemorrhage.

Nutrition

Patients with TBI are in a hyper-metabolic state and early initiation of enteral feeding is recommended. Enteral feeding maintains normal gastrointestinal function and as a result preserves the immunological gut barrier [12]. Brain trauma foundation guidelines recommend that full calorific replacement should be achieved by day 7 post-injury [3].

Glycaemic control

Studies have highlighted that hyperglycaemia is associated with worse neurological outcome following TBI [13], but hypoglycaemia is also potentially harmful; a target blood glucose of 6–10mmol/L is recommended.

Ventilator-associated pneumonia

Patients suffering from TBI are at increased risk of VAP because they are often ventilated for prolonged periods, are administered neuromuscular blocking drugs and may have associated chest trauma. The incidence of VAP increases with TBI severity [3].

Raised intracranial pressure

Patients suffering severe TBI and at risk for intracranial hypertension should have an intracranial pressure (ICP) monitor inserted. ICP cannot be reliably predicted by CT scan alone. ICP data are useful in predicting outcome and guiding therapy, and there is an improvement in outcomes in those patients who respond to ICP lowering therapies when ICP increases above 20 mmHg [3]. ICP monitoring is addressed in a separate chapter of this book.

Increased ICP can be treated with medical or surgical interventions. First line interventions include:

- Ensure the patients head is in a neutral midline position to promote venous drainage.
- Tilt bed to 30 degrees, head up.
- Endotracheal tubes are taped and not tied to avoid obstructing cerebral venous drainage.
- Ventilate to normocapnia ($PaCO_2$ 4.5–5 kPa).
- Maintain adequately oxygenation (PaO_2 >13 kPa).
- Maintain normothermia.
- Ensure euvolaemia.
- Ensure adequate sedation +/– paralysis with neuromuscular blocking drugs.

If the first line manoeuvres above do not correct the intracranial hypertension then second line procedures should be considered.

Cerebrospinal fluid drainage

External ventricular drain (EVD) is considered first line treatment in many centres.

Osmolar therapy

In clinical practice there are currently two options—mannitol and hypertonic saline. Mannitol is given in a dose of 0.25–1 g/kg with intermittent boluses appearing to be more effective than continuous infusion. Hypertonic saline may have advantages over mannitol as it does not have the secondary effect of causing hypovolaemia and thus reducing CPP. Hypertonic saline increases intravascular volume and may improve haemodynamic variables.

Acute hyperventilation

Acute hyperventilation should only be considered for a short duration emergency treatment, such as imminent coning. Prolonged hyperventilation may exacerbate the secondary ischaemic injury [3].

Therapeutic hypothermia

The publicly available data suggest there may be a role for cooling of patients with raised intracranial pressure after TBI. Currently, there are two ongoing trials testing prophylactic hypothermia (POLAR-RCT) and titrated hypothermia to reduce ICP (Eurotherm3235Trial). The Eurotherm3235 trial was stopped early because of the concern for patient safety. The results show when hypothermia is used to reduce ICP after TBI, as a second line therapy, it is associated with a higher mortality and poorer recovery [15].

Anticonvulsant therapy

Seizure prophylaxis should be administered to patients at high risk of early post-traumatic seizures for 7 days. Traditionally, phenytoin has been the drug of first choice with an initial loading dose of 15–20 mg/kg and then titrated to plasma phenytoin levels.

Barbiturate coma

Barbituate coma reduces cerebral blood flow (CBF), cerebral metabolic rate, and ICP. Barbiturates should only be considered in patients with refractory raised ICP and who are haemodynamically stable. Extreme caution should be exhibited if therapeutic hypothermia is already initiated. Therapeutic hypothermia markedly alters the pharmacokinetics of barbiturates.

Maintaining CPP

Cerebral perfusion pressure is calculated by subtracting ICP from MAP and should be targeted between 60 and 70 mmHg. Thus, CPP can be maintained either by reducing ICP or increasing MAP. Targeting a CPP above 70 mmHg is associated with an increased risk of ARDS, probably due to the administration of large volumes of resuscitation fluids to maintain MAP.

Hypotension (SysBP <90 mmHg) is common after TBI and worsens patient outcomes [6]. The most common cause of hypotension in patients with TBI is hypovolaemia, either secondary to

Box 343.4 IMPACT Calculators.

Core

- Age
- GCS Motor Score
- Pupil reaction

Core + CT

- Hypoxia
- Hypotension
- CT Classification
- tSAH on CT
- Epidural Mass on CT
- Characteristics from core calculator also included

Lab

- Glucose (3–20 mmol/L)
- Haemoglobin (6–17 g/dl)
- Characteristics from Core + CT model also included.

Adapted from http://www.tbi-impact.org/?p=impact/calc with permission from the IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury) Study Group. The Impact calculator is based on the prediction models for TBI, published by Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, et al. (2008) Predicting Outcome after Traumatic Brain Injury: Development and International Validation of Prognostic Scores Based on Admission Characteristics. *PLoS Medicine*, **5**(8), e165. doi:10.1371/journal.pmed.0050165.

haemorrhage or due to polyuria as a result of diabetes insipidus. Other less common causes of hypotension include direct myocardial injury due to trauma or vasodilatation secondary to spinal cord injury. Fluid resuscitation with isotonic crystalloid solutions, or in the presence of haemoglobin <100 g/L packed red blood cells, to restore euvolaemia is the first line therapy for hypotension. Vasopressors should be administered if euvolaemia fails to correct hypotension, and are then titrated to achieve the desired CPP or MAP.

Corticosteroids

The CRASH study [14] demonstrated that high dose corticosteroids are associated with an increased risk of death and corticosteroids are considered to be contraindicated in patients with TBI.

Prognosis

TBI is a heterogeneous disease and this causes uncertainty when predicting outcome for individual patients. Two prognostic models have been developed, which are encompassed in the CRASH and IMPACT prognostic calculators. The IMPACT model was developed using a dataset that comprised patients with moderate and severe TBI and predicts mortality and unfavourable outcome (death, vegetative state or severe disability). The IMPACT model incorporates three calculators—the core, core + CT, and lab models (Box 343.4). The two CRASH calculators (the basic and the CT models) were created using a larger dataset, but included mild, moderate, and severe TBI, mainly from low–middle income countries (Box 343.5). The CRASH models predict mortality at 2 weeks and unfavourable outcome at 6 months. The calculators are shown in Box 343.5 and can be accessed online at: http://www.tbi-impact.org/?p=impact/calc

Box 343.5 CRASH calculators

- Country (to establish if low—middle income or high income population).
- Age.
- Pupils react to light.
- Major extracranial injury.

CT scan available

- Presence of petechial haemorrhages.
- Obliteration of the third ventricle or basal cisterns.
- Subarachnoid bleeding.
- Midline shift.
- Non-evacuated haematoma.

Adapted from http://www.crash.lshtm.ac.uk/Risk%20calculator/ with permission from The MRC CRASH (Corticosteroid Randomisation after Significant Head Injury) Trial Collaborators and London School of Hygiene & Tropical Medicine.

References

1. Langlois JA, Rutland-Brown W, and Wald MM. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. *Journal of Head Trauma Rehabilitation*, **21**(5), 375–8.
2. Healthcare Improvement Scotland. (2014). Early management of patient with a head injury. Edinburgh: SIGN. Available at|: http://www.sign.ac.uk/guidelines/fulltext/110/index.html (accessed 3 July 2015).
3. Brain Trauma Foundation and American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS) Joint Section on Neurotrauma and Critical Care. (2007). *Guidelines for the Management of Severe Traumatic Brain Injury*, Journal of Neurotrauma, **24**(Suppl 1), S1–S106.
4. Hesdorffer D, Ghajar J, and Iacono L. (2002). Predictor of compliance with the evidence-based guidelines for traumatic brain injury care: a survey of United States trauma centers. *Journal of Trauma*, **52**, 1202–9.
5. Brain Trauma Foundation. (2007). Guidelines for the Pre-hospital Management of Patients with Traumatic Brain Injury, 2nd edn. *Prehospital Emergency Care*, **12**(Suppl 1), S1–S52.
6. Chestnut RM, Marshall LF, Klauber MR et al. (1993). The role of secondary brain injury in determining outcome from severe head injury. *Journal of Trauma*, **34**, 216–22.
7. National Institute for Health and Care Excellence. (2007). Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. London: NICE. Available at: http://www.nice.org.uk/CG056 (accessed 3 July 2015).
8. Patel HC, Bouamra O, Woodford M, et al. (2005). Trends in head injury outcome from 1989 to 2003 and the effect of neurosurgical care: an observational study. *Lancet*, **366**(9496), 1538–44.
9. Association of Anaesthetists Great Britain and Ireland. (2006). *Recommendations for the Safe Transfer of Patients with Brain Injury*. London: AAGBI. Available at: http://www.aagbi.org/sites/default/files/braininjury.pdf (accessed 3 July 2015).

10. Thurman D and Guerrero J. (1999). Trends in hospitalisation associated with traumatic brain injury. *Journal of the American Medical Association*, **282**, 954–7.
11. Cooper DJ, Rosenfeld V, Murray L, et al. (2011). Decompressive craniectomy in diffuse traumatic brain injury. *New England Journal of Medicine*, **364**, 1493–502.
12. Haddad SH and Arabi YM. (2012). Critical care management of severe traumatic brain injury in adults. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, **20**, 12.
13. Jeremitsky E, Omert LA, Dunham CM, Wilberger J, and Rodriguez A. (2005). The impact of hyperglycemia on patients with severe brain injury. *Journal of Trauma*, **58**(1), 47–50.
14. Edwards P, Arango M, Balica L, et al. (2005). Final results of MRC CRASH, a randomised placebo controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. *Lancet*, **365**, 1957–9.
15. Andrews PJ, Sinclair HL, Rodriguez A, et al. (2015). Eurotherm3235 Trial Collaborators. *New England Journal of Medicine*, [Epub ahead of print] PMID: 26444221.

PART 16.4

Spinal cord injury

CHAPTER 344

Assessment and immediate management of spinal cord injury

Simon Finfer and Oliver Flower

Key points

- Spinal cord injury is a devastating injury that predominantly affects previously healthy young men.
- Level of injury and completeness should be assessed and described using the American Spinal Injury Association (ASIA) Impairment Scale.
- Spinal cord injury is often a component of multisystem trauma and immediate management should be prioritize life-threatening injuries.
- Respiratory system complications are common and 75% of patients with injuries at C5 or higher will require tracheal intubation and mechanical ventilation.
- High thoracic and cervical injuries can result in bradycardia and hypotension typical of neurogenic shock, maintaining arterial pressure through normovolaemia and vasopressors may help optimize outcome.

Introduction

Spinal cord injury is a potentially devastating injury that may occur in isolation, but more commonly occurs in the setting of multiple injuries. Depending on the level of the injury and its completeness, patients may be left with paraplegia or tetraplegia with an obvious profound impact for the patient and their family. Acute management is largely supportive and aimed at avoiding preventable secondary injury. Early identification of the injury and appropriate management may result in improved outcome, which is important to reduce disability and thus to reduce the individual, societal, and health care system costs of long-term management.

Epidemiology

Spinal fractures occur in approximately 5% of trauma patients, with 20% of these having an associated spinal cord injury. One-third of affected patients will suffer tetraplegia and half will have complete cord lesions. Motor vehicle accidents, falls and sports injuries are the common causes; 70–80% of patients are male with the 15–35-year-old age group most commonly affected. In developed countries cervical spine injuries account for more than 50% of injuries. In developing countries the proportion and prevalence of cervical injury is lower, possibly due to lower prehospital survival.

Diagnosis

The diagnosis of isolated spinal cord injury may be obvious, for example, and isolated cervical cord injury due to diving into shallow water or suffered as a sporting injury. In such patients, the loss of motor and sensory function below the level of injury combined with diaphragmatic breathing with or without pain at the site of injury makes the diagnosis clinically obvious. However, the majority of spinal cord injuries occur in patient who have suffered multiple injuries and, in such patients, spinal cord injury may not be readily apparent. This is particularly true if the patient has a depressed level of consciousness or sedated to tolerate mechanical ventilation. In conscious patients, the injury may be apparent on physical examination, but the diagnosis may be unclear due to the distracting pain and immobility due to other injuries. Any patient suffering significant trauma should be managed as if they have a spinal injury until it is has been actively excluded. Injuries to the thoracic and lumbar spine result from massive force and abnormality is almost invariably present on plain X-rays. Cervical spinal cord injury can occur in the presence of normal cervical spine X-ray, particularly in children, and this has resulted in considerable controversy over the degree of investigation needed to 'clear' the cervical spine. Obtaining adequate anteroposterior, lateral and odontoid views by plain radiology can be very difficult in the acute setting and plain X-rays have a sensitivity of around 50% for identifying patients with cervical spine injury. In comparison, computed tomography (CT) has a sensitivity of around 98% [1]. In developed countries most multiply-injured patients will undergo CT scanning of the cervical spine, thorax, and abdomen. Injury to the thoracolumbar spine can be excluded by CT with a high degree of confidence even in unconscious patients. Opinion differs on whether a normal CT scan is sufficient to exclude a cervical spinal cord injury in patients who cannot cooperate with examination or who have significant distracting injuries. A normal multidetector row CT scan has a sensitivity of detecting cervical spine injury, including ligamentous injury, of close to 100% [2]. Where doubt exists a magnetic resonance imaging scan (MRI) should be performed. MRI is more sensitive than CT and can delineate soft tissue, as well as bony injury. Example images are given in Fig. 344.1.

Spinal cord injury should be excluded as soon as possible to avoid unnecessary restriction on patient positioning and movement, which may result in avoidable morbidity.

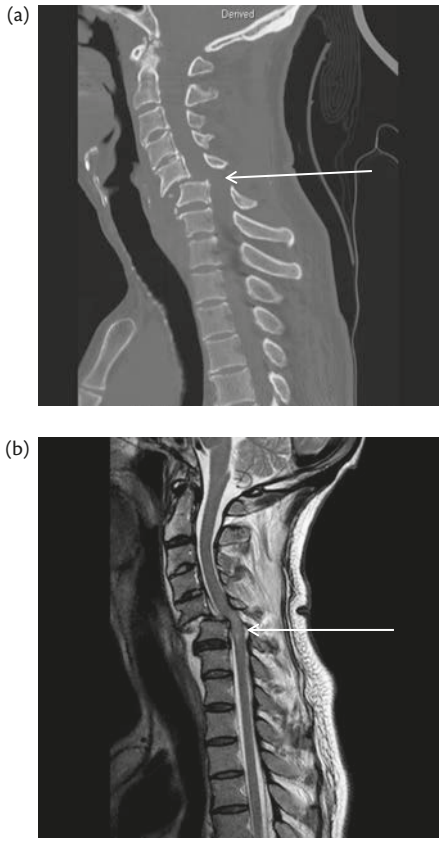


Fig. 344.1 (a) Sagittal CT image showing anteriolisthesis of C5 on C6 (arrow) secondary to bilateral facet joint dislocation (arrow). (b) T2-weighted MRI image of same injury with signal change in the spinal cord (arrow) and disruption of anterior and posterior longitudinal ligaments.

Assessment

Assessment of a patient with a spinal cord injury involves determining the neurological level of injury, and whether the spinal cord injury is complete or incomplete. The neurological level of injury is the most caudal (lowest) spinal cord segment with normal motor and sensory function bilaterally. This level can be quite difficult to determine as the lowest level of motor and sensory function may not appear to be the same, and may also differ from one side to the other. As a result, it is best to describe lowest left- and right-sided motor and sensory levels separately. Complete spinal cord injury is indicated by absence of both motor and sensory function in the lowest sacral segments, which is indicated by the absence of anal tone or sensation. The American Spinal Injury Association (ASIA) impairment scale is a validated instrument for diagnosing and classifying spinal cord injury. A neurological examination incorporating bilateral sensory and motor examination, including digital rectal examination, is performed to determine a single neurological level of injury, the completeness of injury, and the ASIA grade (Fig. 344.2).

Management

Initial assessment

The initial assessment of a patient with a spinal cord injury is no different from any other patient who has suffered trauma and should be a systematic assessment focusing first on the detection and treatment of immediately life-threatening conditions (the primary survey) attending to first life-threatening airway, breathing, cardiovascular, and neurological injuries. A high cervical spinal cord injury (above C5) may result in life-threatening respiratory failure necessitating urgent tracheal intubation and positive pressure ventilation to sustain life. In the presence of pre-existing lung disease or acute lung or chest wall injury lower levels of spinal cord injury may also produce life-threatening respiratory failure. Patients with spinal cord injury have better outcomes if managed in specialist centres; after initial resuscitation, early transfer to one of these centres should be a high priority [3].

Management of the unstable spine

While spinal cord injury can occur in patients with a stable bony spine, the majority of injuries occur in conjunction with spinal fractures and dislocations that are unstable. To prevent further cord injury the initial management is to immobilize cervical spine in a semi-rigid collar and to maintain the whole spine in alignment until the exact anatomy of the injury is delineated through imaging. Immobilizing the spine and maintaining it in alignment may complicate the management of other injuries, particularly chest injuries and adds significantly to nursing work load as the patient must be log rolled or lifted for pressure area, and other nursing care. To protect the thoracolumbar spine the patient has to remain in the supine position with the spine in the anatomical position, although the whole bed can be placed in a reverse Trendelenberg position if the patient is haemodynamically stable. This positioning can compromise weaning from mechanical ventilation and may increase the risk of nosocomial and ventilator-associated pneumonia. For these reasons, the spine should be surgically stabilized as soon as the patient is fit for operation.

Cardiovascular management

Sympathetic innervation of the heart is from the upper thoracic segments via the cervical ganglions, and the peripheral vasculature vasomotor tone is controlled by segmental sympathetic innervation. Thus, spinal cord injury above these levels can result in hypotension due to bradycardia and loss of vasomotor tone, where this compromises tissue perfusion it constitutes neurogenic shock. Cardiac parasympathetic innervation is via the vagus nerve and so is unaffected by spinal cord injury. In patients with multiple injuries, hypovolaemia from blood loss and cardiogenic shock from direct cardiac injury may co-exist, and must be excluded or treated. Hypotension may theoretically cause secondary injury to the spinal cord through impaired perfusion and a number of authors have reported better than expected outcomes in patients treated with protocols that include maintaining mean arterial pressure (MAP) at 85 mmHg or greater for the first 7 days after injury [4,5]. These findings have not been confirmed in randomized trials, but it seems reasonable to maintain arterial pressure at or above 85 mmHg with vasopressors and normovolaemia if this can be achieved without compromising other aspects of patient care.

Respiratory management

Even in the absence of direct chest trauma the respiratory system is the system most often compromised following spinal cord injury and respiratory dysfunction is the commonest cause of morbidity following spinal cord injury. The risk of respiratory failure and the

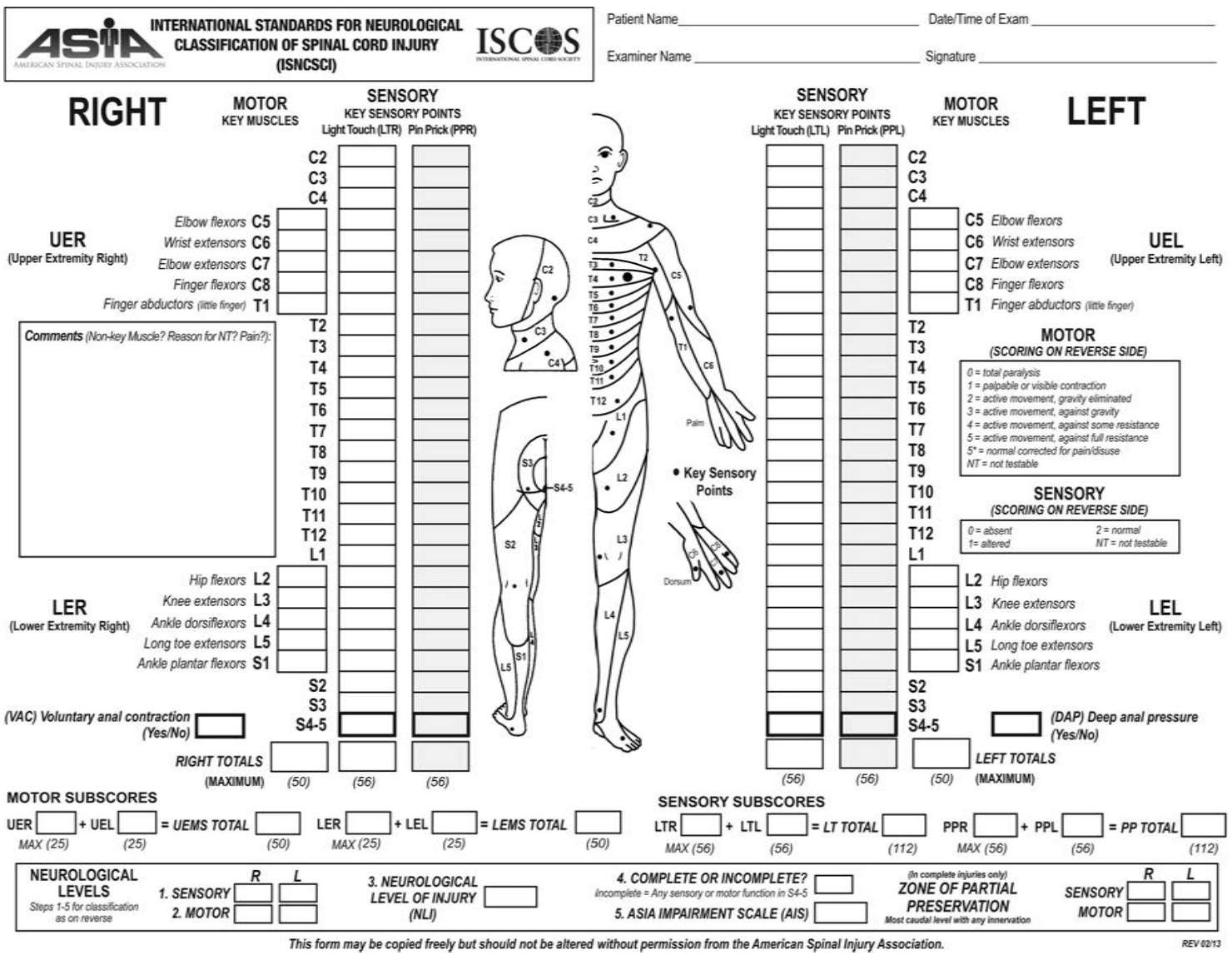


Fig. 344.2 American Spinal Injury Association: International Standards for Neurological Classification of Spinal Cord Injury, (ISNCSCI).

Reproduced with permission from American Spinal Injury Association: *International Standards for Neurological Classification of Spinal Cord Injury*, revised 2013; Atlanta, GA. Reprinted 2013.

need for tracheal intubation increases the higher the injury with around 75% of patients with cervical spinal cord injury being treated with tracheal intubation and mechanical ventilation. Where respiratory function is compromised, but initially adequate, monitoring vital capacity can detect further deterioration and predict the need for mechanical ventilation. Once vital capacity is less than 15 mL/kg body weight, most patients will require mechanical ventilation.

Tracheal intubation

Tracheal intubation may be required urgently because of respiratory failure, decreased level of consciousness with airway compromise or to facilitate the treatment of other life-threatening injuries. Less urgent intubation may be needed for deteriorating respiratory function and secretion clearance. Following trauma, any patient at risk of, or with confirmed, cervical spinal cord injury must haven their neck immobilized during tracheal intubation. The best intubation technique will depend on the availability of equipment and expertise and also on the acuity of the situation. Where time, equipment, and expertise are available, awake fibre optic intubation minimizes the risk of moving the neck. In more urgent situation direct laryngoscopy with manual inline immobilization should be employed. Whilst manual inline immobilization does not eliminate all spinal movement it is likely to be the best option for truly urgent intubation. Video laryngoscopy is now increasingly available and has been shown to improve visualization of the glottis and reduce intubation difficulty in patients with cervical immobilization

Initial management of ventilation

In the acute stage ventilation strategy may be dictated by other injuries, such as traumatic brain injury or acute lung injury. In the absence of such concerns, the ventilation strategy should be tailored to patient comfort and optimizing condition for weaning from mechanical ventilation. In contrast to other conditions, patients with high cervical spinal cord injury appear to tolerate and to be more comfortable when ventilated with large tidal volumes. Tidal volumes in excess of 10 mL/kg ameliorate air hunger and prevent atelectasis. In one uncontrolled study, patients ventilated with tidal volumes in excess of 20 mL/kg suffered fewer respiratory complications and were weaned faster from mechanical ventilation than similar patients ventilated with lower tidal volumes [6]. If high tidal volume ventilation is used dead space tubing must be inserted into the ventilator circuit to prevent profound hypocarbia.

Tracheostomy

The proportion of patients needing tracheostomy after cervical spinal cord injury varies between 20 and 60%, but almost all patients with a complete injury above C5 will require tracheostomy. Tracheostomy may also be required for other injuries, such as severe traumatic brain injury or prolonged weaning after acute lung injury. Where indicated, early tracheostomy will provide better patient comfort and aid weaning from mechanical ventilation. Percutaneous tracheostomy can be performed safely by experienced operators and with care it can be performed even if an unstable cervical spine is being managed conservatively. If an anterior approach to surgical fixation of an unstable cervical spine is planned, percutaneous tracheostomy may have to be delayed, but can be performed safely at a later date. Surgical tracheostomy is an alternate option if expertise in percutaneous tracheostomy is lacking.

Venous thromboembolism

In the absence of prophylaxis venous thromboembolism (VTE) is a near universal complication of spinal cord injury and VTE may be responsible for one in 10 deaths occurring in the first year following spinal cord injury. With prophylaxis, the rate of VTE may be reduced to around 5% with accompanying reductions in resultant morbidity and mortality [7]. Currently, low molecular weight heparin (LMWH) is the preferred pharmacological agent for prophylaxis, and this can be combined with mechanical prophylaxis in the form of anti-embolism stockings and mechanical calf compression. When heparin is contraindicated mechanical prophylaxis can be used alone. Prophylaxis with LMWH should be started as soon as possible, immediately on admission to the ICU if possible and preferably always within 72 hours [8].

Gastrointestinal function and feeding

Acute gastric dilatation, paralytic ileus, constipation, and faecal retention are common complications following spinal cord injury. Optimum bowel management includes ensuring adequate level of hydration, appropriate diet, and a regular regimen of laxatives and daily suppositories. Despite these measures, manual evacuation may be required on a regular basis. Muscle wasting through disuse atrophy is inevitable following spinal cord injury, and cannot be prevented by feeding or overfeeding. The optimal energy and protein intake will vary from patient to patient and normal calculations have to be modified to avoid over feeding. Depending on the level of injury, patients with SCI have resting energy requirement of 50–90% of that estimated using standard calculations, such as the Harris–Benedict equation [9]. Although feeding by the enteral route may initially be difficult to establish, as with other forms of critical illness it is far preferable to parenteral feeding.

Psychosocial issues

Spinal cord injury, particularly high cervical spinal cord injury, is a devastating injury that often affects previously healthy young men. The initial reaction is often one of fear and uncertainty about the future, which may subsequently change to anger and/or depression. In the acute phase there may be uncertainty about the extent and completeness of the injury, and if any doubt exists, definitive statements about the certainty of permanent disability are best avoided. Initially, management is focused on physical issues and communication may be limited due to tracheal intubation and the use of analgesic and sedative agents. Over subsequent days acute physical issues will resolve and psychological issues may come to the fore. Management of these issues require no less skill and experience than managing the physical problems of spinal cord injury. It is often beneficial to nominate a core group of nurses to provide continuity of care and seek the involvement of a psychiatrist experienced in supporting patients with spinal cord injury.

Outlook

Death during the acute phase of spinal cord injury is rare except when due to the presence of other unsurvivable injuries. Patients with thoracic or lumbar injuries may only need short term peri-operative treatment in an intensive care unit. Patients with high cervical spinal cord injury may remain ventilator dependent for weeks or months or indefinitely. Although some patients who remain ventilator-dependent due to a high cervical spinal cord

injury may choose to discontinue ventilation, rather than survive with severe physical disability, discussions, and decisions regarding discontinuing ventilation are conducted once the acute physical problems have been resolved. Overall hospital mortality after spinal cord injury is around 10% with elderly patients and those with co-morbid conditions being at greatest risk of death.

References

1. Holmes JF and Akkinepalli R. (2005). Computed tomography versus plain radiography to screen for cervical spine injury: a meta-analysis. *Journal of Trauma*, **58**(5), 902–5.
2. Panczykowski DM, Tomycz ND, and Okonkwo DO. (2011). Comparative effectiveness of using computed tomography alone to exclude cervical spine injuries in obtunded or intubated patients: meta-analysis of 14,327 patients with blunt trauma. *Journal of Neurosurgery*, **115**(3), 541–9.
3. Casha S and Christie S. (2011). A systematic review of intensive cardiopulmonary management after spinal cord injury. *Journal of Neurotrauma*, **28**(8), 1479–95.
4. Vale FL, Burns J, Jackson AB, and Hadley MN. (1997). Combined medical and surgical treatment after acute spinal cord injury: results of a prospective pilot study to assess the merits of aggressive medical resuscitation and blood pressure management. *Journal of Neurosurgery*, **87**(2), 239–46.
5. Wolf A, Levi L, Mirvis S et al. (1991). Operative management of bilateral facet dislocation. *Journal of Neurosurgery*, **75**(6), 883–90.
6. Peterson WP, Barbalata L, Brooks CA, Gerhart KA, Mellick DC, and Whiteneck GG. (1999). The effect of tidal volumes on the time to wean persons with high tetraplegia from ventilators. *Spinal Cord*, **37**(4), 284–8.
7. Jones T, Ugalde V, Franks P, Zhou H, and White RH. (2005). Venous thromboembolism after spinal cord injury: incidence, time course, and associated risk factors in 16,240 adults and children. *Archives of Physical and Medical Rehabilitation*, **86**(12), 2240–7.
8. Aito S, Pieri A, D'Andrea M, Marcelli F, and Cominelli E. (2002). Primary prevention of deep venous thrombosis and pulmonary embolism in acute spinal cord injured patients. *Spinal Cord*, **40**(6), 300–3.
9. Magnuson B, Peppard A, and Auer FD. (2011). Hypocaloric considerations in patients with potentially hypometabolic disease States. *Nutrition and Clinical Practice*, **26**(3), 253–60.

CHAPTER 345

Ongoing management of the tetraplegic patient in the ICU

Oliver Flower and Raymond Raper

Key points

- Manage traumatic spinal cord injury in a specialist centre.
- Consider the nuances specific to the respiratory care of cervical spinal cord injury.
- Consider early percutaneous tracheostomy.
- Commence venous thromboembolic prophylaxis as soon as possible.
- Involve the patient in discussions regarding long-term ventilation.

Introduction

Traumatic tetraplegia is a devastating injury with major functional and psychosocial implications. Patients who have suffered a traumatic cervical spinal cord injury (CSCI) present unique critical care challenges. Following the initial assessment and management, certain issues are common in the ongoing management of patients during their acute presentation. Survivors of traumatic tetraplegia are at lifelong risk from complications of their neurological deficit and management-related complications of unrelated illnesses. Patients are best managed in centres with specialist medical, nursing, and allied health expertise [1]. The language used when discussing CSCI is important and is clarified in Box 345.1.

Acute CSCI

The management of patients with CSCI must be individualized. Nevertheless, management is best approached in a systematic fashion.

Neurological

A detailed neurological examination should be performed as early as feasible during the admission. The American Spinal Injury Association (ASIA) impairment scale is the most validated instrument for diagnosing and classifying spinal cord injury (SCI). It is currently the only standardized neurological examination available that allows prognostication and has sufficient inter-rater reliability for local and international data collection and comparison. Key findings from examination include a single neurological level of injury (NLOI) and completeness of injury, which specifically refers to whether there is absence of motor or sensory function in the S4/5 region (sacral sparing), highlighting the importance of an adequate sacral and rectal examination for the ASIA impairment scale form. Another important finding is whether there is presence of reflexes such as the bulbocavernosus reflex. This suggests spinal shock is resolving and heralds the potential for complications such as autonomic dysreflexia [2].

Following resolution of spinal shock, muscle spasticity almost invariably occurs and is a consequence of loss of spinal inhibitory signals modifying reflex arcs. Initial treatment consists of enteral baclofen as a muscle relaxant. Some patients require very high oral doses or, in refractory cases, intrathecal administration via an implanted baclofen pump. An alternative agent is tizanidine.

Neuropathic pain is common and can be devastating. Involvement of specialists with expertise in acute pain management is appropriate, although over-focus on the pain can be counterproductive. Useful medications include carbamazepine, gabapentin, and pregabalin, as well as nortriptyline and amitriptyline as part of conventional multimodal analgesia.

Box 345.1 The language of spinal cord injury (SCI)

- **Tetraplegia**: Greek nomenclature, preferred to quadriplegia, which is a mixture of Latin and Greek. Motor and/or sensory deficits affecting upper and lower limbs due to cervical SCI.
- **Paraplegia:** motor and/or sensory deficits affecting only lower limbs due to SCI below the cervical levels.
- **Neurological level of injury (NLOI):** the most caudal (lowest) cord segment with normal motor and sensory function bilaterally. This is distinct from the skeletal level or radiological level of injury.
- **Complete SCI:** absence of motor and sensory function in the lowest sacral segments (i.e. no anal tone or sensation).
- **Zone of partial preservation:** with incomplete SCI, this refers to the spinal segments that have any motor or sensory function below the NLOI.
- **Spinal shock:** the period of flaccid paresis and areflexia following a spinal injury, lasting from 48 hours to weeks, ending with return of reflexes, such as the bulbocavernosus reflex.
- **Neurogenic shock:** a form of distributive (cardiovascular) shock following SCI due to loss of sympathetic tone in peripheral vasculature.

Data from: American Spinal Injury Association: International Standards for Neurological Classification of Spinal Cord Injury, revised 2013; Atlanta, GA. Reprinted 2013; and Ditunno JF et al., 'Spinal shock revisited: a four-phase model', *Spinal cord*, 2004, 42, 7, pp. 383–395. Epub 2004/03/24

Respiratory

Respiratory complications are the leading cause of morbidity and mortality in the short and long term following CSCI. Mechanical ventilation (MV) is required initially in 74% of patients with CSCI. Risk factors for requiring MV in the first week include NLOI at C5 or above, complete SCI, excessive respiratory secretions and pneumonia. MV may be required for days to weeks and approximately 7% of tetraplegic patients remain ventilator dependent on discharge from hospital [3]. The process of liberating these patients from the ventilator requires patience, a long-term plan, and a coordinated team approach involving medical, nursing, and physiotherapy staff [4].

In the acute phase, the mode and settings of MV should be dictated by associated conditions. Brain protection for any associated traumatic brain injury or lung protection for acute lung injury (aspiration pneumonitis, acute respiratory distress syndrome, pulmonary contusion, or infection) will determine the early pattern of ventilator support. Once this phase has past, ventilatory capacity can be evaluated and a regimen aiming for progressive ventilatory weaning, if possible, can be initiated

Specific strategies to assist respiratory function in ventilated patients with acute CSCI are listed in Table 345.1. Following complete CSCI, the intercostal and abdominal muscles are paralysed, and if the NLOI is C5 or above, the diaphragm will also be affected. Unopposed parasympathetic activity results in bronchospasm in susceptible individuals and thick, excessive pulmonary secretions. These should be addressed pharmacologically with bronchodilators and mechanically with humidification, frequent endotracheal suctioning and bronchoscopy as required. The pattern of muscle loss affects expiratory muscles more than inspiratory so expiratory reserve volume is reduced, while residual volume is increased. Assisted coughing and insufflation/exsufflation devices facilitate sputum clearance. Low levels of PEEP help restore functional residual capacity (FRC) and there is some evidence that high tidal volume ventilation facilitates sputum clearance, reduces atelectasis, and shortens the requisite duration of mechanical ventilation. It certainly ameliorates the commonly experienced air hunger, but may necessitate the use of respiratory circuit dead space to prevent hypocarbia. This confounds the addition of active humidification. Forced vital capacity (FVC) is paradoxically improved in the supine position in tetraplegic patients because the weight of the abdominal contents positions the diaphragm higher in the chest, essentially preloading this principal respiratory muscle. This effect can be simulated with an abdominal binder, which is an essential aid as patients move from the supine to the sitting position.

Tracheostomy is required in approximately 60% of patients with CSCI; NLOI and completeness of neurological deficit being the most important predictors of need for tracheostomy. Patients who have a complete injury above C5 invariably require a tracheostomy and individual factors influence the need when the injury is lower or incomplete. An FVC <11.9 mL/kg, requirement for tracheal suctioning more than hourly and a PaO_2/FIO_2 ratio <189 mmHg have been found to predict the need for tracheostomy [5]. A tracheostomy before day 7 can reduce intensive care unit (ICU) length of stay and duration of mechanical ventilation, with the added bonus of facilitated communication and reduced sedation requirements. A percutaneous, dilatational approach performed in ICU is safe and does not increase the rate of surgical wound infection, even after anterior cervical fixation.

Table 345.1 Strategies employed in the respiratory care of tetraplegic patients

Strategy	Rationale
Baseline spirometry measurements	For monitoring and respiratory prognostication. Vital capacity <11.9 mL/kg is predictive of needing prolonged support and tracheostomy
Regular use of bronchodilators	Sympathetic denervation leads to parasympathetic over-activity causing bronchospasm
Use of an humidified circuit	Sympathetic denervation leads to parasympathetic over-activity causing thick tenacious secretions, risking mucous plugging
Keep flat or head down when self-ventilating	With loss of abdominal muscular tone, the upright position causes the abdominal viscera and diaphragm to be drawn so far down that ventilation is difficult. When supine, the viscera push the diaphragm up to position that permits more effective ventilation
Use of abdominal binder	This pushes the abdominal viscera upwards and puts the diaphragm in a more mechanically advantageous position for ventilation
Low positive end-expiratory pressure (PEEP)	High PEEP may push the diaphragm down into a position of mechanical disadvantage, impairing gas exchange
High tidal volume	In the absence of PEEP, higher tidal volumes may prevent atelectasis and segmental collapse. Air hunger is common and may be relieved with higher tidal volumes
Use of dead space in ventilator circuit	High tidal volumes may lead to hypocapnoea unless dead space is introduced into the ventilator tubing
Inspiratory muscle training (IMT)	IMT improves physiological variables and may help to expedite liberation from the ventilator
Low threshold to perform bronchoscopy	Thick tenacious secretions frequently causing plugging of large airways. Sudden desaturation should prompt consideration of therapeutic bronchoscopy
Early tracheostomy	Often necessary for prolonged ventilation; reduces sedation requirements, facilitates weaning from the ventilator, allows ongoing tracheal toilet, improves communication and speech

Data from: American Spinal Injury Association: *International Standards for Neurological Classification of Spinal Cord Injury*, revised 2013; Atlanta, GA. Reprinted 2013; and Ditunno JF et al., 'Spinal shock revisited: a four-phase model', *Spinal Cord*, 2004, **42**(7), pp. 383–95. Epub 2004/03/24.

Many different permutations of progressive ventilator-free breathing (VFB) strategies are used when trying to wean the patient from the ventilator. The key components of these are a clear and documented, consistent approach over weeks to months and avoidance of fatigue by ensuring brief and well-monitored periods of spontaneous breathing. These periods can be progressively extended as tolerated, with adequate rest periods in between. Setbacks such as infections or lobar collapse from mucous plugging may delay the weaning process. Even after successful weaning and decannulation of the tracheostomy, there may be an ongoing requirement for nocturnal non-invasive ventilation, as there is a high prevalence of obstructive sleep apnoea and nocturnal hypoventilation in this population.

There is some evidence supporting the use of inspiratory muscle training devices as part of the weaning process. Once patients are able to tolerate short periods of VFB, regimens using these devices appear safe and provide achievable goals at a time when patients have control of little else.

Respiratory physiotherapy has an important role in preventing infections and expediting the weaning process. Techniques employed include regular turning, deep breathing exercises, incentive spirometry, assisted coughing (with insufflation/exsufflation devices and assisted 'quad' coughing) and mobilization out of bed with an abdominal binder.

Cardiovascular

In the first few days following CSCI, neurogenic shock is common, due to a combination of distributive shock from loss of sympathetic vascular tone and bradycardia from loss of sympathetic innervation to the heart with unopposed cardiac vagal stimulation. There is weak evidence that a mean arterial pressure (MAP) >85 mmHg should be maintained for up to 7 days following injury [6], theoretically improving cord perfusion pressure and preventing secondary spinal cord injury. After initial fluid resuscitation vasopressors, such as noradrenaline are commonly required to meet these targets. Chronic, relative hypotension is expected following CSCI. Anticholinergics like atropine may be required for patients who experience severe bradycardia associated with certain stimuli, such as tracheal suctioning. Rarely, chronotropic infusions (e.g. isoprenaline) or even cardiac pacing may be required for severe bradycardia.

Venous thromboembolism (VTE) is highly prevalent following CSCI. The use of low molecular weight heparin or unfractionated heparin in combination with mechanical measures, such as anti-embolism stockings and sequential calf compression, is recommended for thromboprophylaxis. Low molecular weight heparin (specifically enoxaparin) may be superior to unfractionated heparin with mechanical measures in decreasing the incidence of pulmonary embolism, and have a lower rate of bleeding complications [7]. Adequate VTE prophylaxis is easier if all planned spinal surgical procedures are undertaken as soon as practicable.

Renal

In the initial phase following injury, the bladder is hypotonic and effective drainage is essential to avoid over-distension and injury. Following resolution of spinal shock, bladder spasticity often occurs with detrusor muscle hyperreflexia. To prevent a contracted, low-volume bladder, an anticholinergic agent, such as oxybutynin, tolterodine, or solifenacin should be prescribed. These may be started once the bowels have been opened (as they may worsen constipation). A suprapubic catheter is usually indicated and usually easier to arrange, while the patient is still in the ICU. Bone mineral loss is common following CSCI. This may result in hypercalcaemia, and frequently causes hypercalciuria placing patients at significant risk of developing calcium oxalate nephrolithiasis. A baseline CT of the renal tract can be useful and renal calculi, and urinary tract infections should always be considered as precipitants of autonomic dysreflexia.

Gastrointestinal

Neurogenic bowel is colonic dysfunction resulting from lack of central nervous control. The upper motor neuron bowel syndrome seen following CSCI is characterized by increased colonic wall and anal tone, with loss of external anal sphincter control. This results in constipation and faecal retention. Stool evacuation may be induced by a reflex activity caused by a rectal stimulus, such as an irritant suppository or digital stimulation. These are key components of multifaceted bowel management programmes that also include adequate fluid intake, diet, pharmacology, and occasionally surgery or electrical stimulation. Daily suppositories are commonly required, with polyethylene glycol-based suppositories having advantages over hydrogenated vegetable oil-based bisacodyl suppositories. There is less evidence supporting oral laxatives or additional dietary fibre. Ideally, opioids and other constipating medications should be avoided [8].

Unopposed parasympathetic activity results in hyperacidity. Gastric pH is difficult to control with antihistamines, so a proton pump inhibitor may be indicated for ulcer prophylaxis.

Skin

The development of cutaneous pressure sores is the commonest complication following SCI. They are a source of considerable morbidity and are associated with increased hospital length of stay, life-threatening infections, chronic refractory osteomyelitis, and autonomic dysreflexia. Skin healing in denervated skin is significantly delayed so prevention is vital. Risk factors for pressure ulceration include the degree of immobility, initial hypotension, malnutrition, and prolonged use of spinal boards and hard collars. Preventive measures must be employed, including early use of a pneumatic pressure-relieving mattress, 2-hourly postural change, and a high degree of vigilance for early signs of pressure ulcers [9]. Device-related (especially collar) ulceration can be painful as it tends to affect innervated skin. Occipital ulceration can be particularly devastating and can delay mobilization and respiratory weaning.

Early rehabilitation

Physiotherapy to increase range of movement, particularly in shoulders and hands, may prevent contractures that may significantly affect functional status at a later time. Adhesive capsulitis of the shoulders and deforming hand contractures may be prevented by passive movement exercises and splinting devices. Early mobilization once spinal stability has been achieved is also important for reducing complications such as pressure sores and VTE, as well as addressing the accelerated deconditioning that follows CSCI.

Psychosocial

The psychological and social impact of tetraplegia is immense. The functional loss is huge, and employment and family implications are obvious. An initial grieving response is common and this will be manifest in various ways depending on premorbid characteristics. Situational depression may occur, but antidepressants may not be helpful. It is important for staff to appreciate and communicate that many quadriplegic patients are able to achieve satisfactory levels of function, and are able to enjoy highly meaningful lives and relationships. It is essential not to prejudge patient responses, no matter what views they may have expressed prior to the injury. It is also important not to be overly nihilistic. Psychosocial support should include establishing early effective communication and engendering an environment of trust by open, candid, and

receptive communication. Focusing on what is possible, rather than on what is not possible is recommended. Support from others who have achieved a meaningful life in spite of tetraplegia may be helpful. A psychologist or psychiatrist with experience of assisting patients following SCI should be available.

Ventilator-dependent tetraplegic patients sometimes request to have ventilation discontinued and to be allowed to die. This can create considerable difficulties for staff and families. In principle, mechanical ventilation is a medical treatment and competent patients are legally able to decline medical treatment even if this results in their death. This is the principle of autonomy. The concern, of course, is that the decision may not be stable—it may be impacted by a short-term emotional response to the injury and may change over time if survival is enforced till a different frame of mind is achieved. Some surety is provided if the patient's decision is consistent over time and consistent with any premorbid views. Nevertheless, the right not to be treated in these circumstances is established in law [10] and forcing a patient to undergo unwanted treatment in the hope of a change of mind is not reasonable. Some patients who have died after elective discontinuation of treatment have donated organs for transplantation after death based on their own consent process.

Acute issues in chronic tetraplegia

With improved survival following CSCI, patients with longstanding tetraplegia are now more frequently requiring critical care admissions for a variety of reasons, with different issues to those following initial presentation.

Autonomic dysreflexia

Whilst common, autonomic dysreflexia (AD) is a potential medical emergency that may require intensive blood pressure monitoring and control to avoid a hypertensive intracerebral haemorrhage or myocardial ischaemia. It may occur in any patient with a cord lesion above T6 after spinal shock has resolved. AD is the result of uncontrolled sympathetic discharge in response to noxious stimuli resulting in hypertension, bradycardia, headache, and diaphoresis. Common precipitants are listed in Box 345.2. General management includes primarily detecting and treating the precipitant, sitting the patient up (to induce the orthostatic hypotensive response), loosening clothing, and treatment with anti-hypertensives. One regimen is to give sublingual or transdermal glyceryl trinitrate initially, followed by immediate release nifedipine if this proves insufficient, before intravenous agents, such as sodium nitroprusside or glyceryl trinitrate infusions are required. Some patients may develop chronic, severe AD requiring multiple classes of antihypertensive medications. It must be remembered that in the setting of chronic hypotension, systolic blood pressure of >150 mmHg can be life threatening [11].

Box 345.2 Potential precipitants of autonomic dysreflexia

- Bladder distension.
- Urinary tract infection.
- Renal calculi.
- Faecal impaction.
- Decubitus ulcers with or without infection.
- Foot disease including ingrown toenails.
- Surgical procedures.

Respiratory failure

Because of variably limited reserve, tetraplegic patients commonly develop respiratory dysfunction. This may be precipitated by acute problems, such as pneumonia or pulmonary embolism, but may also present more insidiously due to chronic hypoventilation and recurrent respiratory problems leading to pulmonary hypertension and right heart failure.

Peri-operative care

Because of their limited cardiorespiratory reserve, patients with longstanding tetraplegia may require higher dependency or ICU care following surgery. AD may also complicate surgery, particularly surgery of the bladder or bowel.

Sepsis

Sepsis is another frequent complication in chronic tetraplegia, which may require ICU admission. Common sources include pneumonia, urinary tract infections, and infected pressure areas (often with underlying osteomyelitis). Septic shock may present late as hypotension is masked by chronically low blood pressure. Acute kidney injury may be missed initially as the serum creatinine is commonly low due to low muscle mass and may triple yet still be within the normal reference range. High prevalence of colonisation with multiresistant organisms also complicates treatment of sepsis and should be taken into account when choosing antibiotics.

Complications of intrathecal infusion devices

Continuous intrathecal baclofen infusions from subcutaneously implanted pumps are occasionally used to treat disabling spasticity refractory to conventional measures. If the pump stops working or runs out of drug, baclofen withdrawal syndrome may ensue, with severe spasticity, seizures, hyperthermia, rhabdomyolysis, multi-organ failure and death [12]. This may also occur with the abrupt discontinuation of regular enteral baclofen, which should be avoided or if unavoidable baclofen should be replaced with benzodiazepines. Excessive baclofen administration, which may occur if the pump is changed and a bolus accidentally given, may result in profound coma. Intrathecal devices may also become infected with potentially severe infection of the central nervous system.

References

1. Amin A, Bernard J, Nadarajah R, Davies N, Gow F, and Tucker S. (2005). Spinal injuries admitted to a specialist centre over a 5-year period: a study to evaluate delayed admission. *Spinal Cord*, **43**(7), 434–7.
2. Ditunno JF, Little JW, Tessler A, and Burns AS. (2004). Spinal shock revisited: a four-phase model. *Spinal Cord*, **42**(7), 383–95.
3. Jackson AB, Dijkers M, Devivo MJ, and Poczatek RB. (2004). A demographic profile of new traumatic spinal cord injuries: change and stability over 30 years. *Archives of Physical Medicine and Rehabilitation*, **85**(11), 1740–8.
4. Arora S, Flower O, Murray NP, and Lee BB. (2012). Respiratory care of patients with cervical spinal cord injury: a review. *Critical Care and Resuscitation*, **14**(1), 73.

5. Berney SC, Gordon IR, Opdam HI, and Denehy L. (2011). A classification and regression tree to assist clinical decision making in airway management for patients with cervical spinal cord injury. *Spinal Cord*, **49**(2), 244–50.
6. Casha S and Christie S. (2011). A systematic review of intensive cardiopulmonary management after spinal cord injury. *Journal of Neurotrauma*, **28**(8), 1479–95.
7. Spinal Cord Injury Thromboprophylaxis Investigators. (2003). Prevention of venous thromboembolism in the acute treatment phase after spinal cord injury: a randomized, multicenter trial comparing low-dose heparin plus intermittent pneumatic compression with enoxaparin. *Journal of Trauma*, **54**(6), 1116–24.
8. Krassioukov A, Eng JJ, Claxton G, Sakakibara BM, and Shum S. (2010). Neurogenic bowel management after spinal cord injury: a systematic review of the evidence. *Spinal Cord*, **48**(10), 718–33.
9. Gelis A, Dupeyron A, Legros P, Benaim C, Pelissier J, and Fattal C. (2009). Pressure ulcer risk factors in persons with SCI: Part I: acute and rehabilitation stages. *Spinal Cord*, **47**(2), 99–107.
10. Sensky T. (2002). Withdrawal of life sustaining treatment. *British Medical Journal*, **325**(7357), 175–6.
11. Rabchevsky AG and Kitzman PH. (2011). Latest approaches for the treatment of spasticity and autonomic dysreflexia in chronic spinal cord injury. *Neurotherapeutics*, **8**(2), 274–82.
12. Mohammed I and Hussain A. (2004). Intrathecal baclofen withdrawal syndrome- a life-threatening complication of baclofen pump: a case report. *BMC Clinical Pharmacology*, **4**, 6.
13. American Spinal Injury Association. (2011). International Standards for Neurological Classification of Spinal Cord Injury. Atlanta, GA: ASIA.

PART 16.5

Burns

CHAPTER 346

Pathophysiology and assessment of burns

John A. M. Paro and Geoffrey C. Gurtner

Key points

- Burn injury represents a complex clinical entity with significant morbidity and remains the second leading cause of trauma-related death.
- Thermal insult results in coagulative necrosis of the skin, and the depth or degree of injury is classified according to which skin layers are involved.
- Large burns can initiate a massive hypermetabolic response with systemic effects affecting multiple organ systems.
- Accurate assessment of total body surface area involved in burn injury is critical for prognosis and resuscitation.
- Physical diagnosis remains the gold standard for assessment of burn depth, although other objective measures show promise.

Introduction

Great progress has been made over past decades in the care of burn patients. Burn injuries range in severity from minor to life threatening, and an expanding knowledge of the pathophysiology of burns has led to improved management of a complex clinical entity. This chapter will focus specifically on the local and systemic effects of thermal injury and discuss initial assessment of the burn victim.

Epidemiology

It is estimated that well over one million people in the United States experience some form of burn injury each year. The vast majority of these injuries can be successfully treated on an outpatient basis, resulting in little to no significant morbidity. Some 50,000 burned patients annually, however, require hospitalization in some capacity. Ultimately, 5000 people will die from their injury, making it second only to motor vehicle accidents in the cause of trauma-related deaths [1].

Burn rates remain considerably higher than this in the developing world. Nearly 200,000 deaths, mostly in low-income countries, are attributed to burns [2]. In Western nations, access to care as well as considerable prevention efforts are responsible for a declining incidence and severity of injury [3]. In the UK, the Birmingham Burns Centre has been systematically tracking outcomes for over 75 years, and has helped quantify some of the dramatic improvements in mortality. Since their initial report in 1949, mortality has been halved for patients with comparable burn size and age [4] (Table 346.1).

Burn aetiology

Burns can be classified into five primary causes based on the source of thermal energy transfer. Flame or fire burns are the most common, and account for the majority of reported injuries. Scald injuries result from contact with hot liquids and represent about one-third of known cases. Contact injury with hot or cold surfaces results in nearly 10% of injuries. Burns from noxious chemicals and by the conduction of electricity result in 4% and 3% of injuries, respectively [3]. This distribution is similar in developing countries, with nearly 90% of burns occurring in the home [2].

Pathophysiology

Local changes

Thermal injury to the skin results in coagulative necrosis of the epidermis and the contents below. The extent of destruction is influenced by both the temperature and duration of exposure—skin will absorb the majority of this damage. From superficial to deep, skin includes the following layers:

- **Epidermis**: provides a vapour and bacterial barrier.
- **Dermis**: important for flexibility, strength, and home to hair follicles, nerves, and vasculature.
- **Subcutaneous fat**.
- **Deeper structures**.

Burns are classified according to the extent of damage caused by the thermal insult. First degree burns are those limited to the epidermis, for example, a sunburn. First degree burns heal relatively quickly, without scarring. Second degree burns are further categorized into superficial and deep, based on dermal involvement. An injury involving minimal dermis is also referred to as a superficial partial thickness burn. These injuries take roughly 1–2 weeks to heal, and can result loss of pigment in the affected area. Deep partial thickness burns include more extensive injury to the dermal layer. They require 2–5 weeks to heal spontaneously and can result in substantial scarring and contracture [5].

Third degree burns include injury to epidermis, dermis, and the subcutaneous fat. This is also referred to as full thickness. If the damage extends to underlying tissue, such as muscle, tendon, or bone, this is considered to be a fourth degree burn.

Histologically, the transfer of heat leading to skin injury is classically divided into three zones. The ‘zone of coagulation’ refers to the area of cutaneous necrosis that is irrevocably damaged. This is

Table 346.1 Mortality (all ages) grouped by burn size

%Total body surface area burn	Mortality rate
0.1–9.9	0.6
10–19.9	2.8
20–29.9	8.8
30–39.9	16.4
40–49.9	25.5
50–59.9	36.4
60–69.9	43.3
70–79.9	57.7
80–89.9	74.3
90+	82.8

Adapted from American Burn Association 2011.

surrounded by a 'zone of stasis,' characterized by decreased tissue perfusion and a less severe thermal insult. The viability of this tissue depends on both the body's own local immunochemical response to injury, as well as the timely response of the treating physicians. Finally, a 'zone of hyperaemia' lies peripheral to and below the zone of stasis, and is characterized by vasodilation from a variety of inflammatory mediators released by neighbouring tissue. This zone has minimal injury and should not be victim to further damage.

Systemic changes

It is easy to focus mainly on the local damage and physical findings following a burn injury. Much more is at stake, however, than the local cutaneous damage—a major burn injury will initiate a massive systemic response capable of complete homeostatic disruption. The inflammatory mediators that give rise to the local effects described above can also produce substantial vasodilation in the periphery, leading to increased capillary permeability and multifocal oedema. The systemic inflammatory response provides a substantial contribution to burn-related death.

Hypermetabolism

The hypermetabolic response to a severe burn can last for months following injury. The release of inflammatory hormones leads to a long-standing increase in cardiac output, basal metabolic rate, and oxygen consumption. Clinical manifestations include tachycardia, tachypnoea, and fever. Often, the metabolic rate may be more than double baseline resting energy expenditure [6].

Other hormones released during this phase include catecholamines and cortisol. These have significant effects on mobilization of the body's energy stores and can lead to significant catabolism. Glucose availability is increased through hepatic gluconeogenesis, which is supported by peripheral lipolysis and proteolysis. Early nutrition is essential following significant burn injury to reduce the deleterious effects of this catabolic state. Lean muscle can decrease markedly. Continued lipolysis in an effort to provide more substrates can lead to the development of fatty liver [7]. This metabolic effect has been known to last for as long as 1-year following injury. Ultimately, the body reverts to an anabolic state in an effort to slowly rebuild fat and protein stores.

Immune system effects

Severely-burned patients are at significant risk of infectious complications, both due to prolonged hospital stays, as well as a marked reduction in immune function. Animal models have confirmed an increased susceptibility to infection based on burn size. This appears to be related to altered polymorphonuclear cell surface receptors causing impaired leukocyte adherence, as well as a separate mechanism resulting in a globally decreased bactericidal activity [8].

Differentiating between the systemic effects of a thermal injury and an overt infection can be difficult given the hyperglycaemia, tachycardia, fever, and leukocytosis that often accompany significant burns. Surgical site infection, cellulitis, and pneumonia are all common in patients hospitalized with burns.

Other organ systems

Initial decreased perfusion to the gut can lead to early atrophy of intestinal villi, which disrupts the mucosa, impacts digestion and nutrient absorption, and has profound effects on intestinal permeability. Ultimately, absorption of glucose and amino acids is impaired. Additionally, there is increased translocation of microbes such as *Candida* [9].

Transient oliguria and temporary increases in creatinine concentration occur frequently in the resuscitative stage of post-burn care. This may be related to low flow states seen in the first 24–48 hours following injury and the incidence of transient renal dysfunction varies from 15 to 40% depending on the definition used. There is increasing evidence that early acute kidney injury is a strong predictor of severe renal dysfunction and increased mortality [10].

Assessment

Initial evaluation of a burned patient should be the same as for any victim of trauma. Multiple systems may be affected, and the first priority is to recognize and treat any life-threatening injuries.

Primary survey

It is important to quickly ascertain the stability of the burn victim's airway. Smoke and heated air will cause both direct and indirect damage to a patient's upper airway, and respiratory tract oedema may lead to critical airway obstruction and hypoxaemia. Physical clues of potential airway compromise include singed facial or nasal hair, tachypnoea, expectoration of carbonaceous sputum, and inspiratory or expiratory wheeze. Airway swelling can progress rapidly, and requires constant reassessment throughout the early hospital course. The physician should have a relatively low threshold to secure a definitive airway through tracheal intubation, as upper respiratory swelling will often worsen with fluid resuscitation.

A patent airway alone does not ensure adequate ventilation as deep burns of the chest wall can constrain thoracic mobility thereby limiting ventilation. Monitoring carbon dioxide through capnography is a useful adjunct.

Early haemodynamic assessment is essential, but may be difficult due to the presence of charred extremities and invasive systemic arterial pressure monitoring is often needed. Heart rate can be used as a marker of overall circulation, but is typically elevated in burn injury. Patients with burns must also be fully assessed for other traumatic injuries including spinal injury. Finally, it is critical to

provide full exposure of the patient, typically by cutting and removing all clothing.

Secondary survey

After any potentially life-threatening conditions have been identified and treated, a more thorough head-to-toe physical examination is performed. While all potential sources of traumatic injury must be assessed, the extent and depth of cutaneous damage must be assessed and documented as it has significant impact on both the prognosis and management of burn patients.

Determining extent of injury

The most common method for assessing burn size is the 'rule of nines,' dividing the total body surface area (TBSA) into sections of 9%. Each upper extremity, as well as the head and neck, are 9%. Eighteen per cent is assigned to the chest/abdomen, to the back, and to each lower extremity. The remaining 1% is designated for the genitals and perineum (Fig. 346.1).

A similar method that has been described, especially helpful for smaller and oddly-shaped burns, is to define the area of a patient's full hand (palm and fingers) as 1% TBSA and use this as a mapping template. Some data suggest that an even more accurate assessment involves using only the patient's palm as an estimate of 0.5% body area [11].

Both of the above methods are very useful, particularly in the preliminary evaluation for triage and initiation of resuscitation. They have their limitations and tend to be considerably less accurate in children, who have a different distribution of body surface area (Table 346.2). The rule of nines technique also tends to overestimate burn size [12]. We recommend that, once the patient is stabilized, a more exact measurement of burn size be established using such methods as the Lund–Browder chart or Berkow Formula (Table 346.2).

Determining depth of injury

First degree burns are confined to the epidermis. These are the least serious types of injury, quickest to heal, and perhaps the easiest to diagnose. They blanch when touched, are erythematous and painful, and appear to be like sunburn. Full thickness or third degree burns are dry, insensate, and leathery to the touch.

Differentiating between the two types of second degree burns is more challenging. Superficial partial thickness burns are erythematous and painful as well, and can also blanch to the touch. There is often blistering overlying this type of wound. Sensation is intact, and a pinprick will be felt as sharp. Deep partial thickness burns may demonstrate pallor or mottling, and will not blanch as easily. Sensation remains intact, but diminished—a pinprick may be felt only as pressure (Table 346.3)

These differences are subtle—some studies suggest that experienced burn surgeons are able to accurately classify second degree burns 60–75% of the time [5]. While careful examination by the responsible physician remains the gold standard for burn size and

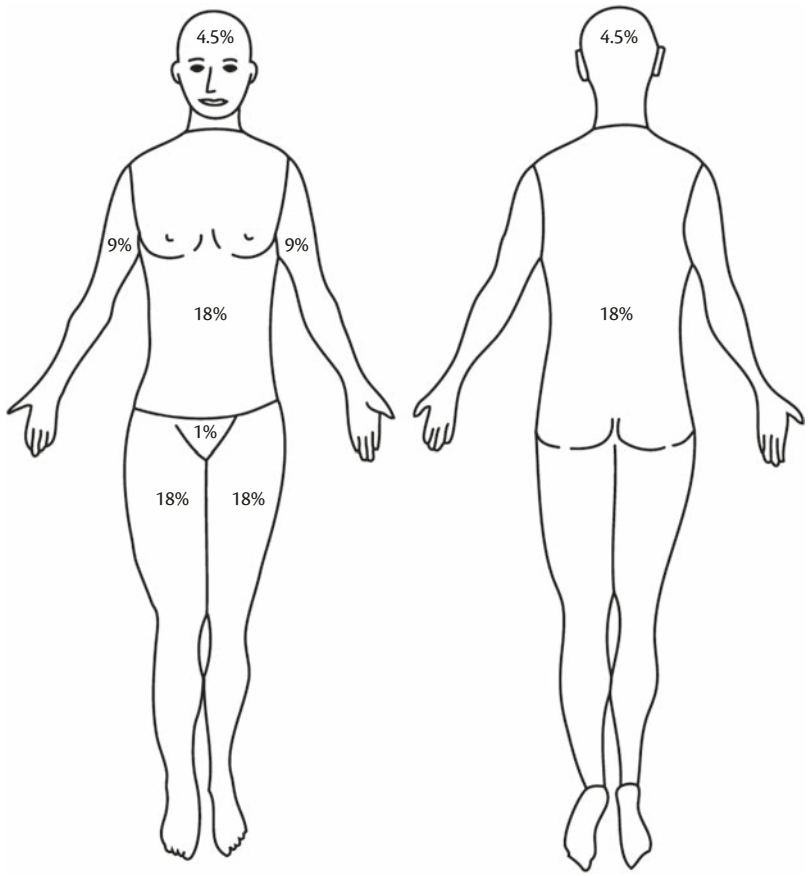


Fig. 346.1 'Rule of nines' chart for estimating body surface area burned in adults.
Reprinted from *The Lancet*, **257**, 6653, AB Wallace, 'The exposure treatment of burns', pp. 501–4, Copyright 1951, with permission from Elsevier.

Table 346.2 Berkow Burn Size estimates by age (percentage body surface area)

Body part	0–1 year	1–4 years	5–9 years	10–14 years	15–18 years	Adult
Head	19	17	13	11	9	7
Neck	2	2	2	2	2	2
Anterior trunk	13	13	13	13	13	13
Posterior trunk	12	13	13	13	13	13
Each buttock	2.5	2.5	2.5	2.5	2.5	2.5
Genitalia	1	1	1	1	1	1
Each upper arm	4	4	4	4	4	4
Each lower arm	3	3	3	3	3	3
Each hand	2.5	2.5	2.5	2.5	2.5	2.5
Each thigh	5.5	6.5	8	8.5	9	9.5
Each leg	5	5	5.5	6	6.5	7
Each foot	3.5	3.5	3.5	3.5	3.5	3.5

This table is adapted from *Sabiston Textbook of Surgery*, Townsend et al., Copyright Elsevier 2007. Data from 'A method of estimating the extensiveness of lesions (burns and scalds) based on surface area proportions', Berkow SG, *Archives of Surgery*, 1924, **8**(1), pp. 138–48. doi:10.1001/archsurg.1924.01120040149006.

depth evaluation, other adjuvant technologies have been piloted and studied. These techniques include histological examination of biopsy specimens, video angiography, vital dyes, video microscopy, and the use of laser Doppler [13,14].

Burn units

Burns units are specialized centres that provide collaborative and team-based approaches to burn care. Patients with substantial burns, burns requiring specialized surgical care, or who have other injuries or significant co-morbidities who should be referred to a burn unit include those with:

Table 346.3 Properties of different burns, according to depth of injury

Burn depth	Skin layers involved	Physical exam	Healing
First degree	Only epidermis	Blanching, painful, and erythematous	Typically within 1 week
Second degree/ superficial partial thickness	Involves minimal portions of dermis	Blanching, painful, and erythematous, with blistering	Epithelialize from retained epidermal structures in 1–2 weeks
Second degree/ deep partial thickness	Injury extends into reticular dermis	Non-blanching, pale and mottled, retains some pain sensation	Heal in 2–5 weeks, with severe scarring
Third degree	All dermis, into subcutaneous fat	Insensate, hard, and leathery	Can only heal from wound edges

- Partial thickness burns greater than 10% total body surface area (TBSA).
- Burns that involve the face, hands, feet, genitalia, perineum, or major joints.
- Third degree burns in any age group.
- Electrical burns, including lightning injury.
- Chemical burns.
- Inhalation injury.
- Burn injury in patients with complex pre-existing medical disorders.
- Any patient with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality.
- Children with burns, who are in a hospital without dedicated paediatric support.
- Burns in patients who require special social, emotional, or rehabilitative intervention.

Conclusion

Burns give rise to complex local and systemic physiological effects, an understanding of those effects, and the ability to accurately quantify the extent of injury, is critical in the understanding and management of patients with burns. These principles provide the foundation for resuscitation and management.

References

1. Pruitt BA, Wolf SE, and Mason AD. (2007). Epidemiological, demographic, and outcome characteristics of burn injury. In: Herndon DN (ed.) *Total Burn Care*. pp. 14–33.Philadelphia, PA: Saunders Elsevier.

2. WHO (World Health Organization) Media Center. (2012). Burns, Fact Sheet. March,. Available at: http://www.who.int/mediacentre/factsheets/fs365/en/index.html (accessed 4 July 2015).
3. American Burn Association. (2011). *National Burn Repository*. C2011. Available at: http://www.ameriburn.org/2011NBRAnnualReport.pdf (accessed 4 July 2015).
4. Rashid A, Khanna A, and Gowar JP. (2001). Revised estimates of mortality from burns in the last 20 years at the Birmingham Burns Centre. *Burns*, **27**, 723–30.
5. Mostrey S, Hoeksema H, Verbelen J, Pirayesh A, and Blondeel P. (2008). Assessment of burn depth and burn wound healing potential. *Burns*, **34**, 761–9.
6. Atiyeh BS, Gunn WA, and Dibo SA. (2008). Metabolic implications of severe burn injuries and their management: a systematic review of the literature. *World Journal of Surgery*, **32**, 1857–69.
7. Hart DW, Wolf SE, Mlcack RP, et al. (2000). Persistence of muscle catabolism after severe burn. *Surgery*, **128**(2), 312–19.
8. Herndon DN and Tompkins RG. (2004). Support of the metabolic response to burn injury. *Lancet*, **363**, 1895–902.
9. Jeschke MG, Mlack RP, Finnerty CC, et al. (2007). Burn size determines the inflammatory and hypermetabolic response. *Critical Care*, **11**(4), R90.
10. Mosier MJ, Pham TN, Klein MB, et al. (2010). Early acute kidney injury predicts progressive renal dysfunction and higher mortality in severely burned adults. *Journal of Burn Care Research*, **31**(1), 83–92.
11. Sheridan RL, Petras L, Basha G, et al. (1995). Planimetry study of the percent of body surface represented by the hand and palm: sizing irregular burns is more accurately done with the palm. *Journal of Burn Care Rehabilitation*, **16**, 605–6.
12. Wachtel TL, Berry CC, Wachtel EE, and Frank HA. (2000). The inter-rater reliability of estimating the size of burns from various burn area chart drawings. *Burns*, **26**, 156–70.
13. Atiles L, Mileski W, Purdue G, Hunt J, and Baxter C. (1995). Laser doppler flowmetry in burn wounds. *Journal of Burn Care Rehabilitation*, **16**, 388–93.
14. Chaterjee JS. (2006). A critical evaluation of the clinimetrics of laser Doppler as a method of burn assessment in clinical practice. *Journal of Burn Care Research*, **27**(2), 123–30.

CHAPTER 347

Management of burns in the ICU

Shahriar Shahrokhi and Marc G. Jeschke

Key points

- Burn critical care is an essential component of modern burn care and significantly improves survival.
- Adequate resuscitation is essential for organ preservation.
- Immediate recognition, as well as early and adequate treatment of inhalation injury decreases detrimental pulmonary sequelae.
- Burn care needs to recognize time patterns for burn patients—prehospital, early, and late management.
- Attenuation of hypermetabolism improves post-burn outcomes.

Introduction

There is no greater trauma than a major burn injury, which can be classified according to different burn causes and different depths. More than 500,000 burn injuries occur annually in the United States per year [1]. Although most of these burn injuries are minor, approximately 40,000–60,000 patients require admission to a hospital or major burn centre for appropriate treatment. The devastating consequences of burns have been recognized by the medical community, and significant resources and research have been dedicated, to improving outcomes [2]. Specialized burn centres and advances in treatment, based on improved understanding of resuscitation, protocolized and specialized critical care, enhanced wound coverage, more appropriate infection control, improved treatment of inhalation injury, and better support of the hypermetabolic response to injury have improved the clinical outcome of this unique patient population over the past years [2,3]. However, a severe burn remains a devastating injury affecting nearly every organ system, and leading to significant morbidity and mortality [2–5]. The management and care of burn patients is complex, entailing many members of various specialties.

Survival of the burn patient depends on:

- **Prehospital care**: adequate and timely response, and treatment, resuscitation, and transport.
- **Initial hospital phase**: admission to a burn centre, escharatomies and fasciotomies, treatment of inhlation injury, and critical care to maintain organ perfusion and function.
- **Later hospital phase**: wound care including burn surgery, infection control, attenuation of hypermetabolism, and maintenance of organ function.

Three critical components have been shown to contribute to increased post-burn morbidity and mortality, and are typical hallmarks of critical care responses:

- Burn shock and resuscitation.
- Inhalation injury.
- Burn hypermetabolism.

Burn shock and resuscitation

The initial management and therapeutic goal is prevention of organ failure, which begins with adequate resuscitation [6]. Burn shock was recognized early on as a predominantly hypovolaemic state, but is now known to be a complex process that includes components of hypovolaemic, distributive, and cardiogenic shock, and which fluid resuscitation alone cannot correct. After thermal injury, inflammatory mediators are released from the burned skin. These include histamine, serotonin, bradykinin, nitric oxide, lipid peroxides, prostaglandins, derived oxygen and nitric oxide free radicals, thromboxane, cytokines (interleukins and tumour necrosis factor (TNF)), and platelet aggregating factors [1,6]. This inflammatory response is proportional to the injury, and the systemic effects of these mediators will become obvious with burns exceeding 20–25% TBSA [7]. The systemic response includes local vasoconstriction, systemic vasodilatation, and massive capillary leak, with subsequent hypovolaemia and haemoconcentration that peaks approximately 12 hours post-burn. Without adequate resuscitation, multi-organ failure and death results [8].

Maintenance of organ perfusion during burn shock depends first on restoration of intravascular volume. The most commonly used algorithm for fluid resuscitation is the Parkland formula, which calculates a total volume of crystalloid to be given over the first 24 hours as 2–4 mL/kg patient weight/% (total body surface area (TBSA) burnt, with half of this amount to be given in the first 8 hours after the burn and the remaining half in the next 16 hours. Thus, as a guideline, a patient weighing 80 kg with 50% TBSA burn would require 2–4 × 80 × 50 mL = 8000–16,000 mL of crystalloid resuscitation in the first 24 hours after the burn [6,8,9]. As recommended by the American Burn Association (ABA), the resuscitation formula is only to be used as a guideline for resuscitation in burn shock. The Parkland formula is deficient in calculating the fluid requirements for resuscitation of patients with large burns, deeper burns, inhalation injury, delays in resuscitation, alcohol or drug use, as well as those with electrical injury leading to inadequate/inappropriate resuscitation.

The endpoints for fluid resuscitation have traditionally been a urine output of 0.5 mL/kg/hour, and a mean arterial pressure (MAP) of >65 mmHg. These endpoints are based on physiological rationale and tradition as there have been no large scale trials of different resuscitation endpoints in patients with severe burns. Currently, there are insufficient data to make evidence-based recommendations regarding the best resuscitation endpoints for patients with severe burns, and survey data suggest that urine output remains the most commonly used endpoint. Even using traditional endpoints for resuscitation, patients with severe burns may receive far greater volumes of crystalloid than predicted by the Parkland formula. Inherent complications of fluid resuscitation in the presence of capillary leak include pulmonary oedema, pleural effusions, pericardial effusions, abdominal compartment syndrome, extremity compartment syndrome, and conversion of burns to deeper wounds. In addition increasing fluid administration in burn patients are associated with increased risk of developing ARDS, pneumonia, bloodstream infections, multi-organ failure, and death [10]. Given the risk of abdominal compartment syndrome with large burns, intra-abdominal pressure monitoring should be considered in patients with burns involving more than 30% TBSA [11].

The role of colloid resuscitation in patients with severe burns is the subject of a long running debate [6,10,11]. Several small studies suggest that colloid resuscitation can result in the administration of less fluid, a less positive fluid balance, and decrease the incidence of intra-abdominal hypertension. Hydroxyethyl starch (HES) is not well studied in burn patients, but smaller studies indicated that HES is associated with increased adverse events. Based on these results and on results from larger trials in the critical care literature the use of HES in burns is not recommended [12]. There are some promising approaches to fluid resuscitation, which involve the modulation of inflammation with the use of antioxidants (specifically ascorbic acid in high doses). In 2000 Tanaka demonstrated in a small open-labelled non-randomized trial that the use of high dose ascorbic acid can lower fluid requirements during resuscitation and decreases the total ventilator days [13]. More recently Kremer et al. demonstrated that administration of high dose ascorbic acid reduces the microvascular barrier dysfunction in vivo [14]. These studies indicate a potential benefit for the resuscitation of burn patients, but one has exercise caution with the use of high vitamin C. This should not be standard, rather a subjective adjunct for burn patients and conducting large multicentre clinical trials to determine whether this should be a standard treatment is highly recommended.

The goals of resuscitation are to stabilize and restore haemodynamic status as soon as possible, and ensure tissue perfusion and oxygenation. To achieve this aim, the clinician can utilize various tools, including a combination of fluids (crystalloids and colloids after 8–12 hours), which aim to restore the intravascular volume, and inotropic and vasopressor agents. Fluids alone may not restore adequate tissue perfusion in all patients. During the initial phase post-burn massive burns may be associated with cardiogenic shock characterized by low cardiac output. The management of initial cardiogenic shock may require a combination of dobutamine and noradrenaline, in doses titrated to target (cardiac index ≥2.5–3 L/min/m^2, mean arterial pressure >60 mmHg) once intravascular volume has been restored as evidenced clinically, as well as by use of non-invasive cardiac output monitors (PiCCO, etc.). A cautious restrictive attitude towards fluids and tight clinical supervision is essential in ensuring optimal outcome. The initial resuscitation should aim to maintain organ perfusion—urinary output 0.5 mL/hour, lack of tachycardia, maintenance of MAP ≥60 mmHg, normal lactate and base excess levels will generally reflect this global condition [1,6,10].

A novel approach for burn patients has been the use of thermodilution catheters to determine cardiac function, systemic vascular resistance, and lung water [15]. The use of these catheters may enable focused and algorithm-driven therapy, which may improve the resuscitation phase, but as of now there are only few small studies published that do not allow major conclusions. However, these systems show promising results to optimize resuscitation.

Inhalation injury

Inhalation injury affects 15–30% of burn patients and is a significant additive variable in burn injury increasing morbidity (ventilator dependence, increased length of hospitalization, etc.) and mortality [3,4,16]. The ideal mode of ventilation for treatment of inhalation injury is yet to be agreed and remains controversial.

The diagnosis ranges from history and physical findings, to examination by bronchoscopy and measurements of serum markers [8,17]. However, there is general agreement that thermal injury associated with being in an enclosed space, loss of consciousness, and severe head and neck burns can have associated inhalation injury. The grading can be established by bronchoscopy, but its relationship to possible mortality, length of ventilatory requirement, and need for tracheostomy remains unclear [8].

A common grading system of inhalation injury developed by Gamelli et al., derived from findings at initial bronchoscopy, is based on the presence of: airway oedema, inflammation, mucosal necrosis, presence of soot and charring in the airway, tissue sloughing or carbonaceous material in the airway [18]. The treatment of inhalation injury should start by immediately securing the airway by endotracheal intubation if early evidence of upper airway oedema is present as airway oedema progresses rapidly in the first 6 hours, and delivering 100% oxygen until adequate oxygenation can be established by monitoring pulse oximetry and arterial blood gases.

Inhalation injury is often associated with inhalation of toxins such as carbon monoxide (CO), and cyanide (CN). The treatment for CO toxicity remains administration of 100% oxygen. The role of hyperbaric oxygen remains controversial, although both physiological data and some randomized-trial data suggest a potential benefit, in particular in terms of reduction of cognitive sequelae [19].

CN toxicity associated with inhalation injury remains a diagnostic dilemma as markers for CN toxicity (elevated blood lactate, elevated base deficit, or metabolic acidosis) can also represent under-resuscitation, associated trauma, CO poisoning or hypoxia. Regardless, aggressive resuscitation and administration of 100% oxygen remains the mainstay of treatment. Controversy remains as to the need for specific antidotes in cyanide poisoning. The use of hydroxocobalamin (a standard of prehospital care in some European centres) has not been as widely accepted in North America. There's minimal evidence for the role of CN antidotes in smoke inhalation injury and, therefore, aggressive supportive therapy aimed at allowing for the hepatic clearance of cyanide without specific antidotes should be the first line of treatment.

Other treatment modalities (β_2-agonist, nebulized heparin, and nitric oxide) have been proposed for inhalation injury. β_2-agonist resulted in improved lung physiology by reducing pulmonary oedema and lung vascular permeability to protein in animal models; however, there's lack of evidence for its use in humans.

Following inhalation injury, casts composed of mucus secretions, airway epithelial cells, inflammatory cells, and fibrin may form within the airway and can cause airway obstruction. In order to improve pulmonary toilet it is essential to prevent and be able to dissolve fibrin deposition. The role of nebulized heparin therapy has been studied in animal models and single-centre trials that demonstrate potential role in inhalation injury, particularly when combined with other anti-inflammatory agents and antithrombin.

Studies in animal models have consistently shown a reduction in pulmonary hypertension associated with inhalation injury with the administration of inhaled nitric oxide. There are limited studies in humans, which have demonstrated an improvement of PaO_2/FIO_2 ratio with the NO. With the current level of evidence the role of NO is unclear in inhalation injury and should only be considered in those who have failed traditional ventilation strategies.

Therefore the treatment guidelines for inhalation injury call for nebulized heparin, acetyl cysteine, adrenaline, and lung protective ventilation.

Post-burn hypermetabolism

The complex metabolic response to burn is extremely profound and one of the central determinants for post-burn survival. Recently, it was shown that this response persists for years [2,4,5]. There's a pronounced increase in catecholamine secretion with a resultant 140–180% increase in the resting metabolic rate, which induces prolonged tachycardia, fever, muscle protein catabolism, and hepatic dysfunction [2,4,5]. This continued hypermetabolic state results in a decrease in lean body mass, compromise of the immune system with resultant increase risk of infection/sepsis, delayed wound healing and prolonged recovery period [2,4,5].

Over the last decade or two various therapies have been studied with the goal to alleviate this catabolic and hypermetabolic state. To-date no single therapy exists to block hypermetabolism, but various therapeutic approaches have been implemented for burn patients [20]:

- Raise ambient temperature.
- Nutrition.
- Early excision and grafting.
- Exercise.
- Adequate organ support.
- Anabolic and/or anticatabolic agents.

Of the systemic therapies the use of anticatabolic β-blocker (propanolol) and anabolic agents such as growth hormone, oxandrolone, insulin, insulin-like growth factor-1, glucagon-like peptide ketoconazole, or the combination of various agents have demonstrated beneficial effects (all reviewed in [20]). Each of the agents have advantages and disadvantages. Currently, three agents should be considered for therapeutic intervention—propranolol will decrease the catecholamine induced post-burn stress, oxandrolone is anabolic and can increase strength and endurance, and finally, insulin is an anabolic hormone regulating post-burn insulin resistance and hyperglycaemia. To summarize, there is no magic bullet to treat hypermetabolism, but it is believed that survival of burn patients depends on the attenuation of the hypermetabolic response using adequate nutrition, early excision and grafting [2], increased ambient temperature, exercise, and administration of anabolic and anti-catabolic agents, such as oxandrolone, insulin, and propranolol [20].

Conclusion

The management of the critically-ill thermally-injured patient can be very complex. The treatments modalities can remain, at times, controversial as there is a lack of high-level evidence. There have been many advances in the field of the critical care of the thermally-injured patient, which would benefit from large-scale multicentre trials. This brief chapter highlights few of the important nuances in the care of these patients and places emphasis on the need for intricate support for the all organ systems in order to improve morbidity and mortality.

References

1. Herndon DN (ed.). (2007). *Total Burn Care*, 4th edn. Philadelphia, PA: Saunders Elsevier.
2. Herndon DN and Tompkins RG. (2004). Support of the metabolic response to burn injury. *Lancet*, **363**(9424), 1895–902.
3. Kraft R, Herndon DN, Al-Mousawi AM, Williams FN, Finnerty CC, and Jeschke MG. (2012). Burn size and survival probability in paediatric patients in modern burn care: a prospective observational cohort study. *Lancet*, **379**(9820), 1013–21.
4. Jeschke MG, Chinkes DL, Finnerty CC, et al. (2008). Pathophysiologic response to severe burn injury. *Annals of Surgery*, **248**(3), 387–401.
5. Jeschke MG, Gauglitz GG, Kulp GA, et al. (2011). Long-term persistence of the pathophysiologic response to severe burn injury. *PLoS One*, **6**(7), e21245.
6. Pham TN, Cancio LC, and Gibran NS. (2008). American Burn Association practice guidelines burn shock resuscitation. *Journal of Burn Care Research*, **29**(1), 257–66.
7. Jeschke MG, Mlcak RP, Finnerty CC, et al. (2007). Burn size determines the inflammatory and hypermetabolic response. *Critical Care*, **11**(4), R90.
8. Latenser BA. (2009). Critical care of the burn patient: the first 48 hours. *Critical Care Medicine*, **37**(10), 2819–26.
9. Greenhalgh DG. (2010). Burn resuscitation: the results of the ISBI/ABA survey. *Burns*, **36**(2), 176–82.
10. Klein MB, Hayden D, Elson C, et al. (2007). The association between fluid administration and outcome following major burn: a multicenter study. *Annals of Surgery*, **245**(4), 622–8.
11. Ivy ME, Atweh NA, Palmer J, Possenti PP, Pineau M, and D'Aiuto M. (2000). Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. *Journal of Trauma*, **49**(3), 387–91.
12. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. (2013). Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. *Journal of the American Medical Association*, **309**(7), 678–88.
13. Tanaka H, Matsuda T, Miyagantani Y, et al. (2000). Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. *Archives of Surgery*, **135**(3), 326–31.
14. Kremer T, Harenberg P, Hernekamp F, et al (2010). High-dose vitamin C treatment reduces capillary leakage after burn plasma transfer in rats. *Journal of Burn Care Research*, **31**(3), 470–9.

15. Branski LK, Herndon DN, Byrd JF, et al. (2011). Transpulmonary thermodilution for hemodynamic measurements in severely burned children. *Critical Care*, **15**(2), R118.
16. Barrow RE, Przkora R, Hawkins HK, Barrow LN, Jeschke MG, and Herndon DN. (2005). Mortality related to gender, age, sepsis, and ethnicity in severely burned children. *Shock*, **23**(6), 485–7.
17. Finnerty CC, Herndon DN, and Jeschke MG. (2007). Inhalation injury in severely burned children does not augment the systemic inflammatory response. *Critical Care*, **11**(1), R22.
18. Endorf FW and Gamelli RL. (2007). Inhalation injury, pulmonary perturbations, and fluid resuscitation. *Journal of Burn Care Research*, **28**(1), 80–3.
19. Weaver LK. (2009). Clinical practice. Carbon monoxide poisoning. *New England Journal of Medicine*, **360**(12), 1217–25.
20. Jeschke MG and Herndon DN. (2013). Burns in children: current standard and new treatments. *Lancet*. 383 (9923), 1168–1178

SECTION 17

Physical disorders

PART 17.1

Drowning

CHAPTER 348

Pathophysiology and management of drowning

Jerome H. Modell and Sean Kiley

Key points

- Drowning is a process beginning with airway submergence under a fluid medium and progressing to aspiration and ultimately death in the absence of intervention.
- Aspiration of both fresh and salt water cause pulmonary oedema, decreased compliance, intrapulmonary shunting, and severe hypoxia.
- Devastating neurological injury resulting from prolonged cerebral hypoxia is proportional to the duration of submersion and delay in effective resuscitation and oxygenation.
- Victims presenting to the emergency department awake and alert, or even stuporous, are likely to have a good neurological outcome with follow-up intensive care. Those presenting comatose are much more likely to have severe neurological deficits.
- Key to survival are timely rescue from the water, immediate initiation of aggressive supportive care regarding airway, cardiovascular, and pulmonary function, and optimization of tissue oxygenation.

Epidemiology

Over the past 50 years, knowledge of the pathophysiology of drowning has expanded greatly [1] and improvement in critical care of drowning victims, emergency medical services, pool safety standards, and lifeguard training have been instrumental in reducing the death rate from drowning in the United States from 3.87 deaths per 100,000 population in 1970 to 1.35 deaths per 100,000 population in 2009 [2]. Factors that contribute to drowning include leaving unattended children at water sites, alcohol or other drug abuse, limited swimming ability, exhaustion, trauma, risky behaviour, deliberate prolonged submersion, exacerbation of existing medical problems (e.g. seizure disorder, cardiac disease, or syncope), and suicide.

Omissions in safety precautions, such as inadequate pool fencing, faulty pool design resulting in victims becoming trapped below the surface of the water, poor pool maintenance causing cloudy water that obscures submerged bodies, lifeguards distracted by socializing and doing administrative chores when on duty, and lifeguards who do not recognize a person in trouble, or have not been properly trained in rescue and resuscitation techniques, all contribute to drowning.

To drown implies death, yet many victims are resuscitated and recover. The terms 'near-drowning', 'drowning without aspiration' or 'dry drowning', 'active and passive, or silent drowning' have been abandoned. The new definitions for 'drowning' and 'the drowning process' were published in 2003 [3].

The drowning process

The drowning process begins when the victim's airway lies below the surface of the liquid, at which time the victim voluntarily holds his or her breath. This is usually followed by an involuntary period of laryngospasm secondary to liquid in the oropharynx or larynx. During this time, the victim is unable to breathe gas, and becomes hypercarbic, hypoxaemic, and acidotic. Respiratory movements become very active, but there is no exchange of air because of the obstruction at the level of the larynx. As the victim's arterial oxygen tension drops further, laryngospasm abates, and the victim actively inhales liquid. Changes occur in the lungs, body fluids, blood–gas tensions, acid–base balance, and electrolyte concentrations, which are dependent on the composition and volume of the liquid aspirated and duration of submersion. Surfactant washout, pulmonary hypertension, and shunting also contribute to development of hypoxaemia [3].

Pathophysiology

The submerged victim holds his or her breath, and/or is in laryngospasm, for approximately 1½–2 minutes before the oxygen in blood perfusing the brain decreases to the extent that laryngospasm can no longer be sustained and ventilation occurs. Consciousness is lost at about the same time due to cerebral hypoxia. If rescued promptly and permitted to breathe air, the individual will not undergo the remainder of the drowning process. If water is aspirated a far more complex occurrence results. Experimentally, it has been shown that cardiac arrest due to hypoxia occurs by 3–4½ minutes [1].

If the victim is rescued, and ventilation and circulation are re-established, acute lung injury usually follows the drowning incident. Studies have shown 2.2–44 mL/kg of water instilled into the trachea of anaesthetized dogs resulted in immediate decrease in the partial pressure of oxygen in arterial blood (PaO_2) that persisted for many hours or even days [4,5]. Likewise, human drowning victims often demonstrate prolonged hypoxia post-event [6].

Rapid hypothermia results from drowning in cold water, which prolongs the length of time they may be submerged and still recover [7].

However, significant hypothermia also can lead to delay in myocardial conduction, dysrhythmias, and cardiac arrest.

Aspiration of water

Once it was thought that approximately 10–15% of human drowning victims died without aspirating liquid. Lunetta et al. in 2004 [8], questioned whether drowning without aspiration actually occurs. They reviewed the autopsies of 578 persons presumed to have drowned, and found evidence of water in the lungs of 98.6% of the victims studied [8]. They concluded drowning requires the aspiration of water. If the heart stops before the individual's airway becomes submerged, water does not passively seep into the lungs. Persons found dead in water without evidence of aspiration at autopsy, probably died of some other cause, such as a homicide or lethal cardiac arrhythmia [8].

Sea water is hypertonic and draws capillary fluid into the lung by osmotic pressure, leading to intra-alveolar oedema [9]. Fresh water aspiration alters the surface tension properties of pulmonary surfactant, rendering the alveoli permeable to fluid and also to collapse [10]. Fresh water is also absorbed into the circulation creating rapid haemodilution [4]. This results in a temporary increase in systemic blood volume, cellular swelling, and haemolysis [4].

Pulmonary oedema occurs with either type of water and decreases compliance, and increases intrapulmonary shunting. The aetiology of this process is fluid-filled, but perfused alveoli when seawater is aspirated and alveolar collapse due to surfactant instability when fresh water is aspirated [11].

Pathological changes caused by drowning are usually reversible if the person is rescued and treated promptly with aggressive pulmonary support, including the use of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) [11]. Acute respiratory distress syndrome (ARDS) and pneumonia increase mortality associated with drowning. If pneumonia is diagnosed, antibiotic treatment should be broad and include coverage for the ecology of organisms in the body of water in which the drowning incident occurred.

Changes in blood volume and serum electrolytes

Differences in tonicity of the aspirated medium produce different effects on intravascular volume. When a large volume of hypotonic fluid is aspirated, it is absorbed quickly and intravascular volume increases in proportion to the volume aspirated [4]. Fluid shifts and redistribution may ultimately result in hypovolaemia. Conversely, aspiration of hypertonic fluid causes immediate shifting of fluid from the intravascular space to the alveoli rapidly creating hypovolaemia [5].

Electrolyte changes during drowning are directly associated with the intravascular volume changes [4,5]. Clinically significant volume or electrolyte abnormalities in survivors are unlikely because they rarely aspirate sufficient volumes of liquid to cause such changes [6].

Cardiovascular effects

If freshwater is aspirated, the resultant hypotonicity of the plasma in the presence of hypoxemia causes red blood cell lysis with release of haemoglobin and potassium. Rarely, serum potassium increases and serum sodium decreases are sufficient to lead to ventricular fibrillation [12]. Arrhythmias related to hypoxia are relieved when oxygenation is re-established [1].

Choi et al. [13] reported that 8.5% of drowned victims had genetic mutations compatible with long QT syndrome. However, Lunetta et al. [14] found QT syndrome founder mutations in *KCNQ1* (*KVLQT1*) and *KCNH2* (*HERG*) genes in only one of 165 consecutive drowning victims. He concluded that long QT-induced arrhythmias resulting in drownings are rare [14].

Neurological effects

Mental status upon arrival at the hospital provides insight regarding long-term neurological effects related to cerebral hypoxia. If the victim is awake and orientated, virtually 100% survive without neurological deficits [15,16]. If they present stuporous, but capable of arousal and have purposeful responsiveness to pain, there is a 90% likelihood that there will not be long-term neurological effects [15,16]. If drowning victims present in coma, the outcomes are worse. Conn et al. [15] found 57% of comatose drowning victims had persistent severe neurological deficits or died and Modell et al. [16] found 44% had severe hypoxic brain damage or died.

The degree of neurological injury is proportional to the duration of submersion and delay in providing effective resuscitation. If effective resuscitation starts within 3 minutes of the onset of submersion, survivability is excellent. However, irreversible cell death usually occurs after about 5 minutes of submersion or inadequate oxygen delivery. There are reports of prolonged cold water immersion in which victims survive neurologically intact [7]. These usually relate to children because they have a large exposed surface area, and cool rapidly thus benefiting from hypothermic protection from hypoxia. The extent of neurological injury is difficult to detect early on, even with imaging. The patient's response to therapy over time is the only true prognosticator.

Shallow water blackout

Craig, et al. [17] studied the breath-holding breaking point in human volunteers and found breath-holding could be prolonged one-and-a-half times longer if it was preceded by hyperventilation. However, during simulated underwater swimming after hyperventilation breath-holding time was reduced to baseline. He concluded although exercise, such as swimming, increased metabolically-produced carbon dioxide, the arterial carbon dioxide tension was decreased in their volunteers because storage was depleted during hyperventilation and the urge to breathe was delayed. With exercise after hyperventilation, arterial oxygen tension decreased to levels incompatible with maintaining consciousness before the level of partial pressure of carbon dioxide in alveolar blood ($PaCO_2$) became unbearable. The victim then begins to breathe under water due to a hypoxic drive, aspirates water, and drowns. This has been termed 'shallow water blackout'.

Treatment

On scene

Treatment for drowning victims begins with immediate rescue from the water. Rescue breathing and support of circulation should begin promptly. Despite anecdotal claims of the use of the Heimlich manoeuvre to treat drowning victims, the Institute of Medicine recommends against the Heimlich manoeuvre because of

its questionable value and it delays initiation of cardiopulmonary resuscitation [18].

Basic life support (BLS) should be instituted immediately and should be followed by advanced cardiac life support (ACLS) as soon as possible. No matter what the patient's appearance after retrieval and resuscitation, transport to the hospital should be immediate, with prompt initiation of oxygen therapy and monitoring with a minimum of pulse oximetry, blood pressure, and ECG. If the patient remains apnoeic and/or in cardiac arrest, ACLS should be continued.

Hospital treatment

Initial treatment should focus on optimizing oxygen delivery to tissues. Oxygen supplementation may be adequate in patients who maintain adequate spontaneous ventilation and circulation. CPAP is effective in recruiting alveoli and reducing intrapulmonary shunt in patients having difficulty maintaining adequate oxygen saturation [12]. Endotracheal intubation and mechanical ventilatory support is required for all comatose patients and those having difficulty maintaining adequate oxygen saturation. Arterial blood gas values must be obtained as soon possible to assess for hypoxia, hypoventilation, and acid–base disturbances. Sodium bicarbonate administration may be necessary to treat profound metabolic acidosis that occurs from anaerobic metabolism.

Severe hypothermia is common and rewarming should be initiated via passive and active external methods, including humidified warm inspiratory gases. Conduction, convection, and radiant warming also may be necessary. Recent data suggests therapeutic hypothermia post-arrest may lead to better outcomes. Walpoth and Daanen recommend rewarming to only 32–34°C for 12–24 hours post-drowning [19].

Haemodynamic monitoring is required when there is concern with fluid balance. Arterial catheters facilitate obtaining serial arterial blood gases. CPAP and/or PEEP should be optimized to improve ventilation/perfusion ratios and to permit F_IO_2 to remain as low as possible to avoid oxygen toxicity. Prophylactic broad spectrum antibiotics are only indicated when the drowning medium is known to be contaminated [1].

Seizures should be treated if present. Studies have been conducted to evaluate the empiric use of mannitol, hyperventilation, barbiturates, and neuromuscular blockade for aggressive cerebral resuscitation [15]. However, outcome benefit has not been demonstrated [16,20]. While intracranial pressure (ICP) monitoring may be used to direct therapy to keep ICP below 20 mmHg, optimizing cerebral perfusion pressure, increased ICP probably reflects damage done at the time of drowning.

References

1. Layon AJ and Modell JH (2009). Drowning: update 2009, *Anesthesiology*, **110**, 1390–401.
2. Center for Disease Control, National Center for Injury Prevention and Control (2009). *United States drowning death and rates per 100,000: all races, both sexes, all ages, ICD-10 Codes: W65-W74, X71, X92, Y21*.
3. Idris AH, Berg R, Bierens J, et al. (2003). Recommended guidelines for uniform reporting of data from drowning: the 'Utstein Style'. *Circulation*, **108**, 2565–74.
4. Modell JH and Moya F. (1966). Effects of aspirated fluid during chlorinated freshwater drowning. *Anesthesiology*, **27**, 662–72.
5. Modell JH, Moya F, Newby EJ, Ruiz BC, and Showers AV. (1967). The effects of fluid volume in seawater drowning. *Annals of Internal Medicine*, **67**, 68–80.
6. Modell JH, Graves SA, and Ketover A. (1976). Clinical course of 91 consecutive near-drowning victims. *Chest*, **70**, 231–8.
7. Modell JH, Idris AH, Pineda JA, and Silverstein JH. (2004). Survival after prolonged submersion in freshwater in Florida. *Chest*, **125**, 1948–51.
8. Lunetta P, Modell JH, and Sajantila A. (2004). What is the incidence and significance of 'dry-lungs' in bodies found in water? *American Journal of Forensic Medicine and Pathology*, **25**(4), 291–301.
9. Modell JH, Calderwood HW, Ruiz BC, Downs JB, and Chapman R, Jr. (1974). Effects of ventilatory patterns on arterial oxygenation after near-drowning in sea water. *Anesthesiology*, **40**, 376–84.
10. Giammona ST and Modell JH. (1967). Drowning by total immersion: effects on pulmonary surfactant of distilled water, isotonic saline and sea water. *American Journal of Diseases of Childhood*, **114**, 612–16.
11. Bergquist RE, Vogelhut MM, Modell JH, Sloan SJ, and Ruiz BC. (1980). Comparison of ventilatory patterns in the treatment of freshwater near-drowning in dogs. *Anesthesiology*, **52**, 142–8.
12. Modell JH, Pellis T, and Weil MH. (2006). Cardiovascular changes. In: Bierens J (ed.) *Handbook on Drowning*, pp. 423–7. Heidelberg: Springer-Verlag.
13. Choi G, Kopplin LJ, Tester DJ, Will ME, Haglund CM, and Ackerman MJ. (2004). Spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes. *Circulation*, **110**, 2119–24.
14. Lunetta P, Levo A, Laitinen PJ, Fodstad H, Kontula K, and Sajantila A. (2003). Molecular screening of selected Long QT Syndrome (LQTS) mutations in 165 consecutive bodies found in water. *International Journal of Legal Medicine*, **117**, 115–17.
15. Conn AW, Montes JE, Barker GA, and Edmonds JF. (1980). Cerebral salvage in near-drowning following neurological classification by triage. *Canadian Anaesthesiologists Society Journal*, **27**, 201–9.
16. Modell JH, Graves SA, and Kuck EJ. (1980) Near-drowning: correlation of consciousness and survival. *Canadian Anaesthesiologists Society Journal*, **27**, 211–15.
17. Craig AB, Jr. (1961). Causes of loss of consciousness during underwater swimming. *Journal of Applied Physiology*, **16**, 583–6.
18. Rosen P, Stoto M, and Harley J. (1994). The use of Heimlich Maneuver in Near-drowning, pp. 397–405. Washington DC: Institute of Medicine.
19. Walpoth B and Daanen H. (2006). Immersion hypothermia, In Bierens J (ed.) *Handbook on Drowning*, pp. 481–5. Heidelberg: Springer-Verlag.
20. Bohn DJ, Biggar WD, Smith CR, Conn AW, and Barker GA. (1986). Influence of hypothermia, barbiturate therapy and intracranial pressure monitoring on morbidity and mortality after near-drowning. *Critical Care Medicine*, **14**, 529–34.

PART 17.2

Electrocution

CHAPTER 349

Pathophysiology and management of electrocution

Jeffrey S. Neiger and Richard G. Trohman

Key points

- Electrocution is a common source of morbidity and mortality, primarily affecting children in the home and young adults via occupational exposure.
- A familiarity with the basic principles of electrical physics helps one understand the typical injuries suffered following electrical shock.
- Exposure to electrical shock can affect a variety of organ systems, including the skin, cardiovascular system, and nervous system.
- Patients who survive initial cardiopulmonary arrest often have a favourable prognosis, and their injuries should be treated aggressively in a specialized burn or trauma unit.
- Because the full degree of injury is not always initially apparent, determination of prognosis can be difficult in electrical shock victims.

Introduction

Electrocution occurs relatively frequently and has a high mortality [1]. Approximately 1000 people die from electrical exposure in the USA annually [1]. Most electrocution victims are children under the age of 6 years who suffer electrical injury in the home and young adults exposed to electricity as a consequence of their occupation, such as miners and construction workers [1]. Patients surviving the initial insult of electric shock account for approximately 3% of the annual admissions to specialized burn units [1].

Physics

There are two methods by which electric power is delivered, alternating current (AC) and direct current (DC). In AC, the form in which electric power is delivered to businesses and residences, the direction of electron flow reverses rapidly in a cyclic fashion. For example, in the USA, standard household current of 110 V flows at 60 cycles per second (60 Hertz (Hz)). In Europe, the power system operates at 220–240 V and a frequency of 50 Hz. Batteries, high tension power lines, and lightning deliver electrical power via DC. In such situations, current flows constantly in one direction across a potential gradient [1].

The primary determinant of damage caused by electrical injury is the amount of current flowing through the body. Additional factors include voltage, resistance, type of current, current pathway, and duration of contact with the electrical source [2]. Joule's law determines the amount of thermal energy delivered, which leads to tissue damage, is a function of the current squared, time, and resistance [1].

Higher resistance tissues, such as skin, bone, and fat, tend to increase in temperature and coagulate. Nerves and blood vessels, which have low resistance, conduct electricity readily. Dry skin has a higher resistance than moist skin, and may suffer extensive superficial tissue damage from electricity, while limiting conduction of harmful current to deeper structures [3]. Moist skin serves as a better current conductor, resulting in less superficial thermal injury, but more extensive damage to internal organs.

Mechanism of injury

In patients exposed to electrical shock, voltage is typically the only variable that is known with certainty [1]. Electrical shocks of 1000 V or more are classified as high voltage and result in more severe injury per time of exposure, while shocks less than 1000 V are considered low voltage. Typical household electricity has 110–230 V, high-tension power lines have over 100,000 V, and lightning strikes can produce 10 million V or more [3].

Electrocution causes injury via four mechanisms:

- Direct effects of current on body tissue, leading to asystole, ventricular fibrillation (VF), or apnoea.
- Blunt mechanical injury from lightning strikes, resulting in muscle contraction or falling.
- Conversion of electrical energy to thermal energy, resulting in burns, protein denaturation and coagulation.
- Electroporation, defined as the creation of pores in cell membranes by means of electrical current, leading to cell death without significant heating [1]. Electroporation occurs with high strength electrical fields (defined as volts per meter).

Contact with DC results in a single muscle contraction, often throwing the person receiving the shock away from the electrical source. When an individual touches an AC electrical source with their hand, repetitive tetanic muscle contraction can cause the hand to grip the source tighter (because of stronger flexor than extensor tone), leading to longer electrical exposure time and greater injury. For this reason, AC is the more frequent cause of electrocution. The amount of AC needed to cause injury varies with the current's

frequency. Skeletal muscle becomes tetanic at lower frequencies, ranging from 15 to 150 Hz [1]. Household electricity (60 Hz) is especially arrhythmogenic, and may lead to the development of fatal ventricular tachyarrhythmias [1].

Typical injuries

Skin

Skin exposed to electrical shock results in four different types of burns: electrothermal burns, arc burns, flame burns, and lightning injuries [1]. Electrothermal burns result in a classic injury pattern, with skin entrance and exit wounds. Skin wounds due to electrical exposure are typically classified by the depth of injury as partial- or full-thickness, or burns involving deeper subcutaneous tissue. High-voltage injuries commonly produce greater damage to deeper tissues, largely sparing the skin surface. Therefore, estimating the area of surface burns as a guide for therapy may lead to critical errors because an apparently 'minor' superficial injury may be associated with massive coagulation necrosis of deeper tissue [4].

An electrical arc is a current spark that travels via (typically) non-conductive matter such as air, across a gap between electrically charged surfaces. It occurs when two surfaces approach each other, before the halves actually touch, or when the surfaces separate from each other by breaking the current path in the circuit. Arcing can generate temperatures of 3000°C to 20,000°C and crosses 2–3 cm for every 10,000 V [5]. Arc injury occurs when the victim becomes part of the arc itself, and leads to characteristic 'crocodile skin' burns in the portions of the body that come in contact with the arc (Fig. 349.1) [6]. These multiple burnt, punched-out lesions of varying depth are a result of the arc 'dancing' across the body surface.

Respiratory

Respiratory arrest following electrical shock may result from inhibition of the central nervous system respiratory centre, prolonged paralysis or tetanic contraction of respiratory muscles, or combined cardiorespiratory arrest secondary to ventricular arrhythmias. If respiratory arrest is not treated promptly by ventilation, secondary hypoxic VF may occur [1]. Parenchymal damage to the lung is rarely seen in patients who suffer electrical injury. However, fatal air embolism may complicate electrical injury to the deep tissues of the neck.

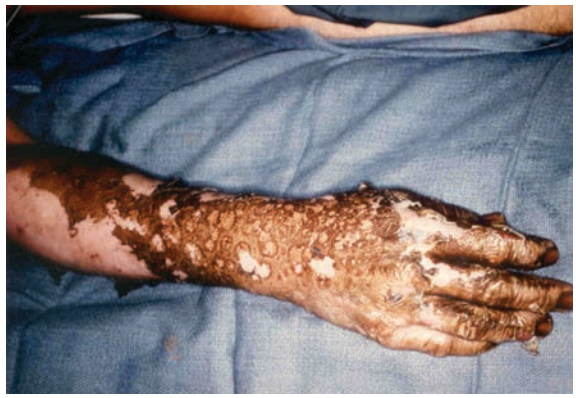


Fig. 349.1. 480-volt arc flash event.
Photos Courtesy of Shermco Industries, Dallas Texas.

Cardiovascular

Electrical shock may induce arrhythmias and conduction abnormalities, as well as myocardial injury due to direct electricity exposure and/or secondary injury due to induced ischemia [1].

Arrhythmias

Low-voltage AC more commonly results in sudden cardiac death due to ventricular fibrillation. In contrast, DC or high-voltage AC shocks are more likely to result in asystole [3]. Experimental studies show AC to be more hazardous than DC applied at the same voltage. Interestingly, with exposure to between 50 and 500 V, the incidence of VF was inversely proportional to voltage, while ventricular tachycardia (VT) and atrial fibrillation (AF) were directly proportional [7]. Potentially fatal arrhythmias are more likely to be caused by horizontal current flow (hand to hand), whereas vertical current (head to foot) usually leads to myocardial tissue damage [1,3]. Most arrhythmias occur shortly after the electrical shock, but delayed ventricular arrhythmias can been seen up to 12 hours following exposure [8]. Subsequent arrhythmias are relatively common (10–46%) among survivors, with sinus tachycardia and premature ventricular complexes being most frequent [1,9]. However, VT and AF have also been reported [1]. Patients who survive electric shock often display non-specific ST-T wave that typically resolve spontaneously [3,10]. Those without initial ECG changes are at a lower risk for subsequent life-threatening arrhythmias [11]. Electrocution injury has also been reported to result in typical Brugada pattern ECG changes, with ST elevations in the right precordial leads (V1–V3) and a right bundle branch block pattern [12]. These changes resolved spontaneously and are of unknown significance regarding the long-term risk of malignant arrhythmias [12].

Conduction abnormalities

Sinus bradycardia and high-degree atrioventricular (AV) block have been reported following electrical shock. AC current injury seems to have a predilection for the sinoatrial (SA) and AV nodes [13]. Some of these conduction abnormalities may persist as long-term sequelae of electrical injury and should be monitored closely in survivors of electrical shock.

Myocardial injury

Myocardial damage may occur after exposure to high or low voltage current. Injury is caused directly by electrothermal injury and electroporation, or secondarily by contusion following lightning strike. Other mechanisms described include coronary spasm leading to ischaemia and hypotensive arrhythmias causing secondary hypoperfusion. Diagnosing myocardial injury can be difficult due to the diffuse nature of myocardial necrosis. Typical symptoms and specific ECG changes are not usually present, myocardial perfusion scans are normal, creatine kinase–MB elevations are of uncertain significance, and troponins have not been well-studied in this setting [1].

Musculoskeletal

Bony tissue has the highest electrical resistance and experiences the most severe electrothermal injuries, including periosteal burns, destruction of bone matrix, and osteonecrosis [3,14]. Fractures and large joint dislocations may be caused by forceful tetanic contractions or falls [14]. Electrothermal injury may lead to rhabdomyolysis and compartment syndrome [15]. The extent of muscle tissue

damage can be assessed by serum creatine kinase level, which generally correlates well with the amount of burned surface area and may be useful as a decision aid for surgical decompression [1].

Neurologic

Electrical shock can result in damage to the central and peripheral nervous system. Loss of consciousness, generalized weakness, autonomic dysfunction, respiratory depression and memory disturbances are frequent manifestations [1]. **Keraunoparalysis** is a specific form of reversible, transient paralysis with associated sensory disturbances and peripheral vasoconstriction seen in some victims of lightning injury [16]. It is important to note that such patients may have fixed and dilated pupils (due to reversible autonomic dysfunction), which should not prompt termination of resuscitation efforts or withdrawal of care. Central nervous system complications also include hypoxic encephalopathy, intracerebral haemorrhage, and cerebral infarction. Although sensorineural hearing loss has been reported, hypoacusis is usually due to rupture of the eardrums, a common consequence of lightning strikes.

Renal

Acute renal failure resulting from rhabdomyolysis and myoglobinuria is a common cause of death following electrocution. Rapid fluid resuscitation to correct hypovolaemia and acidosis can significantly reduce the incidence of acute renal failure in these patients.

Special circumstances

Lightning

Lightning strike is unique because it causes cardiac and respiratory arrest, resulting in 25–30% mortality [17]. Lightning delivers a large amount of DC electricity (up to hundreds of millions of volts and 200 amperes) during a very short period (milliseconds) [1]. Thus, the energy delivered may be less than with other high-voltage electrical injuries because of the short exposure time. Patients rarely sustain extensive tissue destruction or large cutaneous burns.

Lightning strikes have been subdivided into three distinct categories, each with different cardiac effects (Table 349.1) [18].

Although rarely seen, Lichtenberg figures are pathognomonic skin manifestations in persons struck by lightning (Fig. 349.2) [19]. Lichtenberg figures are typically formed by rapid dispersion of charge from the surface of poorly conducting tissues. They are transient in nature and do not cause apparent damage to the epidermis or underlying tissues.

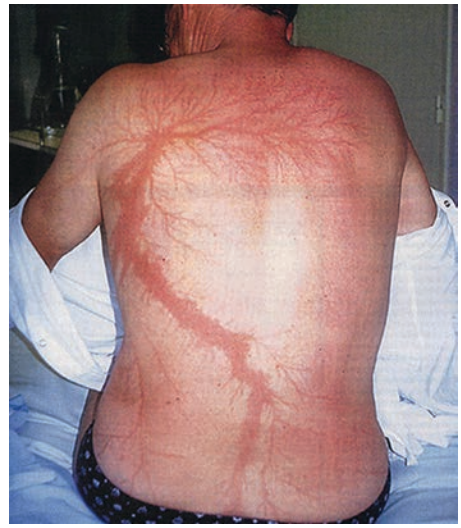


Fig. 349.2 Lichtenberg figures typically formed by rapid dispersion of charge from the surface of poorly conducting tissues.
From *New England Journal of Medicine*, Domart Y and Garet E, 'Lichtenberg figures due to a lightning strike', **343**(21), p. 1536. Copyright © 2000 Massachusetts Medical Society, Reprinted with permission from Massachusetts Medical Society.

Patients with implantable cardiac devices

Isolated reports exist of patients exposed to high-voltage electricity or lightning strike, who were saved from potentially fatal VF by a successful ICD shock [18]. Conversely, the electromagnetic interference caused by electrical exposure may lead to bradycardia or asystole from inhibition of ventricular pacing, or result in inappropriate shocks leading to induction of ventricular arrhythmias. It is important to perform a thorough device interrogation in all patients with pacemakers or ICDs who suffer electrical injury, in order to help clarify the role of the device in treating any resulting arrhythmias, and to ensure proper function of the device and leads following such exposure.

Management

Cardiopulmonary resuscitation

Victims of electric shock should undergo intensive cardiopulmonary resuscitation (CPR) and therapeutic hypothermia. Cardiac arrhythmias and prolonged respiratory arrest may be the only

Table 349.1 Cardiac effects from various types of lightning strikes

Direct strike (Current passes through person from head/upper body to feet)	Side flash (Person in proximity to, but not in contact with object through which current discharges)	Ground strike/step voltage (Lightning strikes ground and dissipates irregularly)
◆ Immediate cardiac arrest due to asystole or hypoxia-induced ventricular fibrillation ◆ Severe biventricular failure/pericardial effusion ◆ Myocardial injury common (75%) ◆ QT prolongation/ST elevation	◆ Sinus tachycardia, ventricular fibrillation ◆ Myocardial injury common (66%) ◆ Non-specific ST-T wave changes	◆ Sinus tachycardia, ventricular fibrillation ◆ Myocardial injury uncommon (12%) ◆ Non-specific ST-T wave changes

Reproduced from Kondur AK et al., 'Implantable cardioverter defibrillators save lives from lightning-related electrocution too!', *Pacing and Clinical Electrophysiology*, **31**, pp. 256–7, Copyright 2008, with permission from John Wiley & Sons, Inc.

clinical problem, especially in patients struck by lightning. In addition, patients who suffer exposure to electrical shock are commonly young, and have few or no comorbid conditions. They may survive prolonged CPR with minimal or no sequelae, especially with appropriate initiation of therapeutic hypothermia protocols. It is important to remember that keraunoparalysis leading to autonomic dysfunction may masquerade as irreversible neurological injury in patients who have been electrocuted.

Prognosis

It is difficult to predict the outcome of patients admitted to the intensive care unit for electrical shock because the full extent of their injuries may not be apparent. Most patients are young and otherwise healthy so a favourable prognosis is likely. Fatal arrhythmias generally occur immediately following the electrical shock. Thus, death in patients who survive to intensive care unit admission following electrical injury is, for the most part, not a result of cardiovascular damage. Most patients surviving cardiopulmonary arrest resume spontaneous breathing within 1 hour. Ventilatory support for patients who have experienced electrical shock should be continued for a reasonable time until cerebral function can be fully assessed [1].

Prediction of neurological outcome following resuscitation from electrical shock is usually based on the presence or absence of findings compatible with anoxic encephalopathy. Recent advancements in post-resuscitation care, especially implementation of therapeutic hypothermia protocols, have significantly increased the proportion of patients who survive with preserved neurological function [20]. Furthermore, commonly accepted guidelines for outcome prediction in hypoxic–ischaemic coma, may not initially apply to patients who survive electrocution. Brainstem reflexes and motor responses may be absent because of keraunoparalysis. Therefore, in patients resuscitated following an electrical shock, prognosis should be assessed very cautiously and may only be reliable several days post-event, when the direct effects of electrical shock are no longer present [1].

The extent and depth of burn injuries affects prognosis [1]. Deeper and more extensive burns may require emergent wound exploration, debridement, and fasciotomy. Rehabilitation of burn victims is also a fundamental component of management. The rehabilitation phase begins when wound coverage is near completion (wounds may require autologous skin grafting) and represents an extension of acute-phase therapy, which includes pain management, wound coverage, positioning, and exercises. Hypertrophic scars are also a concern in patients with electrical burns. Young age, prolonged healing times, deep initial wounds, and pigmented skin are factors that increase the risk for hypertrophic scars [1].

References

1. Spies C and Trohman RG. (2006). Narrative review: electrocution and life-threatening electrical injuries. *Annals of Internal Medicine*, **145**, 531–7.
2. Lee RC, Zhang D, and Hannig J. (2000). Biophysical injury mechanisms in electrical shock trauma. *Annual Review of Biomedical Engineering*, **2**, 477–509.
3. Jain S and Bandi V. (1999). Electrical and lightning injuries. *Critical Care Clinics*, **15**, 319–31.
4. Dougherty W and Waxman K. (1996). The complexities of managing severe burns with associated trauma. *Surgical Clinics of North America*, **76**(4), 923–58.
5. Koller J. (1991). High-tension electrical-arc-induced thermal burns caused by railway overhead cables. *Burns*, **17**, 411–14.
6. Saukko P and Knight B. (2004). Electrical fatalities. In: Saukko P and Knight B (eds) *Knight's Forensic Pathology*, pp. 326–38. London: Arnold.
7. Lown B, Neuman J, Amarasingham R, and Berkovits BV. (1962). Comparison of alternating current with direct electroshock across the closed chest. *American Journal of Cardiology*, **10**, 223–33.
8. Jensen PJ, Thomsen PE, Bagger JP, Nørgaard A, and Baandrup U. (1987). Electrical injury causing ventricular arrhythmias. *British Heart Journal*, **57**, 279–83.
9. Akkaş M, Hocagil H, Ay D, Erbil B, Kunt MM, and Ozmen MM. (2012). Cardiac monitoring in patients with electrocution injury. *Ulus Travma Acil Cerrahi Derg*, **18**(4), 301–5.
10. Lichtenberg R, Dries D, Ward K, Marshall W, and Sanlon P. (1993). Cardiovascular effects of lightning strikes. *Journal of the American College of Cardiology*, **21**, 531–6.
11. Purdue GF and Hunt JL. (1986). Electrocardiographic monitoring after electrical injury: necessity or luxury. *Journal of Trauma*, **26**, 166–7.
12. Wang JG, McIntyre WF, Kong W, and Baranchuk A. (2012). Electrocution-induced Brugada phenocopy. *International Journal of Cardiology*, **160**(3), e35–7.
13. James TN, Riddick L, and Embry JH. (1990). Cardiac abnormalities demonstrated post-mortem in four cases of accidental electrocution and their potential significance relative to nonfatal electrical injuries of the heart. *American Heart Journal*, **120**, 143–57.
14. Butler ED and Gant TD. (1977). Electrical injuries, with special reference to the upper extremities. A review of 182 cases. *American Journal of Surgery*, **134**, 95–101.
15. Rouse RG and Dimick AR. (1978). The treatment of electrical injury compared to burn injury: a review of pathophysiology and comparison of patient management protocols. *Journal of Trauma*, **18**, 43–7.
16. ten Duis HJ, Klasen HJ, and Reenalda PE. (1985). Keraunoparalysis, a 'specific' lightning injury. *Burns including Thermal Injury*, **12**:54–57.
17. Cooper MA. (1980). Lightning injuries: prognostic signs for death. *Annals of Emergency Medicine*, **9**, 134–8.
18. Kondur AK, Afonso LC, Berenbom LD, and Lakkireddy DR. (2008). Implantable cardioverter defibrillators save lives from lightning-related electrocution too! *PACE*, **31**, 256–7.
19. Domart Y and Garet E. (2000). Images in clinical medicine. Lichtenberg figures due to a lightning strike. *New England Journal of Medicine*, **343**, 1536.
20. Oddo M and Rossetti AO. (2011). Predicting neurological outcome after cardiac arrest. *Current Opinion in Critical Care*, **17**, 254–9.

PART 17.3

Altitude- and depth-related disorders

CHAPTER 350

Pathophysiology and management of altitude-related disorders

Daniel S. Martin and Michael P. W. Grocott

Key points

- Acute high-altitude related illnesses include acute mountain sickness (AMS), high altitude pulmonary oedema (HAPE) and high altitude cerebral (o)edema (HACE).
- AMS is common and generally a benign self-limiting condition if managed with rest, no ascent, and symptomatic treatment. Descent is indicated in severe cases.
- HACO and HAPO are rare, but serious conditions that should be considered medical emergencies. Management involves urgent descent, supplemental oxygen (cylinder, concentrator or portable hyperbaric chamber) if available, and specific treatment with dexamethasone (HACO) or nifedipine (HAPO).
- Slow, controlled ascent (adequate acclimatization) is the best prophylaxis against the acute high-altitude related illnesses. Acetazolamide is effective prophylaxis against AMS.
- Other conditions of relevance at altitude include retinal haemorrhage, neurovascular disorders (including transient ischaemic attacks and cerebrovascular accidents), thrombosis, high altitude cough, disordered sleep, cold injury, and sunburn.

Introduction

Ascent to high altitude results in a progressive fall in the partial pressure of oxygen in air as the barometric pressure declines (fraction of inspired oxygen concentration (F_IO_2) remains constant at 0.21). This reduction in oxygen availability has a profound effect on oxygen transport within the body and triggers an adaptive response known as acclimatization. Increases in heart rate (and therefore cardiac output), minute volume, and haemoglobin concentration result in normalization of oxygen delivery, but this process can take days to weeks. The speed and success of acclimatization varies widely, as a consequence of which, some individuals develop acute high altitude-related illness [1]:

- Acute mountain sickness (AMS).
- High altitude pulmonary oedema (HAPO).
- High altitude cerebral oedema (HACO).

There is no clear definition of 'high' altitude and individual responses vary widely. The development of altitude-related illnesses is related to both the absolute elevation and the rate of ascent. Most people begin to notice changes in their physiology (e.g. increased breathlessness on exertion) above approximately 2500 m. Permanent habitation does not commonly occur above 5000 m and this may be because humans are unable to adapt to this degree of hypoxia in the long-term. Altitudes above 8000 m have been referred to as the 'death zone', particularly on Mount Everest (8848 m), and most climbers require supplementary oxygen to function effectively at such great altitudes.

Acute mountain sickness (AMS)

AMS is commonly encountered on ascent to high altitude with 50–60% of those ascending above 4000 m reporting symptoms of AMS. The symptoms are usually self-limiting, but can progress to the more serious high-altitude clinical syndromes if ignored. The symptoms of AMS include:

- Headache.
- Lack of appetite.
- Poor sleep.
- Lethargy.
- Fatigue.

The severity of AMS can range from a mild symptom disturbance to severe debilitation. AMS tends to develop 6–12 hours after arrival at a new altitude. The Lake Louise self-assessment scoring system can be used to assess the presence and progression of AMS and is based upon assigning a score of 0 (no), 1 (mild), 2 (moderate) or 3 (severe) to the symptom domains outlined in the previous list [2]. A score of three or more with the presence of a headache indicates AMS. Headache is considered universal in AMS, and if not present, other possible diagnosis should be considered.

There are a number of factors that increase the likelihood of AMS:

- Rapid ascent to altitude.
- Excessive exercise at altitude.
- Concomitant systematic illness (cold, chest infection, diarrhoea. and vomiting).

- Dehydration.
- Excessive alcohol.
- Previous AMS.

The pathophysiology of AMS is not fully understood. Whether it represents a mild form of HACO or is a discrete entity of its own is a matter of debate. A phenomenon called high-altitude headache has also been proposed, which is defined as headache with no other symptoms of AMS.

Treatment for AMS is to stop the ascent, rest, and monitor the symptoms. If the symptoms resolve over 24–48 hours, it should be safe to continue ascending slowly. If symptoms do not resolve (or worsen) over this time, the individual should descend. If descent is impossible, the administration of supplemental oxygen can be beneficial until descent is feasible. AMS can be treated pharmacologically, primarily with acetazolamide at a dose of 250 mg bd. This carbonic anhydrase inhibitor induces a diuresis with bicarbonate loss, resulting in a metabolic acidosis that is compensated for by hyperventilation, improving partial alveolar pressure of oxygen (P_AO_2) and acclimatization. The side effects of acetazolamide can be troublesome, including paraesthesia of the hands and feet, an unpleasant taste in the mouth, and the need for frequent nighttime urination. It is also a sulfonamide-containing drug, so should be avoided in those with a known sulfonamide allergy. The steroid dexamethasone (4 mg qds) is also effective, but due to the adverse effect profile of steroids, this is usually considered a second-line treatment.

High altitude cerebral oedema (HACO)

As its name suggests, HACO [3] is thought to result from cerebral oedema, which leads to elevated intracranial pressure and, if untreated, death may result from herniation of the brain stem through the foramen magnum. AMS often, but not always, precedes HACO. The prevalence of HACO is far lower than AMS and is probably in the region of 1–2% of those ascending over 4500 m. Clinically, HACO is diagnosed by the presence of any signs that may be related to the central nervous system in an individual at high altitude. Recognized signs of HACO include:

- Ataxia.
- Confusion.
- Drowsiness.
- Behavioural changes.
- Hallucinations.
- Reduced level of consciousness.
- Coma.

Any individual presenting with any of the signs of HACO (with or without a headache) at altitude should be presumed to have HACO until proved otherwise. However, it is important to differentiate the symptoms and signs of HACO from hypothermia, hypoglycaemia, and alcohol intoxication.

There are a number of candidate causal mechanisms explaining the development of HACO including:

- Vasogenic oedema formation.
- Cytotoxic oedema formation.
- Venous congestion.
- The 'tight fit hypothesis'.

Treatment of HACO should start immediately and a descent of at least 500–1000 m should be arranged urgently. Oxygen should be administrated if available or a portable altitude chamber (see Fig. 350.1) can be used if oxygen or immediate descent is not possible. Dexamethasone should be administrated at a dose of 8 mg stat, then 4 mg qds. This may be given po, but should be given parenterally if the individual is unable to swallow or has a decreased conscious level. If able to swallow, acetazolamide should also be

Fig. 350.1 A portable altitude chamber being used at high altitude to achieve 'simulated descent' by increasing the pressure within the bag and thereby increasing the partial pressure of oxygen.
Published with permission of Xtreme Everest.

administrated as per AMS. In severe cases, where the level of consciousness has declined significantly, supportive measures may be required, such as intubation and mechanical ventilation. This can be challenging in a wilderness environment unless the medical team has specifically planned for such an event.

Once evacuated it is important to rule out any other neurological diagnoses, such as a cerebrovascular event, and this is usually achieved by computed tomography (CT) scan. Some individuals continue to complain of altered neurology after descent; they should be closely monitored and followed-up appropriately to exclude alternative causes of cerebral deterioration, including cerebral ischaemia or haemorrhage.

High altitude pulmonary oedema (HAPO)

HAPO [4] is a non-cardiogenic pulmonary oedema that tends to affect people 24–48 hours after arriving at a new altitude. Its prevalence is approximately 2% of those ascending over 4000 m. HAPO tends to be preceded by AMS, but this is not always the case. Symptoms include:

- Persistent cough.
- Excessive shortness of breath (especially after exercise) in comparison with others.
- Chest pain.
- Profound fatigue.

On examination, severe hypoxaemia and widespread chest crepitations are common. Chest X-ray reveals a patchy pattern of pulmonary infiltrates. Some individuals are more susceptible to HAPO than others, and will tend to develop it each time they reach a specific altitude; they are termed 'HAPO susceptible'.

A rise in pulmonary artery pressure occurs when anyone ascends to high altitude. However, those individuals affected by HAPO tend to have a considerably higher pulmonary artery pressure than those who are unaffected. The pathogenesis of HAPO can be explained by a combination of factors:

- Blunted hypoxic ventilatory response.
- Exaggerated and heterogeneous hypoxic pulmonary vasoconstriction.
- Impaired clearance of alveolar fluid.

As with HACO, the treatment of HAPO requires immediate descent to a lower altitude. Exertion should be avoided as this may worsen hypoxaemia. If possible the patient should be carried to a lower altitude. Oxygen is of particular benefit in HAPO as it leads to a rapid reduction in pulmonary artery pressure. A portable altitude chamber can be used if oxygen is unavailable. Nifedipine is the most effective treatment for HAPO, and should be administrated orally at a dose of 10 mg tds. Recently, dexamethasone and sildenafil have also been shown to be effective in the treatment of HAPO. Sildenafil (50 mg tds) should not be administrated with nifedipine as it risks promoting systemic hypotension. Inhaled nitric oxide has also been shown to be effective in treating HAPO and may be useful in an intensive care unit, but is rarely available in the wilderness environment.

Once evacuated, the casualty should be investigated to rule out alternative pathologies, such as pneumonia or pulmonary embolism (PE). Chest X-ray and CT scan will be useful in the first instance and if PE cannot be excluded, a CT pulmonary angiogram should be considered.

Prevention of high altitude illnesses

The most effective way to avoid any of the high altitude illnesses is to ensure a slow ascent to high altitude. Recommendations suggest that individuals travelling above 3000 m should not increase the sleeping elevation by more than 500 m per day and should include a rest day (i.e. no ascent to higher sleeping elevation) every 3–4 days [5]. Metaanalysis and systematic reviews have shown that prophylactic use of acetazolamide in doses between 125 mg and 1 g per day (most commonly 125 or 250 mg bd) reduces the symptoms of AMS during ascent. Dexamethasone is also effective as a prophylactic pharmacological agent, but its use for this purpose should be discouraged due to side effects and its usefulness as a treatment in life-threatening illness. Ginko biloba, a herbal medication, has been shown in some studies to be effective in the prophylaxis of AMS, but there is also data published with conflicting outcomes.

Other pathologies related to high altitude

There are a number of other conditions that can occur at high altitude:

- **Retinal haemorrhage:** reported to occur in 0–79% of those trekking to 5000 m [6]. Usually asymptomatic, but can lead to visual field defects if they involve the macula.
- **Neurological disorders**: transient ischaemic attacks (TIAs), cerebrovascular accidents (CVAs), nerve palsies, and a variety of other neurological conditions have all been reported at high altitude, some with perhaps a greater incidence compared with at sea level.
- **Thrombosis:** the increase in haematocrit that occurs as part of acclimatization may explain the increase in thrombotic events such as deep vein thrombosis (DVT) and PE that have been reported at high altitude.
- **High altitude cough**: this could be multifactorial and related to the effect of reduced humidity at altitude on the respiratory tract mucosa.
- **Disordered sleep**: this is due to periodic breathing that occurs at night. The imbalance between oxygen and carbon dioxide levels controlling ventilation leads to periods of hyperventilation, followed by apnoea and waking.
- **Cold injury**: adiabatic cooling means the temperature falls linearly as altitude is gained. Hypothermia, freezing, and non-freezing cold injury are therefore common at high altitude, but should be preventable.
- **Sunburn**: increased ultraviolet light penetration and the reflective capacity of snow and ice means that skin is easily burnt at high altitude.

References

1. Imray C, Booth A, Wright A, and Bradwell A. (2011). Acute altitude illnesses. *British Medical Journal*, 343.
2. Roach RC, Bärtsch P, Oelz O, Hackett PH, and the Lake Louise AMS Scoring Consensus Committee. (1993). The Lake Louise acute mountain sickness scoring system. In: Sutton JR, Houston CS, Coates G (eds)

Hypoxia and molecular medicine, pp. 272–4. Burlington, VT.: Charles S. Houston.
3. Wilson MH, Newman S, and Imray CH. (2009). The cerebral effects of ascent to high altitudes. *Lancet Neurology*, **8**(2), 175–91.
4. Maggiorini M. (2006). High altitude-induced pulmonary oedema. *Cardiovascular Research*, **72**(1), 41–50.
5. Luks AM, McIntosh SE, Grissom CK, et al. (2010). Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness. *Wilderness Environmental Medicine*, **21**(2), 146–55.
6. Bosch MM, Barthelmes D, and Landau K. (2012). High altitude retinal hemorrhages—an update. *High Altitude Medical Biology*, **13**(4), 240–4.

CHAPTER 351

Pathophysiology and management of depth-related disorders

Peter Radermacher and Claus-Martin Muth

Key points

- Decompression illness comprises decompression sickness resulting from tissue inert gas super-saturation and pulmonary barotrauma due alveolar or airway over-distension.
- Since decompression illness may mimic any other emergency pathology, any emergency coinciding with decompression is 'due to' decompression.
- There are no data on pharmacological treatment, although aspirin is widely used.
- Specific treatment consists of pure O_2 breathing under supra-atmospheric pressures.
- Early treatment initiation is mandatory.

Introduction

Decompression illness (DCI) comprises medical disorders resulting from a decrease in ambient pressure (i.e. decompression). The common characteristic is tissue damage by excess gas during and after decompression. DCI often presents with severe neurological symptoms requiring both intensive care and hyperbaric oxygen therapy (HBO) [1–3]. Although there is a consensus on DCI treatment, there are no randomized control trials supporting current treatment guidelines according to evidence-based-medicine standards [3–5].

Mechanisms of decompression illness

According to Boyle's law, the volume of an enclosed gas will increase as ambient pressure decreases. When expanding intrapulmonary gas, which was inhaled under higher pressure, is not adequately exhaled during decompression, airway over-distension can cause pulmonary barotrauma. Depending on the site of tissue rupture, gas may track along the perivascular sheaths and cause mediastinal emphysema or pneumothorax. Gas may also pass into the pulmonary vasculature with subsequent arterial gas embolism into the cerebral or (rarely) the coronary circulation. According to Henry's law, body tissues saturate with N_2 (or any other inert gas used, e.g. He) at elevated ambient pressure, because of the proportional relationship between the amount of physically-dissolved gas in a liquid and the partial pressure of that gas above the liquid. During decompression, the decrease in ambient pressure may exceed the elimination rate of N_2, resulting in tissue super-saturation and, ultimately, gas bubble formation. Normally, the venous system transports these bubbles to the lungs, where they are eliminated. **Decompression sickness** (DCS) arises when gas bubbles cause mechanical tissue compression or venous embolization. Finally, paradoxical gas embolism may occur through transpulmonary passage of venous gas bubbles or via extra- or, to a lesser extent, intrapulmonary right-to-left shunts. A patent foramen ovale (PFO) is the most common pathway in divers [6].

Pathology

Gas bubbles can cause vascular obstruction or tissue compression due to an expanding volume, resulting in tissue ischaemia and oedema. Increased diffusion distances impeding gas elimination will aggravate the damage. This depends largely on the kinetics of the gas contained within the bubble, and the size and location of the embolus. Interactions between the blood–gas interface and the endothelium will result in further tissue damage, mediated by activation of complement, platelets, and neutrophils. These secondary effects trigger an inflammatory cascade, ultimately causing endothelial damage with capillary leakage, fluid loss from the intravascular space, and haemoconcentration.

Clinical manifestations and presentation

The large majority of DCI occurs during scuba diving. During a rapid ascent with large pressure changes, arterial gas embolism from pulmonary barotrauma is a frequent complication accounting for more than one-third of all recreational scuba-diving fatalities [2]. Severe DCS is most common after long, deep scuba-dives, but may occur after any decompression when there is a significant venous gas load, especially in the presence of right-to-left shunts [7]. Post-diving altitude exposure during long distance commercial flights or by driving across mountains imposes an additional DCS risk [8]. DCS presents with a large variety symptoms, ranging from skin itching and vague constitutional symptoms to shock and cardiopulmonary arrest. The central nervous nitrogen saturation and elimination kinetics and its limited ischaemia

tolerance favour the development of neurological symptoms. Sensory symptoms including numbness, tingling, paraesthesiae, and abnormal sensation are more common than severe neurological symptoms, that typically develop progressively, beginning with mild paraesthesia, followed by regional numbness, weakness and, occasionally, paresis of the affected limbs [1]. Symptoms usually occur within hours after decompression, but may also present immediately. Respiratory DCS presenting with coughing, chest pain, dyspnoea, and haemoptysis may occur when a high venous gas load overwhelms the pulmonary bubble filter, inner ear DCS presents as vertigo, tinnitus, and hearing loss [9]. In contrast to DCS, arterial gas embolism typically presents as a stroke-like syndrome with unilateral neurological symptoms, depending on the affected areas of the brain. Cognitive symptoms and unconsciousness are most frequently observed, seizures, focal motor deficits, visual disturbance, and sensory changes are also common [10]. Bubbles may, however, occlude any artery including the coronary or skeletal muscle vasculature. Spinal cord lesions with sensory or motor paraplegia are more likely to result from DCS. Arterial gas embolism and DCS can be discriminated according to the onset of symptoms, with gas embolism predominantly developing within a few minutes after or even during decompression. Nevertheless, symptoms of arterial gas embolism may be indistinguishable from DCS or even non-diving-related disorders. Finally, severe neurological DCS may be superimposed on gas embolism.

Diagnostic evaluation

The term DCI allows assigning a diagnosis without differentiating between arterial gas embolism and DCS. This is particularly helpful since outcome of severe DCI largely depends on time to treatment. Definitive therapy should not be delayed, especially as no specific tests are available [11]. History and physical examination, including neurological examination, are mandatory for the initial assessment. The temporal relation of the patient's complaints to decompression, including information on time to onset of symptoms, is crucial. Laboratory investigations are useful to evaluate haemoconcentration and dehydration, serum creatine kinase activity was reported as a marker of the severity of arterial gas embolism. A chest X-ray allows evaluating the presence of a pneumothorax, the drainage of which is mandatory prior to recompression [12].

Treatment of DCI

For ethical reasons, no controlled prospective studies in humans are available comparing treatment with '**no treatment**' [4,5]. Therefore, assessment of effective treatment for DCI must rely on empirical evidence and data from animal studies. Immediacy of treatment is crucial and comprises rapid gas elimination and the correction of hypoxia, which is best achieved by hyperbaric oxygen therapy [1,3,12]. An algorithm for treatment is shown in Fig. 351.1.

Initial treatment

Animal studies and diving accident statistics indicate that early normobaric hyperoxia with inspiratory O_2 concentrations close to 100% improves clinical outcome, because it prevents further inert gas uptake and increases the diffusion gradient of inert gas from the bubble into the tissue. Therefore, 100 % O_2 should be administered via a tightly fitting face mask, either from a demand-valve regulator or by a closed-circuit apparatus. In addition, fluid resuscitation is useful to counteract haemoconcentration and dehydration [13]—divers are prone to dehydration because of fluid loss through respiration and increased diuresis during the scuba dive resulting from the immersion-induced increase in intrathoracic blood volume. Intravascular accumulation of gas bubbles and subsequent endothelial damage with capillary leakage will aggravate dehydration. Depending on the patient's level of consciousness, mild DCI may be managed by oral fluids; otherwise, intravenous administration is recommended [10,12]. Adequate fluid resuscitation will allow continued inert gas washout from tissues due to maintenance of microvascular flow.

Patients with DCI should be kept supine, unless a head-down position is required for circulatory support. Thermal control of the patient is necessary as **hyperthermia** worsens neurological outcome, while **hypothermia** impairs tissue nitrogen elimination due to peripheral vasconstriction. Frequently, patients require transport from remote locations. Since altitude exposure precipitates a recurrence of symptoms due to additional N_2 release and bubble growth under reduced pressure, transport should take place in airplanes maintaining sea level cabin pressure. Ground or helicopter transportation at a flight level as low as considered '**safe**' by the pilot are preferable, with hyperbaric oxygen therapy given at the nearest location possible.

Definitive treatment

Recompression will reduce excess intracorporeal gas and increase the driving force for its return into solution. However, recompression per se causes only limited bubble shrinkage, especially as gas emboli do not maintain a spherical shape when trapped in vessels. Hyperbaric oxygen therapy accelerates gas elimination, both by raising the ambient pressure and creating systemic hyperoxia. Hyperbaric oxygen therapy requires patient placement in an environment pressurized at two to three times sea-level atmospheric pressure, while breathing 100% O_2. This usually results in an arterial PO_2 up to 2000 mmHg (267 kPa) and an amount of O_2 physically dissolved in the blood of approximately 60 mL/L. The improved outcome of DCI after hyperbaric oxygen treatment results from its physiological effects, i.e. an increased diffusion gradient for O_2 into the gas bubble and for N_2 out of the bubble, improved tissue O_2 delivery, hyperoxic vasoconstriction, and inhibition of $ß_2$-integrin-dependent neutrophil adherence.

There are no randomized studies in humans comparing recompression breathing air with hyperbaric oxygen therapy. In experimental animals, however, bubble shrinkage was faster during recompression breathing O_2. Clinical experience suggests that recovery from DCI is inversely related to the time to initiation of hyperbaric oxygen therapy [11]. Most improvement occurs when treatment is started within minutes, although improvement was still observed when treatment began hours later. Repetitive recompression treatments should be considered as long as there is clinical improvement, but the more hyperbaric treatments are needed to relieve symptoms, the less likely they are to be effective.

Several empirically derived hyperbaric oxygen treatment schedules are in use, which differ with respect to maximal pressure, duration, and the breathing gas mixture [14]. The most common treatment algorithm ('**U.S. Navy treatment Table 6**'; see http://www.eubs.org/documents/DHM%20vol42%20no3%20suppl%20deep%20tables.pdf) comprises cycles of 100 % O_2 breathing at

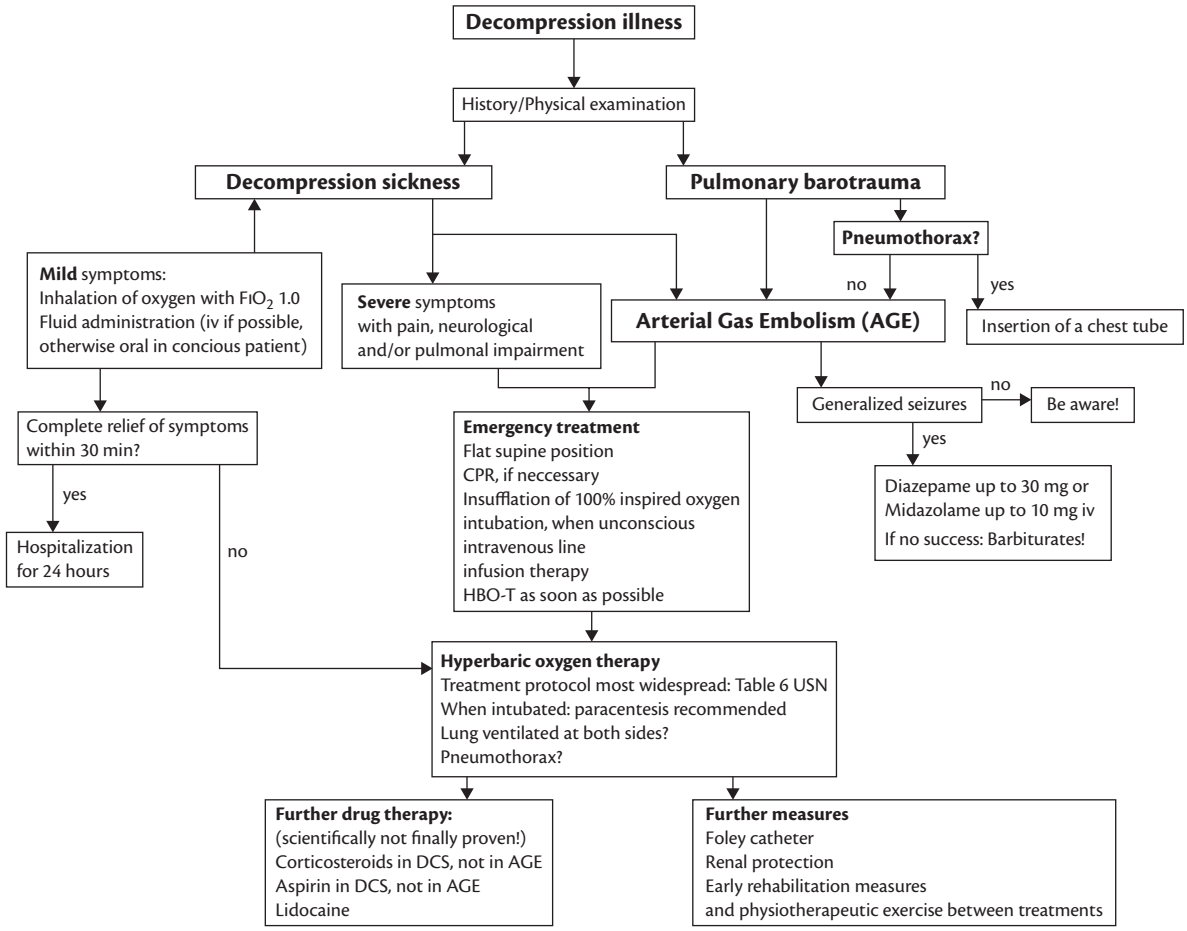


Fig. 351.1 Flow chart for management of DCI.

With kind permission from Springer Science + Business Media: *Intensive Care Medicine*, 'Evaluation and management of decompression illness-an intensivist's perspective', **29**, 2003, pp. 2128–36, Tetzlaff et al., Figure 2, copyright 2003 European Society of Intensive Care Medicine.

18 m sea water (0.28 MPa) and 9 m sea water (0.19 MPa) with a total recompression time of approximately 4 hours 45 minutes [1]. There is an ongoing discussion on the best recompression regimen, and various other treatment algorithms are discussed, e.g. recompression to 50 m seawater, while breathing O_2-enriched gas mixtures using N_2 ('nitrox') or He ('heliox') as carrier gas has been recommended for arterial gas embolism and severe cases of DCS [14]. However, no clear advantage has been shown.

Adjunctive measures

There are scarce data on the efficacy of pharmacologic interventions [4,5]. Nevertheless, **aspirin** is frequently used due to its analgesic, anti-inflammatory and anti-platelet aggregating properties [15]. **Anticoagulants** have been advocated to counteract haemoconcentration and coagulopathy. Low-dose heparin or low-molecular-weight heparin may be given in patients with leg weakness due to DCI as a prophylaxis against deep vein thrombosis [12]. **Corticosteroids** have been recommended for arterial gas embolism to counteract brain oedema. However, cerebral arterial gas embolism provokes cytotoxic brain oedema, which, in general, is unresponsive to corticosteroids. Again, no study date is available. The non-steroidal anti-inflammatory drug **tenoxicam** reduced the number of recompressions required [4], but further studies are needed. Recent ovine and porcine studies showed that intravenous **perfluorocarbon** emulsions reduced both morbidity and mortality. This approach is still highly experimental, and any recommendation must be cautioned. Finally, **lidocaine** improved neuronal recovery in feline air embolism. Mechanisms are not completely understood, but may largely be attributed to a reduction in intracranial pressure and improved cerebral blood flow. Clinical data are confined to one single trial showing cerebral protection in cardiac surgery, with bolus lidocaine administration (1.5 mg/kg) and maintaining a therapeutic concentration thereafter.

Intensive care in the hyperbaric environment

Certain issues must be considered for the management of critically-ill patients in a hyperbaric chamber. Limited access due to narrow space, noise, decreased ambient lighting and altered sound transmission impair clinical observation [12,16]. For ECG and invasive blood pressure monitoring electrical connections are necessary across the chamber wall to the outside physiological monitor [12,16]. While transcutaneous pulse oximetry is of only

limited value due to hyperoxia, transcutaneous PO_2 sensors may provide information on adequate tissue oxygenation. Intravenous lines should be placed prior to hyperbaric oxygen treatment since the hyperbaric chamber environment complicates insertions. Any untreated pneumothorax contraindicates hyperbaric exposure, since it will result in a life-threatening tension pneumothorax during decompression due to gas expansion [12,16]. Therefore, a chest tube must be inserted, and the appropriate instruments must be readily available inside the chamber. During hyperbaric therapy chest tubes should be removed from vacuum drainage and a Heimlich valve inserted [16].

Cardiopulmonary resuscitation during hyperbaric therapy imposes significant risks both for patients and medical staff, especially when cardiac defibrillation is needed: First, there is a significant risk of catastrophic fire due to the elevated PO_2 of the pressurized chamber atmosphere. Secondly, the medical staff are exposed to increased tissue N_2 uptake. It is therefore strongly recommended to avoid electric defibrillation inside the chamber and slowly decompress with the attendants breathing 100 % O_2 from 9 m sea water until reaching surface pressure [12,16].

For fluid administration by gravity, plastic containers should be used instead of glass bottles. Massive gas embolism can result during decompression and, hence, all fluid containers must be vented. The use of flow-controlled automatic infusion pumps is possible, when the device is equipped with a battery as a power supply for minimized risk of fire inside the chamber. Nevertheless, there are substantial variations in performance and accuracy of infusion pumps under hyperbaric conditions [17].

Patients should be sedated and, if indicated, intubated before therapy starts and the chamber pressurized. Total intravenous anaesthesia is the method of choice. Air has to be evacuated from the endotracheal cuff prior to hyperbaric exposure, and the cuff must be filled with an equivalent amount of liquid (e.g. distilled water) to achieve an appropriate seal [12,16]. The endotracheal tube must be tightly secured and stabilized in place with documentation of its depth and auscultation of bilateral breath sounds. Unintended tube displacement may cause bronchial obstruction and subsequent over-inflation of the unvented part of the lung with consecutive barotrauma and/or a sudden drop in blood pressure due to decreased venous return [12,16].

Intubated patients will need myringotomy or, in case of repeated hyperbaric treatments, tympanostomy, as they are unable to actively equilibrate their middle ear by the Valsalva manoeuvre. Patients with a nasal endotrachial tube can suffer from barotrauma of the sinuses during compression [16].

Ventilated patients will frequently require deep sedation or even muscle relaxation because of limited options in terms of ventilation mode. A pressure-controlled ventilatory mode is preferable when controlled ventilation is used to avoid over-estimation of tidal volume and minute ventilation (most ventilators use mass-flow measurements). A higher level of inspiratory pressure support is often needed to compensate for increased work of breathing resulting from the compression-related rise in gas density [16,18–20].

References

1 Melamed Y, Shupak A, and Bitterman H. (1992). Medical problems associated with underwater diving. *New England Journal of Medicine*, **326**, 30–5.

2 Tetzlaff K, Reuter M, Leplow B, Heller M, and Bettinghausen E. (1997). Risk factors for pulmonary barotrauma in divers. *Chest*, **112**, 654–9.

3 Vann RD, Butler FK, Mitchell SJ, and Moon RE. (2011). Decompression illness. *Lancet*, **377**(9760), 153–64.

4 Bennett MH, Lehm JP, Mitchell SJ, and Wasiak J. (2010). Recompression and adjunctive therapy for decompression illness: a systematic review of randomized controlled trials. *Anesthesia & Analgesia*, **111**, 757–62.

5 Bennett MH, Lehm JP, Mitchell SJ, and Wasiak J. (2012). Recompression and adjunctive therapy for decompression illness. *Cochrane Database of Systematic Reviews*, **5**, CD005277.

6 Gempp E, Blatteau JE, Stephant E, and Louge P. (2009). Relation between right-to-left shunts and spinal cord decompression sickness in divers. *International Journal of Sports Medicine*, **30**, 150–3.

7 Wilmshurst P and Bryson P. (2000). Relationship between the clinical features of neurological decompression illness and its causes. *Clinical Science*, **99**, 65–75.

8 Freiburger JJ, Denoble PJ, Pieper CF, Uguccioni DM, Pollock NW, and Vann RD. (2002). The relative risk of decompression sickness during and after air travel following diving. *Aviation, Space, and Environmental Medicine*, **73**, 980–4.

9 Klingmann C. (2012). Inner ear decompression sickness in compressed-air diving. *Undersea & Hyperberbaric Medicine*, **39**, 589–94.

10 Muth CM and Shank ES. (2000). Gas embolism. *New England Journal of Medicine*, **342**, 476–82.

11 Ball R. (1993). Effect of severity, time to recompression with oxygen, and re-treatment on outcome in forty-nine cases of spinal cord decompression sickness. *Undersea & Hyperbaric Medicine*, **20**, 133–45.

12 Tetzlaff K, Shank ES, and Muth CM. (2003). Evaluation and management of decompression illness—an intensivists' perspective. *Intensive Care Medicine*, **29**, 2128–36.

13 Boussuges A, Blanc P, Molenat F, Bergmann E, and Sainty JM. (1996). Haemoconcentration in neurological decompression illness. *International Journal of Sports Medicine*, **17**, 351–5.

14 Shupak A, Melamed Y, Ramon Y, Bentur Y, Abramovich A, and Kol S. (1997). Helium and oxygen treatment of severe air-diving-induced neurologic decompression sickness. *Archives of Neurology*, **54**, 305–11.

15 Bessereau J, Coulange M, Genotelle N, et al. (2008). Place de l'aspirine dans le traitement médicamenteux de l'accident de désaturation. *Thérapie*, **63**, 419–23.

16 Muth CM, Radermacher P, and Shank ES. (2002) When HBO meets the ICU—intensive care patients in the hyperbaric environment. In: Bakker DJ and Cramer FS (eds) *Hyperbaric Surgery*, pp. 111–58. Flagstaff: Best Publishing.

17 Lavon H, Shupak A, Tal D, et al. (2002). Performance of infusion pumps during hyperbaric conditions. *Anesthesiology*, **96**, 849–54.

18 Blanch PB, Desaultes DA, and Gallagher TJ. (1991). Deviations in function of mechanical ventilators during hyperbaric compression. *Respiratory Care*, **36**, 808–14.

19 Lefebvre JC, Lyazidi A, Parceiro M, et al. (2012). Bench testing of a new hyperbaric chamber ventilator at different atmospheric pressures. *Intensive Care Medicine*, **38**(8), 1400–4.

20 Stahl W, Radermacher P, and Calzia E. (2000). Functioning of ICU ventilators under hyperbaric conditions—comparison of volume- and pressure-controlled modes. *Intensive Care Medicine*, **26**, 442–8.

PART 17.4

Temperature related disorders

CHAPTER 352

Pathophysiology and management of fever

Gabriele Bassi and Roberto Fumagalli

Key points

- Temperature control and fever played a cornerstone role in mammal evolution.
- Fever is a beneficial host response to infection and may play a potential protective role during sepsis in critically-ill patients.
- High fever may be detrimental during non-septic conditions, especially in neurological patients.
- Definitive evidence on the efficacy and safety of pharmacological and mechanical antipyretic methods in critically-ill patients is lacking.
- Bedside assessment of every case is required when dealing with fever control in critically-ill patients so as to prevent the routine use of antipyretics.

Physiology of core temperature

Understanding and assessing physiological core temperature

Most of the energy intake of the human body is used to maintain a constant body core temperature of 37° C [1]. Core temperature, in humans, is strictly regulated within a few tenths of 1°C. It is interesting that almost all mammals have a similar average temperature and even poikilothermic ('cool blooded') species maintain the same core temperature by applying behavioural adaptations to environmental thermal changes [2]. These observations led to the concept that thermic homeostasis plays a pivotal role in all biochemical processes and human evolution [3].

Normal body temperature should generally be considered as 37°C [4]. However, there is almost 1°C circadian oscillation around 37°C with a nadir in the early morning and a zenith in the late afternoon. This physiological daily variation is much higher than the few tenths of a degree centigrade threshold, which as general rule, triggers compensatory mechanisms in response to environmental or clinical conditions [3].

Core body temperature is most accurately measured by an intravascular thermistor, using the pulmonary artery catheter as a gold standard. Urinary bladder catheter thermistor, oesophageal probe, rectal probe are nearly equally accurate while infrared ear thermometry is generally accepted, although not so precise. Temporal artery and axillary thermometers are, on the other hand, less reliable [4].

Regulation of core temperature: general considerations

Following a thermodynamic view, body temperature is the result of the constant thermic exchange between core and surrounding environment through conduction, radiant heating, and evaporation [1]. Since a behavioural response in critically-ill patients is not usually possible, the relative contribution of each single mechanism should be taken into account when trying to control core temperature. Similarly, knowledge of autonomic responses to thermic disturbance may help clinicians to optimize fever control or therapeutic hypothermia. The main autonomic responses against heat are perspiration and pre-capillary vasodilatation. The former enhances heat loss by evaporation, while the latter drives the opening of arteriovenous shunts leading to the dissipation of heat from the core to the environment [2]. The main autonomic responses against cold are, on the contrary, vasoconstriction and shivering. The first preserves core heat accumulation, while the second is a last resort reflex, which induces a production of heat by rapid muscle contractions. The vasoactive response is highly metabolically efficient, since it protects core temperature from environmental changes without requiring fluid loss, as in perspiration, or high oxygen consumption as in shivering. The role of the vasoactive response may be lost when dealing with major burns, where skin arteriovenous shunts may be lost.

Our thermal physiology is 'asymmetrical' [5]. Normal core temperature is closer to the upper (protein denaturation point) than the lower (freezing of water) limit of tolerance. Despite the asymmetry, thermoregulatory defence (vasodilatation and vasoconstriction) is triggered by the same inter-threshold range of ≈0.2°C [2]. This strict regulation has been traditionally described as the result of a complex integration of peripheral thermosensor signals with the central thermosensitive neurons of the pre-optic anterior hypothalamus. The hypothalamus triggers the autonomic and behavioural responses when the core temperature exceeds the actual inter-threshold range [1].

Among drugs generally used in critically-ill patients propofol linearly reduces shivering and the vasoconstriction threshold with a dose-dependent correlation while midazolam reduces the set point of 'hypothalamic thermistor' with no effects on amplitude of the inter-threshold of compensatory mechanism activation [2]. An interesting point is that muscle paralysis obviously precludes shivering, but does not reduce fever nor does it prevent vasoactive autonomic defence to core temperature changes [6]. Finally, when

dealing with deliberate cooling (e.g. therapeutic hypothermia), clinicians may consider the role played by skin warming receptors in the autonomic response. Since skin thermosensors contribute more than 20% of the effective thermoregulation, shivering may be prevented by warming hands, face or even the whole skin surface [2].

Role of fever in ICU

Physiology of fever

According to the physiological thermoregulatory mechanism, fever has been described as a 'complex, coordinated autonomic, neuroendocrine, and behavioural controlled response, orchestrated largely by the hypothalamus, which is adaptive and used by nearly all vertebrates as part of the acute-phase reaction to immune challenge' [7]. It differs from uncontrolled conditions such as heat stroke and malignant hyperthermia in that fever is a stereotypical response induced by a rapid modification of the threshold of the core hypothalamic thermistor. Infection, trauma, and tissue injury may cause the release of endogenous pyrogens (IL6, IL1, TNF-α) [8] from macrophages. It has been assumed that these pyrogens break through the blood–brain barrier via an active carrier or a leak at the hypothalamic level and induce the synthesis of prostaglandin E_2 from the organum vasculosum of the laminae terminalis [1–3,5,8]. Prostaglandin E_2 slows down the priming of warm sensitive neurons in the pre-optic nucleus resetting the thermistor threshold and triggering a heat-preserving autonomic response. The mechanism is appropriately regulated by a feedback of biochemical pathways that enhance the level of endogenous antipyretics (arginine vasopressin, glucocorticoids, α-melanocyte-stimulating hormone) preventing excessive core temperature increase and thus restoring a normal thermistor threshold [3].

The febrile response evolved hundreds of millions of years ago and has played a pivotal role in mammal evolution [3]. Fever, as far as physiological body temperature regulation is concerned, has always covered a major biological role as demonstrated by evidence that even cool-blooded animals move to a hotter environment in order to increase core body temperature after experimental bacterial inoculation. From a biochemical point of view, fever induces production of heat shock proteins leading to an important modulation of the inflammatory response during septic shock. Heat shock proteins, in fact, downregulate the activity of the pro-inflammatory nuclear transcriptor NF-κB, which has been reported to be linked to mortality in septic shock [8].

Fever and outcome

Experimental studies have shown reduced bacterial growth, stronger resistance to virus infection, and an overall association with survival within a physiological rise in body temperature [8,9].

A recent review summarizes the results of the main papers on the role of fever and temperature abnormalities in critically-ill patients. A final conclusion was not reached on the association between fever and outcome [10]. Aetiology of fever (infective versus non-infective), specific populations (neurological, trauma, and mixed) and the use of different methods to control fever (drugs versus cooling) represent confounding factors.

Neurological critically-ill patients

During brain injury, fever may increase neuronal excitotoxicity, accelerated free radical production and produce profound alterations in the blood-brain barrier [11]. An increasing body of evidence supports the negative impact of fever on morbidity and mortality during the acute phase of ischaemic brain injury, intra-cerebral haemorrhage, and cardiac arrest. ICU length of stay is prolonged in brain injury and subarachnoid haemorrhage with a linear correlation with temperature [12]. Thus, fever control in neurological critically-ill patients would be generally advised, at least in the acute phase.

High fever

Two of the larger case studies on the association between fever and mortality [13,14] in non-neurological non-selected ICU populations demonstrated that high fever (≥39.3°C and ≥39.5°C) was independently associated with increased intensive care unit mortality. Conversely, fever below 39.3°C had no impact on survival in both studies. These results were not confirmed by a recent survey on two very large, independent, multicentre, geographically distinct and representative databases [15]. A protective role on hospital mortality of high peak fever (39–39.4°C) in the first 24 hours after admission was shown. However, the advantage of fever was restricted to the subgroup of patients with infection, while higher peak temperatures were associated with an increased risk of in-hospital mortality in patients with a non-infection diagnosis. The results of the three studies are difficult to compare since neurological patients were not excluded in the last one and patients with fever related to infection were not isolated in the first two. Nevertheless, there is widespread acceptance that high peak fever, unrelated to infection, may have a different physiological role compared with rising temperature during the sepsis process.

Hypothermia

In spite of conflicting results on the role of fever in most, if not all, experimental and clinical studies, the occurrence of hypothermia is related to increased ICU and hospital mortality [8–12,14,15]. The adjusted odds ratios for in-hospital mortality increased from 1.3 to 3 and 2.8 in the infection and non-infection group, respectively, for temperature drop from 36.4°C to less than 36°C [15]. Since it has been estimated the incidence of hypothermia on ICU admission is 10% for mild hypothermia (35.0K35.9°C), 5% for moderate hypothermia (32–35.9°C) and 1% for severe hypothermia (<32°C), ICU personnel must prevent excessive heat loss and maintain strict temperature monitoring [16].

Clinical management of fever in ICU

Definition and epidemiology of fever in ICU

The American College of Critical Care Medicine and the Infectious Diseases Society of America stated body temperature of 38.3°C in immunocompetent patients admitted to ICU should warrant further investigation to determine whether infection is present [4]. This led to a wide discussion on the epidemiology of high body temperature in ICU. Frequency of fever changed from 9.3% [15] to 70% [12] according to different thresholds, case mix and sites of measurement. Infection related admissions in the same studies ranged from 10.8% [15] to 50% [12], while fever (defined as temperature ≥38.5°C) was recorded in 16.9% of patients among the infection group and 9.3% in the non-infection group [15]. Fever in ICU is quite common and, perhaps, one of the most used criteria for infection assessment in critically-ill patients. Since the prognostic value of fever may differ in infection and non-infection populations, clinicians should take into account a wide spectrum of non-infective clinical conditions, which could

be associated with a rise in body temperature. Non-infectious aetiologies of fever may include pulmonary embolism, drug and transfusion reactions, pancreatitis, endocrine disturbance, myocardial infarction, trauma, and cerebrovascular injuries.

Decision making for fever control

Kluger concluded the function of fever wouldn't have persisted for millions of years if it had not been adaptive [3]. Despite this teleological consideration, clinical studies have demonstrated a significant reduction in oxygen consumption (from a mean of 359.0 ± 65.0 to 295.1 ± 57.3 mL O_2/min) and cardiac output (from a mean of 8.4 ± 3.2 to 6.5 ± 1.8 L/min) once temperature decreased from 39.4 to 37°C [17]. Furthermore, fever control may improve comfort, reduce heart rate, pulmonary shunt, and vasoactive drug requirement. Thus, a rationale for fever suppression exists when dealing with oxygen delivery dependent conditions, were improved supply-demand balance may reduce tissue hypoxic injury. On the other hand, short-term prompt beneficial effects of fever control may give way to potential long-term adverse impact on ICU and hospital outcome, particularly in septic patients. Controversy on the need for fever suppression in the critically ill still remains open and warrants further investigation.

As in other open issues in critical care, the decision-making strategy in the context of fever management must be supported by individual case assessment. The following general rules are proposed.

Excluding septic fever

Outcome in septic shock has been widely demonstrated to be associated with few time- dependent interventions (e.g. early targeted shock resuscitation and early antibiotic therapy). In this context fever or, more generally, temperature abnormalities, should trigger appropriate, prompt, and cost effective investigations as stated in published guidelines. Fever, as a clinical sign after antibiotic therapy, may direct clinical judgment and may represent a natural host defence reaction [3].

Balancing fever control

Antipyretic therapy may be justified when the metabolic cost exceeds the potential physiological benefits. This could be the case in non-septic fever where high temperature has been associated with increased mortality [15]. Nevertheless, even patients with septic shock may benefit from fever control by external cooling [18]. Neurological and paediatric patients may require special consideration, especially if fever is particularly high. Rationale for temperature control in this population is well documented [11].

Options for antipyretic strategy

Although several drugs have proved to be effective in fever suppression, a definitive recommendation on a first line pharmacological strategy is still lacking. A recent systematic review and meta-analysis concluded there was not enough evidence to estimate the effect of pharmacological antipyresis on mortality in critically-ill patients [19]. Low-dose infusion of diclofenac proved to be more effective, haemodynamically better tolerated with a lower impact on hepatic function than bolus administration in neurosurgical patients [12]. Despite acetaminophen being widely used in more than 65% of critically-ill patients, further investigations are advocate to assess safety and association with mortality. Finally, non-pharmacological methods must be considered. Contrasting, but promising results were observed using external cooling. Henker demonstrated minimal effects in temperature control with cooling blankets in comparison with acetaminophen [20], while Schortgen concluded that external cooling was effective in fever control in septic shock, with a beneficial impact on mortality potentially due to a vasoactive sparing effect [18].

References

1. Guyton AC and Hall JE. (2000). *Textbook of Medical Physiology*. Philadelphia, PA: Saunders Company.
2. Sessel DI. (2009). Thermoregulatory defense mechanisms. *Critical Care Medicine*, **37**, S203–10.
3. Kluger MJ, Kozak W, Conn CA, Leon LR, and Soszynski D. (1998). Role of Fever in Disease. *Annals of the New York Academy of Science*, **856**, 224–33.
4. O'Grady NP, Barie PS, Bartlett JG, at al. (2008). Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. *Critical Care Medicine*, **36**, 1330–49.
5. Andrej A and Romanovsky AA. (2007). System functional architecture of the thermoregulatory thermoregulation: some concepts have changed. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **292**, R37–46.
6. Frank SM, Higgins MS, Fleisher LA, et al. (1997). Adrenergic, respiratory, and cardiovascular effects of core cooling in humans. *American Journal of Physiology*, **272**, R557–62.
7. Saper CB and Breder CD. (1994). Neurologic basis of fever. *New England Journal of Medicine*, **330**, 1880–6.
8. Ryan M and Levy M. (2003). Clinical review: fever in intensive care unit patients. *Critical Care*, **7**, 221–5.
9. Mackowiak PA. (2000). Physiological rationale for suppression of fever. *Clinical Infectious Diseases*, **31**, S185–9.
10. Moritok E and Kiyoshi M. (2012). Fever in non-neurological critically ill patients: a systematic review of observational studies. *Journal of Critical Care*, **27**(5), 428–33.
11. Greer DM, Funk SE, Reaven NL, et al. (2008). Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. *Stroke*, **39**, 3029–35.
12. Fumagalli R, Bellani G, and Perri A. (2009). Which drugs for the control of fever in critical patients. *Current Drug Targets*, **10**, 881–6.
13. Laupland KB, Shahpori R, Kirkpatrick AW, et al. (2008). Occurrence and outcome of fever in critically ill adults. *Critical Care Medicine*, **36**, 1531–5.
14. Kiekkas P, Velissaris D, Karanikolas M, et al. (2010). Peak body temperature predicts mortality in critically ill patients without cerebral damage. *Heart Lung*, **39**, 208–16.
15. Young PJ. (2012). Early peak temperature and mortality in critically ill patients with or without infection. *Intensive Care Medicine*, **38**, 437–44.
16. Laupland KB, Zahar JR, Adrie C, et al. (2012). Determinants of temperature abnormalities and influence on outcome of critical illness. *Critical Care Medicine*, **40**, 145–51.
17. Manthous CA, Hall JB, Olson O, et al. (1995). Effect of cooling on oxygen consumption in febrile critically ill patients. *American Journal of Respiratory and Critical Care Medicine*, **151**, 10–14.
18. Schortgen F, Clabault K, Katsahian S, et al. (2012). Fever control using external cooling in septic shock: a randomized controlled trial. *American Journal of Respiratory and Critical Care Medicine*, **185**(10), 1088–95.
19. Jefferies S, Weatherall M, Young P, et al. (2011). The effect of antipyretic medications on mortality in critically ill patients with infection: a systematic review and meta-analysis. *Critical Care Resuscitation*, **13**, 125–31.
20. Henker R, Rogers S, Kramer DJ, et al. (2001). Comparison of fever treatments in the critically ill: a pilot study. *American Journal Critical Care*, **10**, 276–80.

CHAPTER 353

Pathophysiology and management of hyperthermia

Abderrezak Bouchama

Key points

- Hyperthermia is a state of elevated core temperature above 40°C secondary to failure of thermoregulation.
- Hyperthermia is a cardinal feature in heatstroke, malignant hyperthermia, and neuroleptic malignant syndrome.
- High temperature induces direct cellular death and tissue damage as a function of the degree of hyperthermia and its duration.
- Rapid cooling is the primary therapeutic goal in hyperthermia, particularly when it is associated with central nervous system alteration and/or haemodynamic instability.
- Pharmacological cooling with dantrolene sodium is crucial in the treatment of malignant hyperthermia.

Introduction

Hyperthermia is a failure of thermoregulation due to excess heat gain that overwhelms the heat dissipating mechanisms [1,2]. Whereas in fever, the body core temperature seldom exceeds 40°C, the body core temperature in hyperthermia can rise rapidly above 40°C and reach a temperature as high as 47°C (1,3,4). Hyperthermia has many causes, but it is the hallmark of heatstroke, malignant hyperthermia, and neuroleptic malignant syndrome (Box 353.1) (1,3–6). Hyperthermia requires immediate cooling, because heat per se is cytotoxic, and the severity of tissue damage is related to the degree of hyperthermia and its duration [1].

Normothermia, fever and hyperthermia

In humans, the hypothalamus regulates body temperature within the narrow range of approximately 36.6°C ± 0.38°C [2]. Thermal control is achieved through communication between thermoreceptors in the skin and body core, and thermosensitive neurons in the pre-optic/anterior hypothalamus. The peripheral receptors transmit temperature information through direct neural connections or via blood to the hypothalamus, which adjusts the heat loss or gain accordingly. When a temperature increase is perceived, the hypothalamus initiates three mechanisms of temperature regulation:

- Cutaneous vasodilatation.
- Increased sweating.
- Decreased heat production.

The hypothalamic set-point remains normal and the body attempts to dissipate excessive heat. In contrast, during fever the temperature set point is raised through release of prostaglandins, largely PGE_2, into the anterior hypothalamus by circulating pyrogenic cytokines, such as TNFα and IL-1β [2]. In this case, the mechanisms for raising the body temperature are activated, including vasoconstriction and shivering, until the blood and core temperature are elevated to match the hypothalamic set point. Hyperthermia occurs when the production of heat exceeds its dissipation, or there is impairment in heat dissipating mechanisms (Box 353.1).

Pathophysiology

The clinical and metabolic alterations in hyperthermia include change in mental status, haemodynamic instability, disseminated intravascular coagulation, rhabdomyolysis, and lactic acidosis that can culminate in multiple organ system failure and, if left untreated, death [1,3,5]. These alterations result from an interplay between the pathophysiological changes initiated by the underlying condition together with those associated with hyperthermia (Box 353.1). Heat induces direct cytotoxicity, ischaemia-reperfusion injury, and an uncontrolled activation of inflammation and coagulation.

Heat cytotoxicity

Both in vitro and in vivo studies demonstrate high temperature causes direct damage to most cellular structures and their function resulting in cell death by necrosis [1,7,8]. Similarly, excessive heat induces apoptotic cell death, particularly of the lymphoid organs [7,8]. The extent of cell death and tissue damage is proportional to the degree of hyperthermia and its duration.

Ischaemia-reperfusion injury

Hyperthermia presents a major strain to the cardiovascular system [9]. When hyperthermia is sensed, cutaneous blood flow increases markedly, consuming up to 70% of the cardiac output, so that heat is transported from the core in order to be dissipated at the skin surface. This active cutaneous vasodilatation mediated by the hypothalamus results in a marked increase in cardiac output together with splanchnic vasoconstriction to maintain blood pressure. In experimental models for hyperthermia, splanchnic hypoperfusion results in ischaemia of the gastrointestinal organs followed by reperfusion injury during the sudden splanchnic vasodilatation that precedes the onset of hemodynamic collapse and hyperthermia [10].

Box 353.1 Causes of hyperthermia

Principal conditions

- Heatstroke.
- Malignant hyperthermia.
- Neuroleptic malignant syndrome.

Drugs affecting thermoregulation

- **Recreational drugs**: amphetamine, metamphetamine, cocaine, and monoamine oxidase inhibitors.
- **Anticholinergic medications**: anti-depressants, antihistamines, antipsychotics and antiparkinsonics.
- **Serotonergic medications*:** tricyclic antidepressant, monoamine oxidase inhibitors, serotonine and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors.

Diseases affecting thermoregulation

- Thyrotoxicosis.
- Phaeochromocytoma.
- Status epilepticus.
- Cerebrovascular accidents.

*Other medications with serotonergic activity used in intensive care unit include linezolid, fentanyl, meperidine, tramadol, metoclopromide, and valproate.

Activation of inflammation and coagulation

Heat activates host innate immunity and heat shock responses to protect against tissue injury and promote repair and healing [1]. There is clinical and experimental evidence to suggest excessive inflammation and coagulation activation may contribute to organ dysfunction/damage. Widespread haemorrhage and thrombosis, margination, and transmural migration of leukocytes, and endothelial cell activation and/or injury in vascular beds of most organs of the body are prominent features in human and experimental animal studies of heatstroke [7].

Principal hyperthermic conditions

Heatstroke

Heatstroke is a life-threatening illness characterized by hyperthermia associated with central nervous system abnormalities, such as stupor, confusion, or coma following exposure to a high ambient temperature (non-exertional or classic heatstroke) or strenuous physical exercise (exertional heatstroke) [1]. Although prevalent in hot climates, classic heatstroke occurs sporadically in epidemic form in temperate zones during heat waves. The heat wave that affected Europe in the summer of 2003 led to an unprecedented 70,000 excess deaths, of which one-third was attributed to heatstroke [11].

Clinical findings

Hyperthermia and neurological alteration are the hallmark of heatstroke. The rectal temperature is greater than 42°C in most cases. The neurological abnormalities include delirium and restlessness, deep coma, and seizures. Tachycardia and tachypnoea are common and are accompanied by distributive shock in a third of the cases. Cardiogenic shock-like syndrome in hyperthermia is rare. Hypoxemia without overt lung injury is common, but can progress to full blown acute respiratory distress syndrome.

Biochemical findings

A mixed respiratory alkalosis and metabolic acidosis predominate in patients with classic heatstroke. Hypophosphataemia and hyperglycaemia are the most frequent abnormalities. Creatine kinase is moderately elevated with no overt rhabdomyolysis. Exertional heatstroke is characterized by severe lactic acidosis, hyperphosphataemia, hypocalcaemia, and renal failure. Twenty-four hours after cooling of the body to normal temperature, a third of patients with hyperthermia may progress to one or more organ failures. Mortality and permanent brain damage in classic heatstroke survivors can reach up to 60 and 30%, respectively.

Malignant hyperthermia

Malignant hyperthermia is a complication encountered during anaesthesia for patients suffering from inherited autosomal dominant muscle disorders [3,4]. The incidence of malignant hyperthermia is 1:50,000 adults undergoing anaesthesia, and 1:15,000 children because of the frequency of congenital myopathies. Early diagnosis and treatment with dantrolene sodium and cooling reduce the mortality from 70% to less than 10% [3,4].

Clinical findings

An abnormally high cytosolic calcium concentration in skeletal muscle triggered by inhalational anaesthetic agents (halothane, sevoflurane, desflurane, isoflurane, and enflurane) or depolarizing muscle relaxants (succinylcholine) cause most of the cases of malignant hyperthermia in humans. This alteration in the regulation of intracellular calcium has been linked in some susceptible families to a series of mutations in the ryanodine receptor-calcium release channel gene, but not in others suggesting that malignant hyperthermia is a heterogeneous genetic disorder [4].

The clinical manifestations are seen within 30 minutes of anaesthesia in most of the cases. The earliest event is a rise in end-tidal CO_2 as a result of increased skeletal muscle metabolism. Muscle fasciculation and increased tone are detected early in the masseters and pterygoid muscles after administration of a paralysing agent. Tachycardia is another early sign, and is associated with labile blood pressure and ventricular arrhythmias. If the patient is not treated, hyperthermia, and severe lactic and respiratory acidosis occur within minutes, leading to widespread tissue damage and death.

Biochemical findings

Laboratory data include lactic and respiratory acidosis, hypoxaemia, hyperglycaemia, and overt rhabdomyolysis with hyperkalaemia and hypercalcaemia.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome is a rare and potentially fatal idiosyncratic reaction to neuroleptic and psychotropic medications, characterized by the development of hyperthermia, muscular rigidity, altered levels of consciousness and autonomic dysfunction [5]. The incidence and mortality of neuroleptic malignant syndrome are difficult to estimate because there is no universally accepted

definition. The risk is estimated to range from 0.1 to 3.2% and the mortality ranges from 10 to 30% [5].

Clinical findings

Neuroleptic malignant syndrome typically develops within 1–3 days of starting a course of neuroleptic drug treatment. Although, all types of dopamine receptor antagonists used in the treatment of psychosis have been implicated, the butyrophenone haloperidol accounts for half of the reported cases [5].The syndrome is characterized by four classical signs—hyperthermia, rigidity, autonomic instability, and altered level of consciousness. The rectal temperature is usually less than 40°C, although temperatures higher than 41°C have been reported and there is profuse sweating.

Biochemical findings

Laboratory data are not diagnostic; however, elevation of serum creatine kinase levels several hundred-fold is considered confirmatory of neuroleptic malignant syndrome. Elevation of creatine kinase is associated with myoglobinuria and may result in renal failure. Leukocytosis with left shift, and haemoconcentration, has also been recorded. Brain imaging and CSF studies are usually normal, and this helps to rule out other diagnoses, such as infection and brain structural diseases [5].

Treatment of hyperthermia

General approaches

Hyperthermia is a true medical emergency with rapid (hours) progression to multiple organ system failure and death. The primary therapeutic goal is to reduce body temperature as quickly as possible, particularly when hyperthermia is associated with central nervous system alteration and/or haemodynamic instability using cooling methods (Box 353.2). Support of airway, breathing, and circulation should be initiated concomitantly with cooling because mental status alteration with inability to protect the airway, circulatory, and respiratory failure are early complications of hyperthermia. Identification of the cause of hyperthermia is crucial since the therapeutic approach depends, in large part, on the aetiology. The second therapeutic objective is to treat the late or post-cooling complications of hyperthermia.

Cooling methods

Cooling comprises three simultaneous steps including:

- Cessation of the causative mechanism of hyperthermia, namely moving patient with heatstroke from hot environment to a cooler place and discontinuation of the offending medications (anaesthetic agents or neuroleptic drugs) that triggered malignant hyperthermia or neuroleptic malignant syndrome, respectively.
- Initiation of physical cooling.
- If indicated, the use of pharmacological treatment to accelerate cooling (Box 353.2)(1,3,5,12).

Physical cooling

Rapid dissipation of heat is accomplished by increasing the temperature gradient (conduction), water vapour pressure (evaporation), and velocity of air (convection) between the skin and the surrounding air [1]. Several external or internal techniques have been devised based on these principles (Box 353.2) [13,14].

Box 353.2 Methods of cooling

Surface cooling

Techniques based on conductive cooling*

- Ice pack applied to head, neck, and groin.
- Cold water or air circulating cooling blankets.
- Water circulating gel-coated energy transfer pads.†
- Immersion in cold water.

Techniques based on evaporative and convective cooling

- Fanning undressed patient at room temperature (20–22°C).
- Wetting of the body surface during continuous fanning.

Internal cooling

Techniques based on conductive and convective cooling

- Infusion of normal saline or ringer lactate solution at 4°C.†
- Cooling catheters using ice-cold fluids circulating in a closed circuit.†
- Extracorporeal circulation cooling system.†
- Iced gastric and peritoneal lavage.‡

Pharmacologic cooling§

- Dantrolene sodium.
- Dopamine agonists (bromocriptine and amantadine).
- Antipyretics (acetaminophen, aspirin, and non-steroidal anti-inflammatory drugs).

*Conductive cooling lower the skin temperature <30°C, triggering cutaneous vasoconstriction and shivering. Keeping skin temperature around 33°C with concomitant spray of tepid water or hot air, and/or vigorous massaging of the skin is recommended.

†New generation of cooling methods used for the induction of hypothermia post-cardiac arrest. Their efficacy has not been tested in hyperthermic conditions.

‡Cooling techniques investigated essentially in animals.

§Dantrolene is administered intravenously at a dose of 2.5 mg/kg and repeated at 5-min intervals until temperature, heart rate, and muscle rigidity are controlled or a maximum total iv dosage of 10 mg/kg is reached. Dopamine agonists are advised in neuroleptic malignant syndrome, but their efficacy has not been established by controlled trials. Antipyretics have no role in hyperthermic conditions.

Systematic reviews assessing the optimal cooling method in heatstroke identified the lack of solid evidence as most of the studies were observational case series [13,14]. Nonetheless, they suggest immersion in iced water is effective in young people suffering from exertional heatstroke. In classic heatstroke, evaporative- and conductive-based cooling techniques were found to be equivalent. There is also no evidence of a specific endpoint temperature at which to halt cooling. A rectal temperature of less than 39°C appears to be safe in terms of mortality in heatstroke, but associated long-term morbidity, particularly neurological, has not yet been established. At present, there are no data available on the optimal

cooling methods in malignant hyperthermia or neuroleptic malignant syndrome.

Pharmacological cooling

Dantrolene sodium, a hydantoin derivative, is the primary pharmaceutical agent for prevention and treatment of malignant hyperthermia. Dantrolene binds to ryanodine receptors and reduces the release of Ca^{2+} from the sarcoplasmic reticulum, thereby reversing skeletal muscle rigidity and increased metabolism [3,4]. Dantrolene is administered intravenously at a dose of 2.5 mg/kg, and repeated every 5 minutes until temperature, heart rate, and muscle rigidity are controlled or until a maximum total intravenous (iv) dosage of 10 mg/kg is reached.

No pharmacological treatment has been found to be beneficial in heatstroke, including dantrolene sodium and antipyretics [1,15]. The administration of dantrolene sodium and dopamine agonists, such as bromocriptine and amantadine, have been advocated in neuroleptic malignant syndrome to reduce muscle rigidity and to restore central dopaminergic activity, respectively, but their efficacy has not been established by controlled trials [12].

Treatment of complications

Non-specific resuscitative measures similar to those used in other critical care conditions may be needed in hyperthermia to support its late complications. These include management of liver failure, rhabdomyolysis, acute kidney injury, disseminated intravascular coagulation, and acute respiratory distress syndrome

References

1. Bouchama A and Knochel JP. (2002). Heat stroke. *New England Journal of Medicine*, **346**(25), 1978–88.
2. Mackowiak PA.(2000). Temperature regulation and the pathogenesis of fever. *Principles and Practice of Infectious Diseases*, **6**, 703–18.
3. Denborough M. (1998). Malignant hyperthermia. *Lancet*, **352**(9134), 1131–6.
4. Jurkat-Rott K, McCarthy T, and Lehmann-Horn F. (2000). Genetics and pathogenesis of malignant hyperthermia. *Muscle and Nerve*, **23**(1), 4–17.
5. Guze BH and Baxter LR, Jr. (1985). Current concepts. Neuroleptic malignant syndrome. *New England Journal of Medicine*, **313**(3), 163–6.
6. McAllen KJ and Schwartz DR. (2010). Adverse drug reactions resulting in hyperthermia in the intensive care unit. *Critical Care Medicine*, **38**(6 Suppl.), S244–52.
7. Roberts GT, Ghebeh H, Chishti MA, Al-Mohanna F, El-Sayed R, and Bouchama A. (2008). Microvascular injury, thrombosis, inflammation, and apoptosis in the pathogenesis of heatstroke: a study in baboon model. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **28**(6), 1130–6.
8. Sakaguchi Y, Stephens LC, Makino M, et al. (1995). Apoptosis in tumors and normal tissues induced by whole body hyperthermia in rats. *Cancer Research*, **55**(22), 5459–64.
9. Rowell LB. (1983). Cardiovascular aspects of human thermoregulation. *Circulation Research*, **52**(4), 367–79.
10. Hall DM, Buettner GR, Oberley LW, Xu L, Matthes RD, and Gisolfi CV. (2001). Mechanisms of circulatory and intestinal barrier dysfunction during whole body hyperthermia. *American Journal of Physiology: Heart and Circulatory Physiology*, **280**(2), H509–21.
11. Robine JM, Cheung SL, Le Roy S, et al. (2008). Death toll exceeded 70,000 in Europe during the summer of 2003. *Comptes Rendus Biologies*, **331**(2), 171–8.
12. Rosenberg MR and Green M. (1989). Neuroleptic malignant syndrome. Review of response to therapy. *Archives of Internal Medicine*, **149**(9), 1927–31.
13. Bouchama A, Dehbi M, and Chaves-Carballo E. (2007). Cooling and hemodynamic management in heatstroke: practical recommendations. *Critical Care*, **11**(3), R54.
14. Smith JE. (2005). Cooling methods used in the treatment of exertional heat illness. *British Journal of Sports Medicine*, **39**(8), 503–7; discussion 7.
15. Bouchama A, Cafege A, Devol EB, Labdi O, el-Assil K, and Seraj M. (1991). Ineffectiveness of dantrolene sodium in the treatment of heatstroke. *Critical Care Medicine*, **19**(2), 176–80.

CHAPTER 354

Pathophysiology and management of hypothermia

Colin Ferguson

Key points

- Accidental hypothermia is uncommon, but may present in any age group in any season of the year.
- Profound hypothermia results in circulatory arrest.
- The threshold for ventricular fibrillation is lowered at about 30°C.
- Treatment relies on maintaining a circulation and rewarming by any means available.
- A local preplanned multidisciplinary protocol is key to good outcomes.

Introduction

Accidental hypothermia is defined as a core temperature of <35°C. It is an uncommon condition presenting with varying severity, either alone or secondary to some other illness. Although precise figures for incidence and outcome are not available, the approximate incidence quoted is 0.3/100,000 per year in the USA and 0.13/100,000 in France. As a result of the low incidence, evidence-based treatment protocols and pathways based on cohorts of patients do not exist. Since the severely cold patient may be in cardiac arrest, areflexic, and in coma, decision making regarding treatment, its initiation and continuation, may be difficult. An agreed local protocol to inform local practice when encountering these rare patients is essential.

Traditionally hypothermia is classified into mild (33–35°C), moderate (28–33°C) and severe (<28°C), but these are not distinct clinical syndromes. A more recent classification into stages I–IV based on level of consciousness, shivering and vital signs has emerged from alpine medicine [1] and a treatment algorithm based on it has been published recently [2].

Pathophysiology of hypothermia

Physiological changes in the various systems are shown in Table 354.1. In the central nervous system, cooling initially affects higher functions and may lead the patient to not take action to prevent continuing heat loss. Behaviour becomes more bizarre as temperature falls, pupils dilate, and reflexes are depressed until, in severe hypothermia, the patient is in coma with absent eye and peripheral reflexes. In the circulation initial tachycardia and hypertension ('cold stress') are replaced, as the patient cools, with gradually worsening hypotension and bradycardia, prolongation of the cardiac cycle, atrial and re-entry arrhythmias, and eventually, ventricular fibrillation and asystole. The threshold for ventricular fibrillation is reduced at about 30°C, which is an important temperature to note since resuscitation of the pulseless patient requiring CPR is self-evidently more hazardous. The 'J' or Osborn wave, a characteristic ST segment deformation on the ECG, occurs at 32–33°C, but is not pathognomic and occurs in other conditions, such as subarachnoid haemorrhage and hypercalcaemia. In the respiratory system there is initial tachypnoea progressing, as the patient cools, to hypoventilation and apnoea with pulmonary oedema. Importantly, airway reflexes are depressed during moderate hypothermia exposing the patient to the risks of aspiration and its consequences; securing the airway should be considered early in treatment. In the kidneys there is initial cold diuresis owing to reduced tubular resorption, and later oliguria and anuria.

Box 354.1 shows a range of other pathophysiogical changes, many due to reduced enzyme action, in hypothermic patients. Coagulopathy is prominent and platelet function is depressed, but conventional tests of clotting are not helpful since they are carried out at normothermia in the laboratory. All membrane pumps slow such that the barriers between body compartments become porous with consequences for fluid management. Changes in protein binding, liver metabolism, and excretion make drug effects unpredictable. Loss of fluid from the circulation increases blood viscosity and metabolic acidosis develops with a shift in the oxygen dissociation curve. A raised serum amylase is common and may accompany frank pancreatitis presenting during treatment of the hypothermia. Wischnewsky ulcers (multiple haemorrhagic lesions) are seen in the gastric mucosa.

Clinical features and causes

The clinical presentation of hypothermia may be primary, where the cold injury is the major pathology, or secondary, where patients develop hypothermia incidental to another illness (Box 354.2). This is particularly important in trauma patients. A study from an Australian Major Trauma Centre showed hypothermia increased the risk of death threefold in these patients [3] and Gentilello [4] showed that aggressive warming using a femoral arteriovenous shunt in trauma patients with a mean Injury Severity Score of 37 and temperature of 33.2°C reduced mortality and length of hospital stay. Of more general interest, fluid requirements in the warmed group were almost halved in the first 24 hours, from 15 to 8 L.

Table 354.1 Physical signs in hypothermia

	Central nervous	Cardiovascular	Respiratory
Mild (33–35°C)	◆ Apathy ◆ Dysarthria ◆ Ataxia ◆ Impaired judgement ◆ Amnesia (34°C)	◆ Tachycardia + hypertension ◆ Bradycardia + hypotension ◆ Prolonged cardiac cycle ◆ Prolonged QT interval	Tachypnoea
Moderate (28–33°C)	◆ Reduced consciousness ◆ Bizarre behaviour ◆ Hallucinations ◆ Dilated pupils ◆ Hyporeflexia	◆ Atrial arrhythmias ◆ J wave (32–33°C) ◆ VF threshold reduced <30°C	◆ Hypoventilation ◆ Loss of airway reflexes
Severe (<28°C)	◆ Coma ◆ Absent eye reflexes ◆ Peripheral areflexia	◆ Re-entry arrhythmias ◆ VF ◆ Asystole	◆ Congestion ◆ Oedema ◆ Apnoea

Box 354.1 Other changes

- Coagulopathy.
- Reduced platelet function.
- Reduced liver metabolism.
- Reduced Na/K pumps.
- Hyperglycaemia.
- Increased viscosity.
- Acidosis.
- Left shift dissociation carve.
- Hyperamylasaemia.
- Pancreatitis.
- Wischnewsky ulcers.

Box 354.2 Clinical setting, primary or secondary

- **Recreational**: especially hills or water.
- Trauma.
- Drugs, alcohol, self-poisoning.
- **Urban**: old, poor.
- Cerebrovascular accidents.
- Spinal cord transection.
- Hypothalamic disease.

The adage that the patient is 'not dead until they are warm and dead' has emerged from reports of patients with profound hypothermia, in cardiac arrest and areflexic in deep coma, making uncomplicated recoveries after resuscitation and rewarming. It is certainly not possible to prognosticate on the basis of temperature alone and consideration of such cases is informative. Gilbert [5] reported the case of a 29-year-old woman whose lowest temperature was recorded as 13.7°C. She fell while skiing in Norway and was rescued by air by a team that were able to provide advanced life support from physicians from the moment of rescue. She received CPR for three-and-a-half hours, was rewarmed on cardiopulmonary bypass (CPB) and spent some weeks in the ICU, including a period of ECMO, but at the time of the publication was returning to work as a physician. Stoneham [6] reported a 30-year-old man rescued by road ambulance without a specialist crew. His lowest recorded temperature was 23.0°C and he received CPR for four-and-a-half hours. He was rewarmed with warmed gases, warmed fluids, and a heating blanket, and left the hospital 5 days after admission, apparently unharmed. The lowest recorded temperature is 9°C [7], in a patient in whom hypothermia was induced as an adjunct to the treatment of ovarian cancer. The patient was anaesthetized and cooled to the point of asystole, then rewarmed. She was unharmed by the treatment and survived a few weeks before dying from effects of malignant ureteral obstruction

Other prognostic indicators have been suggested, such as hyperkalaemia, but none have been established as generally applicable. Faced with the hypothermic patient in cardiac arrest, the reasonable response is to initiate resuscitation, exclude lethal injury and rewarm. Although some methods of rewarming (e.g. CPB and ECMO) are not generally available, the cases previously mentioned illustrate that, if perfusion is maintained and heat supplied to the patient, a successful outcome is possible with a variety of methods. Many patients will be hypothermic without serious circulatory compromise, especially in secondary hypothermia.

Rewarming methods

Rewarming methods (Box 354.3) are classified as passive or active and the latter subdivided into external, core, and extracorporeal. Rates of warming in degrees per hour for different methods are not helpful since the rate of rewarming has not been shown to affect outcome. The aim of treatment is a live patient not a rate of temperature change. Passive external warming consists of placing the patient in a warm environment with blankets and a hat, and is suitable for the

Box 354.3 Rewarming methods

- Passive external.
- Active external.
- Forced air.
- Warm water.
- Core infusions.
- Humidification.
- Cavity lavage.
- Extra corporeal.
- Haemofiltration.
- CPB.
- ECMO.

mildest cases. Active warming should be considered for patients with a temperature of 32°C or less, in that it transfers heat more rapidly; patients in this temperature range may be approaching the VF threshold, especially if they continue to cool. Resuscitation without a stable circulation is much more difficult. Active external warming is most easily achieved with forced air blankets. They are generally available in many designs and have been shown to be effective. Commercial devices designed for therapeutic hypothermia may have a warming function (e.g. Arctic Sun™). Immersion in warm water is simple for small children and has been used successfully in adults. Active core warming may be achieved by the use of warmed infusion fluids, although this will not provide a great deal of heat, and by lavage of various body cavities. Gastric, colonic, mediastinal, pleural, bladder, and peritoneal lavage have all been used, and the choice depends on local familiarity. Peritoneal lavage has the advantage of warming the liver directly and also the heart through the diaphragm. Humidified gas in ventilated patients may also be used with temperatures of up to 60°C described, although not all humidifiers have this facility. Extracorporeal methods include continuous veno-venous haemodiafiltration, cardioplumonary bypass and extracorporeal membrane oxygenation. While continuous veno-venous haemodiafiltration is commonly available and has been used successfully, CPB is the technique with the most experience, having been in use since the late 1960s. Reported mortality varies from 22 to 75%, but survivors have a good neurological outcome [8]. There may be problems with access via the femoral route and bleeding if heparinization is needed, although heparin-bonded circuits may circumvent this. Extracorporeal membrane oxygenation (ECMO) has entered the field in the last few years. It has the advantage of being portable and better outcomes have been reported after its use [9]. Although reported experience is limited, as familiarity with the technique increases its place will be established and, in specialist hands, it offers the possibility of definitive treatment from the moment of rescue.

Most hospitals lack the ability to perform ECMO and CPB so the establishment of referral networks and liaison with rescue services within regions, similar to trauma networks, is needed to ensure optimal availability of these extracorporeal techniques to appropriate patients. All hospitals need a local pre-planned multidisciplinary protocol to use what facilities they have to treat patients with hypothermia and consider transfer possibilities. Even where CPB is available prior consensus is required in patient selection and the process to be followed. An evidence base may be developed by the use of a registry between hospitals, either nationally or internationally.

Assessment and resuscitation

Assessment of the hypothermic patient includes evaluation of haemodynamic stability and other injuries to exclude lethal injuries, in particular in the patient in cardiac arrest. Resuscitation and rewarming should then commence according to the local protocol that has been devised to optimize the facilities and teams available in the hospital. Since the ventricular fibrillation threshold is reduced at about 30°C and cardiac arrest will complicate management and worsen outcome, it would seem sensible to get the patient warmer than this as soon as possible. Passive external warming may be adequate above 32°C, but at this temperature, active warming should be used. Below 30°C internal warming should be considered, the aim being to rewarm the patient as quickly as possible without complications.

Resuscitation consists of oxygenation and intubation and ventilation if needed. There is no evidence that malignant arrhythmia is a risk in the well-oxygenated patient during intubation. Chest compressions should be carried out in the usual manner bearing in mind that, in the profoundly hypothermic patient, these may be needed for hours such that a team of staff or a mechanical device may be needed. The guidelines for management of fibrillation in hypothermia differ between the American Heart Association and the European Resuscitation Council [10,11]. A compromise position would be up to three doses of vasopressor and defibrillation while the core temperature remains below 30°C and subsequent doses guided by clinical response. Fluids will be required during resuscitation and may be needed in large volumes because of losses and inter-compartmental shifts. All fluids should be warmed to 38–42°C. The situation during rewarming will be unstable and require close monitoring of vital signs, electrolytes, glucose, and blood gases. Vasopressors may be needed if there is hypotension due to vasodilatation. However, they bring with them the potential for arrhythmia and peripheral vasoconstriction. Acid–base management should be by the alpha-stat method in adults, aiming to keep pH normal without temperature compensation on the blood gas measurements [12]. Other problems occurring during rewarming include coagulopathy and hypophosphataemia. Drug doses should be small and titrated to effect. Drug handling is changing moment by moment as the patient warms, and drugs given early in resuscitation may act later in unexpected ways. With this in mind, intramuscular drugs should be avoided. Complications are to be expected, such as lung injury, renal injury, and consequences of coagulopathy. Patients will require at the least a period of close observation in the intensive care unit, if not some period of organ support. There is no consensus nor good evidence as to whether a period of therapeutic hypothermia (between 32 and 34°C for some hours) is beneficial in patients being rewarmed from profound hypothermia with cardiac arrest.

References

1. Durrer B, Brugger H, and Syme D. (2003). The medical on-site treatment of hypothermia: ICAR-MEDCOM recommendation. *High Altitude Medicine & Biology*, **4**, 99–103.
2. Brown J, Brugger H, Boyd J, and Paal P. (2012). Accidental hypothermia. *New England Journal of Medicine*, **367**, 1930–8.

3. Ireland S, Endacott R, Cameron P, Fitzgerald M, and Eldho P. (2011). The incidence and significance of accidental hypothermia in major trauma—a prospective observational study. *Resuscitation*, **82**, 300–6.
4. Gentilello L, Cobean R, Offner P, Soderberg R, and Jurkovich G. (1992). Continuous arteriovenous rewarming: rapid reversal of hypothermia in critically ill patients. *Journal of Trauma*, **32**(3), 316–27.
5. Gilbert M, Busund R, Skagseth A, Nilsen PÅ, and Solbø JP. (2000). Resuscitation from accidental hypothermia of 13.7 degrees C with circulatory arrest. *Lancet*, **355**, 375–6.
6. Stoneham M and Squires S. (1992). Prolonged resuscitation in acute deep hypothermia. *Anaesthesia*, **47**, 784–8.
7. Niazi SA and Lewis FJ. (1958). Profound hypothermia in man: report of a case. *Annals of Surgery*, **147**, 264–6.
8. Walpoth BH, Walpoth-Aslan BN, Mattle HP, et al. (1997). Outcome of survivors of accidental deep hypothermia and circulatory arrest treated with extra corporeal blood warming. *New England Journal of Medicine*, **337**, 1500–5.
9. Morita S, Inokuchi S, Yamagiwa T, et al. (2011). Efficacy of portable and percutaneous cardiopulmonary bypass versus that of conventional internal warming for patients with accidental deep hypothermia. *Critical Care Medicine*, **39**, 1064–8.
10. Soar J, Perkins GD, Abbas G, et al. (2010). European Resuscitation Council Guidelines for Resuscitation 2010 Section 8: cardiac arrest in special circumstances: electrolyte abnormalities, poisoning, drowning, accidental hypothermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. *Resuscitation*, **81**, 1400–33.
11. Vanden Hoek TL, Morrison LJ, Shuster M, et al. (2010). Part 12: cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*, **122**(Suppl.), 829–61.
12. Aziz KAA and Meduoye A. (2010). Is pH-stat or alpha-stat the best technique to follow in patients undergoing deep hypothermic circulatory arrest? *Interactive Cardiovascular and Thoracic Surgery*, **10**, 271–82.

PART 17.5

Rhabdomyolysis

CHAPTER 355

Pathophysiology and management of rhabdomyolysis

Josep M. Grau and Esteban Poch

Key points

- Rhabdomyolysis must be understood as an acute clinicobiological syndrome, with many traumatic and non-traumatic causes.
- Isolated raised creatine kinase values (even to thousands) does not imply a rhabdomyolysis syndrome.
- Acute kidney injury can occur in up to 50% of patients with rhabdomyolysis and can be life threatening.
- The mainstays of therapy of rhabdomyolysis is aggressive volume repletion in order to avoid hypovolaemic shock and acute kidney injury, and control of plasma potassium.
- Acute compartment syndrome must be suspected in particular in traumatic rhabdomyolysis, with closely monitoring of compartment pressure.

Introduction

Rhabdomyolysis is a potentially life-threatening syndrome characterized by the breakdown of skeletal muscle due to physical, biological, or toxic injury resulting in release of intracellular content into the circulatory system. It is associated with myalgia, muscle tenderness, swelling, and/or stiffness accompanied by weakness and raised levels creatine kinase (CK), myoglobin, phosphate, and potassium, sometimes with acute kidney injury (AKI) [1,2].

In non-traumatic muscle injury, isolated elevation of CK, even to 5–10 times normal, does not necessarily imply rhabdomyolysis. Most of the muscular dystrophies and some cases of myositis may present with extremely high CK, but never representing rhabdomyolysis. Rhabdomyolysis must be always understood as an acute syndrome, while muscular dystrophies, myositis, and connective-tissue disorders are chronic disorders.

Causes

The causes of rhabdomyolysis are summarized in Box 355.1. With respect to the category of drugs and toxins, hypolipaemiant-related rhabdomyolysis merits a comment, since such drugs are commonly prescribed. Any statin, in particular, when associated with other hypolipaemiant drugs such as fibrates can be responsible for severe rhabdomyolysis, especially in old people with chronic kidney disease [3]. Such a syndrome must be clearly differentiated from the necrotizing autoimmune statin-mediated myopathy, actually understood as a myositis variant [4].

Trauma-related rhabdomyolysis may occur after significant blunt trauma (physical assault) or crush injury (disasters such as bombings, earthquakes, building collapse, and train accidents), high-voltage electrical injury (electrocution), and extensive third-degree burns [5,6]. Rhabdomyolysis is actually noted to occur only after the acute compression of the muscle is relieved releasing the necrotic muscle components into the circulation [1].

Most reported infectious causes of rhabdomyolysis, besides the two mechanisms referred to in Box 355.1, represent isolated raised CK levels without the complete rhabdomyolysis syndrome.

Pathophysiology and clinical features

The pathogenesis of rhabdomyolysis involves direct sarcolemmal injury (e.g. trauma) and/or adenosine triphosphate (ATP) depletion within the myocyte with an increase in intracellular calcium and myocyte toxicity [1]. Sarcolemmal calcium is strictly regulated by a series of pumps, channels, and exchangers that maintain low levels of calcium when the muscle is at rest and allow its' necessary increase for actin-myosin binding and muscle contraction (Fig. 355.1). ATP depletion impairs the function of these pumps, resulting in a persistent increase in sarcolemmal calcium that leads to persistent contraction and energy depletion, and the activation of calcium-dependent neutral proteases and phospholipases, with eventual destruction of myofibrillar, cytoskeletal, and membrane proteins followed by lysosomal digestion of fibre contents and, ultimately, breakdown of the myofibrillar network resulting in disintegration of the myocyte. In addition, mitochondrial function is affected. In traumatic rhabdomyolysis, additional injury is produced by ischaemia-reperfusion and inflammation by neutrophils that infiltrate damaged muscle [1].

The damaged muscle is able to absorb and sequester huge amounts of extracellular fluid through the leaky sarcolemma. Because muscle represents 40% of body weight, sequestration of extracellular fluid leading to hypovolemic shock can occur without extensive muscle damage [7]. Besides this, sequestration of extracellular fluid and Na^+ produces muscle oedema, which can lead to a compartment syndrome in muscles contained within a fibrous, non-distensible fascia. Sequestration of circulating calcium typically produces hypocalcaemia in the early phases of the clinical picture, which can be symptomatic.

Box 355.1 Frequent causes of rhabdomyolysis (multiple causes may co-exist)

Drugs and toxins

- Alcohol, cocaine, heroin, amphetamines, antiretrovirals, hypolypemiant agents.
- Spider venom, snake bite, massive bee venom.

Trauma and related injuries

Crush injuries and disasters, burn injuries, electrical injuries.

Excessive muscular activity

Marathon, body-builders, status epilepticus, military recruits.

Temperature extremes

Neuroleptic malignant syndrome, malignant hyperthermia syndrome.

Muscle ischaemia

- Localized (tourniquets, thrombosis, embolism, compartment syndrome).
- Generalized (hypotension and shock).

Infection

- Secondary to sepsis (hypoxia, dehydration).
- Direct bacterial or fungal invasion.

Electrolyte and endocrine abnormalities

- Hyponatraemia, hypokalaemia, hypophosphataemia.
- Hypothyroidism.

Genetic Disorders

Mostly recurrent rhabdomyolysis starting during childhood:

- Deficiencies in glycogenolytic enzymes (McArdle's disease).
- Abnormal lipid metabolism (CPT II deficiency).
- Mitochondrial primary diseases.

Unknown

Sometimes recurrent.

Adapted from *New England Journal of Medicine*, Bosch X et al., 'Rhabdomyolysis and acute kidney injury', **361**(1), pp. 62–72. Copyright © 2009 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Conversely, due to the damage of the sarcolemma, intramuscular components leak to the circulation. Potassium efflux from cells can produce life-threatening hyperkalaemia (muscle contains 75% of the total body potassium), and myoglobin release, which is oxidized and has nephrotoxic properties. In addition, purines are released forming uric acid that can contribute to kidney damage. Phosphate is also released to the circulation, producing hyperphosphataemia, especially if renal function is affected.

Hypovolaemic shock is often aggravated by the systemic effects of muscle injury with inflammation, release of nitric oxide and other vasodilators, and the cardiotoxic and vasodilatory effects of hypocalcaemia, acidosis, and hyperkalaemia [7].

AKI is the most serious complication of rhabdomyolysis in up to 50% of patients [1]. The pathogenesis implies renal vasoconstriction associated with hypovolaemic shock, and activation of sympathetic nervous system antidiuretic hormone and the renin angiotensin system, all of which favour renal salt and water conservation. In addition, myoglobin-induced oxidative injury increases vasoconstrictors and decreases vasodilators. Kidney injury results from a combination of ischaemia due to renal vasoconstriction, direct tubular toxicity mediated by myoglobin-associated oxidative injury, which is enhanced in acidic urine, tubular damage due to ischaemia, and distal tubule obstruction due to precipitation of the complex myoglobin–Tamm–Horsfall protein in addition to sloughed tubular cells forming casts. Clinically, myoglobinuria-associated AKI is manifest by features of ischaemic-toxic acute tubular necrosis, with oliguria or anuria. Characteristically, patients display red-brownish urine, with a positive dipstick test for blood (representing myoglobinuria) and normal sediment (absence of or few red cells). The presence of AKI increases the risk of clinically significant hyperkalaemia and other accompanying electrolyte disorders, typically with unusually high levels of plasma creatinine, uric acid, and phosphate. The risk of AKI not only depends on the level of plasma CK (usually higher than 20,000 IU/L), but also on the severity of the accompanying shock, acidosis and infection, since chronic elevation of CK in patients with myopathies is not usually associated with kidney damage.

Management

Medical

The main goal of therapy is the early restoration of intravascular volume to avoid the development of AKI [8,9]. Box 355.2 summarizes recommendations for the management of patients with rhabdomyolysis. Patients often require very high volumes of fluid, about 10–20 L/day. Delay in receiving supportive therapy is associated with higher incidence of AKI and mortality [8,10]. With respect to the volume to be administered, it is very important to take into account the context in which rhabdomyolysis takes place. In a disaster-associated crush syndrome, affected individuals are often young and previously healthy and can tolerate very high volumes of fluid which can be life-saving [11]. On the contrary, in rhabdomyolysis, either toxic or traumatic, occurring in the hospital setting, especially if subjects are elderly, the amount of fluid to be administered must be programmed and monitored with caution.

Administration of normal or half-normal saline seems universal, but the use of bicarbonate is not supported by scientific evidence. There are empirical advantages of alkalinization, based on animal studies. It is known that precipitation of myoglobin with Tamm–Horsfall protein in the renal tubule is favoured by acidic urine. Alkalinization also inhibits redox cycling of myoglobin and lipid peroxidation, ameliorating tubule injury, and it has been shown that met-myoglobin only induces vasoconstriction in an acidic medium in the isolated perfused kidney. The principal, and probably only, disadvantage of alkalinization is the reduction in ionized calcium, which can exacerbate the symptoms of the initial hypocalcaemic phase of rhabdomyolysis. However, the clinical benefits of alkalinization over simple volume repletion are not firmly established. In the largest series of trauma patients

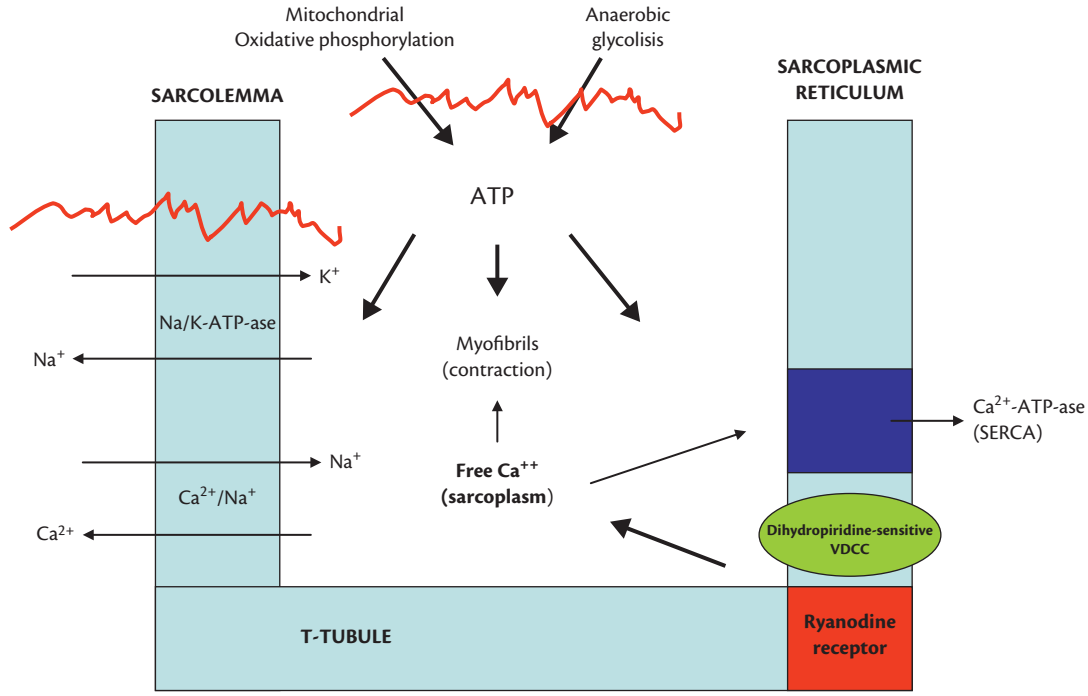


Fig. 355.1 Pathogenesis of rhabdomyolysis. Low sarcolemmal calcium is maintained by the action of the membrane Na–Ca exchanger, which allows the exit of calcium in exchange for sodium. The driving force for this exchange is the sodium concentration gradient maintained by the action of sarcolemmal Na,K-ATPase. In addition, the sarco(endoplasmic) reticulum calcium pump (SERCA) actively sequesters calcium in the sarcoplasmic reticulum and keeps sarcolemmal calcium low. The pathways leading to a rapid increase in sarcolemmal calcium necessary for contraction are the ryanodine receptor and the dihydropyridine-sensitive voltage-dependent Ca^{2+} channel. ATP depletion (red stripe), that impairs the function of these pumps, or physical damage to the sarcolemma (red stripe), both resulting a persistent increase in sarcolemmal calcium that leads to persistent contraction and energy depletion and the activation of calcium-dependent neutral proteases and phospholipases, with eventual destruction of myofibrillar, cytoskeletal, and membrane proteins.

SERCA, sarcoplasmic (endoplasmic) reticulum calcium pump; VDCC, voltage dependent Ca^{2+} channel.

[12], rhabdomyolysis developed in 85% of cases and administration of bicarbonate plus mannitol did not prevent renal failure, dialysis, or mortality, although the results suggested that it may be beneficial in patients with peak CK values >30,000 IU/L. In the only published randomized prospective trial comparing Ringer's lactate to normal saline [13], sodium bicarbonate was added in both groups if urine pH was <6.5 after 12 hours of volume repletion, and no benefits were observed.

Massive infusion of normal saline can contribute to metabolic acidosis via hyperchloraemia. Therefore, administration of both normal saline and sodium bicarbonate seems reasonable in those with metabolic acidosis. If bicarbonate is used, urine pH, serum bicarbonate, sodium, calcium, and potassium should be monitored, and if the urine pH does not rise after 4–6 hours of alkali perfusion or symptomatic hypocalcaemia develops, alkalinization should be discontinued and hydration continued with normal saline alternating with 5% glucose [1,8].

The use of diuretics is still controversial, but if used, they should be restricted to volume-replete patients. Mannitol may have several beneficial effects [14]. First, as an osmotic diuretic it increases urinary flow and the flushing of nephrotoxic agents through the renal tubules. Secondly, as an osmotic agent it creates a gradient that extracts fluid accumulated in injured muscles, improves hypovolaemia, and may prevent compartmental syndrome. Thirdly, it is a free radical scavenger. Most data on the benefits of mannitol have been obtained from animal studies that show the protective effect of mannitol may be attributable to its osmotic diuretic action rather than other mechanisms. No randomized, controlled trial has confirmed its benefit. In addition, high accumulated doses of mannitol (>200 g/day or accumulated doses >800 g) have been associated with AKI due to renal vasoconstriction and tubular toxicity, known as osmotic nephrosis. If mannitol is to be used, plasma osmolality and the osmolal gap (that is, the difference between measured and calculated serum osmolality) should be monitored frequently and therapy discontinued if adequate diuresis is not achieved or the osmolal gap rises above 55 mOsm/kg. Mannitol should not be given to anuric patients, or patients with renal failure with extracellular volume overload, particularly if they are elderly [1]. Loop diuretics also increase urinary flow and may decrease the risk of myoglobin precipitation, but no study has shown a particular benefit.

Electrolyte abnormalities must be treated promptly, especially correction of hyperkalaemia, which occurs very early in the course of the disease. Rapidly rising potassium levels (>1 mmol/L/day), even within the normal ranges can herald dangerous hyperkalaemia. Measures that cause a shift of potassium from the extracellular to the intracellular space (hypertonic glucose-insulin and bicarbonate) are only temporarily effective. The only means of removing potassium from the body are diuresis, intestinal potassium binders, or dialysis. In contrast, early hypocalcaemia should not be treated unless symptomatic or severe hyperkalaemia is also present. Calcium-containing phosphate binders should be used with caution to treat hyperphosphataemia, since the calcium load

Box 355.2. Steps in the medical management of rhabdomyolysis

- Check for extracellular volume status, central venous pressure, and urine output.*
- Measure blood chemistry (creatine kinase, creatinine, Na^+, K^+, Ca^{2+}, P, uric acid, albumin), and blood cell count.
- Perform a urine dipstick test and examine the urine sediment. Measure urine electrolytes and creatinine.
- Initiate volume repletion with normal saline promptly at a rate of approximately 400 mL/h (200–1000 mL/h depending on the setting and severity), with monitoring of the clinical course and of central venous pressure.
- Target urine output of approximately 3 mL/kg body weight/hour (200 mL/hour).
- Check serum potassium level frequently.
- Correct hypocalcaemia only if symptomatic (e.g. tetany or seizures) or if severe hyperkalaemia occurs.
- Investigate the cause of rhabdomyolysis.
- Check urine pH; if it is less than 6.5, alternate each litre of normal saline with 1 L of 5% dextrose plus 100 mmol of sodium bicarbonate. Avoid potassium and lactate-containing solutions.
- Consider treatment with mannitol (up to 200 g/day and cumulative dose up to 800 g). Check for plasma osmolality and plasma osmolal gap. Discontinue if diuresis (>20 mL/hour) is not established.
- Maintain volume repletion until myoglobinuria is cleared (as evidenced by clear urine or a urine dipstick testing result that is negative for blood).
- Consider renal replacement therapy if there is resistant hyperkalaemia of more than 6.5 mmol/L that is symptomatic (as assessed by electrocardiography), rapidly rising serum potassium, oliguria (<0.5 mL of urine/kg/hour for 12 hours), anuria, volume overload, or resistant metabolic acidosis (pH < 7.2).

*In the case of the crush syndrome (e.g. earthquake, building collapse), institute aggressive volume repletion promptly before evacuating the patient.

could favour the precipitation of calcium-phosphate in injured muscle [1,8].

If the patient develops AKI severe enough to produce hyperkalaemia and/or acidosis resistant to medical treatment, renal replacement therapy is indicated, principally with intermittent haemodialysis. Due to the molecular weight of myoglobin (17 kDa), conventional haemodialysis with regular dialysers has little effect in removing myoglobin. However, due to the pathogenic role of myoglobin in rhabdomyolysis-induced AKI, preventive extracorporeal elimination of this molecule has been studied. While plasmaphoresis has shown no significant benefit, continuous veno-venous haemofiltration or haemodiafiltration, especially with super high-flux filters and high volumes of ultrafiltration, have shown some efficacy in removing myoglobin in case reports. High-cut-off pore dialysers, which are permeable to proteins such as free light chain immunoglobulins, may remove myoglobin effectively [15]. However, until large positive randomized trials become available, preventive removal of myoglobin in rhabdomyolysis (to prevent AKI) cannot be recommended.

Other therapies with anecdotal evidence are the use of antioxidants and free radical scavengers (pentoxyfylline, vitamin E, vitamin C) to ameliorate the toxic effects of oxidized myoglobin.

Surgical

Compartment syndrome occurs when increased pressure within a compartment compromises the circulation and function of the tissues within that space. Acute compartment syndrome is a surgical emergency and most often develops after significant trauma, in particular with long bone fractures, but may also occur following minor trauma or even from non-traumatic causes.

About 70% of acute compartment syndrome are due to long bone fractures, especially with comminuted fractures of the tibia and bones of the forearm [16]. Direct trauma to a tissue compartment (crush injury), severe thermal burn, penetrating trauma, or injury to vascular structures (either arterial or venous) may also be responsible for acute compartment syndrome as may ischaemia-reperfusion injury, sometimes occurring few hours or days after revascularization procedures such as by-pass surgery, embolectomy, or thrombolysis.

The development of acute compartment syndrome includes rapid progression of signs and symptoms over a few hours. Therefore, serial evaluation is mandatory. The most important symptoms are pain (out of proportion to apparent injury) and paresthaesias. The compartment is tense with skin pallor, diminished sensation, and muscle weakness or paralysis.

Compartment pressures should be measured, and a difference between diastolic blood pressure and the compartment pressure of 30 mm Hg or less requires an immediate surgical approach [17], including relieving all external pressure on the compartment, analgesics as required, as well as oxygen supplementation. Fasciotomy to fully decompress all involved compartments is the definitive treatment for acute compartment syndrome.

References

1. Bosch X, Poch E, and Grau JM. (2009). Rhabdomyolysis and acute kidney injury. *New England Journal of Medicine*, **361**(1), 62–72.
2. Melli G, Chaudhry V, and Cornblath DR. (2005). Rhabdomyolysis: an evaluation of 475 hospitalized patients. *Medicine (Baltimore)*, **84**(6), 377–85.
3. Khan FY. (2009). Rhabdomyolysis: a review of the literature. *Netherlands Journal of Medicine*, **67**(9), 272–83.
4. Grable-Esposito P, Katzberg HD, Greenberg SA, Srinivasan I, Katz J, and Amato AA. (2010). Immune-mediated necrotizing myopathy associated with statins. *Muscle & Nerve*, **41**, 185–90.
5. Hatamizadeh P, Najafi I, Vanholder R, et al. (2006). Epidemiologic aspects of the Bam earthquake in Iran: the nephrologic perspective. *American Journal of Kidney Disease*, **47**(3), 428–38.
6. Sever MS, Vanholder R, and Lameire N. (2006). Management of crush-related injuries after disasters. *New England Journal of Medicine*, **354**(10), 1052–63.

7. Vanholder R, Sever MS, Erek E, and Lameire N. (2000). Rhabdomyolysis. *Journal of the American Society of Nephrology*, **11**(8), 1553–61.
8. Better OS and Abassi ZA. (2011). Early fluid resuscitation in patients with rhabdomyolysis. *Nature Review: Nephrology*, **7**(7), 416–22.
9. Better OS and Stein JH. (1990). Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. *New England Journal of Medicine*, **322**(12), 825–9.
10. Ward MM. (1988). Factors predictive of acute renal failure in rhabdomyolysis. *Archives of Internal Medicine*, **148**(7), 1553–7.
11. Gunal AI, Celiker H, Dogukan A, et al. (2004). Early and vigorous fluid resuscitation prevents acute renal failure in the crush victims of catastrophic earthquakes. *Journal of the American Society of Nephrology*, **15**(7), 1862–7.
12. Brown CV, Rhee P, Chan L, Evans K, Demetriades D, and Velmahos GC. (2004). Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? *Journal of Trauma*, **56**(6), 1191–6.
13. Cho YS, Lim H, and Kim SH. (2007). Comparison of lactated Ringer's solution and 0.9% saline in the treatment of rhabdomyolysis induced by doxylamine intoxication. Emergency Medical Journal, **24**(4), 276–80.
14. Zager RA, Foerder C, and Bredl C. (1991). The influence of mannitol on myoglobinuric acute renal failure: functional, biochemical, and morphological assessments. *Journal of the American Society for Nephrology*, **2**(4), 848–55.
15. Ronco C. (2005). Extracorporeal therapies in acute rhabdomyolysis and myoglobin clearance. *Critical Care*, **9**(2), 141–2.
16. White TO, Howell GE, Will EM, Court-Brown CM, and McQueen MM. (2003). Elevated intramuscular compartment pressures do not influence outcome after tibial fracture. *Journal of Trauma*, **55**(6), 1133–8.
17. Hammerberg EM, Whitesides TE Jr, and Seiler JG, 3rd (2012). The reliability of measurement of tissue pressure in compartment syndrome. *Journal of Orthopaedic Trauma*, **26**(1), 24–31.

SECTION 18

Pain and sedation

PART 18.1

Pain

CHAPTER 356

Pathophysiology and assessment of pain

Rebecca E. Martin and Ross D. MacPherson

Key points

- Pain is a complex physiological phenomenon with the nociceptive nervous system, both peripheral and central, demonstrating significant plasticity and sensitization.
- Modulation of nociceptive signals occurs at multiple levels within the nociceptive system and the resultant subjective experience of pain is an integration of both excitatory and inhibitory nociceptive processes.
- Visceral pain is usually diffuse and poorly localized with convergence of both non-visceral and other-visceral afferents onto the same second order neuron in the dorsal horn of the spinal cord.
- In the critical care setting communication regarding a particular individual's pain experience is difficult and numerous assessment tools have been developed to guide clinicians.
- The use of pain assessment tools to titrate analgesia drug dosages improves clinical outcomes, including reduction in ventilator time and intensive care unit stay.

Introduction

Pain is a complex phenomenon that serves a protective function by modifying behaviour to avoid tissue damage, with acute pain acting as a 'teaching signal' in development to improve survival. Pain is defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or defined in terms of such damage' [1]. It is distinct from the other internal senses of the body, i.e. the somatosensory system—touch, thermal, proprioception, and pain—in that it is unpleasant at threshold. This unpleasantness, which defines pain as an experience, being both sensory and emotional, distinguishes pain from nociception, the neural process encoding noxious stimuli [1]. The IASP notes that the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of suitable pain-relieving treatment, emphasizing the need for appropriate assessment and management of pain when caring for unconscious patients and those with communication barriers. Insight into mechanisms of nociception assists such clinical assessment of pain and this chapter introduces the reader to basic concepts of nociception and the assessment of pain in critical care.

The nociceptive system demonstrates rapid and significant plasticity in response to peripheral inputs with both peripheral and central changes leading to amplification of signal processing, a process referred to as sensitization. This creates both reduction in the threshold of nociception and increased suprathreshold effects, demonstrated clinically as allodynia, pain due to a stimulus that does not normally provoke pain, and hyperalgesia, increased pain from a stimulus that does normally provoke pain. Treatment goals extend beyond the removal of the pain response to a noxious stimulus, referred to as analgesia, but also attempts to preserve the protective functions of the somatosensory system, i.e. return sensitivity to baseline with antihyperalgesia and anti-allodynia effects as outlined in Fig. 356.1 [2].

An important advance in our understanding of these processes was Melzack and Wall's 1965 'gate theory' of pain [3], which proposed that modulation of sensory inputs within the spinal dorsal horn, including activity in non-nociceptive neurons, leads to either an increase or a decrease in the volume of nociceptive signals transmitted to the brain. Further understanding has since recognized the significance of descending influences from the brain, both facilitatory and inhibitory, providing a more comprehensive understanding of the sensory/discriminative, affective/motivational, and cognitive/evaluative components of pain perception and behaviour [4].

Peripheral mechanisms of nociception

A peripheral nociceptive neuron is a sensory neuron capable of encoding noxious stimuli with its cell body located in the dorsal root, trigeminal, or nodose ganglia. These neurons are anatomically pseudo-unipolar, with a central projection to either the spinal cord or the medullary dorsal horn. In addition, they have a peripheral projection terminating in 'free' unencapsulated nerve endings in the tissues. Primary afferent nociceptors are most commonly discussed in terms of their morphology and electrophysiological characteristics. Aδ fibre mechanothermal sensory neurons have myelinated, medium to small diameter fibres and C-fibre polymodal sensory neurons have non-myelinated, slowly conducting fibres. Aδ fibres, being myelinated, conduct at a faster rate and are associated with pricking, sharpness, and possibly aching pain. C-fibre nociceptors, the most numerous subclass, are typically polymodal, with populations responding to chemical, thermal, and mechanical stimuli and are associated with the perception of slow, burning pain. [5]

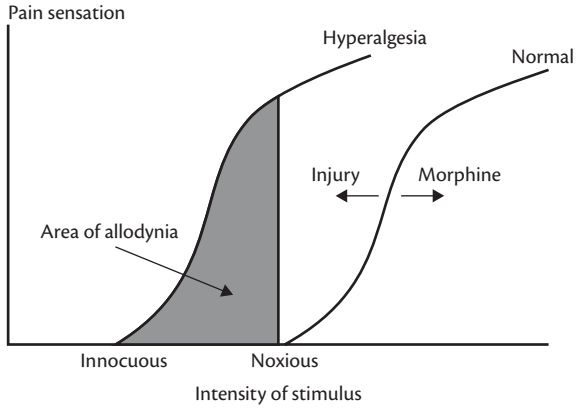


Fig. 356.1 Dose–response curve showing terminology.
Reprinted from *Annals of Emergency Medicine*, **35**(6), Ducharme J, 'Acute pain and pain control: state of the art', pp. 592–603, Copyright 2000, with permission from Elsevier and American College of Emergency Physicians.

Nociceptors have free nerve endings without specialized transducing structures so the main processes of signal transduction are intrinsic to the nerve terminal itself. For detection of noxious thermal, mechanical, or chemical stimuli, they must produce activation of the peripheral nociceptive terminal, transforming the noxious energy into generator potentials that contribute to action potentials that are then propagated along the primary afferent nociceptor. Transmission of this electrophysiological impulse is initially to the dorsal horn (DH) of the spinal cord (or of the medulla). For the perception it must be further transmitted via the brain stem and thalamus to the multitude of higher centres in the brain involved with processing nociception. Modulation of the signal occurs at multiple levels and the resultant subjective experience of pain is an integrated result of both excitatory and inhibitory nociceptive processes, in the context of the particular individual's experience.

In the clinical setting of actual or potential tissue damage, such as occurs with inflammation, infection, or ischaemia, multiple chemical mediators are released by damaged cells, from the degranulation of mast cells, from the secretions of inflammatory cells, and from sympathetic nerve terminals, as well as by the induction of enzymes such as cyclo-oxygenase-2 [6]. In addition to directly activating the primary afferent neuron, they may also modify and enhance the response characteristics of the peripheral terminal, known as 'peripheral sensitization'. An area of increased sensitivity within the area of injury occurs, which is manifest clinically as primary 'hyperalgesia'.

This inflammatory and sensitizing 'soup' of chemical mediators, acting directly via ionotropic chemoreceptors, such as those from the transient receptor potential (TRP) group and others, forms generator potentials in the nociceptive free nerve ending that contribute to membrane depolarization. They may also act via G protein-coupled receptors such as those sensitive to prostaglandins, serotonin, and bradykinin. Following activation, phosphorylation of channels as a result of changes in intracellular kinase cascades, results in alterations of channel kinetics, and threshold and sensitization of the nociceptor. [6]

When the activated nociceptive afferent transmits impulses centrally toward the spinal cord it also produces antidromic impulses in its collateral fibres, this releases transmitters in the periphery that contribute to neurogenic inflammation [4,7]. Release of substance P and calcitonin gene-related peptide (CGRP) from these antidromic fibres plays a pivotal role in the vicious cycle of peripheral sensitization as they both activate and sensitize nociceptors, which in turn leads to further release of substance P and CGRP [4]. Subsequent further activation and sensitization occurs as a result of increased capillary permeability, extravasation of bradykinin, release of 5-hydroxytryptamine (5HT) from platelets and histamine from mast cells.

Once a noxious stimulus has produced activation of the nerve terminal (signal transduction), and a generator potential equal to or above threshold has been produced, an action potential will be initiated and propagated by voltage-gated sodium channels (VGSCs). Different subtypes of VGSC exist, with NaV1.8 and NaV1.7 underlying nociceptor action potential generation, whereas propagation primarily involves the NaV1.6 subtype, which is not specific to nociception [7]. Following injury, changes in the kinetics and expression of different VGSCs contribute to hyper-excitability of nerves seen in different pain states [6,8].

Visceral nociceptors also have free nerve endings and sensitize. Some organs, such as the liver, brain, and lung lack sensory innervation, and do not respond to traumatic stimuli. Effective stimuli for visceral nociception differ: with thermal and mechanical stimuli generally ineffective, whereas pathological distention of hollow viscera or the capsules of solid organs, as well as ischaemia and infection producing nociceptive activity. Visceral afferents may travel via spinal nerves (e.g. splanchnic) or autonomic nerves (vagus) with the overall visceral input to the spinal cord being <10% of all afferent inputs [9]. Visceral pain is usually diffuse and poorly localized with convergence of both non-visceral and other visceral afferents onto the same second order neuron in the dorsal horn.

Spinal cord

Somatosensory afferents, with their cells bodies in the dorsal root ganglia, enter the CNS via the laminated dorsal horn of the spinal cord, which acts as a complex nociceptive processing unit. Although some fibres traverse a few segments in Lissauer's tract, most terminate in the superficial DH laminae I and II, with some Aδ fibres projecting more deeply to lamina V. Aβ fibres (light touch) synapse in laminae III and IV. There is convergent input of both nociceptive and tactile afferents into lamina V, either directly or via interneurons. Projection neurons may be nociceptor-specific (NS) with small receptive fields, predominantly in lamina I; low threshold, responding to innocuous stimuli only, predominantly in lamina III; or wide dynamic range (WDR) neurons, which have large receptor fields and converging inputs that are both nociceptive and non-nociceptive, predominantly in lamina V [9].

All primary sensory afferents exert excitatory synaptic effects on their second order neurons in the DH, mostly via glutamate release acting on α-amino-3-hydroxy-5-methyl-4-isaxazole-proprionic acid (AMPA) receptors. The N-methyl-D-aspartate (NMDA) subtype of glutamate receptor is minimally active in its resting state with its channel blocked by a magnesium 'plug'. However, with intense, sustained input, tissue damage or nerve injury, the magnesium blockade is removed from the NMDA channel, and an increase in the stimulus to response profile of the DH neurons is seen, called central sensitization. This plasticity is initiated by increased intracellular calcium, both via the NMDA channel and

release from intracellular stores. Changes in DH sensitivity and/or the functional connectivity of Aβ fibres, and increased descending facilitation contribute to extended sensitivity beyond the area of tissue damage or 'secondary hyperalgesia'. 'Wind up' refers to a rapid and reversible increase in responsiveness during a train of inputs, whereas 'long-term potentiation' (LTP) is a more long-lasting activity-dependent modification of individual synapses. Processes underlying secondary hyperalgesia, wind-up, and LTP are similar, but they are distinct phenomena that may all contribute to central sensitization [10–12].

Spinal modulation of activity involves the endogenous opioid system, excitatory, and inhibitory interneurons, descending influences from supraspinal sites, as well as influences from non-neuronal cells, such as microglia. Inhibitory interneurons are themselves activated by the primary afferent and act both pre- and post-synaptically. The predominant effect is post-synaptic inhibition via $GABA_A$ and glycine receptors acting on ligand gated Cl^- channel and also via G protein coupled receptors such as $GABA_B$, adenosine, and opioid receptors. Glutamate release from the primary afferent terminal may also be supressed by similar mechanisms acting pre-synaptically [12]. Voltage-gated calcium channels (VGCCs), especially the N-type, modulate neuronal excitation and transmitter release, and in chronic pain conditions are more active [8].

Central

The output from the spinal cord dorsal horn is transmitted to areas of the brain involved in sensory, emotional, autonomic, and motor processing via spinothalamic, spinobulbar, and spinomesencephalic tracts. There is no one area of the cortex identifiable as being solely responsible for pain with multiple brain regions and an extensive cortical network involved.

Pain assessment in the critical care setting

If your patient is able to communicate in any meaningful way at all, pain management becomes, at least in theory, a much more straightforward process. The patient can describe the nature and intensity of his or her pain and, more important, can tell you if any strategies that have been initiated have actually worked.

This situation is unusual in the critical care setting, and trying to accomplish this same end-point in a patient who is unable to communicate has been a challenge that many groups have tried to take on over the years.

Nurses have been particularly active in this area, and almost all of the early studies and most reviews will be found in the nursing, as opposed to medical literature, reflecting the importance placed in pain management by those staff directly caring for the patient.

There have been a number of important assessment tools proposed by various groups over the years. The Behavioural Pain Scale (BPS) [13] looks at the parameters of compliance with ventilation, facial expression, and upper limb movement to try and gauge the level of pain. While the Critical Care Pain Observation tool [14] also utilized facial expression and ventilator compliance they also proposed that body movement and muscle tension were important parameters. The Non-Verbal Pain Scale [15] was essentially adapted from a similar pain scale used in children and uses three behaviours and two physiological domains. Many of these tools have been the subject of assessment and modification, with the behavioural pain scale (BPS) being the most widely accepted system.

No matter what tool is employed assessment of pain in the non-verbal patient is no easy task. Pain levels must be assessed frequently throughout the day and particularly following painful procedures and turning. To quote one source on the subject, Mularski [16] has said 'for (pain assessment systems) to be effective . . . they must be ardently, frequently, and regularly implemented, as well as appropriately reviewed in the clinical titration of analgesia.'

Nevertheless, despite the difficulties in formulating and assessing these various pain measurement scales, there is evidence that their use is beneficial. Chanques et al. [17] and, more recently, Payen et al. [18] have both demonstrated that simply applying currently available methods for evaluation and management of pain in the intensive care unit (ICU) will most likely result in a reduction in both ventilator time, and time of ICU admission. Interestingly an earlier paper by Payen et al. [19] showed that despite a range of assessment tools being available, they had not been widely accepted in the ICU environment.

One point that comes through in all of these reviews, is that the validity of assessment tools declines in patients who are heavily sedated and are even less applicable in the paralysed patient, a situation where provision of adequate analgesia and sedation is of paramount importance. Nevertheless, despite all these difficulties, there must be a continued attempt to refine and promote such assessment systems. Even today, it appears that most hospitals do not utilize assessment protocols for analgesia in the ICU, despite these tools being available. Furthermore, it has been clearly demonstrated that by deciding on analgesia drug dosage, based on assessment, rather than intuition, will result in a reduction both in ventilator days and length of ICU stay [13]. Although as yet unproven, one group has suggested that if this strategy is followed, there may well be further reductions in delirium and ventilator-associated pneumonia [20].

References

1. Merskey H and Bogduk N. (1994). *Classification of Chronic Pain, IASP Task force on Taxonomy*. Seattle: IASP Press.
2. Ducharme J. (2000). Acute pain and pain control: state of the art. *Annals of Emergency Medicine*, **35**(6), 592–603.
3. Melzack R and Wall PD. (1965). Pain mechanisms: a new theory. *Science*, **150**(3699), 971–9.
4. Siddall PJ and Cousins MJ. (2009). Introduction to pain mechanisms: Implications for neural blockade. In: Cousins MJ, Carr BD, Horlocker TT, and Bridenbaugh PO (eds) *Cousins and Bridenbaugh's Neural Blockade in Clinical Anaesthesia and Pain Medicine*, 4th edn, pp. 661–92. Philadelphia: Lippincott Williams & Wilkins.
5. Meyer RA, Ringkamp M, Campbell JN, and Raja SN. (2006). Peripheral mechanisms of cutaneous nociception. In: McMahon SB and Koltzenburg M (eds) *Wall and Melzack's Textbook of Pain*, 5th edn, pp. 3–34. New York: Elsevier Churchill & Livingstone.
6. Macintyre PE, Schug SA, Scott DA, Visser EJ, Walker SM, and APM:SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2010). *Acute Pain Management: Scientific Evidence*, 3rd edn. Melbourne: ANZCA & FPM.
7. Gold MS and Gebhart G. (2010). Peripheral pain mechanisms and nociceptor sensitisation. In: Fishman SM, Ballantyne JC, and Rathmell JP (eds) *Bonica's Management of Pain*, 4th edn, pp. 24–34. Philadelphia: Lippincott Williams & Wilkins.
8. Porreca F. (2012). Nociceptors, the spinal dorsal horn and descending modulation. In: Tracey I (ed.) *Pain 2012: Refresher Courses*, 14th World Congress on Pain, pp. 3–14. Seattle: IASP Press.

9. Beaulieu P. (2008). Applied physiology of nociception. In: Macintyre PE, Walker SM, and Rowbotham DJ (eds) *Clinical Pain Management Acute Pain*, 2nd edn, pp. 3–19. London: Hodder Arnold.
10. Walker SM. (2008). Mechanisms of inflammatory hyperalgesia. In: Macintyre PE, Walker SM, Rowbotham DJ (eds) *Clinical Pain Management Acute Pain*, 2nd edn, pp. 20–31. London: Hodder Arnold.
11. Sandkuhler J and Gruber-Schoffnegger D. (2012). Hyperalgesia by synaptic long term potentiation (LTP): an update. *Current Opinion in Pharmacology*, **12**(1), 18–27.
12. Salter MW. (2012). Dorsal horn plasticity and neuron-microglia interactions. In: Tracey I (ed.) *Pain 2012: Refresher Courses*, 14th World Congress on Pain, pp. 15–25. Seattle: IASP Press.
13. Payen J-F, Bru O, Bosson JL, et al. (2001). Assessing pain in critically ill sedated patients by using a behavioural pain scale. *Critical Care Medicine*, **29**, 2258–63.
14. Gelinas C, Fillion L, Puntillo KA, Viens C, Fortier M. (2006). Validation of the Critical-care pain Observation Tool in adult patients. *American Journal of Critical Care*, **15**, 420–7.
15. Odhner M1, Wegman D, Freeland N, Steinmetz A, Ingersoll GL. (2003). Assessing pain control in nonverbal critically ill adults. *Dimensions in Critical Care Nursing*, **22**, 260–7.
16. Mularski RA. (2004). Pain management in the Intensive Care Unit. *Critical Care Clinics*, **20**, 381–401.
17. Chanques G, Jaber S, Barbotte E, et al. (2006). Impact of systemic evaluation of pain and agitation in an intensive care unit. *Critical Care Medicine*, **34**, 1691–9.
18. Payen J-F, Bosson JL, Chanques G, Mantz J, Labarere J, and DOLOREA Investigators. (2007). Pain assessment is associated with decreased duration of mechanical ventilation in the intensive care unit. *Anesthesiology*, **111**, 1308–16.
19. Payen J-F, Chanques G, Mantz J, et al. (2007). Current practices in sedation and analgesia for mechanically ventilated critically ill patients. *Anesthesiology*, **106**, 687–95.
20. Kumar AV and Brennan TJ. (2009). Pain assessment, sedation and analgesic administration in the Intensive care unit (Editorial). *Anesthesiology*, **111**, 11867–8.

CHAPTER 357

Pain management in the critically ill

Ross D. MacPherson

Key points

- There have been very few well conducted trials specifically examining pain management in the intensive care unit setting, and evidence for much of what we do is lacking.
- Pain causes significant sympathetic nervous system stimulation that can impact on all organ systems.
- The pharmacokinetics of analgesic agents, and indeed all drugs, can be altered in the critically-ill patient, although again definitive studies are few.
- An understanding of the pharmacokinetics of infusions of commonly used drugs will aid in competent prescribing.
- Whilst analgesia will usually provide some degree of sedation, sedation never equates to analgesia.

Introduction

Providing guidelines for the management of pain in the ICU presents a unique set of problems. In the first place there have been few well conducted trials on this subject and most reviews can suggest little more than general guidelines—those seeking Level 1 evidence on this topic will be disappointed, and even traditional sources of high quality evidence-based information on pain management, such as the IASP can offer little more. Of course, this will come as no surprise since the intensive care unit (ICU) population represents such a heterogeneous sample that trying to provide guidelines is very difficult. Furthermore, at stages during the patient's ICU stay, the physician will be faced primarily with decisions focusing on respiratory and cardiovascular management often of life-threatening conditions, and the problems related to pain management tend to be overlooked. It must be understood that sedation does not equate with analgesia, and while analgesia agents almost always will provide a degree of sedation, the reverse is never true. Finally, apart from the subjective feeling associated with pain, it should be understood that it is also associated with significant sympathetic nervous system activation resulting in effects on all physiological systems including respiratory, cardiovascular, gastrointestinal, and endocrine.

However, all these issues should not deter us from making a considered attempt to optimize pain management in the ICU patient. It has already been clearly identified that acute pain that is poorly managed in the ICU frequently progress to chronic pain problems having a significant impact on the patient's life following discharge from hospital [1]. Furthermore, as has been shown in the section 'Pain Assessment in the Critical care Setting' in Chapter 356, 'Pathophysiology and Assessment of Pain' adequate pain management is associated with a reduction in time involving mechanical ventilation, and earlier discharge from the ICU to the general ward [2].

Routes of administration

There are numerous routes of administration available for analgesic agents. However, most of these are unsuitable for use in the critical care setting. The major advances in, for example, sustained release oral opioid preparations, and transdermal fentayl or buprenorphine are useful where pain is established and ongoing, but take time to alter dosage, and in the case of transdermal products take many hours to achieve steady state. In general, the absorption of drugs by the oral route is unpredictable in the critically ill. For these and other reasons the intravenous route has been favoured for the management of pain in the ICU and this will be the main focus of this chapter.

Pharmacokinetics

Although detailed data are lacking, it may be that the pharmacokinetic behaviour of drugs in critically-ill patients have significant deviations from that seen in other populations. Apart from significant impairment of drug metabolism and excretion that may arise from hepatic and renal impairment in this group, there are a number of other associated factors that can affect drug disposition, the importance of which is difficult to quantify. Large shifts in the volumes and composition of body fluid compartments, reductions in albumin and glycoprotein concentrations, and acid–base disturbances can all contribute to unexpected drug behaviour [3].

Of particular interest in the ICU patient is the pharmacokinetics associated with the use of prolonged infusion.

Empirically, it has been noted that it often needed a considerable amount of time for the clinical effects of drugs that had been administered by long-term infusion for some time to wear off. It was clear that for some drugs the time taken for clearance from the body was heavily-dependent on the duration of the intravenous infusion.

In contemporary pharmacokinetics, the term context sensitive half time has been coined to describe the time taken, following the cessation of an intravenous infusion, for the blood level of a drug

to decline by half **following a particular period of infusion**. The 'context' in this case refers to the duration of the infusion. This is not a constant value (in most cases), but the time needed for a decrement in the body of a particular drug is dependent (in part) upon the time of the preceding infusion.

As can be seen in Fig. 357.1, fentanyl is generally taken as an agent with a relatively short half-life, however, as its infusion is prolonged, the time taken for the drug to be cleared increases substantially [4]. The reasons for these changes are complex, but usually involve saturation of elimination pathways (as in the case of thiopentone), or in the case of fentanyl its high lipophilicity results in the saturation of peripheral drug compartments [5].

The difficulties with morphine infusions are well known to intensivists. The primary metabolites of morphine, the -3 and -6 glucuronide are both renally cleared, and the 6 glucuronide possesses significant analgesic and sedative effects, accentuated when the metabolite accumulates in renal impairment.

Opioids

Opioids remain the mainstay of pain management in critically-ill patients. Apart from avoiding pethidine (meperidine), any of the other agents can be used, although each has its own set of individual characteristics.

Morphine is readily available and inexpensive, an important point to remember. Of the opioids, it is one of the more sedating agents, and will produce metabolites that may have prolonged activity.

Hydromorphone was initially synthesized over a century ago and has recently undergone a revival of interest. It can be given by a number of routes of administration, and while it also undergoes glucuronidation, the metabolites produced are inactive, making it an attractive prospect in patients with renal impairment [6].

Remifentanil is the newest opioid to join the stable and has a unique pharmacokinetic profile. Its metabolism by non-specific esterases (not to be confused with pseudocholinesterase) in the plasma results in a half-life that is measured in minutes, and a very stable context-sensitive half-time. It has found a niche in certain anaesthetic procedures providing a degree of haemodynamic stability and impressive analgesia. Its use is not without hazards, however, and reports of hypotension, bradycardia, and muscle rigidity have all been reported. Using remifentanil requires some finesse, since its analgesic effects are so short lived, other longer-acting agents must be added to the regime prior to its cessation, or the consequence will be a hypertensive patient in severe pain. There have been a number of promising studies of remifentanil use in the critical care setting [7]. One area where remifentanil could make a big impression is to facilitate undertaking brief, but painful procedures in the ICU. The remifentanil infusion can be commenced, titrated to effect and continued through the procedure e.g. chest tube or tracheostomy, and ceased at the conclusion.

Drugs to avoid

Pethidine (meperidine)

This drug has no role to play in modern pain management. It has no advantages at all over other available opioids. It has a high risk of dependence, is metabolized to a toxic metabolite with a long half-life, and has considerable anti-cholinergic side effects. Importantly, toxicity can occur even at so-called 'therapeutic' dosage levels. It is an unsafe drug and should be avoided [8].

Codeine

Codeine, which has also had its adherents over the years, mainly in the arena of neurosurgery is also a drug of limited efficacy. While some codeine/paracetamol combinations provide superior analgesia to paracetamol alone, codeine as a sole agent has very poor analgesic qualities [9]. Furthermore, most agree that it only exerts its analgesic efficacy by conversion to morphine a feat that cannot be accomplished by about 10% of the population who are lacking the appropriate CYP2D6 enzyme system. It has a low ceiling effect and is very constipating.

Methadone

While methadone is not exactly a drug to be avoided in the acute pain setting, it is a drug that needs to be used with caution on account of its unpredictable, complex, and variable pharmacokinetics.

Methadone is a racemic compound with the (R) isomer having a high affinity for the opioid receptor, while the (S) isomer has antagonistic effects on the NMDA receptor (like ketamine). It has a high lipid solubility and is highly redistributed to fat tissues over time, accounting for its long half-life. It has no active metabolites (despite

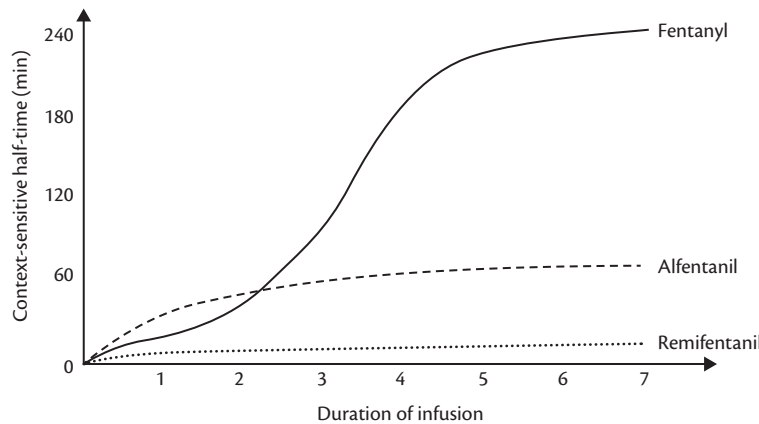


Fig. 357.1 Context-sensitive half-times of remifentanil, fentanyl, and alfentanil.

Reproduced from Roberts F and Freshwater-Turner D, 'Pharmacokinetics and anaesthesia', *Continuing Education in Anaesthesia Critical Care and Pain*, 2007, **7**(1), pp. 25–9, by permission of Oxford University Press and the British Journal of Anaesthesia.

a complex array of P450 cytochromes involved in its metabolism) and lacks the euphoric effects of traditional opioids. However, its analgesic half-life (4–8 hours) is considerably less than its elimination half-life (that can be up to 150 hours). Thus, dosing is difficult to predict and over administration can lead to accumulation, and the potential risk of increased respiratory depression. Methadone in high levels has also been implicated to initiate torsades de pointes. The risk of this event is increased in patients with pre-existing QT prolongation, hypokalaemia, and hypomagnesaemia. With so many other options available, methadone is an unlikely candidate for first line pain management in the ICU [10,11].

Adjunct agents

Paracetamol

Paracetamol is the foundation stone of modern pain management. Provided a few simple rules are adhered to, this agent enhanced the quality of opioid-induced analgesia and has an excellent side effect profile. With the parenteral form of paracetamol now available in most countries, the problems associated with administration have now been overcome. The dose should be capped at 1 g qds, and this dose should be reduced in the critically ill, elderly, or cachectic patients where the dosage should be based on paediatric guidelines (i.e. 15 mg/kg). Liver function tests should be monitored closely and the drug suspended in the face of any abnormality. The only other issue that has arisen in recent times is the possibility of increased toxicity with intravenous paracetamol in the malnourished patient where stores of glutathione, needed for paracetamol metabolism to non-toxic products, may be diminished

Ketamine

Ketamine has much to recommend it as an analgesic agent in the critically ill. It has enjoyed a re-emergence as an analgesic agent, and well known as an agent with effects at multiple receptor sites, notably the NMDA receptor.

In the past, the well-known psychomimetic effects have limited the use of ketamine. However, these effects are generally held to be a dose-related phenomenon, and since the amounts needed when ketamine is used as an analgesic agent are an order of magnitude less than when used as an anaesthetic agent, such effects are much less problematic. It is perhaps most useful as an adjunct to opioid analgesia when dosing seems to be increasing without appreciable increase in efficacy. It has a wide range of other benefits [12]. For example, in most patients (provided that they are not in severe shock) the mild sympathominetic effects tend to maintain blood pressure and cardiac output. It should be noted that these effects are centrally mediated and ketamine in fact is a direct myocardial depressant when administered in vitro. Additional benefits include the fact that it has a relatively fixed context-sensitive half time, is a mild bronchodilator, had anti-inflammatory properties, reduces opioid-induced hyperalgesia, and may reduce the emergence of chronic pain syndromes [10]. In some countries isomeric ketamine is available. The S(+) isomer is associated with improved analgesia coupled with a reduction in psychomimetic effects.

Tramadol

Tramadol use in the ICU has been restricted probably because of concerns about possible epileptogenic effects, and variable clinical efficacy. Despite these worries, tramadol should not be forgotten as an adjunct to opioid-based analgesia. It is essentially devoid of traditional opioid adverse effects, such as tolerance and dependence, and it is available in a wide variety of dosage forms. Furthermore, it is one of the few 'traditional' analgesics that has been shown to have some efficacy in the management of neuropathic, as well as nociceptive pain, making it useful in mixed pain conditions [9,13]. Serotonin syndromes is unlikely when the drug is used at the recommended dosage, and is generally encountered only at either excessive dosage or when the drug is used in combination with other serotonergic agents. The M1 metabolite of tramadol has considerable activity, and its generation is also determined on pharmacogenetic grounds, with some patients unable to synthetize this particular metabolite. The significance of this is still unclear, but it may be responsible for reduced activity of the drug.

Non-steroidal anti-inflammatory agent (NSAIDs)

NSAIDs tend to be avoided in the ICU setting, primarily because of fears concerning renal dysfunction and bleeding. While these are often quite well founded, NSAIDs should not be disregarded completely, as they are capable of providing outstanding analgesia without the usual opioid related adverse effects [14]. The key to minimizing adverse effects is to choose an agent with a short half-life such as diclofenac or ibuprofen, and to limit treatment to 3 days at a time [15]. Unlike aspirin, the platelet effects of NSAIDs are reversible, and platelet function will return to normal within hours of cessation of a short half-life agent. Furthermore, most renal impairment is associated in patients in who prostaglandins play a major role in maintaining blood flow i.e. the volume depleted. Maintaining an appropriate fluid volume and urine output will minimize the risk of adverse events.

Other modalities

There are some pain modalities that are perhaps under-utilized in the ICU. The first is the use of spinal opioids. Opioids (especially the less lipid soluble morphine) can be delivered into the CSF in doses orders of magnitude smaller than those given by any peripheral route and deliver substantial analgesia for up to 24 hours following surgical procedures. Its activity does seem to be somewhat site specific, but when ICU admission is anticipated following, for example, major urogenital, or lower limb surgery this can be considered.

The other area which has undergone a revival is the use of peripheral nerve blocks. Peripheral nerve blocks have always been part of anaesthetic technique, but technical difficulties often stood in the way of consistent results. However, with the advent of ultrasound, there has been a revival of the use of both single shot and continuous local anaesthetic infusions. Despite the popularity of these as a means of provision of analgesia there are some other factors that need to be considered. The first is that evidence as to the efficacy of the wide range of blocks currently employed is lacking. Furthermore, the process is not risk free and even with ultrasound usage, perineural haematoma or intraneuronal injections are still a major cause of morbidity. The chances of these occurring are significantly higher in the anaesthetized or sedated subject [16]. Finally, the ability to provide these blocks is still determined by the Hospital having anaesthetists with sufficient skills and equipment to be able to undertake these procedures.

Gabapentin was initially developed as an anti-epileptic agent and has since been used as a mood stabilizer and a treatment option for neuropathic pain. However, it has been increasingly used as an adjunct to general anaesthesia as there is mounting evidence that even low doses in the peri-operative period can both reduce pain perception and opioid requirements. There is also evidence that its administration can prevent the progression to chronic pain. Although an oral solution exists in some countries, there is currently no parenteral dosage form available, a fact that may limit its utility [17].

Transition to ward care

As soon as practical, patients should be transferred to a patient-controlled analgesia (PCA) device, where this is part of the usual pain management routine. PCAs have been about for more than a decade now and are an established part of acute pain management. It is interesting to note that while PCA analgesia has a high degree of patient acceptance, studies have consistently shown that in terms of adverse effects, complication, quality of pain management, and overall opioid usage, they provide no particular advantage over conventional opioid management [14,15]. Despite this, they are important in establishing a patient-centred analgesia regime. Patient education is critical for PCA analgesia to be successful, and this should be initiated well before ward discharge if possible. Pethidine must never be used in a PCA prescription, but apart from that any other opioid can be used. Although it may be counter intuitive, numerous reports have shown that a background added to a PCA has no impact on overall analgesia and should be avoided in adults.

Conclusion

Opioids delivered by infusion remain the mainstay of pain management in the ICU. Of the various opioids available hydromorphone and remifentanil provide probably the optimum degree of analgesia coupled with minimal adverse effects.

There is always room for input from specialists in pain management, and if your institution has an acute pain team, they should be encouraged to include the ICU as part of their referral base. Early involvement of the acute pain team in complex pain management issues within the critical care setting will always be beneficial, and they can provide ongoing input with pain management, as well as providing a continuum of care for the patient moving from the critical care to the general ward environment.

References

1. Desbiens NA and Wu AW. (2000). Pain and suffering in seriously ill hospitalised patients. *Journal of the American Geriatric Society*, **48**, S183–6.
2. Payen J-F, Bosson JL, Chanques G, Mantz J, Labarere J, and DOLOREA Investigators. (2007). Pain assessment is associated with decreased duration of mechanical ventilation in the intensive care unit. *Anesthesiology*, **111**, 1308–16.
3. Barr J and Donner A. (1995). Optimal intravenous dosing strategies for sedatives and analgesics in the intensive care unit. *Critical Care Clinic*, **11**(4), 827–47.
4. Roberts F and Freshwater-Turner D. (2007). Pharmacokinetics and anaesthesia. *Continuing Education in Anaesthesia and Critical Care Pain*, 7(1), 25–9.
5. Hill S. (2004). Pharmacokinetics of drug infusions. *Continuing Education in Anaesthesia and Critical Care Pain*, **4**(3), 76–80.
6. Devlin JW and Roberts RJ. (2009). Pharmacology of commonly used analgesics and sedatives in the ICUL benzodiazepines, propofol and opioids. *Critical Care Clinic*, **25**, 431–49.
7. Battershill AJ and Keating GM. (2006). Remifentanil: a review of UTS analgesic and sedative use in the intensive care unit. *Drugs*, **66**(3), 365–85.
8. Pattullo G and MacPherson RD. (2011). Pethidine: the case for its withdrawal. Publication of the Australasian and New Zealand College of Anaesthetists Melbourne, 17–27 (Monograph).
9. Moore RA and McQuay HJ. (1997). Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. *Pain*, **69**, 287–94.
10. Trescott AM, Datta S, Lee M, and Hansen H. (2008). Opioid pharmacology. *Pain Physician*, **11**(2 Suppl.), S133–53.
11. Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, and Mehler PS. (2002). Torsades de pointes associated with very high dose methadone. *Annals of Internal Medicine*, **137**, 501–4.
12. Panzer O, Moitra V, and Sladen RN. (2011). Pharmacology of sedative-analgesic ag1ents: dexmetadomidine, remifentanil, ketamine, volatile anesthetics and the role of peripheral mu antagonists. *Anesthesiology Clinic*, **29**, 587–605.
13. Duehmke RM, Hollingshead J, and Cornblath DR. (2006). Tramadol for neuropathic pain. *Cochrane Database of Systematic Reviews*, 3, Art. No.: CD003726. DOI: 10.1002/14651858.CD003726.pub3
14. Ong, CKS, Lirk, P, Tan CH, and Seymour RA. (2007). An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clinical Medicine & Research*, **5**(1), 19–34.
15. McQuay HJ, Edwards JE, and Moore RA. (2002). Evaluating analgesia: the challenges. *American Journal of Therapy*, **9**, 179–87.
16. Bernards CM, Hadzic A, Suresh S, and Neal JM. (2008). Regional anesthesia in anesthetised or heavily sedated patients. *Regional Anesthesia and Pain Medicine*, **33**, 449–60.
17. Ho KY, Gan TJ, and Habib AS. (2006). Gabapentin and postoperative pain—a systematic review of randomized controlled trials. *Pain*, **15**, **126**, 91–101.

PART 18.2

Sedation

CHAPTER 358

Sedation assessment in the critically ill

Giovanni Mistraletti and Gaetano Iapichino

Key points

- Continuous sedation monitoring is mandatory—it guarantees patient comfort, leads the adequate use of sedatives and helps staff in communication.
- The sedation assessment is devoted to reaching an awake, calm, and cooperative state as soon as possible during the intensive care unit (ICU) stay, thus permitting the patient's early mobilization.
- Instrumental monitoring (electroencephalography, blood dosage, electromyogram) failed in bedside assessment of sedation state in conscious ICU patients. Actigraphy could offer some advantages.
- Among many different validated scales, each unit has to choose and use the most suitable for local needs. The Richmond Agitation-Sedation Scale is the most used all around the world.
- A sudden fluctuation of consciousness is the main challenge in sedation assessment. Repeated measurements are necessary to guide the adequate therapy.

The key importance of a sedation target

Patient comfort is a primary goal in the intensive care unit (ICU), and includes adequate pain control, anxiolysis, and prevention and treatment of delirium. The appropriate target level of sedation primarily depends on a patient's acute disease process, and on the therapeutic and supportive interventions required. After the first days of ICU stay, characterized by clinical stabilization and invasive procedures, the sedation target is a calm patient, awake during the day and asleep at night. The use of deep levels of sedation to facilitate mechanical ventilation or painful procedures should be minimized with ventilation setting optimization and adequate analgesia, rather than deepening unconsciousness [1,2].

Achieving and maintaining the appropriate balance of sedation and analgesia is frequently challenging. Without rational and agreed upon 'target levels' of sedation, it is probable that different members of the health care team will have disparate treatment goals, increasing the chance for iatrogenic complications and potentially delaying recovery [3].

The target level of sedation should be discussed and defined at the beginning of each staff shift, and re-evaluated regularly as the clinical condition of the patient changes. The pharmacological treatment should be written with the appropriate flexibility to allow titration to the desired endpoint, anticipating fluctuations in sedation requirements throughout the day. Frequent monitoring with validated tools improves communication among clinicians and plays an important role in detecting and treating pain, agitation, and delirium, while avoiding excessive or prolonged sedation [4].

An ongoing change in perspective

Recognition that heavy sedation may increase mortality and morbidity has led to a new model in which the emphasis is on maximizing the comfort of the patients, while they remain awake, interactive, and orientated. This new model relies on strategies, such as daily interruptions of sedation, analgesia-based sedation, enteral sedation, avoidance of paralytic agents, early physiotherapy, and use of validated tools for sedation assessment [5].

Sedation assessment with objective methods

Several objective methods for sedation assessment in critically-ill patients have been proposed, but none have yielded satisfying results. Most of them are currently still under evaluation.

Electroencephalograhy, electromyography, and auditory-evoked potential

The continuum from wakefulness to sleep involves a progressive decrease in alpha bands and an increase in beta, theta, and delta bands. Electroencephalogram (EEG) interpretation requires recognition of patterns and is made more difficult by different drug interferences.

Bispectral index (BIS) monitor is a four-channel EEG monitor, which generates a single number that correlates with depth of consciousness. It has been developed for degree of hypnosis monitoring during general anaesthesia. Correlation between BIS and validated ICU sedation scales is poor because of great BIS value variability and the electromyography (EMG) interference [6].

Based on the analysis of EEG signal irregularity, the entropy monitor (GE Healthcare, Fairfield, CT, USA) also utilizes the EMG signal, which may provide information useful for assessing whether a patient is responding to an external, painful stimulus. The prediction probability values of this monitor in differentiating between consciousness and unconsciousness are comparable with those for BIS, without adding useful information to sedation assessment.

Auditory-evoked potentials (AEP) are electrophysiological responses of the nervous system to standard sensory stimulation evoked by using headphones. An EEG pattern is recorded after each stimulus. These three methods may have a role in monitoring sedation levels only in patients needing deep sedation, or receiving neuromuscular blocking drugs, as in this circumstance sedation scales cannot be used [6].

Plasmatic drug concentration

Monitoring blood drug values is useful when a correlation between plasmatic concentration and pharmacological effect at the site of action has been well established [7]. However, critically-ill patients may be affected by renal and hepatic dysfunctions that impair their ability to metabolize and excrete drugs. Hypoxia, inflammatory mediators and abnormal diets are common in critically-ill patients, and all affect enzymatic function. Finally, ICU patients may present multi-organ dysfunctions that alter their response to drugs. In conclusion, this method cannot be recommended for sedation monitoring.

Lower oesophageal contractility and frontalis muscle electromyogram

Spontaneous, non-propulsive lower-oesophageal contractility (LOC) is definitely stress related and increases in frequency as the dose of anaesthetic is reduced. Deepening of anaesthesia resulted in progressive suppression of LOC. However, LOC has great inter-variability and is affected by drugs such as atropine. The electromyogram responsiveness is not sufficiently sensitive to monitor sedation in ICU patients [7].

Actigraphy

Actigraphy provides a continuous measure of bodily movements and was initially developed to measure sleep–wake cycles. This small electronic device containing an accelerometer continuously senses and records minimal movements, summarizing such data in numerical form.

Wrist actigraphy provides useful non-specific observations in ICU patients; even if it does not discriminate the lack (or the excess) of analgesics and sedatives from other acute neurological dysfunctions, preliminary observations suggest that the measurement of bodily movements could provide a timely indication of acute changes in neurological status, generating motor agitation or hypoactive behaviour, and it could prevent the insufficient or excessive use of sedatives [8].

This objective method is relatively new in this context. It presents interesting properties, worthy of future investigation [9].

Sedation assessment with subjective methods

Individual assessments of sedation, performed at the bedside by nurses or physicians, can be hampered by a lack of objectivity. Guidelines recommend establishing a sedation target and regularly redefining it for each patient, using a validated sedation assessment scale, with documentation of regular assessment and response.

Sedation scales: useful guides in consciously-sedated patients

Sedation scales are used to assess the depth of sedation, awareness, agitation, and response to stimuli. Use of such a scale is a key component of sedation algorithms [10]. It must be used to manage agitation and to establish a target level of sedation for medication titration, in order to promptly detect oversedation when the target level is exceeded. All sedation algorithms recommend to use a sedation scale, with Ramsay Sedation Scale (RSS), Richmond Agitation-Sedation Scale (RASS), and Riker Sedation Agitation Scale (SAS) being the most common [11].

Old and unvalidated sedation scales

The use of a scale to assess level of consciousness dates to the introduction of a 6-point scale by Ramsay et al. (RSS) almost 40 years ago [12]. Nowadays, it continues to be a widely-used scale for monitoring sedation in daily practice. This instrument identifies situations of agitation or sleep visually. Some experts consider that it is more a scale of consciousness than a tool for the measurement of sedation. RSS has been extensively tested, but it has never been validated. Moreover, it does not grade agitation. Consequently, this scale is excessively subjective and has poor validity.

Many other scales have been proposed [13], some of them are not validated. They are not recommended for clinical use.

The validated bedside sedation scales

The ideal scoring system should be easy, reliable, sensitive, and with minimal inter-observer variability. Moreover, it should give no or minimal additional discomfort to the patient. Even though a complex scoring system is not suitable for the ICU, oversimplification risks neglecting important information. Most of the proposed tools are a compromise between accuracy and time required for evaluation of sedation [14].

Recently, developed scales often combine the sedation/arousal domain with an assessment of agitation, like the SAS, the RASS, the Motor Activity Assessment Scale, the Observers' Assessment of Alertness and Sedation, the Nursing Instrument for the Communication of Sedation [15], and the Bloomsbury Sedation Score (Fig. 358.1).

Unlike other validated instruments, the RASS separates verbal from physical stimulation so that the patient's level of arousal may be graded according to the potency of the stimulus. Interestingly, RASS is valid for assessing patient's sedation over time, which has not been studied previously for other sedation scales. Moreover, RASS was validated both in spontaneously breathing/mechanically-ventilated, and in sedated/not-sedated critically-ill patients.

The multi-item sedation scales

The Adaptation to the Intensive Care Environment (ATICE) scale consists of five items—awareness and comprehension combined in a conscious domain, calmness, ventilator synchrony, and facial relaxation are combined in a tolerance domain. As for ATICE, the Minnesota Sedation Assessment Tool evaluates the level of consciousness of patients receiving invasive mechanical ventilation. It measures arousability, spontaneous muscle activity and global sedation quality. The Vancouver Interaction and Calmness Scale consists of two five-item subscales quantifying separately calmness and interaction with operators.

These more complex scoring systems are usually adopted in clinical trials to evaluate a new drug or a new objective tool for sedation assessment, whereas in daily practice easily applied scores are usually preferred.

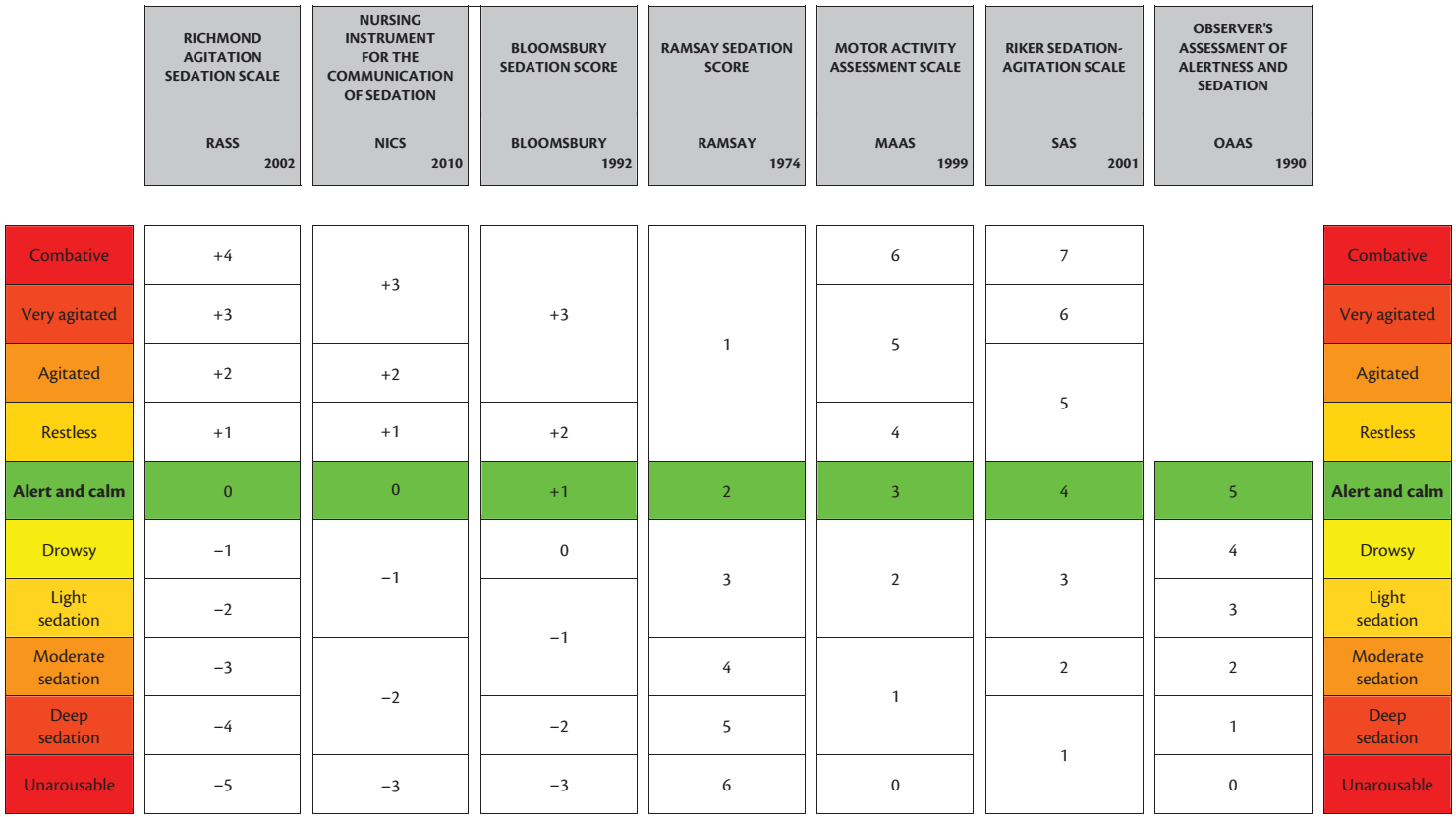


Fig. 358.1 Sedation/agitation scales in the intensive care unit.

 RASS: Richmond Agitation-Sedation Scale reproduced with permission from the American Thoracic Society: Sessler CN et al., 'The Richmond agitation–sedation scale validity and reliability in adult Intensive Care Unit Patients', American Journal of Respiratory Critical Care Medicine, 2002, 166, pp. 1338–1344; NICS: Data from Mirski MA et al., 'Validity and reliability of an intuitive conscious sedation scoring tool: The nursing instrument for the communication of sedation', *Critical Care Medicine*, 2010, **38**(8), pp. 1674–84; Bloomsbury: Data from Armstrong RF et al., 'Critical care algorithm: Sedation, analgesia, and paralysis', *Clinical Intensive Care*, 1992, **3**, pp. 284–7; Ramsay: Data from Ramsay MAE et al., 'Controlled sedation with alphaxalone- alphadolone', *British Medical Journal*, 1974, **2**, pp. 656–9; MAAS: Data from Devlin JW et al., 'Motor activity assessment scale: A valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit', *Critical Care Medicine*, 1999, **27**(7), pp. 1271–5; SAS: Data from Riker RR et al., 'Prospective evaluation of the Sedation-Agitation Scale in adult ICU patients', *Critical Care Medicine*, 1999, **27**, pp. 1325–9; OAAS: Data from Chernik DA et al., 'Validity and Reliability of the Observer's: Assessment of Alertness/Sedation Scale: Study with: Intravenous Midazolam', *Journal of Clinical Psychopharmacology*, 1990, **10**(4), pp. 244–51.

Choosing and implementing an evaluation scale

Desirable features of a good sedation instrument for use in the ICU include:

- Rigorous multidisciplinary development.
- Ease of administration, recall and interpretation.
- Well-designed discrete criteria for each level.
- Sufficient sedation levels for effective drug titration.
- Assessment of agitation.
- Demonstration of inter-rater reliability and validity in relevant patient populations [3].

Each ICU has to choose the best tools for its patient population, and to plan specific intervention to introduce it in daily care [16].

Teaching protocols used for implementation of sedation scales have shown good results among ICU caregivers. Different methods have been used to implement evaluation tools in clinical practice. Typically, they are based on introductory in-service training for nurses and operators followed by graded, staged educational interventions at regular intervals.

Web-based, freely-available teaching interventions have been recently proposed (www.icudelirium.org, www.sedaicu.it).

Emerging problems and suggested solutions

Fluctuation of consciousness

ICU patients are prone to sudden changes in their state of consciousness due to the effects of drugs, sleep disruption, organic, and metabolic disease or delirium. Assessment of sedation once a shift is indispensable, but not sufficient. Among the different possibilities (minimal/maximal level, prevalent level, worst level), it is important to state the duration of each value within the observed shift. Sedation and agitation need to be reassessed both on a regular basis and during any clinical modification, to promptly capture all the modifications requiring intervention.

Sedation and agitation without patient awakening

It is relatively common for patients to manifest sudden aggressive behaviour when recovering from sedation and without fully awakening. For this reason, together with the effort in joining and maintaining an adequate level of conscious sedation, it is important to boost interdisciplinary communication between nurses and physicians, in order to be aware of and prevent these problems.

Differentiating sedation, coma, and physiological sleep

Making a sedation assessment during the night is frequently challenging. Most analgesics and sedatives are known to make patients sleepy, but without reaching a restorative, physiological sleep [17]. If a critically-ill patient appears calm and keeps his/her eyes closed during the night, he/she should not be stimulated just to make a sedation assessment. He/she could be observed during unavoidable procedures happening in the ICU during the night, in order to discriminate normal sleep (with arousals due to noise and light) from sedation or coma.

Acknowledgements

The authors thank Linda Canali and Paolo Martini for editing the English.

References

1. Cigada M, Corbella D, Mistraletti G, et al. (2008). Conscious sedation in the critically ill ventilated patient. *Journal of Critical Care*, **23**(3), 349–53.
2. Strom T and Toft P. (2011). Time to wake up the patients in the ICU: a crazy idea or common sense? *Minerva Anestesiologica*, **77**(1), 59–63.
3. Sessler CN, Grap MJ, and Ramsay MA. (2008). Evaluating and monitoring analgesia and sedation in the intensive care unit. *Critical Care*, **12**(Suppl. 3), S2.
4. Martin J, Franck M, Fischer M, and Spies C. (2006). Sedation and analgesia in German intensive care units: how is it done in reality? Results of a patient-based survey of analgesia and sedation. *Intensive Care Medicine*, **32**(8), 1137–42.
5. Martin J, Heymann A, Basell K, et al. (2010). Evidence and consensus-based German guidelines for the management of analgesia, sedation and delirium in intensive care—short version. *German Medical Sciences*, **8**, Doc02.
6. Haenggi M, Ypparila-Wolters H, Buerki S, et al. (2009). Auditory event-related potentials, bispectral index, and entropy for the discrimination of different levels of sedation in intensive care unit patients. *Anesthesia and Analgesia*, **109**(3), 807–16.
7. Mondello E, Siliotti R, Gravino E, Coluzzi F, David T, and Sinardi AU. (2005). Sedation monitoring in ICU. *Minerva Anestesiologica*, **71**(9), 487–96.
8. Mistraletti G, Taverna M, Sabbatini G, et al. (2009). Actigraphic monitoring in critically ill patients: preliminary results toward an 'observation-guided sedation'. *Journal of Critical Care*, **24**(4), 563–7.
9. Grap MJ, Hamilton VA, McNallen A, et al. (2011). Actigraphy: analyzing patient movement. *Heart & Lung: the Journal of Critical Care*, **40**(3), e52–9.
10. Sessler CN and Varney K. (2008). Patient-focused sedation and analgesia in the ICU. *Chest*, **133**(2), 552–65.
11. Patel SB and Kress JP. (2012). Sedation and analgesia in the mechanically ventilated patient. *American Journal of Respiration and Critical Care Medicine*, **185**(5), 486–97.
12. Ramsay MA, Savege TM, Simpson BR, and Goodwin R. (1974). Controlled sedation with alphaxalone-alphadolone. *British Medical Journal*, **2**(5920), 656–9.
13. De Jonghe B, Cook D, Appere-De-Vecchi C, Guyatt G, Meade M, and Outin H. (2000). Using and understanding sedation scoring systems: a systematic review. *Intensive Care Medicine*, **26**(3), 275–85.
14. McGrane S and Pandharipande PP. (2012). Sedation in the intensive care unit. *Minerva Anestesiologica*, **78**(3), 369–80.
15. Mirski MA, LeDroux SN, Lewin JJ, 3rd, Thompson CB, Mirski KT, and Griswold M. (2010). Validity and reliability of an intuitive conscious sedation scoring tool: the nursing instrument for the communication of sedation. *Critical Care Medicine*, **38**(8), 1674–84.
16. Brush DR and Kress JP. (2009). Sedation and analgesia for the mechanically ventilated patient. *Clinics in Chest Medicine*, **30**(1), 131–41, ix.
17. Brown EN, Lydic R, and Schiff ND. (2010). General anesthesia, sleep, and coma. *New England Journal of Medicine*, **363**(27), 2638–50.

CHAPTER 359

Management of sedation in the critically ill

Bhakti K. Patel and John P. Kress

Key points

- Once adequate analgesia is confirmed, the need for sedation should be considered.
- Metabolism of sedatives in critical illness can be unpredictable and achieving optimal sedation without coma is a moving target.
- Choice of sedative can have clinical implications, including incidence of delirium, duration of mechanical ventilation, and intensive care unit length of stay.
- Sedative requirements vary over time and among patients necessitating regular assessment of depth of sedation and goal-directed titration.
- A sedation strategy should be employed to achieve the least amount of sedation for patient comfort that allows interaction with care providers.

Introduction

Achieving adequate sedation in the intensive care unit (ICU) strikes a balance between comfort and tolerance of the ICU setting without excessive and prolonged sedation. Patients undergoing mechanical ventilation experience pain and discomfort from their underlying medical condition(s) and the necessary procedures and nursing care required for their recovery. Once adequate pain control is assured, some patients may not require sedation at all [1]. Non-pharmacological interventions, such as verbal reassurance or repositioning may help comfort the agitated or restless patient, although these efforts alone may be inadequate or impractical, and the need for sedation paired with analgesia becomes the rule.

Sedation should be titrated to reproducible clinical goals to avoid the risk of excessive sedation as these highly potent medications often have unpredictable pharmacology in the setting of critical illness resulting in drug accumulation, drug–drug interactions and prolonged drug effect. The risks of prolonged and excessive sedation include increased duration of mechanical ventilation, ICU length of stay [2], ventilator associated pneumonia [3], and ICU-acquired weakness [4]. Therefore, titration of sedatives with either protocol driven assessment of sedative needs or daily interruption of sedatives is warranted to achieve patient comfort and avoid the complications of excessive and prolonged sedation. A 2013 consensus guideline paper on pain, agitation, and delirium has been published [5].

Sedation medications

Sedation requirements vary among patients and also with time for an individual patient. The variability of sedative pharmacology is explained in part by accumulation of sedatives in tissue stores, perturbation of metabolism of sedatives with hepatic and renal dysfunction that occurs with critical illness, and drug–drug interactions. The ideal sedative has rapid onset and offset of action, minimal accumulation in tissue stores, and less adverse effects such as delirium. Therefore, when choosing a sedative these ideal properties and the patient characteristics that affect drug metabolism (i.e. hepatic/renal dysfunction) should be considered.

Benzodiazepines

Benzodiazepines (e.g. lorazepam, midazolam, and diazepam) have potent anxiolytic, sedative, and hypnotic effects depending on the degree of binding to the γ-aminobutyric acid (GABA) receptor. Midazolam is slightly more lipophilic than lorazepam and as such crosses the blood–brain barrier more quickly. However, this rapid, but prolonged benzodiazepine effect is explained by its lipophilicity allowing accumulation in adipose tissue preventing metabolism. Furthermore, liver dysfunction that disrupts the CYP450 metabolism of benzodiazepines and renal dysfunction that contributes to the accumulation of the active metabolites of midazolam explains the prolonged sedative effect of benzodiazepines, and midazolam in particular [6].

Benzodiazepines have adverse effects including suppression of respiratory drive by shifting the CO_2 response curve to the right and rarely cause paradoxical agitation in the elderly. There also has been an emerging literature, which suggests that the prolonged sedative effects of benzodiazepines are an independent risk factor for delirium with an apparent dose related effect [7]. Given the considerable morbidity and mortality associated with this increased risk of ICU delirium, the effect of sedative choice on mortality and clinical outcomes of septic patients has also been studied. A subgroup analysis of septic patients randomized to lorazepam versus dexmedetomidine, found an increased risk of delirium, less ventilator free days and increased mortality in patients receiving lorazepam [8]. Although benzodiazepines have been first-line agents for sedation, randomized controlled trials comparing them with newer agents, such as propofol or dexmedetomidine clearly show that benzodiazepines lead to worse outcomes, including delirium, oversedation, delayed extubation, and longer time to discharge [9,10].

Propofol

Propofol is another sedative that modulates neurotransmitter release including GABA, but the exact mechanism is not well understood. Propofol has sedative, hypnotic, and amnestic effects. In contrast to benzodiazepines, however, propofol's pharmacokinetics favour rapid onset and offset allowing rapid awakening after discontinuation [6]. Thus, propofol's favourable pharmacological profile in one Canadian study of 69 mechanically-ventilated patients was shown to shorten duration of mechanical ventilation in comparison to midazolam [11]. Propofol's effect on reduced duration of mechanical ventilation persisted even in comparison to intermittent dosing of lorazepam [12], which suggests favourable pharmacodynamics of propofol over benzodiazepines independent of dosing strategy. Other similar studies have consistently demonstrated the superiority of propofol over benzodiazepines in terms of shorter time to mental status recovery, liberation from the ventilator, and cost-effectiveness [13].

Propofol is hydrophobic with delivery in a lipid emulsion and thus should be counted as a caloric source providing 1.1 kcal/mL of nutrition with regular monitoring for hypertriglyceridaemia. Propofol can induce hypotension by decreasing vascular tone especially in hypovolaemic patients. Rarely propofol infusion syndrome characterized by bradycardia, heart failure, rhabdomyolysis, hyperkalaemia, and metabolic acidosis has been described at high and prolonged infusion rates. There remains considerable debate on the appropriate dosing to avoid this rare complication, but most recommend maintaining dosages less than 4–5 mg/kg/hour.

Dexmedetomidine

Dexmedetomidine is a central α2 agonist that inhibits norepinephrine release. It has sedative and analgesic effect without causing respiratory depression, making it a potentially ideal drug for ICU sedation. Riker and colleagues demonstrated that although dexmedetomidine and midazolam achieved similar levels of sedation, dexmedetomidine sedation was associated with less ICU delirium and on average almost 2 more days free of mechanical ventilation [9]. In a recent study combining the results from two randomized controlled trials comparing dexmedetomidine to midazolam and propofol, respectively, Jakob and colleagues found non-inferiority of this sedative in achieving light to moderate sedation. Dexmedetomidine appeared to reduce the median duration of mechanical ventilation in comparison to midazolam, but not propofol. The main advantage demonstrated was improved communication between patient and nursing staff [10]. Other similar studies suggest that dexmedetomidine further decreased the need for additional opiates and sedatives, thus decreasing the time in comatose state, days of mechanical ventilation, length of ICU stay, and days with delirium. The main side effect of this sedative is bradycardia and hypotension most prominent during initial bolus dosing. Dexmedetomidine is an attractive sedative that allows the patient to remain awake, calm, and interactive without the associated complications of sedation. For occasional patients with very high levels of agitation, it may not be adequate as a sole agent.

Sedation strategies

Active titration of sedatives to match the dynamic and individualized needs of patients requires use of a standard assessment tool to measure the depth of and ongoing need for sedation over time. Such sedation assessment tools should ideally be simple, easy to use and remember, have discriminatory criteria for each level to aid in titration of sedatives, inter-user reliability, and validity across patient populations. Many sedation scales are available with varied strengths/limitations. Two of the more commonly utilized scales are the Ramsey and Richmond Agitation Sedation scale. Once the appropriate sedative is chosen, a validated sedation scale and strategy should be used to titrate these medications to achieve an awake, calm, and interactive patient able to undergo cognitive and neuromuscular evaluation. This shift in sedation goals to light (Ramsey score 1–2) over deep sedation (Ramsey score 3–4) is well tolerated and results in less ventilator days and shorter ICU length of stay [14]. There are a variety of sedation strategies to achieve these goals.

Daily interruption of sedatives

Daily interruption of sedatives is a strategy that seeks to achieve awakening as early as possible. Both sedatives and analgesia medications are discontinued until the patient demonstrates awakening or exhibits distress (agitation, ventilator asynchrony, hypertension, or tachycardia), which mandates resumed drug administration at half of the previous dose. This strategy was originally studied in a randomized controlled trial of 128 patients on mechanical ventilation, which demonstrated that daily interruption of sedation decreased the number of days on mechanical ventilation, allowed assessment of neurological status, and decreased the need for diagnostic neurologic testing [15]. A more recent trial comparing a nursing sedation algorithm in conjunction with daily interruption of sedatives to a nursing algorithm alone found no differences in ventilator days or length of stay. This trial used benzodiazepines and opiates at relatively high doses compared with other trials, which may have offset the effects of sedative interruption [16].

Patient-targeted sedation protocols

Patient-targeted sedation protocols provide a structured assessment of pain and sedation needs coupled with an algorithm that directs titration of these medications. Brook and colleagues compared a bedside nursing protocol designed for early detection of pain, preferential use of intermittent dosing of medications with reservation of continuous infusions for patients with inadequate response to intermittent therapy, and early de-escalation of continuous infusions to intermittent therapy. This strategy demonstrated shorter duration of mechanical ventilation, length of ICU and hospital stay, and need for tracheostomy in comparison to usual care [17].

Similarly, DeJonghe and colleagues used a comprehensive patient assessment tool, Adaption to the Intensive Care Unit Environment (ATICE), to guide sedative and analgesia infusions to optimize patient tolerance of the ICU environment. This sedation assessment tool incorporated tolerance of the ICU environment as demonstrated by ventilator synchrony, calmness, and facial relaxation in addition to standard assessment of consciousness [18]. Similar to other sedation tools it demonstrated high internal consistency across disciplines and validity. Alterations in patient tolerance prompted adjustment of ventilator settings and administration of opiates or sedatives, depending on the specific derangement in ICU tolerance. Once tolerance was demonstrated, the level of consciousness was addressed with titration of sedatives and opiates to achieve

an awake and interactive patient. Use of this algorithm in 102 patients without acute brain injury demonstrated shorter duration of mechanical ventilation and time to arousal [19]. Incorporation of ventilator synchrony as part of tolerance of the ICU environment highlights the importance of adjusting ventilator settings to improve patient–ventilator interaction prior to increasing sedatives.

No sedation

Given the growing evidence suggesting the benefits in decreasing the depth and duration of sedation, a no sedation strategy was recently studied. Strom and colleagues randomized 140 patients to no sedation (intermittent morphine with propofol rescue if agitation persisted) versus the control group who received usual care sedation (propofol for 48 hours followed by midazolam with intermittent morphine, using a daily interruption protocol). The results were interpreted with intention to treat analysis and demonstrated an increase in ventilator free days and decrease in hospital and ICU length of stay [1]. This strategy of no sedation was well tolerated as long-term follow-up of these patients suggested no increased incidence of post-traumatic stress disorder in comparison to daily interruption of sedation [20].

Conclusion

Achieving optimal sedation in mechanically-ventilated patients is difficult given the unpredictable metabolism of sedatives, and dynamic and variable sedative needs for individual patients. Choice of sedative and depth of sedation has implications for duration of mechanical ventilation and its associated complications. A strategy that employs goal-directed sedation favouring an awake and interactive patient with aggressive titration of medications has been associated with improved ICU outcomes.

References

1. Strom T, Martinussen T, and Toft P. (2010). A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet*, **375**, 475–80.
2. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, and Sherman D. (1998). The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest*, **114**, 541–8.
3. Cook DJ, Walter SD, Cook RJ, et al. (1998). Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Annals of Internal Medicine*, **129**, 433–40.
4. DeJonghe B, Cook D, Sharshar T, Le- faucheur J, Carlet J, and Outin H. (1998). Acquired neuromuscular disorders in critically ill patients: a systematic review. *Intensive Care Medicine*, **24**, 1242–50.
5. Barr J, Fraser GL, Puntillo K, et al. (**2013**). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical Care Medicine*, **41**(1), 278–80.
6. Devlin JW and Roberts RJ. (2009). Pharmacology of commonly used analgesics and sedatives in the ICU: benzodiazepines, propofol, and opioids. *Critical Care Clinics*, **25**, 431–49, vii.
7. Pandharipande P, Shintani A, Peterson J, et al. (2006). Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*, **104**, 21–6.
8. Pandharipande PP, Sanders RD, Girard TD, et al. (2010). Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori–designed analysis of the mends randomized controlled trial. *Critical Care*, **14**, R38.
9. Riker RR, Shehabi Y, Bokesch PM, et al. (2009). Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *Journal of the American Medical Association*, **301**, 489–99.
10. Jakob SM, Ruokonen E, Grounds RM, et al. (2012).Dexmedetomidine vs Midazolam or propofol for sedation during prolonged mechanical ventilation: Two randomized controlled trials. *Journal of the American Medical Association*, **307**(11), 1151–60.
11. Hall RI, Sandham D, Cardinal P, et al. (2001). Propofol vs midazolam for ICU sedation: a Canadian multicenter randomized trial. *Chest*, **119**, 1151–9.
12. Carson SS, Kress JP, Rodgers JE, et al. (2006). A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Critical Care Medicine*, **34**, 1326–32.
13. Patel SB and Kress JP. (2012). Sedation and analgesia in the mechanically ventilated patient. *American Journal of Respiratory and Critical Care Medicine*, **185**, 486–97.
14. Treggiari MM, Romand JA, Yanez ND, et al. (2009). Randomized trial of light versus deep sedation on mental health after critical illness. *Critical Care Medicine*, **37**, 2527–34.
15. Kress JP, Pohlman AS, O'Connor MF, and Hall JB. (2000). Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New England Journal of Medicine*, **342**, 1471–7.
16. Mehta S, Burry L, Cook D, et al. (2012). Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. *Journal of the American Medical Association*, **308**(19), 1985–92.
17. Brook AD, Ahrens TS, Schaiff R, et al. (1999). Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Critical Care Medicine*, **27**, 2609–15.
18. De Jonghe B, Cook D, Griffith L, et al. (2003). Adaptation to the Intensive Care Environment (ATICE): development and validation of a new sedation assessment instrument. *Critical Care Medicine*, **31**, 2344–54.
19. De Jonghe B, Bastuji-Garin S, Fangio P, et al. (2005). Sedation algorithm in critically ill patients without acute brain injury. *Critical Care Medicine*, **33**, 120–7.
20. Strom T, Stylsvig M, and Toft P. (2011). Long-term psychological effects of a no-sedation protocol in critically ill patients. *Critical Care*, **15**, R293.

SECTION 19

General surgical and obstetric intensive care

PART 19.1

Optimization strategies for the high-risk surgical patient

CHAPTER 360

Identification of the high-risk surgical patient

Rupert Pearse and Stephen James

Key points

- High-risk patients account for over 80% of peri-operative deaths.
- Age, co-morbid disease, limited functional capacity, and an emergency presentation for major surgery are hallmarks risk.
- The magnitude, duration, and consequences of post-operative morbidity are determined by a complex interplay between the indication for surgery, the resulting tissue injury, and patient factors.
- A number of methods including risk scoring and cardiopulmonary exercise testing can be used to identify the high-risk group.
- Efforts should be made throughout the peri-operative period to prevent the occurrence of any post-operative complications, as they all carry significant long-term implications.

The high-risk surgical population

Over 230 million patients undergo major surgery each year with mortality varying from 1% to 4% [1,2]. The low overall post-operative mortality conceals the sub-group of high-risk patients who account for over 80% of post-operative deaths [3,4]. In the UK, over 170,000 high-risk non-cardiac surgical procedures are performed each year, following which 100,000 patients develop complications resulting in over 25,000 deaths before hospital discharge [3–5]. Clinicians often fail to both identify patients at high risk of complications and allocate them to an appropriate level of peri-operative care, in particular intensive care [3,4]. Importantly, patients who develop complications but survive, will still suffer a substantial reduction in functional independence and long-term survival [6–8]. In a recent large North American study, mortality in an unselected population of surgical patients doubled from 2.0 to 4.3% between 30 and 365 days after surgery [8]. By one year, 47% of surviving patients had been readmitted to hospital.

As understanding of the impact of poor surgical outcomes has improved, it has become clear that a robust approach to pre-operative assessment of surgical risk is essential.

The high-risk surgical patient

Age, co-morbid disease, limited functional capacity, and emergency presentation are the hallmarks of the high-risk surgical patient. For example, an 80-year-old patient undergoing emergency gastrointestinal surgery would have a mortality risk of up to 50% and a complication rate close to 100%. While adverse events due to failures in surgical or anaesthetic technique receive much attention, they are comparatively infrequent. However, most patients develop some degree of post-operative morbidity as a result of physiological, endocrine, and inflammatory changes associated with the tissue injury of surgery. The magnitude, duration, and consequences of post-operative morbidity are determined by a complex interplay between the indication for surgery, the resulting tissue injury, and patient factors, such as cardiopulmonary reserve and active co-morbid disease. In some patients, the burden of post-operative morbidity will result in a recognized diagnosis, such as pneumonia or myocardial infarction, but many will also experience non-specific injury to one or more organ system such as the heart, kidneys, or brain that are only detected through increased observation and serial measurements, e.g. serum creatinine. This subclinical injury may be not be severe enough to satisfy accepted definitions of a complication or to require treatment in a critical care unit, but is associated with reduced long-term survival.

Much understanding of peri-operative complications revolves around the considerable changes in oxygen consumption that occur in this period. Although effective anaesthesia and invasive ventilation may decrease oxygen consumption, pathological abnormalities, including shivering, pain, and agitation can result in a significant imbalance between delivery and consumption, commonly seen in the first few hours after major surgery and often indicated by low central venous oxygen saturation. It has been suggested that poor global oxygen delivery is associated with reduced tissue perfusion and oxygenation, and hence post-operative complications. There is some evidence to suggest regional oxygen imbalance is associated with complications such as surgical wound infection. Increases in heart rate and arterial pressure, when coupled with systemic inflammation and the procoagulant state, may also result in myocardial injury in patients with pre-existing coronary artery disease. A large proportion of these events are silent in nature, masked by wound pain, analgesia, and residual anaesthesia, although their prognostic impact is still great.

Reasons to identify the high-risk surgical patient

Clear assessment of peri-operative risk is an important component of informed consent and may alter the surgeon's recommendation

to undergo surgery. The use of natural frequencies and a clear expression of the reference class, e.g. 'seven in one hundred patients like you' improves comprehension and the key elements of a discussion should be clearly documented. Unfortunately, a lack of information on what a patient wants to know concerning risk before consenting to surgery, tends to present the information that is most readily available. Quality of life data from observational studies can be used to describe outcomes of importance to most patients. We should avoid jargon or unclear terms.

Risk stratification can be used to determine the level of monitoring and peri-operative care required. Although risk stratification is widely believed to improve outcome there are no large prospective studies that can support this claim. It is also becoming clear the presence of a complication within 30 days of surgery is more important than any pre- or intra-operative risk factor in determining short- and long-term survival [7]. This supports the need for post-operative risk identification to detect and treat the earliest signs of problems. Outcome measures are therefore increasingly being used to underpin quality improvement frameworks. The focus on reducing the incidence of post-operative complications is predicated on the assumption this will lead to global improvements in quality and patient experience.

Risk assessment based on clinical criteria

The majority of patients are evaluated according to a clinician's subjective assessment of clinical history, physiology, and the extent of surgery. This tries to predict the interplay between the tissue injury-induced inflammatory response and the patient's pre-existing disease state. The most important comorbid diseases are heart failure, renal impairment, diabetes, liver cirrhosis, and malignancy.

The kidneys are affected by the interplay of haemodynamic, toxic, and inflammatory changes of the peri-operative course and can be seen as a marker for the global insult of surgery. Acute kidney injury (AKI) occurs in nearly 1% of patients with no pre-existing renal disease and is now well classified [9]. AKI is associated with increased long-term mortality in a variety of settings even if complete resolution occurs. Pre-existing renal disease risk factors alongside the nature of surgery (emergency, intra-peritoneal, or involving profound haemodynamic changes) are associated with a higher incidence of AKI.

Venous thromboembolism is responsible for a significant proportion of post-operative morbidity and the typical high-risk patient will have a number of important risk factors. Advanced age, malignancy, chemotherapy, immobility, and major surgery all contribute to endothelial damage, blood stasis and hypercoagulability, the key aetiological triad.

Other complications, such as respiratory failure or pneumonia, may be associated with a recognizable pattern of obesity, chronic obstructive pulmonary disease (COPD), compromised intra-operative lung mechanics and poorly-controlled pain. Similarly, malnutrition, diabetes, and obesity are associated with higher levels of wound infection. Procedures associated with the highest incidence of morbidity include all vascular or dual cavity procedures, gastrointestinal or extensive liver resection, joint replacement, and complex cardiothoracic surgery.

Beyond this familiar approach to risk assessment the need to perform a surgical procedure as an emergency is a very important factor in predicting risk (Table 360.1) [5]. This relates to the more serious nature of acute pathology, the lack of opportunity to optimize medical management of co-morbid illnesses and the presence of hypovolaemia, which may be severe. In addition, the dependence on junior medical staff often working outside office hours with minimal supervision and delays in access to an operating theatre may further hamper efforts to deliver optimal care.

Table 360.1 Impact of urgency on high-risk patients from a national prospective audit

Risk	30-day mortality
Immediate (within 1 hour)	1 in 4
Urgent (within 4 hours)	1 in 8
Expedited (within 48 hours)	1 in 16
Elective (not seen in pre-admission clinic)	1 in 20
Elective (seen in pre-admission clinic)	1 in 140

Data from Findlay G et al., Knowing the risk; a review of the peri-operative care of surgical patients, London: National Confidential Enquiry into Patient Outcome and Death, 2011. Available at: http://www.ncepod.org.uk/2011report2/downloads/POC_fullreport.pdf

Risk evaluation and corresponding strategies

Shortcomings in the identification of high-risk patients have led to investment in improvement options. One simple approach is to place those at highest risk of mortality in a pathway with the most monitoring and care. A mortality >10% could lead to an automatic intensive care referral with high dependency care being used for procedures with a mortality of 5–10%. Such an approach would include the vast majority of patients likely to sustain significant complications.

A number of risk stratification systems exist. The American Society of Anesthesiologists Physical Status (ASA-PS) score is based on subjective assessment of systemic disease, and is the most simple and commonly used tool. More complex alternatives use physiological and surgical variables to estimate predicted mortality and include the Charlson Age Co-morbidity Index, the Physiologic and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) scoring system for general surgery or the EuroSCORE for cardiac surgery [10–12]. These scores can then be used to set thresholds for admission to critical care, although, in some cases, elements of the operative component will need to be estimated in advance.

An appreciation of the central role of cardiac function in the development of complications after non-cardiac surgery led to the Lee Revised Cardiac Risk Index [13]. Like all pre-operative scoring systems, they are modelled on short-term (30-day or in-hospital) event rates and there is no evidence to suggest they accurately forecast medium- or long-term outcomes. Most risk scoring systems work well for audit against expected outcome rates, but are less accurate in stratifying an individual patient's peri-operative risk.

The World Health Organization (WHO) surgical safety checklist was introduced in 2008 to reduce the most common and avoidable risks that could endanger a patient's life. Before induction of anaesthesia, before surgery, and at the end of the operation an identified

member of the team completes a number of checks in the presence of the surgical team. This ensures the team is familiar with each other and has discussed the anticipated course of events, including any expected major blood loss or anticipated critical events, and the need for antibiotic prophylaxis or imaging.

Patient-reported exercise capacity

Exercise capacity is perhaps the best predictor of longevity in the non-surgical setting and American College of Cardiology/American Heart Association (ACA/AHA) guidelines propose a pre-operative assessment of the activities of daily living as a means to evaluate this. However, subjective assessments of exercise capacity have not been shown to closely correlate to objective measures and have poor predictive accuracy for post-operative cardiac events or death. The Duke Activity Status Index and the Veterans Specific Activity Questionnaire are tools that provide a more reliable prediction of exercise capacity, but are still weak predictors of post-operative complications [14]. Therefore, these methods cannot be used as comprehensive guides to the identification or management of the high-risk surgical patient.

Exercise capacity measurement

Cardiopulmonary exercise testing (CPET) involving a cycle ergometer with simultaneous spirometry, electrocardiography, pulse oximetry, and blood pressure measurement is the standard technique for objective assessment. CPET provides a safe global assessment of the cardiovascular, respiratory, neuropsychological, and skeletal muscle systems, and has an established role in the assessment of heart failure and respiratory limitation. It can be used pre-operatively, even in the majority of patients awaiting joint replacement, and accurately detects myocardial ischemia, anaerobic threshold (ATh) and peak oxygen consumption (VO_2 peak). These three factors are predictive of post-operative complications and death in a number of different surgical settings, although large blinded studies of the predictive accuracy of this test have not been performed [15–17]. In practice, an ATh of <11 mL/min/kg or a VO_2 peak <15 mL/min/kg may be considered an indicator of high-risk, while an AT of <8 mL/min/kg or VO_2 peak <12 mL/min/kg indicates a very high risk from surgery. In either case, enhanced peri-operative care is essential.

Screening for high-risk surgical patients using plasma biomarkers

An interesting emerging technology is the use of pre-operative plasma biomarkers together with clinical data to allow a basic assessment of peri-operative risk category (low, intermediate, or high). This information could guide the use of more detailed clinical evaluation and diagnostic tests. Promising candidates include B-type natriuretic peptide (BNP or NT-proBNP), glomerular filtration rate estimated from serum creatinine (eGFR), C-reactive protein, and cardiac troponins. These biomarkers reflect levels of pre-existing organ dysfunction or pro-inflammatory states, which predispose to complications. A systematic review confirms the potential of NT-proBNP to predict short and medium term post-operative outcomes [18]. Clinical implementation is currently limited.

Box 360.1 End of surgery care bundle

- Use care bundle if POSSUM score likely to predict a mortality ≥5% OR if the patient has deteriorated during surgery.
- Risk score the patient using POSSUM.
- Check arterial blood gases to assess lactate, acid-base status, and the ratio of arterial oxygen concentration to the fraction of inspired oxygen (P:F ratio).
- Summarize fluids given and draft ongoing fluid requirements.
- Use a nerve stimulator and reverse muscle relaxant.
- Check and document temperature, plan further correction as necessary.
- Surgeon and anaesthetist to decide preferred level of care jointly and discuss any further therapeutic options.
- Recommend that all patients with a mortality risk ≥10% to go to level 2 or 3 care.
- Consider level 2 or 3 if the risk is 5–10% or there are other concerns.

Data from Anderson I et al., *The Higher Risk General Surgical Patient—Towards Improved Care for a Forgotten Group*, London: Royal College of Surgeons of England, 2011.

Post-operative assessment of risk

Late or unplanned admission to critical care carries with it a much higher mortality than planned admission [4]. Therefore, towards the end of higher risk surgery, much of which is emergent, time can be taken to re-evaluate the patient. One option is to use the surgical Apgar score [19]. This takes into account the estimated blood loss, lowest mean arterial pressure, and lowest heart rate to produce a ten point score for the prediction of 30-day complications and mortality. Another option is to employ an end of surgery care bundle (Box 360.1) [20]. Regular senior clinical input, active monitoring to detect the early signs of complications and the adherence to an enhanced recovery program are measures that can be used later in the post-operative course.

References

1. Weiser TG, Regenbogen SE, Thompson KD, et al. (2008). An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet*, **372**(9633), 139–44.
2. Pearse RM, Rhodes A, Moreno R, et al. (2011). EuSOS: European surgical outcomes study. *European Journal of Anaesthesiology*, **28**(6), 454–6.
3. Jhanji S, Thomas B, Ely A, Watson D, Hinds CJ, and Pearse RM. (2008). Mortality and utilisation of critical care resources amongst high-risk surgical patients in a large NHS trust. *Anaesthesia*, **63**(7), 695–700.
4. Pearse RM, Harrison DA, James P, et al. (2006). Identification and characterisation of the high-risk surgical population in the United Kingdom. *Critical Care*, **10**(3), R81.
5. Findlay G, Goodwin A, Protopappa K, Smith N, and Mason M. (2011). *Knowing the Risk; a Review of the Peri-operative Care of Surgical Patients*. London: National Confidential Enquiry into Patient Outcome and Death.
6. Head J, Ferrie JE, Alexanderson K, Westerlund H, Vahtera J, and Kivimaki M. (2008). Diagnosis-specific sickness absence as a predictor

of mortality: the Whitehall II prospective cohort study. *British Medical Journal*, **337**(oct02 2), a1469–a.
7. Khuri SF, Henderson WG, Depalma RG, Mosca C, Healey NA, and Kumbhani DJ. (2005). Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Transactions of the Meeting of the American Surgical Association*, **123**(&NA), 32–48.
8. Jencks SF, Williams MV, and Coleman EA. (2009). Rehospitalizations among patients in the Medicare fee-for-service program. *New England Journal of Medicine*, **360**(14), 1418–28.
9. Kheterpal S, Tremper KK, Englesbe MJ, et al. (2007). Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. *Anesthesiology*, **107**(6), 892–902.
10. Charlson ME, Pompei P, Ales KL, and MacKenzie CR. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases*, **40**(5), 373–83.
11. Copeland G, Jones D, and Walters M. (1991). POSSUM: a scoring system for surgical audit. *British Journal of Surgery*, **78**(3), 355-60.
12. Nashef SAM, Roques F, Sharples LD, et al. (2012). EuroSCORE II. *European Journal of Cardiothoracic Surgery*, **41**(4), 734–44; discussion 44–5.
13. Lee TH, Marcantonio ER, Mangione CM, et al. (1999). Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*, **100**(10), 1043–9.
14. Snowden CP, Prentis JM, Anderson HL, et al. (2010). Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major elective surgery. *Annals of Surgery*, **251**(3), 535–41.
15. Older P, Hall A, and Hader R. (1999). Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly. *Chest*, **116**(2), 355–62.
16. Older P, Smith R, Courtney P, and Hone R. (1993). Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. *Chest*, **104**(3), 701–4.
17. Hennis PJ, Meale PM, and Grocott MP. (2011). Cardiopulmonary exercise testing for the evaluation of perioperative risk in non-cardiopulmonary surgery. *Postgraduate Medical Journal*, **87**(1030), 550–7.
18. Rodseth RN, Padayachee L, and Biccard BM. (2008). A meta-analysis of the utility of pre-operative brain natriuretic peptide in predicting early and intermediate-term mortality and major adverse cardiac events in vascular surgical patients. *Anaesthesia*, **63**(11), 1226–33.
19. Gawande AA, Kwaan MR, Regenbogen SE, Lipsitz SA, and Zinner MJ. (2007). An Apgar score for surgery. *Journal of the American College of Surgery*, **204**(2), 201–8.
20. Anderson I, Eddlestone J, Lees N, et al. (2011). *The Higher Risk General Surgical Patient—Towards Improved Care for a Forgotten Group*. London: Royal College of Surgeons of England.

CHAPTER 361

Peri-operative optimization of the high risk surgical patient

Monty Mythen and Michael P. W. Grocott

Key points

- Flow-based cardiovascular variables, such as cardiac output and oxygen delivery predict perioperative outcome better than alternative, predominantly pressure-based, measures (e.g. heart rate, blood pressure, central venous pressure).
- Targeting flow-based goals, using fluid boluses with or without additional blood or vasoactive agents, in patients undergoing major surgery has been shown to improve outcome in some studies.
- Early studies used pulmonary artery catheters to monitor blood flow, but newer studies have used less invasive techniques such as oesophageal Doppler monitoring and pulse contour analysis.
- Meta-analysis of the current evidence suggests that this approach is unlikely to cause harm, may not reduce mortality, but does reduce complications and duration of hospital stay.
- Large multi-centre clinical trials are underway.

Introduction

The terms 'peri-operative optimization' and 'goal-directed therapy' (GDT) are commonly used to describe a bundle of care where additional therapy is given with the aim of increasing global blood flow to predefined explicit goals. The origins of this approach are usually ascribed to William Shoemaker, a Surgeon from the USA. Shoemaker et al. observed that survivors of high-risk major surgery had significantly higher cardiac index, oxygen delivery (DO_2) and oxygen consumption (VO_2) measured with a pulmonary artery catheter (PAC), compared with non-survivors. While the oxygen flux measures discriminated between survivors and non-survivors, the commonly measured haemodynamic variables (heart rate (HR), blood pressure (BP), urine output (UO), and central venous pressure (CVP), etc.) did not.

In a follow-up randomized controlled trial (RCT), the same group demonstrated a dramatic (some would say incredible) reduction in mortality (33% to 4%) when the interventional group was given additional fluid and, if required, an intravenous dobutamine infusion, with the aim of achieving specific goals for cardiac index (2.5 L/min/m^2), DO_2i (600 mL/min/m^2) and VO_2i (170 mL/min/m^2) guided by PAC [1]. There followed a series of single-centre trials that tested a similar approach and obtained similar results, notably from Boyd et al. and Wilson et al. [2,3].

In the 1990s, relatively non-invasive cardiac output monitoring became more readily available and reliable. In particular, the oesophageal Doppler monitor (ODM) developed by Singer and Bennett opened the way for testing a similar approach in a lower risk group of patients [4]. Mythen and Webb tested optimization of cardiac stroke volume measured with the ODM by the administration of additional colloid boluses compared with standard of care, and found improved indices of tissue perfusion and better clinical outcomes (reduced complications and length of hospital stay) in a small study of patients undergoing cardiac surgery [5]. There followed a number of single-centre RCTs using the ODM to guide administration of fluid boluses to achieve 'optimal' stroke volume, commonly without additional vaso-active drugs, with broadly similar results in terms of morbidity and length of hospital stay [6–8]. More recently, alternative cardiac output measurement devices have been tested with similar results [9].

Possible mechanisms and face validity

The beneficial effects are thought to result from avoiding hypovolaemia, tissue hypoperfusion, and tissue hypoxia with consequent minimization of inflammatory pathway activation. Predictors of poor outcome following major surgery include age, co-morbidities, poor functional capacity (low VO_2 at anaerobic threshold), the magnitude of tissue trauma, and surrogates of tissue hypoperfusion and hypoxia, such as lactic acidosis and low venous oxygen saturations. Studies using gastric tonometry to measure gut mucosal perfusion demonstrated occult splanchnic perfusion in patients undergoing elective major surgery that was not detectable with routine haemodynamic variables (e.g. HR, BP, UO), but was associated with reduced cardiac stroke volume suggesting central hypovolaemia. The same patients also demonstrated increased systemic inflammation. Pro-actively treating patients with a goal-directed approach that includes fluid boluses to avoid central hypovolaemia and results in a relative increase in oxygen flux should improve indices of end-organ perfusion, avoid complications and improve outcome. This is a central tenet of this approach, but the physiological goals used are diverse (e.g. specific DO_2 value versus maximum stroke volume versus oxygen extraction ratio or mixed venous oxygen saturation). Thus, the literature is difficult to interpret.

What does the evidence show?

A recently published Cochrane systematic review and meta-analysis summarized the clinical effects of increasing perioperative blood

flow using fluids with or without inotropes/vasoactive drugs to explicit defined goals in adults [10]. The authors included randomized controlled trials of adult patients (aged 16 years or older) undergoing surgery. The review included 31 studies of 5292 participants (Table 361.1). There was no difference in mortality at the longest follow-up: 282/2615 (10.8%) died in the control group and 238/2677 (8.9%) in the treatment group, RR of 0.89 (95% CI: 0.76–1.05; p = 0.18). However, the intervention did reduce the rate of three morbidities (renal failure, respiratory failure, and wound infections). The number of patients with complications was also reduced by the intervention. The authors also concluded that it was unlikely that the intervention causes harm [10] and that although the balance of current evidence does not support widespread implementation of this approach to reduce mortality, it does suggest that complications and duration of hospital stay are reduced [10].

The practice of GDT

Ideally, GDT using advanced haemodynamic monitoring should be used for all patients undergoing major surgery, but this is not practical or affordable. Thus, a risk-adapted approach is commonly recommended (see Box 361.1). The level of monitoring and intensity and duration of care should be tuned to the risk of the patient in the context of the risk of the surgery. At the highest level, a full raft of haemodynamic and other monitors are utilized including cardiac output measurement, care is delivered by a team of the most experienced clinicians and is continued into the post-operative period in a higher dependency unit. Treatment algorithms vary, but a common component is administration of additional fluid boluses to treat objective evidence of central volume deficit (e.g. reduced stroke volume measure or stroke volume variation during controlled ventilation). The addition of a vasoactive agent (e.g. dopexamine) to achieve a predetermined level of DO_2 is also advocated by some groups.

Indicators of central hypovolaemia include:

- Blood and/or fluid loss.
- Tachycardia.
- Hypotension.
- Cool peripheries.

Table 361.1 Protocol to increase global blood flow compared to control for surgical patients. Summary of findings for the main comparison. Protocol to increase global blood flow compared with control for surgical patients

Patient or population: surgical patients
Settings: hospital
Intervention: protocol to increase global blood flow
Comparison: control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (grade)	Comments
	Assumed risk	Corresponding risk				
	Control	Protocol to increase global blood flow				
Mortality (longest follow-up)	11 per 100	10 per 100 (8–11)	RR 0.89 (0.76–1.05)	5292 (31 studies)	⊕⊕⊖⊖ low1,2	p = 0.18
Mortality (hospital or 28-day)	7 per 100	6 per 100 (5–7)	RR 0.81 (0.65–1.00)	5292 (31 studies)	⊕⊕⊖⊖ low1,2	p = 0.06
Number of patients with complications	40 per 100	27 per 100 (23–32)	RR 0.68 (0.58–0.80)	1841 (17 studies)	⊕⊕⊖⊖ low1,2	p < 0.00001
Length of hospital stay		The mean length of hospital stay in the intervention groups was 1.16 lower (1.89–0.43 lower)		4729 (27 studies)	⊕⊕⊖⊖	p = 0.002

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1. The majority of studies are unblinded due to the nature of the intervention and, hence, it is suggested 'unclear risk for most of the studies'.

2. Most studies had small number of patients.

CI, confidence interval; RR, risk ratio.

Box 361.1 Recommendations for the use of intra-operative fluid management technologies

The Enhanced Recovery Partnership recommends that all anaesthetists caring for patients undergoing intermediate or major surgery should have cardiac output measuring technologies immediately available and be trained to use them.

The use of intra-operative fluid management technologies are recommended from the outset in the following types of cases:

- Major surgery with a 30-day mortality rate of ≫1%.
- Major surgery with and anticipated blood loss of greater than 500 mL.
- Major intra-abdominal surgery.
- Intermediate surgery (30-day mortality ≫0.5%) in high-risk patients (age ≫80 years, history of left ventricular failure, myocardial infarction, cerebrovascular accident, or peripheral arterial disease).
- Unexpected blood loss and/or fluid loss requiring ≫2 L fluid replacement.
- Patients with ongoing evidence of hypovolaemia and or tissue hypoperfusion (e.g. persistent lactic acidosis).

- Low CVP.
- Low cardiac output.
- Reduced stroke volume.
- Systolic or pulse pressure variation (during intermittent positive pressure ventilation (IPPV)).
- Pre-load responsiveness.
- Low central venous O_2 saturation.
- Surrogate measures of tissue hypoxia (e.g. lactic acidosis).

Central hypovolaemia should respond to intravascular volume expansion therapy (i.e. a fluid bolus).

Consensus and ongoing controversies regarding GDT

There is broad consensus, certainly amongst proponents of 'enhanced recovery' or 'fast track' surgery that a goal-directed approach, individualized for each patient, risk adapted to be consistent with locally-developed guidelines and regular audited, results in better patient outcomes [11,12]. Furthermore, it is now recognized that peri-operative fluid management is a serious issue that, if poorly done, can cost higher risk patients their lives: too much or too little fluid is not in the patient's best interest. There is also broad agreement that the judicious use of vasopressors is appropriate for anaesthesia-induced hypotension. However, little, if any of this is supported by the highest levels of evidence. Thus, there are many areas of ongoing controversy, including choice of advanced haemodynamic monitor, the importance (or not) of blood transfusion as part of the intervention (and the target Hct), the use of colloid or crystalloid fluids, the use of vasoactive agents to increase DO_2, the use of vasopressors to target BP, and choice of target flow goals (numerical value of DO_2 versus maximizing SV or oxygen extraction measure—all conceptually different). Given the uncertainty about which goals to choose, and in the context of dramatically reduced use of the PAC, the best current evidence based recommendation is to target SV using colloid boluses [11,12].

The paucity of data from large RCTs to inform these decisions underlines the need for further research. The largest study to date was the Sandham study [13]. This was a RCT of the use of PACs in high-risk surgical patients. It was a multicentre study of 3803 eligible patients, of whom 1994 were randomized into two groups. Overall, there was no difference in mortality between patients who were managed with a pulmonary-artery catheter (7.8% mortality) compared with those managed using a central venous pressure catheter (7.7%). Patients managed with a PAC had a higher rate of pulmonary embolism (8 events versus 0 events; $p = 0.004$), but there was a trend towards less renal failure in patients managed using a PAC. All patients were admitted to intensive care in the post-operative period, which was not the standard of care, i.e. both groups underwent a minimum post-operative intensive care unit stay of 24 hours. Patients were a mixture of ASA grade III and IV cases, of which the majority were major vascular (around 50%) and abdominal (around 20%). This is often referred to as an optimization study, although the title of the paper talks about it being a study of randomization to PAC or no PAC. The haemodynamic algorithm for the PAC group is a set of suggested interventions, namely the administration of fluid boluses, vasoactive drugs and/or packed red blood cells, but only around 50% of patients received any intervention. The haemodynamic goals chosen were lower than those reported to produce benefit in previous studies and the majority of patients do not achieve the protocol goals in the pre- and intra-operative period. Only in the post-operative period did around 50% of patients get above the 600 mL/min/m^2 for oxygen delivery. In other words, this study was probably not designed to evaluate GDT. Of note, this study was also not properly controlled (no PAC in control group), there was loss to follow-up and, notwithstanding the reported 'no-harm' signal, there was some evidence of clinical benefit with PAC usage (reduced renal failure) [13]. At the time of writing the 'OPTIMISE' trial—a large multicentre UK trial looking at dopexamine supplemented goal-directed therapy—has completed recruitment and the results are eagerly anticipated.

In England, an Enhanced Recovery after Surgery program was rolled out nationally from 2009 to 2012 [11,12]. This programme strongly recommended a goal-directed approach to peri-operative fluid management with the development, implementation, and regular audit of local algorithms that incorporated a low threshold for the use of advanced haemodynamic monitors [11,12]. The programme delivered the goals of reduced length of hospital stay for four categories of major surgery (colorectal, gynaecology, orthopaedic, and urology), reduced bed usage, no increase in readmissions and improved patient satisfaction. A recently published DELPHI consensus process conducted in England confirmed the use of advanced haemodynamic monitors and goal-directed

peri-operative fluid management was strongly supported [12]. The results of large multicentre studies are anticipated.

References

1. Shoemaker WC, Appel PL, Kram HB, Waxman K, and Lee TS. (1988). Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest*, **94**, 1176–86.
2. Boyd O, Grounds RM, and Bennett ED. (1993). A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *Journal of the American Medical Association*, **270,** 2699–707.
3. Wilson J, Woods I, Fawcett J, et al. (1999). Reducing the risk of major elective surgery: randomized controlled trial of preoperative optimization of oxygen delivery. *British Medical Journal*, **318,** 1099–103.
4. Singer M, Clarke J, and Bennett ED. (1989). Continuous hemodynamic monitoring by esophageal Doppler. *Critical Care Medicine*, **17**(5), 447–52.
5. Mythen MG and Webb AR. (1995). Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Archives of Surgery*, **130,** 423–9.
6. Sinclair S, James S, and Singer M. (1997). Intraoperative intravascular volume optimization and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *British Medical Journal*, **315,** 909–12.
7. Gan TJ, Soppitt A, Maroof M, et al. (2002). Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology*, **97,** 820–6.
8. Wakeling HG, McFall MR, Jenkins CS, et al. (2005). Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *British Journal of Anaesthesia*, **95,** 634–42.
9. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, and Bennett ED. (2005). Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Critical Care*, **9,** R687–93.
10. Grocott MPW, Dushianthan A, Hamilton MA, et al. (2012). Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery. *Cochrane Database of Systematic Reviews*, **11,** CD004082.
11. Mythen MG, Swart M, Acheson N, et al. (2012). Perioperative fluid management: Consensus statement from the enhanced recovery partnership. *Perioperative Medicine*, **1**, 2. Available at: http://www.perioperativemedicinejournal.com/content/1/1/2.
12. Knott A, Pathak S, McGrath JS, et al. (2012). Consensus views on implementation and measurement of enhanced recovery after surgery in England: Delphi study. British Medical Journal, **2**(6), p. ii: e001878.
13. Sandham JD, Hull RD, Brant RF, et al. (2003). A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *New England Journal of Medicine*, **348,** 5–14.

PART 19.2

General post-operative intensive care

CHAPTER 362

Post-operative ventilatory dysfunction management in the ICU

Paolo Chiarandini and Giorgio Della Rocca

Key points

- Mechanical ventilation impairs respiratory function and gas exchange, even in normal subjects.
- Lung protective strategies (low tidal volume, recruitment manoeuvres, positive end-expiratory pressure) should always be adopted.
- Avoid post-operative residual curarization (PORC).
- Extubate early and avoid unnecessary mechanical ventilation to prevent pneumonia.
- Adequate analgesia and post-operative NIV in high-risk patients could help respiratory recovery and reduce complications.

Introduction

Alterations in respiratory function and gas exchanges are frequently seen in patients during anaesthesia and in the post-operative period. Hypoxaemia occurs frequently during general anaesthesia, even in patients with normal lungs, and peri-operative ventilatory dysfunction is a common and recognized problem after surgery. It contributes to surgical morbidity and mortality. Patients' pre-operative respiratory status, types of surgery (abdominal, thoracic, laparoscopic), length of procedure, and anaesthesia (mechanical ventilation, use of inhalational anaesthetics, excessive fluid administration, narcotic, and muscle relaxant use), all contribute to impairment of respiratory function (e.g. airway patency, ventilatory drive suppression, ventilation/perfusion mismatch, shunt, and atelectasis).

Ventilatory dysfunction in anaesthesia

In the anaesthetized patient there is an increase in shunt (both 'true shunt' and 'venous admixture') from 1–2% (awake) to 8–10% impairing ventilation/perfusion ratio (V/Q) and gas exchange [1]. Changes in lung volumes and respiratory mechanics also occur. Supine position and loss of respiratory muscle tone reduces end-expiratory lung volume (up to 40%) and functional residual capacity (FRC). In patients in whom closing volume is near to FRC during spontaneous breathing (elderly and chronic obstructive pulmonary disorder (COPD) patients), air trapping and auto-PEEP can develop reducing tidal ventilation when mechanically ventilated. Compliance is also reduced from a mean of 95 to 60 mL/cmH_2O, partially due to the reduction in FRC [2]. An increase in resistance is then observed. Areas of atelectasis appear in almost 90% of anaesthetized patients [3]. Consequently, a decrease in PaO_2/FIO_2 ratio can be observed. This is often not clinically relevant with haemoglobin saturation rarely decreasing below 90%, because of the use of relatively high inspiratory oxygen fractions (FIO_2 0.4). In patients in whom respiratory reserve is already diminished, either before surgery or because of surgery (i.e. lung resections), a decrease in PaO_2/FIO_2 ratio can reduce blood oxygenation in a pathological way, requiring even higher FIO_2.

Lung protective strategies in anaesthesia

Tidal volume (V_t) during spontaneous ventilation in healthy subjects is around 6 mL/kg of ideal body weight. In past years V_t of 10–15 mL/kg were frequently used during mechanical ventilation to avoid atelectasis formation, and considered safe if a plateau pressure below 30 cmH_2O was maintained. However, an excessive stretch of alveolar walls (**volutrauma**), along with increased transpulmonary pressure (**barotrauma**), the cyclic opening and closing of alveoli (**atelectrauma**) and inflammatory mediators (**biotrauma**), can induce inflammation or sensitization of the lung to ventilator-induced lung injury (VILI). The concept of 'protective ventilation' was developed in anaesthetized patients. The goal of mechanical ventilation during anaesthesia is to provide good oxygenation and CO_2 removal, and keep tidal volume and pressures as close as possible to physiological values or as low as possible, while avoiding atelectasis formation with recruitment manoeuvres and PEEP [4]. Unfortunately, at the moment, prospective randomized controlled trials have not yet demonstrated particular clinical targets.

There are several methods published to recruit alveoli, mainly based on sustained pressure for a single or multiple periods. These include intermittent 'sighs', and progressive changes in PEEP and/or tidal volume for fixed periods. Most of them result in improvement in alveolar gas exchange, but there is no consensus in one prevailing among the others [5].

There is no agreement on appropriate PEEP levels during anaesthesia. The goal is to prevent atelectasis formation, reduce airway

closure, elevate FRC, and avoid high oxygen concentrations. This must be counterbalanced by the haemodynamic effects of PEEP on venous return and the right heart. There is general clinical consensus that PEEP levels of 5–10 cmH_2O are well tolerated by patients. A recent systematic review on this topic, published by the Cochrane Anesthesia Review Group, failed to demonstrate a statistically significant impact of intra-operative PEEP on post-operative mortality and respiratory complications. However, a trend to an increase in PaO_2/FIO_2 ratio and a decrease in post-operative atelectasis appears, without increasing barotrauma and cardiac complications [6].

Atelectasis

There are three mechanisms contributing to the development of atelectasis—compression of lung tissue, absorption of alveolar air, and impairment of surfactant function [7]. All three mechanism can cause atelectasis independently or together. Airless regions in the lungs can be detected 5 minutes after induction of anaesthesia. Once these regions develop, reopening them can require airway pressures up to 40 cmH_2O [8]. Factors associated to the development of atelectasis intra-operatively are type of anaesthesia, use of muscle relaxants, position, time ventilated, inspired oxygen concentration, patient's age, and obesity. Development of atelectasis intra-operatively is associated with decreased lung compliance, impairment of oxygenation, increased pulmonary vascular resistance, and development of lung injury. The adverse effects of atelectasis persist in the post-operative period and can impact patient recovery. Atelectasis can persist for 2 days after major surgery.

Residual neuromuscular blockade

Muscle activity, mainly diaphragmatic, creates the driving force during inspiration in spontaneous breathing and modifies chest diameters to allow ventilation in such a way that is not equally distributed to all lung regions. General anaesthesia reduces FRC and neuromuscular blockade agents (NMBA) commonly used in general anaesthesia, especially in abdominal surgery, can worsen this effect.[9] In recent years, studies focusing on the effects of new antagonizing drugs for muscle blockade, have evidenced the clinical importance of post-operative residual curarization (PORC) in the early phases after surgery. The use of short-acting NMBA reduces post-operative pulmonary complications [10]. The use of clinical or subjective criteria to define decurarization (protrusion the tongue, sustained head raising for 5 seconds, vital capacity below normal, etc.) are non-specific and often unreliable. Only the use of objective monitoring tools (e.g. quantification of the train of four (TOF) ratio) can significantly decrease the incidence of PORC. The use of sugammadex (a novel and specific reversal drug) should be considered against the old cholinesterases inhibitors, such as neostigmine to reduce the incidence of PORC.

Acute lung injury (ALI)/adult respiratory distress syndrome (ARDS)

Mechanical ventilation in anaesthesia and acute respiratory failure (and its most severe form adult respiratory distress syndrome (ARDS)) share three features in common—hypoxaemia, altered chest mechanics/compliance, and consolidation/atelectasis. The basis of acute lung injury (ALI)/ARDS are inflammation of lung units and destruction of microscopic architecture, while mechanical ventilation causes alterations primarily modifying the functioning of the lungs. Clinical and experimental data show a link between the two, demonstrating mechanical ventilation can induce inflammation of the lungs and damage to the ultrastructure. This is the focus of lung protective ventilatory strategies. No clinical monitoring tool is currently able to determine when the normal lung starts injuring, probably because there is a continuum of injury triggers to the alveoli from the first positive pressure air insufflation to the last. These injury triggers depend on pressure and volume used, and time of use. Pre-operative lung status and systemic inflammation developing during surgery are also important.

Post-operative ventilatory dysfunction

Pneumonia

This is the most important infective complication that affects the respiratory system. The incidence varies from 9 to 40% and depends on different factors such as age, pre-operative status (BMI and smoking history), type of surgery, and history of cancer [10]. Atelectasis formation and pneumonia are presumed to be linked, although no experimental or clinical study has clearly demonstrated a causative effect. Nonetheless, some studies have shown reducing atelectasis formation reduces post-operative pneumonia. The best strategy to reduce the incidence of pneumonia in surgical patients is to restore physiological functions as quickly as possible. This is part of the peri-operative surgical strategy called 'fast-track surgery' that comprises a bundle of techniques aimed at shortening recovery phase and reducing complications. Early extubation is one of the most important, along with early mobilization, less-invasive surgical techniques, avoidance or fast removal of drain-tubes and catheters, etc. [11].

When mechanical ventilation must be prolonged after surgery, the risk of ventilator-associated pneumonia (VAP) increases. VAP is defined as a pulmonary infection that arises 48–72 hours after endotracheal intubation, and is a subset of hospital-acquired pneumonia (HAP). VAP represents more than 85% of ICU HAP. There are a lot of factors associated with VAP. The Institute for Healthcare Improvement (IHI) has proposed the concept of 'ventilator bundles' to allow clinicians to focus on selected evidence-based interventions that minimize the risk of pneumonia in ventilated patients—elevation of the head of the bed, daily sedation interruption, peptic ulcer disease prophylaxis and deep vein thrombosis prophylaxis. Diagnosis of VAP should be based on early and accurate identification of patients with pulmonary infection, timely collection of cultures, and initiation of antibiotics (often broad-spectrum antibiotics). The use of scores to identify infected patients, such as the Modified Clinical Pulmonary Infection Score (CPIS), has been recommended as has the use of customized antibiotic-treatment algorithm or guidelines based on local isolates and susceptibility profiles [12].

Pulmonary embolism

Before the extensive introduction of deep vein thrombosis (DVT) prophylaxis and early mobilization, the incidence of clinically relevant episodes of pulmonary embolism, was one of the major cause of morbidity and mortality in surgical patients. Since most thrombi are asymptomatic, the real incidence of DVT and pulmonary embolism (PE) is not clearly understood. However, when PE is clinically relevant, the impact on mortality,

morbidity, and health care resource utilization is so high that prevention is the most efficient therapeutic approach. Guidelines from the American College of Chest Physicians recommended routine thromboprophylaxis with low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin for patients at moderate risk, with LMWH for patients at higher risk, and with graduated compression stockings and/or intermittent pneumatic compression for those with significant risk of bleeding [13]. In patients with suspected PE, the gold standard for diagnosis is chest CT-angiography, being other diagnostic test such as chest radiography, D-dimer dosage, electrocardiogram, or echocardiography, less sensitive.

Therapeutic strategies to improve post-operative pulmonary function

Strategies to improve post-operative pulmonary function or to minimize risk of complications should cover the full peri-operative period. Pre-operatively, there is no general consensus on the utilization of risk stratification scores. The same is true for functional tests (spirometry) or laboratory examinations. Clinical evaluation remains the best way to assess patient status and to guide further diagnostic work-up. Patient education measures like smoking cessation/reduction, have not given successful results if not instituted at least 2 months before surgery. Teaching the patient the proper use of manoeuvres designed to increase lung volumes after surgery seem to work better [14]. Intra-operatively, unnecessary manoeuvres that affect/damage chest and respiratory muscle integrity (type of surgical incision, use of devices to lift the thoracic cage, electrocauterization to the diaphragm) must be avoided. Protective ventilation and strategies to 'keep the lung open' (PEEP, low V_t, low pressures, and recruiting manoeuvres) should be adopted.

In the post-operative period, best results can be attained by increasing lung volumes by means of chest physiotherapy, use of incentive spirometry devices, and intermittent positive pressure breathing. In reviews and meta-analyses, no method demonstrated superiority over others, but all demonstrated the ability to decrease the frequency of post-operative pulmonary complications by a factor of two. Adequate post-operative analgesia must be assured to patients to allow good patient co-operation. Many studies have tried to demonstrate the advantage of one analgesic technique (regional versus intravenous, opioids versus local anaesthetics) over another. At the moment, no clear general recommendation can be made, except in COPD patients and thoracic surgery where epidural analgesia seems advantageous, together with a multimodal approach (e.g. anti-inflammatory agents and analgesics) [15]. The use of non-invasive ventilation in the early post-operative period, including continuous positive airway pressure with helmet or face-mask, seems a good and reasonable way to help patients' respiratory recovery and reduction of atelectasis, especially in high risk patients and those who have pre-operative respiratory dysfunction [16]. Data in general, cardiac, and thoracic surgery are encouraging, but populations studied and non-invasive ventilation strategies utilized, do not allow a recommendation for extensive use.

References

1. Hedenstierna G. (2003). Alveolar collapse and closure of airways: regular effects of anaesthesia. *Clinical Physiology & Functional Imaging*, **23,** 123–9.
2. Don H. (1977). The mechanical properties of the respiratory system during anesthesia. *International Anesthesiology Clinics*, **15**(2), 113–36.
3. Lundquist H, Hedenstierna G, Starndberg A, Tokics L, and Brismar B. (1995). CT-assessment of dependent lung densities in man during general anaesthesia. *Acta Radiologica*, **36,** 626–32.
4. Kilpatrick B and Slinger P. (2010). Lung protective strategies in anaesthesia. *British Journal of Anaesthesia*, **105**(S1), 108–16.
5. Tusman G and Bohm SH. (2010). Prevention and reversal of lung collapse during the intra-operative period. *Best Practice & Research Clinical Anaesthesiology*, **24**(2), 183–97.
6. Imberger G, McIlroy D, Pace NL, Wetterslev J, Brok J, and Moller AM. (2010). Positive end-expiratory pressure (PEEP) during anaesthesia for the prevention of mortality and postoperative pulmonary complications. *Cochrane Database Systematic Review*, **9,** CD007922.
7. Duggan M and Kavanagh BP. (2005). Pulmonary atelectasis: a pathogenic perioperative entity. *Anesthesiology*, **102**(4), 838–54.
8. Tusman G, Bohm SH, Tempra A, et al. (2003). Effects of recruitment maneuver on atelectasis in anesthetized children. *Anesthesiology*, **98**(1), 14–22.
9. Berg H, Roed J, Viby-Megensen J, et al. (1997). Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anesthesiologica Scandinavica*, **41**(9), 1095–103.
10. Canet J, Gallart L, Gomar C, et al. (2010). Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology*, **113**(6), 1338–50.
11. Olsen MF and, Wennberg E. (2011). Fast-track concepts in major open upper abdominal and thoracoabdominal surgery: a review. *World Journal of Surgery*, **35**(12), 2586–93.
12. Valencia M and Torres A. (2009). Ventilator-associated pneumonia. *Current Opinion in Critical Care*, **15**(1), 30–5.
13. Guyatt GH, Eikelboom JW, Gould MK, et al. (2012). Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients: antithrombotic Therapy and Prevention of Thrombosis, 9th edn. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, **141**(2 Suppl.), 185S–94S.
14. Lawrence VA, Cornell JE, Smetana GW, and American College Physicians. (2006). Strategies to reduce postoperative pulmonary complications after noncardiothoracic surgery: systematic review for the American College of Physicians. *Annals of Internal Medicine*, **144**(8), 596–608.
15. Popping DM, Elia N, Marret E, Remy C, and Tramer MR. (2008). Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. *Archives of Surgery*, **143**(10), 990–9.
16. Chiumello D, Chevallard G, and Gregoretti C. (2011). Non-invasive ventilation in postoperative patients: a systematic review. *Intensive Care Medicine*, **37**(6), 918–29.

CHAPTER 363

Post-operative fluid and circulatory management in the ICU

Claudia Ebm and Andrew Rhodes

Key points

- Post-operative complications are common and can be reduced with appropriate circulatory management.
- Optimal management of volaemic status is the most important part of circulatory management.
- Functional haemodynamic measurements are useful in predicting volume responsiveness.
- Titrating resuscitation to achieve an optimal cardiac index and oxygen delivery has been shown to improve outcomes.
- Modern haemodynamic monitors can provide this information in a near non-invasive fashion.

Introduction

Post-operative outcomes relate at least in part to the intra- and post-operative management of the circulation. Optimizing haemodynamics and ensuring adequate blood flow through the use of intravenous (iv) fluids and circulatory support remains an essential part of the peri-operative strategy. Although fluid therapy can be titrated very easily in many patients who are at low risk of post-operative complications, those with a limited cardiovascular or respiratory reserve represent more of a challenge. For such high-risk populations, which account for up to 15% of all surgical patients and more than 80% of all post-operative complications and deaths, a sophisticated haemodynamic strategy is important [1]. Demand-orientated 'individualized' fluid administration and consecutive inotropic or inodilator therapy can help to optimize oxygen delivery and, hence, reduce complication rates and duration of hospital stay [2–4].

A sophisticated post-operative strategy requires knowledge of the pathophysiological abnormalities that commonly occur in high-risk surgical patients. Haemodynamic derangements, either directly linked to peri-operative volume depletion or as a consequence of an inflammatory response to tissue trauma, lead to a decrease in preload, impaired cardiac contractility and low cardiac performance. Local malperfusion induced by such circulatory failure with increased requirements for oxygen due to the stress response, cause a net oxygen debt, cellular hypoxia, local tissue damage, and may ultimately result in multiple-organ failure (MOF), and death. Thus, the objective of fluid and circulatory therapy is to maintain the microvascular blood flow in order to balance oxygen supply with increased demand.

Post-operative fluid balance

The optimal circulatory strategy aims to correct intravascular volume deficits, while avoiding excessive fluid administration. Precisely estimating requirements for fluid administration is a challenge and fluid overload is often a reflection of poor fluid prescribing practices based on historical misunderstanding of post-operative physiology. This may be caused by the belief that pre-operative fluid depletion due to starvation and intra-operative fluid and electrolyte loss has to be corrected aggressively to avoid haemodynamic instability and organ malperfusion. This often results in an overall positive fluid balance, often far greater than actual losses require. Following the initial post-operative 'resuscitation' many authors have therefore explored the use of a restrictive fluid strategy in the subsequent period.

In 1990, Lowell et al. [5] reported the negative consequences of fluid overload and these results were confirmed in more recent studies showing that restrictive post-operative fluid regimens reduce hospital length of stay and complication rates [6,7]. Lobo has also compared restrictive (4 mL/kg/hour) versus liberal (12 mL/kg/hour) fluid regimens in high-risk surgical patients and observed lower complication rates (20.0 versus 41.9%, $p = 0.046$) associated with the restrictive regimen [8].

It is apparent that no single 'recipe' can be used to prescribe iv fluids for all patients' needs. The optimal practice, especially in patients with limited cardiovascular reserve, is to titrate fluids individually to monitored variables in the initial phase, then move rapidly to enteral fluids with the avoidance of large volumes of crystalloids. In this context, 'goal-directed therapy' can be used to titrate fluid administration individually and in light of the cardiovascular response to a given fluid challenge (Fig. 363.1).

Goal-directed therapy

Goal-directed therapy (GDT) is pragmatic stepwise strategy to guide and manipulate fluid and inotropic support by using flow and perfusion related measurements. GDT is based on the idea

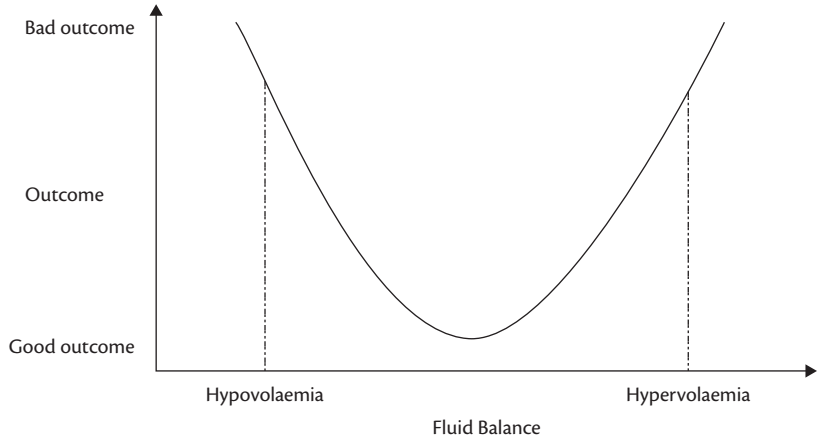


Fig. 363.1 The effect of total fluid balance on clinical outcome.

that optimal fluid therapy combined, in some circumstances with a vasodilator or positive inotropic agent, increases oxygen delivery to predefined goals. In particular, 'haemodynamic optimization' refers to optimizing tissue perfusion by manipulating stroke volume (SV), haemoglobin (Hb), and arterial oxygen saturation (SaO_2) to improve oxygen delivery (DO_2).

Aims of post-operative goal-directed therapy

The main aim of post-operative GDT is to improve cardiac performance, taking into account the pathophysiological alterations in high risk surgical patients. Haemodynamic optimization uses flow-related (cardiac output (CO) or DO_2) and perfusion (central or mixed venous oxygen saturation (SvO_2)) endpoints to guide fluid administration. The specific endpoints (targets) used have arisen from historic recognition that patients in low flow states have poorer outcomes. Shoemaker et al. [9], in a seminal work, identified the median values of cardiac index (4.5 L/min/m^2), oxygen delivery index (600 mL/min/m^2), and oxygen consumption index (170 mL/min/m^2) for survivors following major surgery and then used these targets as endpoints for resuscitation and demonstrated significant reduction in mortality. Although some of these endpoints, and the mechanisms to achieve them, have been refined over the subsequent twenty years, the main principles of this targeted approach to individualized management of the circulation remain the same.

Shoemaker's findings precipitated a series of trials targeting haemodynamic variables in order to improve outcome. In 2005, Pearse published a study in high-risk surgical patients treated with goal-directed therapy (GDT) in the post-operative recovery phase. This study advocates early resuscitation using predefined endpoints to guide fluid resuscitation coupled with manipulating cardiac output, afterload and contractility. Pearse et al. [4] randomized 122 patients to receive either conventional fluid plus circulatory management or early goal-directed therapy (EGDT) to achieve an oxygen delivery index of >600 mL/min/m^2. Individualized fluid resuscitation was commenced immediately after major surgery and maintained up to 8 hours. Although, the GDT group required more iv colloids (1907 SD ± 878 mL versus 1204 SD ± 898 mL; $p < 0.0001$) and inotropic support (dopexamine (55 patients (89%) versus 1 patient (2%); $p < 0.0001$), complication rates (44 versus 68%, $p < 0.0001$) and hospital length of stay (11 versus 14 days, $p = 0.001$) were significantly reduced in the treatment arm.

GDT can vary in a number of ways— timing (pre-, intra-, and post-operative), targets used (oxygen delivery, oxygen extraction, cardiac output, stroke volume, SvO_2, lactate), strategy (fluids and/or inotropic support), and monitoring techniques.

Timing

The original optimization studies all started in the pre-operative period and then continued through surgery into the intensive care unit (ICU) afterwards. This approach is intuitively sensible as it pre-empts problems in the circulatory system before they occur. However, for practical and logistic reasons (lack of ICU capacity and organizational difficulties) the technique never became popular and was rarely possible. Many authors have, therefore, begun to look at the effects of implementing such a strategy in the intra-operative phase or in the immediate post-operative period. GDT should be started as soon as possible and continued into the post-operative period. Although this is a pragmatic solution, it cannot be substituted for poor pre- and intra-operative practice, and it must be recognized that even optimal management in the post-operative period will never be able to compensate completely for prolonged circulatory dysfunction that has been poorly managed before the end of surgery.

Strategy

The first step in the haemodynamic management of post-operative patients is to assess tissue perfusion and oxygenation. Static measurements (central venous pressure (CVP), mean arterial pressure (MAP), urine output, pulmonary artery occlusion pressure (PAOP), etc.) have traditionally been used to estimate intravascular volume status and identify patients who are at risk of developing tissue malperfusion. However, in critically-ill patients such indices do not provide a reliable basis for preload optimization. In such situations, rather than relying on predefined absolute values, dynamic measurements can be used to predict the change in flow.

Dynamic measurements in these circumstances use one of three types of variable:

- Volume challenge.
- An assessment of preload reserve via either pulse pressure variation (PPV) or stroke volume variation (SVV).
- A passive leg raise manoeuvre [10].

Most authors have advocated the use of the 'fluid challenge', whereby a small volume of iv fluid is rapidly administered and the direct effects on changes in cardiac index monitored. More recently, the functional approach to predicting volume responsiveness has been described and used. Variations in pulse pressure (>13–15%) and stroke volume (>10%), induced by changes in intrathoracic pressure during a full respiratory cycle, have the ability to evaluate the current intravascular filling status, predict the response to fluid administration and enable the accurate administration of fluids. Fluid bolus will continue until the patient's preload is optimized. This is physiologically characterized by a move towards the flat part of the Frank–Starling curve, and clinically seen as a stagnant or decreasing SVV or PPV. In this phase, further fluid challenge would be harmful. However, such dynamic measurements are only efficacious in patients who are not breathing spontaneously and are in sinus rhythm. These circumstances are rarely applicable to the post-operative setting where other methodologies have to be used. Passive leg raising may be a practical alternative to assess the need for further fluid resuscitation. After a patient's legs are elevated to 45°, real-time changes in cardiac performance (stroke volume or cardiac output) are measured.

Haemodynamic monitoring

Technological advances allow for a more precise method to estimate cardiac output in order to detect subclinical volume depletion earlier. Cardiac output can be monitored using invasive methods, based on thermodilution techniques or the Fick method, or minimal-invasive methods that include oesophageal Doppler, transoesophageal echocardiography, lithium dilution, pulse contour analysis, or more experimental techniques, such as bioimpedance and bioreactance. While each of these has its own inherited strengths and weaknesses, the ideal system in the post-operative ICU setting should be non-invasive, continuous, accurate, reliable, and applicable to non-sedated patients.

More than 30 years ago, the pulmonary artery catheter (PAC) was introduced to monitor and manipulate the cardiovascular system in unstable patients. The widespread use of the PAC has become the topic of extensive debate, triggered by an absence of studies demonstrating a clear outcome benefit, as well as its unfavourable risk/benefit profile. Over the last decade a number of less invasive alternative tools emerged, with potential to replace the PAC. Several studies have shown oesophageal Doppler-guided optimization has the potential to improve outcome in the intra-operative phase. In the post-operative phase, however, the need for sedated patients limits its practicability. Many authors have thus started to look at less invasive techniques, such as arterial pressure-based devices that translate the arterial pressure signal line into flow-related information (pulse contour analysis).

Methodology for non-cardiac surgical patients

GDT should be initiated in the immediate post-operative phase and continued for up to 8 hours. The initial phase of optimization is characterized by rapid fluid administration. Small intravenous boluses of fluid (250 mL) are given to test the patient's preload reserve. This is repeated until the SV or CO fails to increase by a value of 10–15% from the baseline over an observation period of 20 minutes. Boluses can be repeated if the targeted endpoints subsequently increase again. As such, the physiological endpoint achieved is more of importance than the exact type of fluid. This concept has been described as 'stroke volume maximization'.

In some patients, perfusion is still inadequate despite optimal fluid loading. Several authors have used an oxygen delivery cut off of 600 mL/min/m^2 to identify this. In this group, low doses of inotropes have been shown to be beneficial in terms of reducing post-operative complications [2,11,12]. Dopexamine hydrochloride has been extensively studied the inotropic agent for this indication and a recent meta-analysis has revealed significant benefits with this approach.

Methodology for cardiac surgical patients

Post-cardiac surgical optimization has used different endpoints to the non-cardiac population. In this group, it is rarely possible to achieve an indexed value of oxygen delivery (DO_2I) of 600 mL/min/m2 and the use of increased doses of inotropic agents may be harmful. Authors have therefore chosen to either normalize the lactate and/or mixed venous oxygen saturation or just cardiac index, aiming for values greater than those previously shown to be been predictive of poor outcomes. While Polonen [13] used a SvO_2 >70% and lactate (<2 mmol/L) as therapeutic goals in the immediate post-operative phase, McKendry [14] focused on achieving a stroke volume index >35 mL/m^2. Whatever the endpoints, the technique used remains similar, and has resulted in reduced complications and length of stay for the high-risk cardiac patient.

References

1. Pearse R, Harrison D, James P, et al. (2006). Identification and characterisation of the high-risk surgical population in the United Kingdom. *Critical Care*, **10**, R81.
2. Donati A, Loggi S, Preiser JC, et al. (2007). Goal directed intraoperative therapy reduces morbidity and length of hospital stay in high risk surgical patients. *Chest*, **132**(6), 1817–24.
3. Gan TJ, Soppitt A, Maroof M, et al. (2002). Goal-directed intraoperative fluid administration reduced length of hospital stay after major surgery. *Anaesthesiology*, **97**(4), 820–6.
4. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, and Bennett ED. (2005). Early goal directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial. *Critical Care*, **9**(6), 687–93.
5. Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, and Bistrian BR. (1990). Postoperative fluid overload: not a benign problem. *Critical Care Medicine*, **18**, 728–33.
6. Brandstrup B, Tonnesen H, Beier-Holgersen R, et al. (2003). Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Annals of Surgery*, **238**, 641–8.
7. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, and Allison SP. (2002). Effect of salt and water balance on recovery of

gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet*, **359**(9320), 1812–18.
8. Lobo SM, Ronchi LS, Oliveira NE, et al. (2011). Restrictive strategy of intraoperative fluid maintenance during optimization of oxygen delivery decreases complications after high-risk surgery. *Critical Care*, **15**, 226.
9. Shoemaker WC, Montgomery ES, Kaplan E, and Elwyn DH. (1972). Physiological patterns in surviving and non-surviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. *Archives of Surgery*, **106**(5), 630–6.
10. Cecconi M, Parsons A, and Rhodes A. (2011). What is a fluid challenge? *Current Opinion in Critical Care*, **17**(3), 290–5.
11. Boyd O, Grounds M, Bennett D, et al. (1993). A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high risk surgical patients. *Journal of the American Medical Association*, **270**, 2699–707.
12. Lobo SM, Salgado PF, Castillo VG, et al. (2000). Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. *Critical Care Medicine*, **28**, 3396–404.
13. Polonen P, Ruokonen E, Hippelainen M, Poyhonen M, and Takala J. (2000). A prospective, randomized study of goal-oriented haemodynamic therapy in cardiac surgical patients.2000. *Anesthesia & Analgesia*, **90**(5), 1052–9.
14. McKendry M, McGloin H, Saberi D, et al. (2004). Randomized controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimization of circulatory status after cardiac surgery. *British Medical Journal*, **329**(7460), 258.

CHAPTER 364

Enhanced surgical recovery programmes in the ICU

Michael J. Scott and Monty Mythen

Key points

- Enhanced recovery programmes (ERPs) are evidence-based peri-operative care pathways.
- Patient-centred care delivered by a multidisciplinary team improves consistency and quality of care, resulting in reduced length of stay.
- Evidence is emerging that ERPs reduce the incidence of medical complications.
- Minimally invasive surgery, individualized analgesia, and goal-directed fluid therapy are key elements for optimal outcomes to ensure early gut function and mobility.
- The use of critical care facilities within ERPs is desirable to deliver optimal post-operative care in high risk patients or in patients who have complications.

History and development of enhanced recovery pathways

Enhanced recovery after surgery (sometimes termed 'fast-track' surgery) was introduced in the 1990s by Kehlet in Copenhagen, Denmark. At that time it was standard practice for patients undergoing colonic resection surgery to be left with drips and nasogastric tubes and no enteral nutrition for days post-operatively. He focused on a multimodal approach to reduce the stress response to surgery to enable early post-operative rehabilitation. His results of getting patients home after open colonic resection within 48–72 hours seemed extraordinary at a time when the length of stay for patients undergoing colorectal surgical resection was 1–2 weeks. In order to facilitate this, many different pre-operative, peri-operative, and post-operative elements were used. Rather than focusing on the surgery itself he focused on enhancing recovery by implementing evidence based practice in the fields of analgesia, anaesthesia, nutrition, reduction of surgical stress, and early ambulation [1]. He involved anaesthesiologists, nurses, and physical therapists as active participants of the care team.

The overall aim of an ERP is to deliver an evidence-based peri-operative care pathway to improve outcome. The ERP aims to reduce surgical stress and enhance post-operative physiological function with a resulting early return of enteral diet and mobilization. The increase in adoption of laparoscopic techniques in colorectal surgery together with ERPs has led to reduced length of stay with Rockall's group demonstrating that ultra-short length of stay of 23 hours are possible even in complex colorectal resections [2].

ERP elements and grading of evidence in colorectal surgery

Table 364.1 lists the 20 most recent ERP Elements, their recommendation with evidence level and recommendation grade for elective colonic surgery [3].

Evidence base for enhanced recovery programmes

There are few large randomized controlled studies comparing ERPs with standard pathways. Fig. 364.1 shows the results a Cochrane review looking at the evidence base for reduction in length of stay and reduction in complications [4]. This showed a mean reduction of 2.51 days and a risk ratio favouring ER to reduce complications of 0.52.

Many of the ER elements have been accepted and adopted into standard surgical practice. The difference between 'new' enhanced recovery programmes (ERPs) and standard surgical pathways has therefore reduced, which has affected the ability for future studies to identify differences. It is also important to look at compliance in the treatment group, as well as which ERP elements have been included in the standard control group. The compliance and efficacy of certain elements, such as epidural analgesia and fluid management can be difficult to compare between groups due to practical implementation and efficacy.

Although it is recognized that it is the combination of all the ERP elements that leads to improved outcomes, there has been interest in trying to identify if certain elements are more important than others to obtain improved outcomes. A review by Gustafsson looked at 114 variables in a single centre using enhanced recovery over 6 years [5]. The association between adherence to the ERP protocol and post-operative symptoms, complications, and length of stay following major colorectal cancer was compared. Comparing patients from 2002–4 to 2005–7, there was an increase in compliance with ERP elements from 43.3 to 70.6% with resulting reduction of post-operative complications (odds ratio 0.73) and unwanted symptoms (odds ratio 0.53). Restriction of intravenous fluid and oral carbohydrate loading were major independent predictors. The proportion of adverse post-operative outcomes was

Table 364.1 Guidelines for perioperative care in elective colonic surgery: enhanced recovery after surgery (ERAS®) society recommendations

Item	Recommendation	Evidence level	Recommendation grade
Pre-operative information, education and counselling	Patients should routinely receive dedicated preoperative counselling Pre-operative general medical optimisation is necessary before surgery	Low	Strong
Pre-operative optimization	Smoking and alcohol consumption (alcohol abusers) should be stopped 4 weeks before surgery	**Alcohol**: low **Smoking**: high	Strong
Pre-operative bowel preparation	Mechanical bowel preparation should not be used routinely in colonic surgery	High	Strong
Pre-operative fasting and carbohydrate treatment	Clear fluids should be allowed up to 2 hours and solids up to 6 hours prior to induction of anaesthesia	**Solids and fluids**: moderate	**Fasting guidelines**: strong
	Pre-operative oral carbohydrate treatment should be used routinely. In diabetic patients carbohydrate treatment can be given with the diabetic medication	**Carbohydrate loading, overall**: low carbohydrate loading, diabetic patients: very low	**Pre-operative carbohydrate drinks**: strong **Pre-operative carbohydrate drinks, diabetic patients**: weak
Pre-anaesthetic medication	Patients should not routinely receive long- or short-acting sedative medication before surgery because it delays immediate post-operative recovery	High	Strong
Prophylaxis against thromboembolism	Patients should wear well-fitting compression stockings, have intermittent pneumatic compression, and receive pharmacological prophylaxis with LMWH. Extended prophylaxis for 28 days should be given to patients with colorectal cancer	High	Strong
Antimicrobial prophylaxis and skin preparation	Routine prophylaxis using intravenous antibiotics should be given 30–60 minutes before initiating surgery. Additional doses should be given during prolonged operations according to half-life of the drug used Preparation with chlorhexidine-alcohol should be used	High	Strong
Standard anaesthetic protocol	A standard anaesthetic protocol allowing rapid awakening should be given	**Rapid awakening**: low	Strong
	The anaesthetist should control fluid therapy, analgesia and haemodynamic changes to reduce the metabolic stress response	**Reduce stress response**: moderate	
	Open surgery: mid-thoracic epidural blocks using local anaesthetics and low dose opioids	**Open surgery**: high	
	Laparoscopic surgery: spinal analgesia or morphine PCA is an alternative to epidural anaesthesia	**Laparoscopic surgery**: moderate	
PONV	A multimodal approach to PONV prophylaxis should be adopted in all patients with >2 risk factors undergoing major colorectal surgery. If PONV is present, treatment should be given using a multimodal approach	Low	Strong
Laparoscopy and modifications of surgical access	Laparoscopic surgery for colonic resections is recommended if the expertise is available	**Oncology**: high. **Morbidity**: low. **Recovery/LOSH**: moderate	Strong
Nasogastric incubation	Post-operative nasogastric tubes should not be used routinely. Nasogastric tubes inserted during surgery should be removed before reversal of anaesthesia	High	Strong
Preventing intra-operative hypothermia	Intra-operative maintenance of normothermia with a suitable warming device and warmed intravenous fluids should be used routinely to keep body temperature >36°C	High	Strong

(*continued*)

Table 364.1 Continued

Item	Recommendation	Evidence level	Recommendation grade
Peri-operative fluid management	Patients should receive intra-operative fluids (colloids and crystalloids) guided by flow measurements to optimize cardiac output	**Balanced crystalloids**: high. **Flow measurement in open surgery**: high. **Flow measurement in other patients**: moderate	Strong
	Vasopressors should be considered for intra- and post-operative management of epidural-induced hypotension provided the patient is normovolaemic	**Vasopressors**: high	
	The enteral. route for fluid post-operatively should be used as early as possible, and intravenous fluids should be discontinued as soon as is practicable	**Early enteral route**: high	
Drainage of peritoneal cavity after colonic anastomosis	Routine drainage is discouraged because it is an unsupported intervention that is likely to impair mobilization.	High	Strong
Urinary drainage	Routine transurethral bladder drainage for 1–2 days is recommended	Low	**Routine bladder drainage**: strong
	The bladder catheter can be removed regardless of the usage or duration of thoracic epidural analgesia		**Early removal if epidural used**: weak
Prevention of post-operative ileus	Mid-thoracic epidural analgesia and laparoscopic surgery should be utilized in colonic surgery if possible	**Thoracic epidural and laparoscopy**: high	**Thoracic epidural, fluid overload, nasogastric decompression, chewing gum, alvimopan**: strong
	Fluid overload and nasogastric decompression should be avoided	**Chewing gum**: moderate	
Post-operative analgesia	**Open surgery**: TEA using low-dose local anaesthetic and opioids	**TEA, open surgery**: high **Local anaesthetic and opioid**: moderate	Strong
	Laparoscopic surgery: an alternative to TEA is a carefully administered spinal analgesia with a low-dose, long-acting opioid	**TEA not mandatory in laparoscopic surgery**: moderate	
Peri-operative nutritional care	Patients should be screened for nutritional status and, if at risk of under nutrition, given active nutritional support	**Post-operative early enteral feeding, safety**: high. **Improved recovery and reduction of morbidity**: low	**Post-operative early feeding and feeding and peri-operative ONS**: strong
	Peri-operative fasting should be minimized. Post-operatively patients should be encouraged to take normal food as soon as lucid after surgery	**Peri-operative ONS (well-fed patient)**: low. **Peri-operative ONS (malnourished patient)**: low.	**IN**: IN could be considered in open colonic resections, weak
	ONS may be used to supplement total intake	**IN**: low	
Post-operative glucose control	Hyperglycaemia is a risk factor for complications and should therefore be avoided	**Using stress reducing elements of ERAS to minimize hyperglycaemia**: low	**Using stress reducing elements of ERAS to minimize hyperglycaemia**: strong
	Several interventions in the ERAS protocol affect insulin action/resistance, thereby improving glycaemic control with no risk of causing hypoglycaemia	**Insulin treatment in the ICU**: moderate	**Insulin treatment in the ICU (severe hyperglycaemia)**: strong. **Insulin treatment in ICU (mild hyperglycaemia)**: weak
	For ward-based patients, insulin should be used judiciously to maintain blood glucose as low as feasible with the available resources	**Glycaemic control in the ward setting**: low	**Insulin treatment in the ward setting**: weak

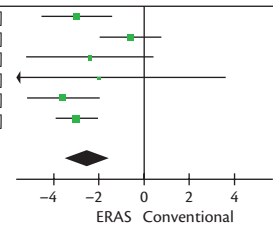
LMWH, low molecular weight heparin; PCA, patient controlled analgesia; PONV, post-operative nausea and vomiting; TEA, thoracic epidural analgesia; ONS, oral nutritional supplementation; IN, intravenous nutrition; ERAS, enhanced recovery after surgery; ICU, intensive care unit.

Adapted from *Clinical Nutrition*, **31**, 6, Gustafsson et al., 'Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations', p. 783–800, Copyright 2012, with permission from Elsevier and The European Society for Clinical Nutrition and Metabolism.

Length of hospital stay:

Study or Subgroup	ERAS Mean [days]	ERAS SD [days]	ERAS Total	Conventional Mean [days]	Conventional SD [days]	Conventional Total	Weight	Mean Difference IV, Random, 95% CI [days]
Anderson 2003	4	1.8	14	7	2.1	11	19.3%	−3.00 [−4.56, −4.11]
Delaney 2003	5.2	2.5	31	5.8	3	33	21.7%	−0.60 [−1.95, 0.75]
Gatt 2005	6.6	4.4	19	9	4.6	20	9.6%	−2.40 [−5.22, 0.4.2]
Khoo 2007	5	8.5	35	7	14.75	35	3.1%	−2.00 [−7.64, 3.64]
Muller 2009	6.7	4.84	76	10.3	4.97	75	19.2%	−3.60 [−5.17, 2.03]
Serclova 2009	7.4	1.3	51	10.4	3.1	52	27.1%	−3.00 [−3.92, −2.08]
Total (95% CI)			**226**			**226**	**100.0%**	**−2.51 [−3.54, −1.47]**

Heterogeneity: Tau^2 = 0.80; Chi^2 = 11.04, df = 5 (P = 0.05); I^2 = 55%
Test for overall effect: Z = 4.76 (P < 0.00001)



Complications:

Study or Subgroup	ERAS Events	ERAS Total	Conventional Events	Conventional Total	Weight	Risk Ratio M-H, Random, 95% CI
Anderson 2003	5	14	7	11	14.1%	0.56 [0.24, 1.29]
Gatt 2005	9	19	15	20	33.9%	0.63 [0.37, 1.08]
Khoo 2007	9	35	18	35	23.3%	0.50 [0.26, 0.96]
Serclova 2009	11	51	27	52	28.6%	0.42 [0.23, 0.75]
Total (95% CI)		**119**		**118**	**100.0%**	**0.52 [0.38, 0.71]**
Total events	34		67			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.17, df = 3 (P = 0.76); I^2 = 0%
Test for overall effect: Z = 4.07 (P < 0.0001)

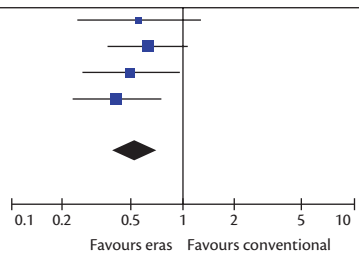


Fig 364.1 Length of stay and complications after surgery. Results of a Cochrane review (4).
Reproduced from Spanjersberg WR et al., 'Fast track surgery versus conventional recovery strategies for colorectal surgery', *Cochrane Database of Systematic Reviews*, **2**, p. 49, copyright 2011, with permission from John Wiley & Sons, Inc., and the Cochrane Collection.

significantly reduced with increasing adherence to the ERP protocol. It is therefore important even in centres with established ERPs to maintain high levels of compliance to the ERP elements using audit tools.

Those centres that have a high rate of operation completion with laparoscopic surgery and have adopted enhanced recovery with goal directed fluid therapy have a particularly good 5-year survival rate for colorectal disease [6]. It is unclear whether this is due to the reduction in stress response at the time of surgery, reduction in post-operative complications, the fact that patients receive chemotherapy sooner after primary surgery, or a combination of all these factors [7].

Controversies in ERPs

It is still unclear if all the ERP elements are necessary to obtain optimal outcomes. However, a lot of the elements interact with each other positively, which goes some way to explain why a higher compliance with the number of elements has shown an improvement in outcome.

Patients staying on the pathway are relatively straight forward and normally fulfil their pre-operative discharge goal, although when patients develop complications the outcome is more dependent on the surgical team identifying and treating the complication.

There remains controversy as to whether the elderly or those patients with significant co-morbidities are suitable for ERPs. If enhanced recovery reduces peri-operative stress and improves restoration of post-operative function, then these groups may well have most to benefit from ERPs.

Spread and adoption of ERPs

The demonstrated benefits of ERPs have led to a rapid spread and adoption by many surgical units throughout many countries. There have been publications in rectal surgery and pancreaticoduodenectomy with recommendations for other surgical specialties to follow [8].

In the United Kingdom the Department of Health set up the Enhanced Recovery Partnership Programme in 2009 to encourage adoption of ERPs. Initially the four specialties of colorectal, gynaecology, urology, and musculoskeletal surgery were rolled out. The programme was successful in bringing down length of stay and delivering high levels of patient satisfaction, while maintaining the same level of readmission rates. There has also been widespread adoption of the general principles and creation of ERPs in many of the other surgical specialties, including hepatobiliary, oesophagogastric, and breast, head, and neck surgery. The development of ERPs is now established in emergency specialties, such as fractured neck of femur and emergency laparotomy. The UK has been the first country to embed ERPs as a standard of care approved by all the relevant stakeholders including the Department of Health, health commissioning boards, and the Royal Colleges responsible for teaching and training.

The role of critical care in ERPs

There is wide variation in the use of intensive care within enhanced recovery pathways. The variation is not just between countries, but within surgical units in the same country due to different approaches to where to manage surgical patients post-operatively. There are a

variety of issues, including resource allocation, staffing issues, and practicalities of where goal-directed fluid therapy (GDFT) can be delivered. GDFT is done by using flow monitoring devices, such as the Oesophageal Doppler™ or arterial waveform analysis where fluid boluses of around 250 mL are given to see if the stroke volume increases by 10% or more [9]. This maintains the patient on the optimal part of the Starling curve and avoids relative hypovolaemia and splanchnic hypoperfusion. No more fluid is given if there is no increase in stroke volume and the clinical parameters and assessment are within the desired range. Maintaining normovolaemia in the immediate peri-operative period after cellular injury is also important. There is an increase in oxygen consumption, and cells need oxygen and nutrients to start repairing injury. There are often fluid shifts and changes in vascular capacitance, and resistance due to the use of vasopressors and regional anaesthesia. Oxygen debt during this post-operative period is highly likely to lead to complications. Currently, it is only really practical to achieve flow monitoring in the post-operative period when patients are awake with arterial pulse contour wave devices or utilizing oxygen extraction from central venous catheters. Once the period of fluid redistribution is complete intravenous fluid should be restricted to a minimum with the resumption of enteral intake as soon as tolerated and according to the surgical procedure.

It is accepted that a high-risk patient undergoing major surgery benefits from critical care and pre-emptive haemodynamic intervention, as do patients having high-risk surgery [10]. However, there is still a large group of patients who are neither high risk nor undergoing high risk surgery who have a high mortality and morbidity from surgery [11]. The problem is predicting which of those patients will need critical care and benefit from increased resource allocation. In reality, it is not always possible to predict this until the surgical procedure is complete and an assessment of the patient's condition has taken place. Therefore, assessment at the end of surgery plays an important role of where to place the patient post-operatively. The current economic pressure on health care systems to deliver more care for the same money makes ERPs attractive; however, the extra resources and costs needed to provide critical care post-operatively means it may not be practical to provide it for all patient groups.

In 2005, Khuri published data from the USA on eight types of operation identifying the predictors of 30-day mortality and long term survival [12]. It showed that a major post-operative complication had more of an effect on long-term life expectancy than pre-operative risk (Fig. 364.2). Birkmeyer has shown that the cost of inpatient episodes in the USA is much higher in centres with higher rates of complications and the average cost of a complication is $10,000 [13]. This further supports the use of critical care to support enhanced recovery pathways to optimize fluids and analgesia in the immediate post-operative period. Investment of resources at this time should lead to a reduction in complications and respective cost saving as well as benefiting the patient. Fig. 364.3 shows a practical approach to integrating goal-directed fluid therapy and utilization of critical care services in an enhanced recovery pathway.

Conclusion

Enhanced recovery pathways deliver patient-centred, evidence-based care. As well as improving patient experience and reducing length of stay there is increasing evidence that it reduces post-operative medical complications [14,15]. In order to achieve this well-structured pathways and trained multidisciplinary teams are needed with ongoing audit of compliance to maintain high quality results. ERPs enable more patients to be treated with improved outcomes with the same resources.

The use of critical care within ERPs is variable depending on local policy and patient and surgical risk factors, and whether there are significant surgical or medical issues immediately after surgery. The use of goal-directed fluid therapy may increase the use of critical care immediately post-operatively because of the lack of provision of this equipment and staff trained to use it in post-anaesthesia units or on surgical wards, but the reduction in complications may prove to be cost beneficial.

The increasing standardization of peri-operative care pathways using ERPs around the world opens up the possibility of

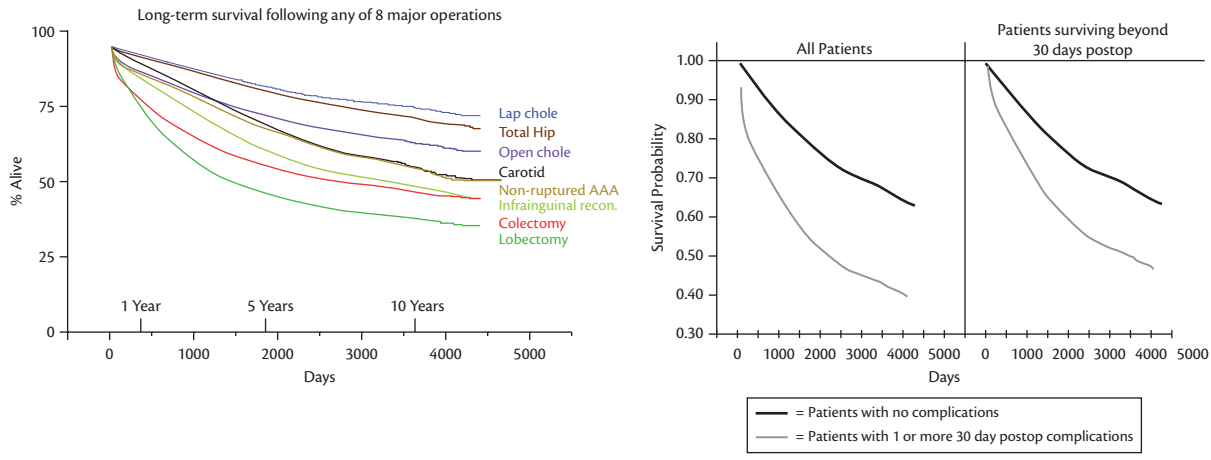


Fig 364.2 Long-term survival following surgery.

Reproduced from Khuri SF, 'Determinants of long-term survival after major surgery and the adverse effect of postoperative complications', *Annals of Surgery*, **242**(3), pp. 326–41; discussion 41–3, copyright 2005, with permission from Wolters Kluwer Health.

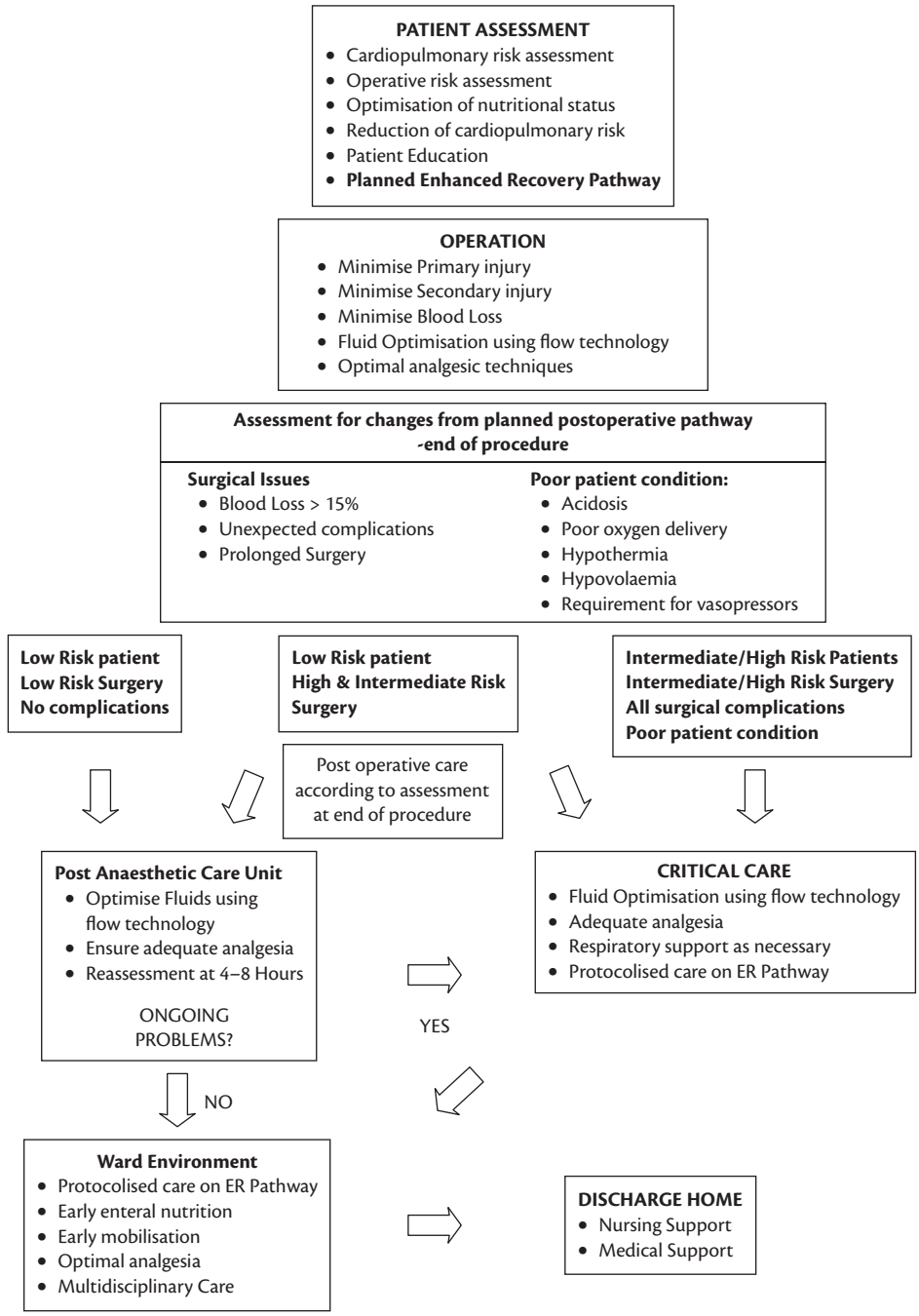


Fig 364.3 A protocol for combining an enhanced recovery pathway with flow-directed fluid administration and critical care.

performing multicentre randomized controlled studies to identify key treatment components or strategies, and quantify their effect on short- and long-term outcomes.

It is likely that enhanced recovery principles will be incorporated into critical care pathways in the future.

References

1. Kehlet H and Wilmore DW. (2002). Multimodal strategies to improve surgical outcome. *American Journal of Surgery*, **183**(6), 630–41.
2. Levy BF, Scott MJ, Fawcett WJ, and Rockall TA. (2009). 23-hour-stay laparoscopic colectomy. *Diseases of the Colon and Rectum*, **52**(7), 1239–43.
3. Gustafsson UO, Scott MJ, Schwenk W, et al. (2012). Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery after Surgery (ERAS®) Society recommendations. *Clinical Nutrition*, **31**(6), 783–800.
4. Spanjersberg WR, Reurings J, Keus F, and van Laarhoven CJ. (2011). Fast track surgery versus conventional recovery strategies for colorectal surgery. *Cochrane Database Systematic Reviews*, **2**, CD007635.
5. Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, and Nygren J. (2011). Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. *Archives of Surgery*, **146**(5), 571–7.
6. Day A, Smith R, Jourdan I, Fawcett W, Scott M, and Rockall T. (2012). Retrospective analysis of the effect of postoperative analgesia on

survival in patients after laparoscopic resection of colorectal cancer. *British Journal of Anaesthesia*, **109**(2), 185–90.
7. Fawcett WJ, Mythen MG, and Scott MJ. (2012). Enhanced recovery: more than just reducing length of stay? *British Journal of Anaesthesia*, **109**(5), 671–4.
8. Lassen K, Coolsen MM, Slim K, et al. (2012). Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society Recommendations. *Clinical Nutrition*, **31**(6), 817–30.
9. Mythen MG and Webb AR. (1995). Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Archives of Surgery*, **130**(4), 423–9.
10. Hamilton MA, Cecconi M, and Rhodes A. (2011). A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesthesia & Analgesia*, **112**(6), 1392–402.
11. Pearse RM, Moreno RP, Bauer P, et al. (2012). Mortality after surgery in Europe: a 7 day cohort study. *Lancet*, **380**(9847), 1059–65.
12. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, and Kumbhani DJ. (2005). Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Annals of Surgery*, **242**(3), 326–41; discussion 41–3.
13. Birkmeyer JD, Gust C, Dimick JB, Birkmeyer NJ, and Skinner JS. (2012). Hospital quality and the cost of inpatient surgery in the United States. *Annals of Surgery*, **255**(1), 1–5.
14. Jones C, Kelliher L, Dickinson M, et al. (2013). Randomized clinical trial on enhanced recovery versus standard care following open liver resection. *British Journal of Surgery*, **100**(8), 1015–24.
15. Walter CJ, Collin J, Dumville JC, Drew PJ, and Monson JR. (2009). Enhanced recovery in colorectal resections: a systematic review and meta-analysis. *Colorectal Disease*, **11**(4), 344–53.

PART 19.3

Obstetric intensive care

CHAPTER 365

Obstetric physiology and special considerations in ICU

Patrick J. Neligan and John G. Laffey

Key points

- A series of physiological and anatomic changes occur during pregnancy that make the mother vulnerable to a variety of insults arising from underlying disease, pregnancy related diseases, or coincidental disease.
- Early pregnancy is characterized by endocrine-related changes that alter cardiopulmonary and respiratory function to match the metabolic demands of the enlarging fetus. Later pregnancy is characterized by mechanical anomalies resulting from the presence of an expanding uterus that enlarges into the abdomen and abuts the chest wall.
- The physiological changes of pregnancy are significant, and may delay the diagnosis of critical illness and necessitate modifications to standard management approaches.
- There are two patients, mother and fetus. The fetus is generally robust despite maternal illness, and therapeutically what is good for the mother is generally good for the fetus.
- Trauma is the most common cause of non-obstetrical maternal death.

Introduction

Pregnancy is a normal physiological process that is defined by the presence of the uteroplacental complex. In order for pregnancy to commence and continue, the woman must possess sufficient physiological reserve to host an enlarging fetus that makes progressively greater metabolic demands. A series of physiological and anatomic changes occur in the mother during the course of the pregnancy that make her vulnerable to a variety of insults arising from underlying disease, pregnancy-related diseases, or coincidental disease. The intensivist must be aware of these changes as they impact upon our ability to care for these patients. In addition, intensivists must be able to recognize abnormal physiology, such as occurs in pre-eclampsia, which may result in life-threatening complications.

This chapter will outline the major physiological changes of pregnancy, and then consider how these changes impact on the care of the pregnant patient with non-obstetric critical illness.

Normal physiology of pregnancy

See Table 365.1 for physiological changes in various systems during pregnancy.

Respiratory system

As pregnancy progresses there is an increase in minute ventilation, resulting in relative hypocarbia ($PaCO_2$ is 5–10 mmHg below 'normal'). This is brought about by a 40% rise in tidal volume and a 15% rise in respiratory rate (2–3 breaths/minute); alveolar ventilation is about 70% greater [1]. In later pregnancy there is a profound reduction in functional residual capacity (FRC), resulting from reduced chest wall compliance associated with upward pressure from the uterus [1]. Consequently, administration of anaesthetics or sedatives may result in rapid development of hypoxaemia. The PaO_2 remains within normal limits throughout pregnancy. However, oxygen consumption increases progressively, so that at term mixed venous oxygen content may be significantly below normal. Oxygen consumption increases by up to 60% during labour.

The airway of the pregnant woman similarly undergoes significant changes that become more dramatic as parturition approaches—increased blood and plasma volume result in mucosal oedema and hypervascularity of the upper airways. This results in pharyngolaryngeal and vocal cord oedema and a friable mucosa. When 242 pregnant women's airways were examined at 12 weeks and subsequently at 36 weeks gestation, the percentage with Mallampati Class IV ('difficult') airways had increased by 34% [2]. Hence, difficult tracheal intubation is more likely encountered as term approaches.

Cardiovascular system

Significant changes occur in the cardiovascular system during pregnancy, due to increased vascular capacity particularly within the uterus, placenta, and breast tissue [3]. Consequently, blood volume increases progressively from 6–8 weeks gestation to 34 weeks with little change thereafter. There is physiological anaemia—the plasma volume increases 40–50%; the red cell mass increases only 20–30%. Cardiac output increases by approximately 25%, principally as a result of an increase in stroke volume (by one-third) and heart rate (by one-sixth). Total peripheral resistance falls, so the circulation is hyperdynamic. Blood pressure is normal or slightly below normal; hypertension is almost always pathological in pregnancy. Central venous pressure in the superior vena caval distribution remains 'normal', but femoral venous pressure may be higher than normal due to compression of the inferior vena caval system. There is significant venous distension, although this has little impact in critical illness [3].

Table 365.1 Physiological changes in various systems during pregnancy

System	Changes
Respiratory system	◆ Increased alveolar ventilation (70%) ◆ Relative hypocarbia ($PaCO_2$ 25–32 mmHg) ◆ Reduced FRC ◆ Increased O_2 consumption ◆ Reduced SvO_2.
Cardiovascular system	◆ **Increased cardiac output (20%)**: increased stroke volume 30%, Increased heart rate 15% ◆ Reduced total peripheral resistance ◆ Normal CVP in SVC distribution ◆ **Elevated CVP in IVC distribution**: aorto–caval compression ◆ Increased circulating volume ◆ Increased plasma volume (40–50%) ◆ **Increased red cell mass (20–30%)**: physiological anaemia
Gastrointestinal and metabolic	◆ Reduced lower oesophageal sphincter tone ◆ Reduced gastric pH: elevated risk of gastro-pulmonary aspiration ◆ Increased metabolism: • Carbohydrate^{+++} • Protein^{++} • Fat^{+} ◆ Hyperinsulinaemia and hypoglycaemia
Kidney	◆ Increase renal blood and plasma flow (50–60%) ◆ Increased glomerular filtration (50–60%) ◆ Reduced serum urea and creatinine ◆ Glycosuria ◆ Mild proteinuria
Haematopoietic system	◆ Reduced haemoglobin and haematocrit ◆ Slightly elevated leucocyte and platelet count ◆ Increased fibrinogen and clotting factors ◆ **Reduced fibrinolytic activity**: increased clotting tendency

Gastrointestinal and metabolic systems

The combination of decreased lower oesophageal sphincter tone during pregnancy, increased intra-abdominal pressure, delayed gastric emptying, and reduced gastric pH in labour, result in elevated risk and severity of gastropulmonary reflux. Pregnancy is a hypermetabolic–hypercatabolic state. There is a dramatic increase in basal metabolic rate with profound increase in glucose utilization, and lesser increases in fat and protein metabolism. Pregnant women are hence relatively hypoglycaemic. However, a cohort of patients will develop insulin resistance/hyperinsulinaemia associated with the release of human placental lactogen, cortisol, and oestrogen, that may manifest as hyperglycaemia or gestational diabetes [4].

Renal function

Renal plasma flow and glomerular filtration rate begin to increase progressively during the first trimester. At term, both are 50–60% higher than in the non-pregnant state in parallel with increases in blood volume and cardiac output. There is elevation in creatinine clearance, and serum levels of urea and creatinine are reduced by 40%. Hence, increasing serum creatinine during pregnancy is abnormal, and poses considerable risk to maternal and fetal health [5]. The dramatic increase in renal blood flow and glomerular filtration may result in overspill glycosuria and proteinuria. The renal calyses and ureters become dilated and atonic as pregnancy progresses, resulting in increased risk of urinary tract infection.

Haematopoietic system

The haemoglobin and haematocrit fall, but total body haemoglobin is increased. This is important as significant maternal blood loss occurs at delivery; the additional volume in the circulation acts as a reserve buffer, while contraction of the uterus autotransfuses the mother. Pregnancy is a hypercoagulable state—there are dramatic increases in fibrinogen and factor VII, X and XII levels [6]. There is also an increase in the number of platelets and a reduction in fibrinolytic activity. During pregnancy neither clotting nor bleeding times are abnormal.

Implications for care of critically ill pregnant patient

Sepsis

While bacteraemia in pregnancy is relatively common—reportedly between 8 and 9% of pregnancies—progression to severe sepsis and septic shock is relatively rare, with rates of sepsis of between 1 in 7654 to 1 in 8338 deliveries reported [7]. Despite this, sepsis is a major cause of maternal death in the United Kingdom, where this is well studied, largely due to a substantial increase in deaths related to Group A streptococcal genital tract sepsis [8]. Obesity and operative vaginal or caesarean delivery appear to be major risk factors [8,9].

Pregnancy predisposes to four different septic complications:

- Pyelonephritis.
- Chorioamnionitis (including septic abortion).
- Endometritis (following Caesarean delivery).
- Pneumonia.

Pyelonephritis results from colonization of the kidney with Gram-negative bacteria secondary to loss of ureteral sphincter tone associated with progesterone. Pneumonia results, at least in part, from aspiration of gastric contents consequent of loss of lower oesophageal sphincter tone and diaphragmatic elevation. Chorioamnionitis results from alterations in the pH and increased glycogen content of the vagina, resulting in loss of the barrier for bacterial entry. Chorioamnionitis may complicate chorionic villus sampling, amniocentesis, or attempted instrumental (septic) abortion.

The clinical manifestations of sepsis during pregnancy are similar to that of the non-pregnant patient. However, these 'classic' signs may be obscured by the cardiovascular alterations of pregnancy. Sepsis may rapidly progress in the pregnant patient, resulting in coagulopathy, vasoplegia, and evolving multiple organ failure. Purpura fulminans may be associated with Group A Streptococcal infection [10]. Physicians must have a high index of suspicion

for sepsis in any peripartum patient that presents with fever and evidence of organ dysfunction—confusion, oliguria, tachycardia, etc. If goal-directed resuscitation is utilized one must be aware of physiological changes of pregnancy and adjust the goals of the resuscitation accordingly. For example, although central venous pressure remains essentially unchanged during pregnancy, SvO_2 progressively decreases in the later stages. Hence, achieving goals of 70–75% may not be possible—or necessary—in this setting.

Acute respiratory distress syndrome

The physiological changes of pregnancy may predispose to acute respiratory distress syndrome (ARDS) in a number of ways. The most probable cause of acute lung injury in the pregnant patient is infection, either pneumonia or secondary to chorioamneiitis, endometritis, septic abortion, or retained products of conception. Other causes include pre-eclampsia, obstetric haemorrhage, and pulmonary aspiration of gastric contents.

The respiratory system in advanced pregnancy has distinct features that must be considered. Functional residual capacity is decreased secondary to upward displacement of the diaphragm by the gravid uterus, increasing predisposition to hypoxaemia. Hypocapnia is universal, so that what appears to be a normal range $PaCO_2$ (40 mmHg) may actually reflect ventilatory compromise. Hypercapnia is probably tolerated by the fetus better than hypoxaemia. In general, a PaO_2 of >70 mmHg is required to ensure fetal well-being.

Pregnant females are generally excluded from ARDS clinical trials, such as the ARDS network tidal volume study [11], so data regarding management is limited. However, the use of therapeutic goals for the pregnant patient that are similar to those for the non-pregnant patient seems reasonable. Manoeuvres such as prone positioning is possible, but technically difficult to perform in the pregnant patient, could compromise fetal monitoring, and abdominal compression must be avoided to prevent further cephalad displacement of the diaphragm. Recent data, from pregnant patients with H1N1-induced ARDS, reports good overall outcomes, and demonstrated the utility of extracorporeal membrane oxygenation in this population [12].

Thromboembolic and immune-embolic (amniotic fluid or fat embolism) disease may manifest with acute hypoxic respiratory failure, although the pathophysiological changes and clinical history are distinct from classic ARDS.

Thromboembolic disease

Pregnancy is a hypercoagulable state. Pregnant females are at 10 times the risk of thromboembolic disease (TED) compared with non-pregnant women, with approximately one in four deaths associated with pregnancy resulting from pulmonary embolism (PE) syndrome. The risk of death in pregnant patients admitted to the intensive care unit with pulmonary embolism is 23.1% [13]. The risk of venous thromboembolism is roughly equal for each of the trimesters, and slightly elevated in the post-partum period. This is elevated by a factor of 5 if the patient has undergone Caesarean delivery. Multiparous women are at elevated risk, as are the obese, those with endometriosis, and patients with a history of thrombophlebitis or thromboembolism. One in six cases of thromboembolism in pregnancy have antiphospholipid syndrome, an inherited disorder with a 5% risk per patient irrespective of prophylactic measures [14]. Heparin remains the mainstay of treatment for TED in pregnancy, as it does not cross the placenta, while warfarin is teratogenic and should be avoided.

Pre-eclampsia and eclampsia

Pre-eclampsia (PET), a multisystem disease specific to pregnancy, is defined as hypertension and proteinuria appearing after the 20th week of gestation and resolving within 6 to 12 weeks of delivery [15]. It occurs in 2–3% of all pregnancies and is more common in primigravida or the first pregnancy with a particular partner. Other risk factors include a positive family history, pre-existing hypertension, diabetes mellitus, multiple pregnancies, and increasing maternal age and obesity.

Pre-eclampsia is a placental disease that commences early in pregnancy and may result from an autoimmune response of the mother to the placenta [15]. Functionally, the placenta becomes ischaemic secondary to hypoperfusion and hypoxia. Vasoactive substances released by the ischaemic placenta lead to widespread endothelial damage and profound vasospasm in a variety of different organ systems. As pregnancy progresses, the demands on the placenta increase and ischaemia worsens. The mother becomes absolutely and relatively hypovolaemic. Systemic vasoconstriction, hypertension, and renal dysfunction are seen. An imbalance between vasoconstrictive thromboxane and vasodilatory prostacyclin results in platelet dysfunction, activation of the coagulation system, endothelial damage, and further vasoconstriction.

Hypertension and proteinuria are the clinical manifestations of the disease. Late complications include pulmonary oedema, hypertensive encephalopathy, cerebral irritability and seizures (eclampsia). PET is associated with significant morbidity and, if undiagnosed or untreated, mortality, for the mother and fetus. Eclampsia is an extreme complication of PET that is defined by the occurrence of seizures in the absence of other neurological disorders. Treatment includes magnesium sulphate for the prevention of eclamptic seizures [16], and anti-hypertensives such as hydralazine and labetalol [15]. PET is abrogated by delivery of the fetus.

Trauma and cardiac arrest

Trauma is the most frequent non-obstetric cause of death in pregnancy [17]. The most common cause of injury from trauma is motor vehicle crash, followed by domestic violence, gunshot wound or stabbing, and traumatic brain injury from a variety of causes [18]. Regardless of the nature and extent of the injury, trauma is associated with elevated risk of foetal demise, usually secondary to placental abruption, preterm labour, or spontaneous abortion. With penetrating trauma, major bleeding is more likely in pregnancy, as are hepato-splenic injuries, with bowel injuries less common. Placental abruption most frequently occurs during deceleration events—the inelastic placenta shears off the uterus.

During resuscitation, it is essential to avoid aorto-caval compression and to be aware of the risk of gastropulmonary aspiration in advanced pregnancy. The patient should be placed with a 15° angle to the left and the head elevated. Traditional indicators of blood loss or fluid sequestration, such as base deficit, lactate, and haemoglobin concentration may be unreliable in pregnancy and may under-represent the danger to the mother and fetus. Foetal heart monitoring provides good information about both the volume status of the mother and the oxygen delivery to the fetus. Evidence of foetal distress should alert the multidisciplinary team to ongoing blood loss or missed maternal injury. The mother should undergo

pelvic examination for the presence of bleeding, evidence of placental abruption, and to determine the current condition of the cervix. Radiological examination is crucial to determine the extent and severity of injuries, and should not be withheld for fear of injuring the fetus. Uterine shielding should be employed where possible. The highest foetal risk is from the 8th to the 15th gestational weeks. However, exposure to less than 1 RAD of radiation is low risk. A plain X-ray requires 0.2 RAD, while a CT scan requires 0.5 RAD per slice. A test for Rhesus antigenicity (Kleihauer–Betke) should be performed. A Rhesus negative patient with a positive test should be given Rhesus immunoglobulin to prevent iso-immune injury [19].

If cardiac arrest occurs in the third trimester of pregnancy, cardiopulmonary resuscitation is difficult and often ineffective. Drugs and defibrillation regimens should follow standard advanced cardiac life support guidelines. Caesarean delivery within 4 minutes will enhance viability of the fetus, while increasing maternal blood volume and releasing of aorto–caval compression, enhances the likelihood of successful maternal resuscitation [20].

Conclusion

Pregnancy is associated with a variety of physiological changes that both elevate the risk of critical illness, and present the intensivist with challenges with regard to diagnosis and management. Two patients are being treated, but what is good for the mother will benefit the fetus. Diagnostic tests, goals, and interventions are similar to the non-pregnant patient with adjustments to standard strategies based on the physiological changes in pregnancy. Critical care interventions are similar to those for the non-pregnant patient; however, more stringent physiological targets for metabolic, pulmonary, and haemodynamic control may be necessary.

References

1. Hegewald MJ and Crapo RO. (2011). Respiratory physiology in pregnancy. *Clinical Chest Medicine*, **32**, 1–13, vii.
2. Pilkington S, Carli F, Dakin MJ, et al. (1995). Increase in Mallampati score during pregnancy. *British Journal of Anaesthesia*, **74**, 638–42.
3. Neligan PJ and Laffey JG. (2011). Clinical review: special populations—critical illness and pregnancy. *Critical Care*, **15**, 227.
4. Catalano PM. (2010). Obesity, insulin resistance, and pregnancy outcome. *Reproduction*, **140**, 365–71.
5. Podymow T, August P, and Akbari A. (2010). Management of renal disease in pregnancy. *Obstetric and Gynecological Clinics of North America*, **37**, 195–210.
6. Marik PE. (2010). Venous thromboembolism in pregnancy. *Clinical Chest Medicine*, **31**, 731–40.
7. Mabie WC, Barton JR, and Sibai B. (1997). Septic shock in pregnancy. *Obstetrics and Gynecology*, **90**, 553–61.
8. Cantwell R, Clutton-Brock T, Cooper G, et al. (2011). Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *British Journal of Obstetrics and Gynaecology*, **118**(Suppl. 1), 1–203.
9. Acosta CD, Bhattacharya S, Tuffnell D, Kurinczuk JJ, and Knight M. (2012). Maternal sepsis: a Scottish population-based case-control study. *British Journal of Obstetrics and Gynaecology*, **119**, 474–83.
10. Yamada T, Yamamura MK, Katabami K, et al. (2010). Invasive group A streptococcal infection in pregnancy. *Journal of Infection*, **60**, 417–24.
11. (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *New England Journal of Medicine*, **342**, 1301–8.
12. ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System. (2010). Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study. *British Medical Journal*, **340**, c1279.
13. Zwart JJ, Dupuis JR, Richters A, Ory F, and van Roosmalen J. (2010). Obstetric intensive care unit admission: a 2-year nationwide population-based cohort study. *Intensive Care Medicine*, **36**, 256–63.
14. Galarza-Maldonado C, Kourilovitch MR, Perez-Fernandez OM, et al. (2012). Obstetric antiphospholipid syndrome. *Autoimmune Review*, **11**, 288–95.
15. Pettit F and Brown MA. (2012). The management of pre-eclampsia: what we think we know. *European Journal of Obstetrics and Gynecology: Reproductive Biology*, **160**, 6–12.
16. (1995). Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet*, **345**, 1455–63.
17. El-Kady D, Gilbert WM, Anderson J, Danielsen B, Towner D, and Smith LH. (2004). Trauma during pregnancy: an analysis of maternal and fetal outcomes in a large population. *American Journal of Obstetrics and Gynecology*, **190**, 1661–8.
18. El Kady D, Gilbert WM, Xing G, and Smith LH. (2005). Maternal and neonatal outcomes of assaults during pregnancy. *Obstetrics and Gynaecology*, **105**, 357–63.
19. Muench MV, Baschat AA, Reddy UM, et al. (2004). Kleihauer–Betke testing is important in all cases of maternal trauma. *Journal of Trauma*, **57**, 1094–8.
20. McDonnell NJ. (2009). Cardiopulmonary arrest in pregnancy: two case reports of successful outcomes in association with perimortem Caesarean delivery. *British Journal of Anaesthesia*, **103**, 406–9.

CHAPTER 366

Pathophysiology and management of pre-eclampsia, eclampsia, and HELLP syndrome

Muna Noori and Catherine Nelson-Piercy

Key points

- Severe, life-threatening, hypertension requires prompt, effective treatment, which should be reflected in local management protocols.
- Systolic hypertension greater than 150–160 mmHg demands urgent treatment, as it is associated with an increased risk of intracerebral haemorrhage.
- Syntocinon, rather than ergometrine should be used to actively manage the third stage of labour, as the latter drug may cause marked hypertension.
- Women with severe pre-eclampsia need effective multidisciplinary team care, with input from intensive care specialists where appropriate.
- Delivery is the definitive treatment for pre-eclampsia or eclampsia, but should only be undertaken once the maternal condition has been stabilized.

Introduction

Pre-eclampsia is a major, multisystem disorder of human pregnancy that poses a higher risk of future cardiovascular disease [1]. It affects approximately 2–4% of first-time pregnancies in North America, Europe, and Australia [2] and is characterized by new onset hypertension (>140/90 mmHg) and proteinuria (>300 mg/24 hours or a protein:creatinine ratio >30 mg/mmol) that typically develop after 20 weeks gestation [3]. Pre-eclampsia and eclampsia were the second most common causes of direct maternal death in the United Kingdom (UK) between 2006 and 2008, responsible for 19 deaths [4]. In the majority of cases, there was substandard care in the management of hypertension, particularly systolic hypertension [5].

Pre-eclampsia is a syndrome with multiple aetiologies, which poses a challenge in its prediction and in the development of preventative strategies. There are a number of pre-pregnancy risk factors that predispose women to developing pre-eclampsia, including nulliparity, maternal age >40 years, body mass index >35 kg/m^2, pregnancy interval >10 years, previous pregnancy complicated by pre-eclampsia, family history of pre-eclampsia, multiple pregnancies, and pre-existing medical disorders characterized by endothelial dysfunction, such as hypertension and diabetes.

Pathophysiology

Pre-eclampsia is regarded as a two-stage disorder. The first stage results from inadequate placental development early in pregnancy, whereas the second stage is the maternal response to inadequate placental invasion [6].

Healthy pregnancy requires remodelling of spiral arteries at the foeto–maternal interface to create high capacitance, low resistance vessels thereby maximizing blood flow to the growing fetus. In pre-eclampsia, remodelling is incomplete and spiral arteries remain tortuous, muscular, and narrow. The resulting placental hypoperfusion leads to hypoxia, ischaemia, oxidative stress, and widespread endothelial dysfunction [7].

Theoretical mechanisms of pre-eclampsia

Several mechanistic pathways have been shown to contribute to the evolution of pre-eclampsia, including the following.

Impaired nitric oxide synthase activity

The vasodilatation of healthy pregnancy is mediated by nitric oxide (NO), which is produced by conversion of maternal L-arginine to NO by nitric oxide synthase (NOS). Impaired NOS activity is likely to play a major role in the widespread endothelial dysfunction and vasoconstriction that characterizes pre-eclampsia [8].

Exaggerated inflammatory responses

Healthy pregnancy is associated with systemic inflammation which is exaggerated in pre-eclampsia [9].

Prostaglandin imbalances

In contrast to normal pregnancy, pre-eclampsia is associated with relative underproduction of prostacyclin (PGI_2) and overabundance of thromboxane A_2 (TxA_2) [10]. The imbalance between these opposing prostanoids formed the rationale for investigations of 'low dose aspirin' therapy for prevention of recurrent, severe, preterm pre-eclampsia [11].

Immune maladaptation

A strong risk factor for pre-eclampsia is nulliparity, which implies that a previous pregnancy confers some protection from developing the disease [7].

Genetic factors

Pre-eclampsia is more common in women with a family history of pre-eclampsia.

Angiogenic imbalance in the evolution of pre-eclampsia

Recently, the role of angiogenic factors in regulation of angiogenesis and evolution of pre-eclampsia has been highlighted [12]. Healthy pregnancy relies upon an intricate balance between pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), and anti-angiogenic factors that include soluble feline mcDonough sarcoma (FMS)-like tyrosine kinase-1 (sFlt-1, which binds PlGF) and soluble endoglin (sEng). Disturbance of this balance results in the development of pre-eclampsia (Fig. 366.1).

PlGF is expressed in highest quantities in healthy pregnancy and exerts its pro-angiogenic actions by binding to the membrane bound Flt-1 receptor. A soluble form of Flt-1 (sFlt-1) is released by an ischaemic placenta into the maternal bloodstream, where it binds circulating PlGF with high affinity and interferes with PlGF's actions (Fig. 366.1). Levels of PlGF are lower in women with pre-eclampsia whereas levels of sFlt-1 are elevated up to 5–10 weeks prior to its onset [12,13]. Measurement of the ratio of maternal sFlt-1 to PlGF in the first trimester may identify women, who later develop pre-eclampsia, and when measured later in pregnancy, can differentiate women at risk of pre-eclampsia from those who subsequently develop gestational hypertension [14]. Near-patient measurement of PlGF in women with suspected pre-eclampsia presenting before 35 weeks, has a high sensitivity and negative predictive value for pre-eclampsia within 14 days [15].

Endoglin, a cell surface co-receptor for transforming growth factor β1 and β3, regulates endothelial nitric oxide synthase (eNOS) activity and modulates vascular tone. A soluble form of endoglin (sEng) interferes with interactions between TGF-β1 and its receptor, resulting in hypertension and pre-eclampsia. Levels of sEng are elevated prior to onset of pre-eclampsia, and sEng works synergistically with sFlt-1 to cause severe hypertension, proteinuria, HELLP (**h**aemolysis, **e**levated **l**iver enzymes, **l**ow **p**latelets) syndrome and foetal growth restriction (FGR) [16].

Diagnosis

Pre-eclampsia is usually diagnosed through routine antenatal screening for hypertension and proteinuria. Definitions of hypertension are outlined in Box 366.1. Many women are asymptomatic at the time of diagnosis, whereas others develop symptomatic disease, with biochemical and haematological abnormalities including severe headache, visual disturbances, vomiting, liver tenderness, clonus (≥3 beats), papilloedema, HELLP syndrome, platelet count $<100 \times 10^9$/L or abnormal liver enzymes (ALT or AST above 70 IU/L), and acute kidney injury (AKI). Furthermore, a diagnosis of FGR may precede the onset of the maternal syndrome.

Investigations

Disease severity and progression can be monitored with the following:

- Regular assessment of haemoglobin, platelet count, liver function, renal function, and electrolytes.
- Clotting studies if pre-eclampsia is severe or thrombocytopenia is diagnosed.
- Regular urinalysis to assess for proteinuria. If >1+ is detected, a urine protein:creatinine ratio should be measured, or less commonly, a 24-hour urine collection.
- Foetal monitoring to assess growth, amniotic fluid volume and fetal Doppler.

Treatment of hypertension

Hypertension greater than 150/100 mmHg requires treatment in accordance with recent guidelines from the National Institute of Clinical Excellence (NICE), irrespective of whether or not it is

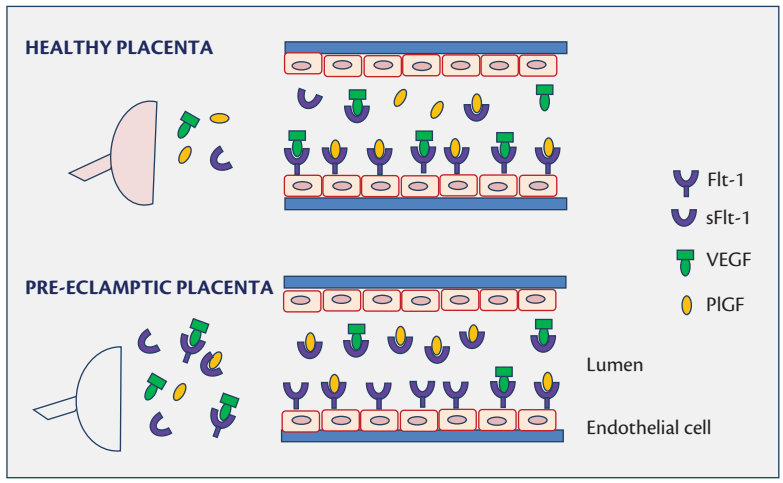


Fig. 366.1 Proposed mechanism of endothelial dysfunction in pre-eclampsia. Soluble Flt-1 binds circulating VEGF and PlGF and antagonizes their pro-angiogenic effects on endothelial cells. In healthy pregnancy, small amounts of VEGF, PlGF, and sFlt-1 are produced. In pre-eclampsia, excessive sFlt-1 binds circulating VEGF and PlGF, and prevents their interaction with endothelial cell-bound Flt-1 receptors. This results in endothelial dysfunction, reduced nitric oxide production, decreased prostacyclin, and the release of procoagulant proteins.

Box 366.1 Definitions of hypertension in pregnancy

- **Chronic hypertension**: hypertension that is present at the booking visit or before 20 weeks or if the woman is already taking antihypertensive medication when referred to maternity services. It can be primary or secondary in aetiology.
- **Gestational hypertension**: new hypertension presenting after 20 weeks without significant proteinuria.
- **Mild hypertension**: diastolic blood pressure 90–99 mmHg; systolic blood pressure 140–149 mmHg.
- **Moderate hypertension**: diastolic blood pressure 100–109 mmHg; systolic blood pressure 150–159 mmHg.
- **Severe hypertension**: diastolic blood pressure 110 mmHg or greater; systolic blood pressure 160 mmHg or greater.
- **Pre-eclampsia**: new hypertension presenting after 20 weeks with significant proteinuria.
- **Severe pre-eclampsia**: pre-eclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or haematological impairment.
- **Significant proteinuria**: greater than 300 mg/24 hours or >30 mg/mmol.

diagnosed in the context of pre-eclampsia. Blood pressure below this threshold requires monitoring, rather than treatment as a diastolic blood pressure much below 80 mmHg may have a negative impact on foetal blood supply [17].

Oral labetalol, the current anti-hypertensive agent of choice, should be commenced when moderate hypertension is diagnosed. Methyldopa and/or oral nifedipine can be used in conjunction with labetalol if monotherapy is ineffective.

Pre-eclampsia: spectrum of disease

Clinical manifestations of severe pre-eclampsia include eclampsia, HELLP syndrome, disseminated intravascular coagulopathy (DIC), cerebrovascular haemorrhages, hepatocellular damage, pulmonary oedema, and adult respiratory distress syndrome (ARDS). Foetal consequences include FGR, foetal distress, placental abruption, and foetal death *in utero*.

Eclampsia

Eclampsia complicates 1% of cases of pre-eclampsia with a UK incidence of 2.7/10,000 maternities [17]. Tonic–clonic seizures are followed by a post-ictal phase. Convulsions may occur antepartum (45%), intrapartum (19%), or post-partum (36%), and arise following localized cerebral vasoconstriction and hypoxia, and are often preceded by hyperreflexia and headache. Eclampsia may be complicated by ischaemic or haemorrhagic stroke with cerebral vasospasm or oedema, or more rarely, by cortical blindness or PRES (posterior reversible encephalopathy syndrome).

Management of eclampsia

The patient should be protected from physical injury during the tonic–clonic phase, with attention to the airway. Although maternal hypoxia during the seizure may result in foetal bradycardia, the mother must be stabilized prior to delivery of the fetus.

The use of intravenous magnesium sulphate should be considered in severe hypertension or severe pre-eclampsia and should be given following an eclamptic seizure, as it reduces the likelihood of recurrent seizures [19]. Diazepam and phenytoin are not recommended to treat eclampsia [17].

Magnesium sulphate is administered as an intravenous loading dose of 4 g followed by an infusion of 1 g/hour maintained for 24 hours. Recurrent seizures should be treated with a further dose of 2–4 g. Lower maintenance doses may be required in AKI to prevent magnesium toxicity, which is characterized by loss of deep tendon reflexes when levels exceed 5 mmol/L, or respiratory depression and arrest at higher concentrations. Deep tendon reflexes and oxygen saturations should therefore be checked hourly to alert staff to possible toxicity, which can be reversed by intravenous calcium gluconate.

HELLP syndrome

HELLP syndrome develops in 5–20% of cases of pre-eclampsia, although milder presentations involving hepatic enzyme derangements and thrombocytopenia, without haemolysis, are more frequent. Features include liver tenderness, vomiting, hypertension, AKI, acidosis, or placental abruption. The pathophysiology of HELLP syndrome is unclear, but is characterized by endothelial cell injury, micro-angiopathic platelet activation and, in 20% of cases, a consumptive coagulopathy. Differential diagnoses to consider include acute fatty liver of pregnancy (AFLP) or haemolytic uraemic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP).

Management of HELLP syndrome

Delivery must be expedited once maternal blood pressure is stabilized. Fresh frozen plasma can be used to correct coagulopathy, while platelet transfusions are reserved for cases that involve active bleeding or to 'cover' surgery. Although corticosteroids given to promote foetal lung maturation prior to preterm delivery transiently improve both haematological and hepatic abnormalities in HELLP syndrome, treatment with steroids for maternal reasons is not advocated. Post-partum, HELLP syndrome usually improves, although it may develop for the first time in 30% of cases.

Management of severe hypertension or pre-eclampsia in a critical care setting

Women with severe hypertension or severe pre-eclampsia should be assessed for referral to the appropriate critical care setting using the criteria outlined in Table 366.1.

Severe hypertension should be treated immediately with one of the following, in accordance with local management protocols.

Intravenous labetalol

Intravenous labetalol given as intermittent boluses followed by an infusion once acute blood pressure control has been achieved.

Intravenous hydralazine

Intravenous hydralazine given by intermittent bolus followed by a maintenance infusion once blood pressure control is achieved. Hydralazine is a vasodilator that can cause tachycardia and headache. If hydralazine is administered intrapartum, preloading with

Table 366.1 Assessment of severity of pre-eclampsia in determining level of critical care required

Level 1	Level 2	Level 3
Pre-eclampsia with mild or moderate hypertension	Stepping down from level 3 or up from level 1	Severe pre-eclampsia
Ongoing conservative antenatal management of severe preterm hypertension	Eclampsia	Ventilatory support required
Step-down treatment following delivery	HELLP syndrome	
	Haemorrhage	
	Hyperkalaemia	
	Severe oliguria	
	Coagulation support	
	Intravenous antihypertensive treatment	
	Initial stabilization of severe hypertension	
	Evidence of cardiac failure/pulmonary oedema	
	Abnormal neurology	

Reproduced from NICE CG107 Hypertension in pregnancy: The management of hypertensive disorders during pregnancy, NICE 2010 (https://www.nice.org.uk/guidance/cg107), originally adapted from the Guideline Development Group from Intensive Care Society, Standards and Guidelines 2002, with permission.

up to 500 mL crystalloid fluid at the time of the first dose should be considered to reduce the risk of profound hypotension, and consequent placental hypoperfusion and foetal distress.

Oral nifedipine

Concurrent use of nifedipine and magnesium sulphate therapy for seizure prophylaxis can cause severe hypotension so must be used with caution. Sublingual nifedipine causes too rapid a fall in blood pressure resulting in placental hypoperfusion and should not be used.

Fluid balance

Volume expansion in women with severe pre-eclampsia may result in pulmonary oedema and should be avoided, including prior to regional anaesthesia. Fluid restriction should be continued intrapartum and post-partum unless there are other ongoing fluid losses, such as haemorrhage.

Oliguria is a common feature of pre-eclampsia, particularly with concurrent use of Syntocinon due to its anti-diuretic effect, and usually does not require treatment. Syntocinon may be administered in a concentrated form via syringe driver, to minimize the volume of fluid being given. Diuretic use should be reserved for cases complicated by pulmonary oedema.

Timing of delivery

Mild and moderate pre-eclampsia can be managed conservatively, particularly prior to 34 weeks, to minimize complications of prematurity. However, in the context of worsening pre-eclampsia or severe hypertension refractory to treatment, delivery should be expedited. Where delivery is planned prior to 36 weeks gestation, corticosteroids should be given to promote foetal lung maturation. A management plan should be agreed by the obstetrician, anaesthetist, and neonatologist.

A diagnosis of severe pre-eclampsia does not preclude induction of labour, although clinical deterioration of the mother or foetal compromise may necessitate urgent delivery by Caesarean section. Although the second stage of labour does not routinely need to be limited in women with stable pre-eclampsia, operative vaginal delivery is advocated if hypertension is uncontrolled.

Post-partum care

Although delivery addresses the underlying cause of pre-eclampsia by removing the placenta, pre-eclampsia may deteriorate post-partum or may develop for the first time after delivery. Women with severe hypertension or pre-eclampsia therefore require intensive monitoring in a critical care setting following delivery, with close attention to blood pressure, fluid balance, haematology, and biochemistry.

Conclusion

Pre-eclampsia is unpredictable and is a leading cause of maternal and fetal morbidity and mortality in the UK and worldwide. The 2006–2008 UK Confidential Enquiry into Maternal Deaths highlighted the largely avoidable causes for maternal deaths from pre-eclampsia, which included poor diagnosis, failure to appreciate the relevance and significance of new onset hypertension and proteinuria, and suboptimal treatment of systolic hypertension. Frontline healthcare professionals need regular training updates in the emergency care of women with pre-eclampsia. Furthermore, this high risk patient group requires multidisciplinary team input, with senior involvement.

References

1. Bellamy L, Casas JP, Hingorani AD, and Williams DJ. (2007). Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *British Medical Journal*, **335**, 974–86.
2. Wallis AB, Saftlas AF, Hsia J, and Atrash HK. (2008). Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987–2004. *American Journal of Hypertension*, **21**, 521–6.
3. ACOG Committee opinion: ACOG Practise Bulletin. (2002). Diagnosis and management of preeclampsia and eclampsia. *Obstetrics and Gynaecology*, **99**, 159–67.
4. Centre for Maternal and Child Enquiries (CMACE). (2011). Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. *British Journal of Obstetrics and Gynaecology*, **118**(Suppl. 1), 1–203.
5. Shennan AH, Redman CW, Cooper C, and Milne F. (2012). Are most maternal deaths from pre-eclampsia avoidable? *Lancet*, **379**(9827), 1686–7.
6. Redman CW and Sargent IL. (2009). Placental stress and pre-eclampsia: a revised view. *Placenta*, **30**(Suppl. A), S38–42.

7. Roberts JM and Redman CW. (1993) Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet*, **341**, 1447–51.
8. Williams DJ, Vallance PJ, Neild GH, Spencer JA, and Imms FJ. (1997). Nitric oxide-mediated vasodilation in human pregnancy. *American Journal of Physiology*, **272**, H748–52.
9. Redman CW, Sacks GP, and Sargent IL. (1999). Preeclampsia: an excessive maternal inflammatory response to pregnancy. *American Journal of Obstetrics Gynecology*, **180**, 499–506.
10. Fitzgerald DJ, Rocki W, Murray R, Mayo G, and FitzGerald GA. (1990) Thromboxane A2 synthesis in pregnancy-induced hypertension. *Lancet*, **335**, 751–4.
11. (2004). CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group (2004). *Lancet*, **343**, 619–29.
12. Levine RJ, Maynard SE, Qian C, et al. (2004). Circulating angiogenic factors and the risk of preeclampsia. *New England Journal of Medicine*, **350**, 672–83.
13. Chaiworapongsa T, Romero R, Espinoza J, et al. (2004). Evidence supporting a role for blockade of the vascular endothelial growth factor system in the pathophysiology of preeclampsia. *American Journal of Obstetrics and Gynecology*, **190**, 1541–7.
14. Noori M, Donald AE, Angelakopoulou A, Hingorani A, and Williams DJ. (2010). Endothelial function and angiogenic factors in hypertensive disorders of pregnancy: a prospective study. *Circulation*, **122**, 478–87.
15. Chappell LC, Duckworth S, Seed PT, et al. (2013). Diagnostic accuracy of placental growth factor in womenwith suspected preeclampsia. *Circulation*, **128**, 2121–2131.
16. Venkatesha S, Toporsian M, Lam C, et al. (2006). Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nature: Medicine*, **12**, 642–9.
17. NICE. (2010). Hypertension in pregnancy: the management of hypertensive disorders during pregnancy, NICE Clinical Guideline 107. London: NICE. Available at: https://www.nice.org.uk/guidance/cg107 (accessed 14 July 2015).
18. Knight M. (2007). Eclampsia in the United Kingdom 2005. *British Journal of Obstetrics and Gynaecology*, **114**, 1072–8.
19. Altman D, Carroli G, Duley L, et al. (2002). Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet*, **359**, 1877–90.

CHAPTER 367

Obstetric Disorders in the ICU

Andrew Levinson and Ghada Bourjeily

Key points

- Venous thromboembolism, post-partum haemorrhage, amniotic fluid embolism, ovarian hyperstimulation syndrome, and obstetric sepsis are rare, but clinically significant complications of pregnancy.
- Knowledge of the physiological changes that occur in pregnancy is crucial when caring for women who are pregnant or immediately post-partum.
- Successful treatment of major obstetrical haemorrhage must focus on identifying and alleviating the cause of major bleeding, resuscitation, and reversal of the coagulopathy.
- When diagnosing pulmonary embolism (PE) in pregnancy, it is imperative to remember that the risk of undiagnosed and untreated PE outweighs the potential fetal oncogenic and teratogenic risk.
- Sepsis remains an important cause of maternal morbidity and mortality. Early recognition and intervention of pregnancy-related sepsis is essential.

Introduction

Critical illness in pregnancy is a rare, but potentially catastrophic event for the mother and fetus. Treatments of critically-ill pregnant patients must take into account the physiological changes in pregnancy and focus on stabilizing the pregnant woman.

Only 1% of all obstetric patients in industrialized countries are admitted to intensive care units (ICU). However, once in the ICU, the mortality of these patients can be high, with current estimates of from 12% to 20%. Acute respiratory distress syndrome (ARDS) remains the leading cause of mortality in pregnant women in the ICU [1]. Disorders specifically related to pregnancy account for 55–80% of admissions of pregnant women to the ICU [2].

In caring for critically-ill pregnant women, it is important to understand the normal physiological changes in pregnancy (Table 367.1). Vital signs that may be interpreted as abnormal, in fact, can be part of the patient's normal physiological response to changes in pregnancy.

Obstetrical haemorrhage

Epidemiology

Severe haemorrhage in both the antepartum and immediate post-partum period is one of the most common obstetric admissions to the ICU. Haemorrhage is also the most common cause of maternal mortality in both the developing world and in industrialized nations [3]. Recent studies suggest that a large percentage of maternal deaths due to obstetrical haemorrhage are preventable if the care provided is more timely and follows best practices.

Pathophysiology

Recognition and management of obstetrical haemorrhage is complicated by the fact that 300–500 cm^3 of blood loss is not uncommon in normal delivery. Tachycardia may be the only initial presenting symptom as patients may not become hypotensive until one-half of blood volume has been lost. Aorto–caval compression by the gravid uterus can also accentuate haemodynamic instability.

Causes of antepartum haemorrhage include placental anatomic abnormalities, uterine rupture, and atony, as well as trauma to the uterus or the lower genital tract and retained products of conception. Risk factors for haemorrhage include obesity, chorioamnionitis, prior caesarean delivery and previous history of post-partum haemorrhage. Coagulopathies can be both a primary impetus or a resulting complication of major obstetrical haemorrhage [4].

Treatment

Successful treatment of major obstetrical haemorrhage requires a coordinated rapid response by all members of the care team (Box 367.1). Effective treatment must focus on identifying and alleviating the cause of major bleeding, resuscitation, and reversal of the coagulopathy. Treatment efforts should focus on obtaining large-bore peripheral intravenous (iv) access and resuscitation to maintain effective circulation and oxygen delivery. If haemorrhage continues, treatment includes administration of prostaglandins, balloon tamponade or packing of the uterus, central venous and arterial access, and the transfusion of red blood cells (RBC), platelets, and fresh frozen plasma (FFP). If bleeding does not respond to medical treatments, interventions to mechanically stop bleeding, such as uterine artery ligation, embolization, or uterine compression sutures are recommended as potential next steps. Studies suggest that there is little evidence that any one measure is superior to another, therefore, management should be based on availability and local expertise. If these measures fail or the patient becomes unstable, emergent hysterectomy becomes inevitable.

Massive transfusion protocols may prevent the unnecessary delay in the administration of life-saving blood products. There is poor quality evidence to support one specific ratio of RBCs, plasma and/or cryoprecipitate, and platelets in massive

Table 367.1 Physiological changes in pregnancy

Cardiac changes	**Change**	**Normal range in pregnancy**
Blood pressure	↓	10–15 mmHg decrease in first 2 trimesters
Blood volume	↑	30–50% increase
Cardiac output	↑↑	5–7 L/m^2/min (40% increase)
Central venous pressure	↔	<13 mmHg
Colloid oncotic pressure	↓	10–15% decrease
Ejection fraction	↔	70%
Heart rate	↑	Increases by 10–20 bpm
Pulmonary artery pressure	↔	≤25 mmHg
Pulmonary capillary wedge pressure	↔	<13 mmHg
Stroke volume	↑	70–100 mL/beat
Systemic vascular resistance	↓	25–30% decrease
Respiratory changes		
ABG's		
pH	↑	Mild respiratory alkalosis
PaO_2	↑	Average 100–105
$PaCO_2$	↓	28–32 mmHg
HCO_3	↓	18–22 mEq/L
A–a gradient	↑	Increase in late gestation to approximately 20 weeks
Oxygen consumption	↑	20% Increase, further increase during labour and delivery
Minute ventilation	↑	50% increase
Respiratory rate	↔	No change
Tidal volume	↑	40–50% increase
Total lung capacity	↓	4–5% decrease
Functional residual capacity	↓	20% decrease by term
Residual volume	↓	
Vital capacity	↔	
Diffusion capacity	↔	Minimal change
Forced expiratory volume in 1 second	↔	
Peak expiratory flow rate	↔	
Haematological changes		
Anti-Xa assay (heparin)	↔	Levels likely drop around mid-gestation
Clotting factors	Most ↑	
Fibrinogen	↑↑	500–600 mg/dL
Hb (haemoglobin)	↓	10–13 g/dL
Platelet count	Gradual ↓ to term	150,000–200,000
PT, PTT, NR	↔	
RBC mass	↑	20%
WBC	↑	10,000–16,000/mm^3

↑ Increase; ↓ decrease; ↔ no change.

Box 367.1 Management caveats

Management team

Intensivist, anaesthesiologist, obstetrician, obstetric internist, neonatologist.

Airway intubation

- Airway assessment even in urgent intubations.
- Difficult airway cart readily available including laryngeal mask airway.

Airway management

- **Avoid aspiration**: elevate head of bed, cricoid pressure, consider bicitra.
- **Lower dose of sedatives/anaesthetics**: hypoxaemia and hypercapnia occur faster in pregnancy.
- **Pre-oxygenate**: manual ventilation may increase risk of aspiration.
- Smaller endotracheal tube size may be necessary.
- Intubation to be performed by the most experienced provider.
- CXR for tube placement with abdominal shield.

Haemodynamics

- **Echocardiography:**
  - Systolic and diastolic dimensions slightly increased.
  - Systolic function slightly increased.
  - Moderate increase in the size of the right chambers and the left atrium.
  - Progressive dilation of pulmonary, tricuspid, and mitral valve annuli.
  - Some degree of pulmonary, tricuspid, and mitral regurgitation.
- **CVP, PAOP**: unchanged; CVP may not correlate with PAOP in pre-eclampsia.

Pharmacokinetics

- Volume of distribution.
- Hepatic clearance.
- Renal clearance.
- No clear recommendations for weight-based dosing.

Resuscitation

- **Airway:**
  - Early intubation.
  - Cricoid pressure until intubation achieved.
- **Breathing**: 100% oxygen.
- **Circulation**: Manual leftward displacement of the uterus.
- **Defibrillation**:
  - Standard ACLS protocol.
  - Ensure removal of fetal monitors.
- **Drugs:**
  - Standard ACLS doses; may need to increase dose of vasopressin.
  - Caution with sodium bicarbonate (may not transfer through placenta readily).
  - Caution with alpha-adrenergic agents (effect on placental perfusion); alpha adrenergic agents use is justified in these circumstances.
- **Delivery:**
  - Initiate peri-mortem delivery if resuscitation unsuccessful.
  - Alert appropriate neonatologist and obstetrician as soon as cardiac arrest occurs.

transfusion, although current clinical practice in trauma patients seems to favour closer to a 1:1:1 ratio [5]. While there are no randomized data to support its use, recombinant factor VIIa has been reported to stop bleeding in women with refractory obstetrical haemorrhage.

Pulmonary embolism

Epidemiology

Venous thromboembolism (VTE) is a common and potentially fatal complication of pregnancy. In the United States the incidence of VTE is 0.6–2 per 1000 pregnancies and the maternal mortality is 1.1 per 100,000 deliveries, making VTE one of the leading causes of maternal mortality. Deep venous thrombosis (DVT) is by far the most common form of VTE in pregnancy [6] and occurs predominantly on the left side.

Pathophysiology

During pregnancy, all Virchow's triad elements are accentuated, including venous stasis, vascular injury, and hypercoagulability. Venous stasis is caused both by hormonal factors and mechanical compression by the growing uterus of the pelvic vessels. Vascular injury can occur with any type of delivery. Hypercoagulability in pregnancy is due to increased levels of procoagulant factors, decreased fibrinolysis, and anticoagulant activity [7].

Diagnosis

When choosing the right diagnostic test, it is imperative to remember that the risk of undiagnosed and untreated PE outweighs the potential fetal oncogenic and teratogenic risk [7]. False-negative results may result in missed diagnosis and high mortality. False positive findings may result in complicated labour plans, unnecessary anticoagulation, and limited contraceptive options.

Approaches to the diagnostic management of suspected PE in pregnancy have not been validated and remain controversial. Current guidelines are based on very low quality clinical evidence [8]. Clinical decision tools and D-dimers have not been validated in pregnancy.

In patients with leg symptoms, compression ultrasonography (CUS) can be done first. Although CUS circumvents the use of radiation, it has low yield in patients without leg symptoms suspected of PE outside pregnancy. Given the higher prevalence of isolated pelvic DVT in pregnancy, the yield of CUS is even lower.

In patients without leg symptoms, current guidelines recommend that chest radiograph (CXR) should be obtained first. If CXR is normal, half-dose perfusion scintigraphy exposes the breasts to less radiation than multidetector computed tomography-pulmonary angiogram (MDCT-PA), and usually shows a high proportion of normal and near normal scans in pregnancy. Ventilation scans are needed only if perfusion scan shows segmental defects (Fig. 367.1). Drawbacks of this approach are the inability to make an alternative diagnosis, the slightly higher, although acceptable, fetal radiation compared with MDCT-PA, and the lack of clinical pretest probability tools to aid in interpreting the findings. In patients with abnormal CXR, ATS guidelines [8] recommend obtaining MDCT-PA. Breast radiation exposure incurred by MDCT-PA can be reduced with breast shields by 30–50% without affecting image resolution. In haemodynamically-unstable pregnant patients, we recommend proceeding directly to MDCT-PA as the first test, as it is fast, can determine clot burden, and rule out other life-threatening diagnoses that can mimic PE such as dissection.

Management

There is a paucity of studies looking at the efficacy of treatments for VTE in pregnancy. Treatment is generally unchanged compared with the non- pregnant population and includes low molecular weight heparin (LMWH), unfractionated heparin (UFH) or thrombolysis, and in rare cases inferior vena cava (IVC) filter placement [9]. LMWH is the preferred therapy. Although pregnancy-specific complications have been described in case studies and small series with thrombolytics, clinicians should not hesitate to use these drugs in pregnancy in conditions associated with high mortality, such as PE with haemodynamic instability or refractory hypoxaemia. Temporary IVC filters can be placed in pregnancy. Labour and delivery should be planned carefully and anticoagulation withheld prior to planned induction of labour depending on the risk of VTE recurrence, the risk of bleeding, and the need for regional anaesthesia [6].

Pregnancy-related infections

Common obstetric infections include endometritis, chorioamnionitis, septic abortion, septic thrombophlebitis, and wound infections. Chorioamnionitis is the infection of the chorioamniotic membranes and the amniotic fluid. Endometritis and wound infections are complications of caesarean deliveries and are likely under-reported. Septic abortion is associated with short-term mortality and morbidity, and long-term complications. The incidence of ICU admissions due to septic abortion has steadily declined since the legalization of abortion in many industrialized countries. Septic thrombophlebitis is in the differential diagnosis of peripartum patients with a fever and is usually treated with anticoagulation, although its clinical significance is controversial. Mastitis is a common infectious complication seen in post-partum women, but is rarely the source of serious complications.

Epidemiology

Sepsis remains an important cause of maternal morbidity and mortality. Morbidity from sepsis occurs in 0.1–0.6 per 1000 pregnancies [10]. In industrialized countries, 2.1% of maternal deaths are estimated to be due to severe sepsis or septic shock. In recent years, the percentage of admissions for maternal sepsis due to non-bacterial maternal infections and antepartum pelvic infections has significantly increased. Obesity, maternal age less than 25, and caesarean section have been identified as risk factors for obstetric sepsis.

Pathophysiology

Physiological changes during pregnancy, including peripheral vasodilatation and tachycardia, may delay the recognition of sepsis in pregnant women. Despite these physiological changes, gravidas likely have a more favourable outcome of sepsis than their non-pregnant counterparts because they are younger, have fewer co-morbidities, and rarely harbour resistant organisms.

Diagnosis and management

Pregnant women are routinely excluded from clinical trials, including those in sepsis. As a result, there is little randomized clinical data to support specific treatments. It is standard practice to follow international guidelines for treatment of severe sepsis and septic shock, such as early-goal directed therapy for rapid fluid resuscitation, with a few caveats. Systolic blood pressure of <90 mmHg is not an uncommon finding in a normal pregnancy due to the reduction in systemic vascular resistance. Studies of haemodynamic changes of pre-eclampsia suggest that CVP may not consistently correlate with pulmonary artery occlusion pressures. However, CVP likely remains the best available approach to assessing intravascular volume. It is unclear whether colloid infusions are superior to crystalloids. It is likely that all vasopressors reduce placental perfusion. The most common organisms isolated in maternal infections are *E. coli*, Enterococci, and β-haemolytic streptococci. Dosing of antibiotics should take into consideration pregnancy pharmacokinetics (Box 367.1). Drugs with a better fetal safety profile should be used when possible. Adequate source control is the key to successful management. Ultrasound can be useful in identifying pelvic sources of infection.

Amniotic fluid embolism

Amniotic fluid embolism (AFE), also known as anaphalactoid syndrome of pregnancy, is an uncommon, but potentially catastrophic complication occurring in labour or the immediate post-partum period. It is characterized by severe cardiopulmonary collapse and subsequent multi-organ dysfunction.

Epidemiology

Current estimates of the incidence of AFE in industrialized countries range from 1.9 to 6.1 cases per 100,000 births, with mortality rates of 20–90%. Proposed risk factors for AFE include advanced maternal age, placental pathologies, complicated labour and delivery, obstetric interventions, uterine trauma, and fetal distress. Whether induction of labour increases the risk of AFE remains controversial [11].

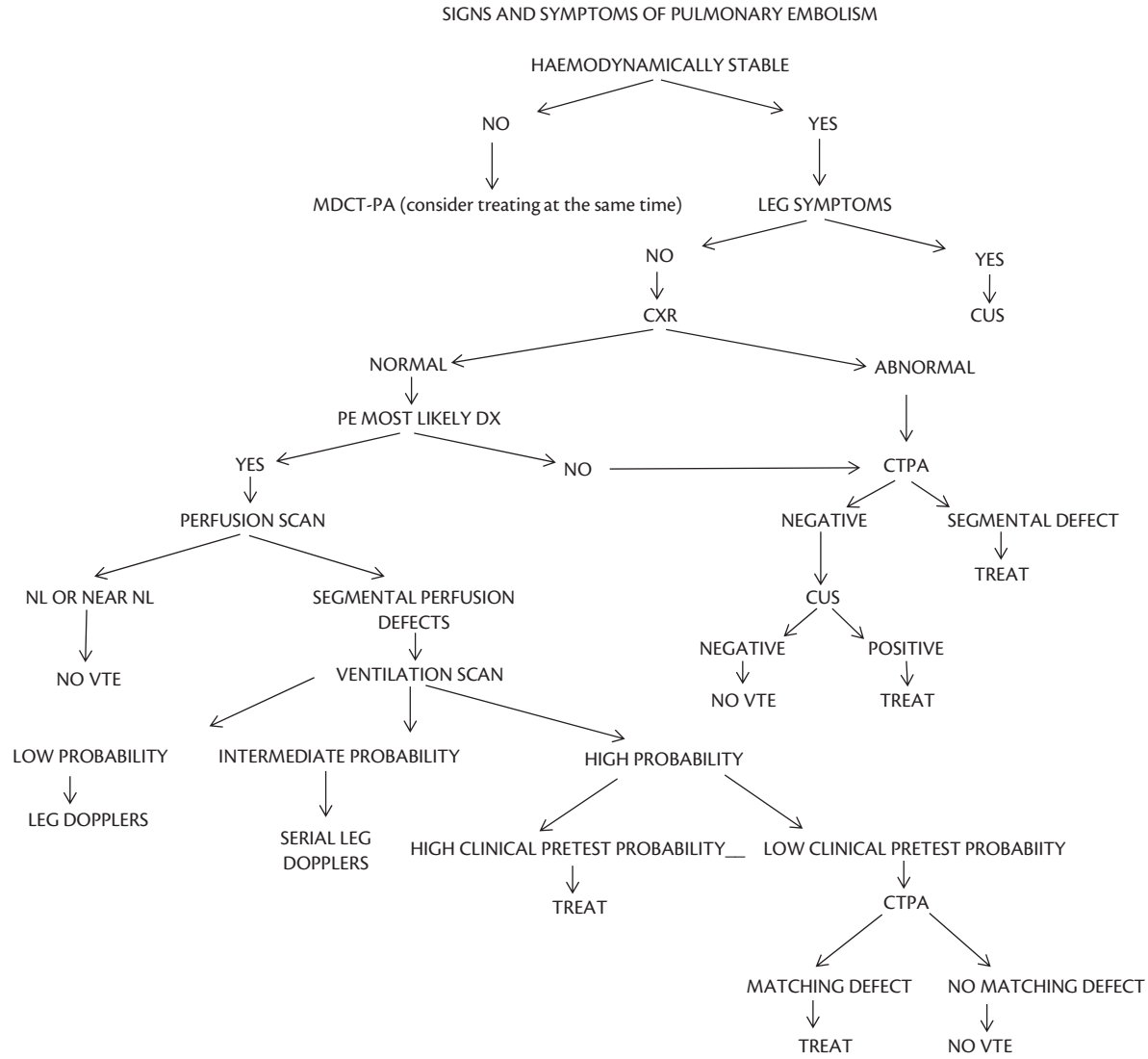


Fig. 367.1 Proposed algorithm for the work-up of pulmonary embolism in pregnancy.
CUS, compression ultrasounds; MDCT-PA, multidetector computed tomography pulmonary angiogram; VTE, venous thromboembolism; PE, pulmonary embolism; NL, normal; CXR, Chest radiograph.

Pathophysiology

The pathogenesis of AFE is poorly understood. Animal studies suggest that amniotic fluid entering the maternal systemic circulation leads to the obstruction or vasospasm of the pulmonary vasculature, and results in cardiopulmonary collapse. Subsequent investigations suggested that elevated pulmonary pressures may, in fact, be secondary to left ventricular dysfunction. A hypothetical biphasic course is proposed where the initial phase of acute pulmonary hypertension and ventricular failure are followed by left ventricular dysfunction. An immunological or inflammatory response to amniotic fluid is another suggested mechanism [12].

Clinical diagnosis

AFE is a clinical diagnosis characterized by the sudden onset of haemodynamic instability, respiratory failure (cardiogenic or non-cardiogenic pulmonary oedema), disseminated intravascular coagulation (DIC), coagulopoathy, encephalopathy, and seizures. In pregnant women with sudden cardiopulmonary collapse, other potential causes such as PE, septic shock, heart failure, and major obstetrical haemorrhage should also be considered. The detection of fetal squamous cells in the pulmonary vasculature has been reported in asymptomatic women at term and is not a specific finding. There is little data to support the use of laboratory testing to establish the diagnosis of AFE.

Management of complications

Treatment of AFE should focus on supportive care and correcting haemodynamic instability. High flow oxygen or mechanical ventilation are usually needed. Hypotension should be rapidly reversed with initial aggressive fluid resuscitation followed by vasopressors. Central venous access and arterial access should be obtained if the patient remains haemodynamically unstable after fluid resuscitation. In refractory shock, invasive or non-invasive means of measuring cardiac output should be considered.

Caesarean should be considered in the case of severe shock with the hope of improving both maternal and fetal outcome [13]. Massive bleeding, coagulopathy, and subsequent DIC should be treated similarly to massive obstetrical haemorrhage. The use of recombinant factor VII has been described in the literature, but caution is advised as one review suggests worse outcomes when it is administered [14]. Experimental treatment with inhaled nitric oxide and other pulmonary vasodilators, exchange transfusion, extracorporeal membrane oxygenation (ECMO), and continuous veno-venous haemofiltration (CVVH) have been described in small series and case reports [15,16], but there is little evidence to support their use routinely.

Ovarian hyperstimulation syndrome

Severe ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of the administration of exogenous gonadotropins in an effort to induce ovulation during assisted reproduction (ART). In the mild and moderate stages, women undergoing ART present with abdominal bloating, mild abdominal pain, nausea and vomiting, small ascites, and mildly enlarged ovaries. All of these signs and symptoms are often self-limiting and managed as an outpatient. In the severe stages, however, massive ovaries, large volume ascites, symptomatic pleural effusions, oliguria, haemoconcentration, and thromboembolism can be life-threatening and require close monitoring in a critical care setting.

Epidemiology

The incidence of moderate OHSS is 3–6% and 0.1–2% for severe OHSS. Risk factors for OHSS include age greater than 30, very high serum oestradiol, multiple ovarian follicles, and pregnancy [17].

Pathophysiology

The pathogenesis of OHSS remains incompletely understood. Oestradiol levels are often elevated, but not currently thought to have a primary role in the pathogenesis, although high levels may be associated with disease severity. Patients are at increased risk of worsening complications if they are newly pregnant because rising levels of endogenous human chorionic gonadotropic hormone may further worsen ovarian hyperstimulation.

Current research suggests that vascular endothelial growth factor (VEGF) plays a major role in the pathogenesis of OHSS by increasing vascular permeability. Other factors, such as angiotensin-II and insulin-like growth factor are thought to also work to increase vascular permeability, leading to the loss of albumin from the intravascular space and the subsequent development of electrolyte imbalances. Ultimately decreased oncotic pressure causes the rapid accumulation of abdominal ascites and pleural effusions. Massive ascites can lead to intra-abdominal hypertension and eventually abdominal compartment syndrome, further worsening organ dysfunction [18]. Patients with OHSS are at elevated risk for VTE, likely due to hormonal influences. These patients have a higher prevalence of upper extremity DVT.

Diagnosis

OHSS is a clinical diagnosis and should include a recent history of ovarian stimulation, and ovulation or exogenous gonadotropin administration. In very rare cases, OHSS can occur spontaneously. Alternative diagnoses such as ovarian torsion and other ovarian pathology, acute appendicitis, and infectious aetiologies should be excluded.

Treatment

There is little evidence to support current treatments for OHSS. Patients with mild and moderate OHSS should have monitoring for weight gain, fluid accumulation, and hepatic and renal function. Patients with severe symptoms of OHSS should receive iv fluid resuscitation to expand intravascular volume, monitoring for worsening intra-abdominal hypertension. Large volume paracenteses may be needed to alleviate symptoms with the goal of improving renal perfusion by decreasing abdominal hypertension. If dyspnoea and large pleural effusions do not improve with paracentesis, therapeutic thoracentesis may be needed. Thromboprophylaxis with UFH or LMWH should be initiated due to the very high incidence of thromboembolic complications.

Conclusion

Specific disorders related to pregnancy account for the vast majority of ICU admissions for pregnant women. Knowledge of the physiological changes that occur in pregnancy is extremely important. A thorough understanding of the effective management practices for the most common obstetrical reasons for ICU admission is essential for providing effective critical care to women in the antepartum and immediate post-partum period.

References

1. Munnur U, Bandi V, and Guntupalli KK. (2011). Management principles of the critically ill obstetric patient. *Clinical Chest Medicine*, **32**(1), 53–60, viii.
2. Bourjeily G and Miller M. (2009). Obstetric disorders in the ICU. *Clinical Chest Medicine*, **30**(1), 89–102, viii.
3. Kuklina EV, Meikle SF, Jamieson DJ, et al. (2009). Severe obstetric morbidity in the United States: 1998–2005. *Obstetrics and Gynecology*, **113**(2 Pt 1), 293–9.
4. Mercier FJ and Van de Velde M. (2008). Major obstetric hemorrhage. *Anesthesiology Clinic*, **26**(1), 53–66, vi.
5. James AH, McLintock C, and Lockhart E. (2012). Postpartum hemorrhage: when uterotonics and sutures fail. *American Journal of Hematology* [Review], **87**(Suppl. 1), S16–22.
6. Miller MA, Chalhoub M, and Bourjeily G. (2011). Peripartum pulmonary embolism. *Clinical Chest Medicine*, **32**(1), 147–64.
7. Bourjeily G, Paidas M, Khalil H, Rosene-Montella K, and Rodger M. (2010). Pulmonary embolism in pregnancy. *Lancet*, **375**(9713), 500–12.
8. Leung AN, Bull TM, Jaeschke R, et al. (2011). An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. *American Journal of Respiratory and Critical Care Medicine* [Practice Guideline], **184**(10), 1200–8.
9. Bates SM, Greer IA, Middeldorp S, et al. (2012). VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* [Practice Guideline], **141**(2 Suppl.), e691S–736S.
10. van Dillen J, Zwart J, Schutte J, and van Roosmalen J. (2010). Maternal sepsis: epidemiology, etiology and outcome. *Current Opinion in Infectious Diseases*, **23**(3), 249–54.
11. Knight M, Berg C, Brocklehurst P, et al. (2012). Amniotic fluid embolism incidence, risk factors and outcomes: a review and recommendations. *BMC Pregnancy and Childbirth*, **12**, 7.
12. Benson MD. (2012). Current concepts of immunology and diagnosis in amniotic fluid embolism. *Clinical Developments in Immunology*, **2012**, 946576.
13. Ramsay G, Paglia M, and Bourjeily G. (2012) When the heart stops: a review of cardiac arrest in pregnancy. *Journal of Intensive Care Medicine*, **28**(4), 204–14.

14. Leighton BL, Wall MH, Lockhart EM, Phillips LE, and Zatta AJ. (2011). Use of recombinant factor VIIa in patients with amniotic fluid embolism: a systematic review of case reports. *Anesthesiology*, **115**(6), 1201–8.
15. Conde-Agudelo A and Romero R. (2009). Amniotic fluid embolism: an evidence-based review. *American Journal of Obstetrics and Gynecology*, **201**(5), 445 e1–13.
16. Dean LS, Rogers RP, 3rd, Harley RA, and Hood DD. (2012). Case scenario: amniotic fluid embolism. *Anesthesiology*, **116**(1), 186–92.
17. Zivi E, Simon A, and Laufer N. (2010). Ovarian hyperstimulation syndrome: definition, incidence, and classification. *Seminars in Reproductive Medicine*, **28**(6), 441–7.
18. Grossman LC, Michalakis KG, Browne H, Payson MD, and Segars JH. (2010). The pathophysiology of ovarian hyperstimulation syndrome: an unrecognized compartment syndrome. *Fertility and Sterility*, **94**(4), 1392–8.

SECTION 20

Specialized intensive care

PART 20.1

Specialized surgical intensive care

CHAPTER 368

Intensive care management after cardiothoracic surgery

Matthew Barnard and Nicola Jones

Key points

- Monitoring and maintaining organ perfusion and cardiac output are as important to survival after cardiac surgery as in all general intensive care patients.
- Cardiac tamponade is common and easily missed. Diagnosis should not be delayed for diastolic collapse.
- Atrial fibrillation is very common after cardiac surgery (30%). Ventricular arrhythmias are uncommon and should raise suspicion of coronary graft compromise.
- Restriction of intravenous fluids and peri-operative protective ventilatory strategies can improve outcome after thoracic surgery.
- Prompt attention to atelectasis, infection, and air leak after thoracic surgery will improve outcome.

Cardiac surgery

Cardiovascular disease has declined over the last 20 years in most developed countries but still accounts for 30% of deaths [1]. Despite substantial changes in patient demographics, altered disease patterns, and novel technological developments, models of future activity suggest that demand for cardiac surgery will continue [2]. Few believe that coronary artery bypass graft (CABG) surgery will be completely eliminated in the next 10–15 years, but models incorporating such a scenario predict that surgery will be sustained due to an ageing population, and a 25% overall increase in valve and non-CABG surgery. Despite a demographic shift towards older and sicker patients, operative mortality has been reduced. The principles of general critical care apply to cardiac surgical patients.

Cardiovascular management

Ischaemia

All cardiac surgical patients are monitored for ischaemia with 5-lead ECG ST analysis confering greater specificity than sensitivity. Troponin levels following cardiac surgery are difficult to interpret. Reference ranges are not well established and troponin-I levels increase significantly in the first 48 hours post-operatively above current diagnostic levels for acute coronary syndromes including patients who have not had myocardial infarction [3]. Diagnostic criteria for ischaemia include clinical symptoms, ECG changes, and echocardiography. New echocardiographic regional wall abnormalities developing since completion of surgery are suspicious of ischaemia. However, wall motion abnormalities also occur in stunning, hibernation, and infarction.

Treatment is with standard therapies including antiplatelet medication, intravenous nitrates and anti-anginal medication. Early consultation with cardiologists and repeat angiography are important if ECG or echo changes are significant or persist beyond 2–3 hours.

Ventricular dysfunction

Impaired left and right ventricular function can be due to pre-existing impairment, aortic cross-clamping with insufficient myocardial protection or peri-operative infarction. Clinical manifestations of reduced cardiac output require assessment of ventricular filling, and global and regional ventricular function. Pulmonary artery catheters provide information on cardiac output and resistances, but do not improve outcome. Assessment with echocardiography identifies regional and global hypokinesia, and should distinguish between hypovolaemia, tamponade, and ventricular outflow obstruction. Doppler interrogation of transmitral flow may demonstrate restrictive LV filling (reduced E wave deceleration and tissue E wave velocity).

Treatment includes addressing underlying causes, and inotropic or mechanical support (Box 368.1). Inotropic therapy includes catecholamines, phosphodiesterase inhibitors and calcium sensitising agents. Hypertrophic left ventricles (hypertension, aortic stenosis, hypertrophic cardiomyopathy) can exhibit preserved systolic function with greatly impaired diastolic function [4]. Catecholamines such as epinephrine can further impair diastolic function leading to a spiral of worsening function and metabolic acidosis. Phosphodiesterase inhibitors are useful in this situation. Effectiveness of treatment is monitored by clinical assessment including arterial pressure, peripheral perfusion, and urine output, together with serial measurements of cardiac output, serum lactate, and echocardiography.

Tamponade

Pericardial collection is common and is suggested by reduced cardiac output, hypotension, tachycardia, elevated central venous pressure, oliguria, acidosis, and elevated lactate. Pericardial collection and tamponade are more common in patients with coagulopathy, pre-operative antiplatelet therapy, re-operations, major aortic surgery, and complex surgery with prolonged bypass time. The spectrum of impairment extends from mild decrease in arterial blood pressure to collapse and cardiac arrest. High clinical suspicion,

Box 368.1 Treatment of ventricular dysfunction

- **Beta-adrenergic agonists**: e.g. dobutamine 2–20 μg/kg/min.
- **Phosphodiesterase III inhibitors**: e.g. milrinone 50 μg/kg followed by infusion 0.5 μg/kg/min.
- Noradrenaline or phenylephrine if systematic vascular resistance low.
- Correction of hypocalcaemia.
- Intra-aortic balloon counterpulsation.
- Pulmonary vasodilator (nitric oxide, epoprostenol) if predominant right ventricular failure.
- Ventricular assist devices.

together with severe haemodynamic compromise indicates a need for immediate chest re-opening. If the clinical condition permits, confirmation should be obtained by transthoracic or transoesophageal echocardiography. It is important to appreciate that the traditional echocardiographic finding of 'right ventricular diastolic collapse' occurs late and is not an essential diagnostic criterion.

Arrhythmias and pacing

Common post-operative arrhythmias include atrial fibrillation, atrial tachycardias, sinus and nodal bradycardias, and heart block. Ventricular arrhythmias are less common, and should provoke consideration and exclusion of ischaemia or bypass graft occlusion.

Atrial fibrillation is the commonest arrhythmia and occurs between post-operative days 1–5 in 30–50% of patients. It is usually self-limiting. Serum potassium and magnesium should be normalized. Treatment includes β-blockers, amiodarone, flecainide, and electrical cardioversion. Atrial fibrillation beyond 24 hours mandates consideration of anticoagulation.

Epicardial pacing electrodes (usually two wires, but can use a single active wire with an indifferent wire attached elsewhere in the body—usually subcutaneously with a hypodermic needle) are applied to either atrium, ventricle, or both during surgery. They are useful for temporary epicardial pacing in the setting of bradycardia, heart block, or to optimize heart rate. Atrial pacing modes are preferred in the presence of intact AV conduction as native ventricular conduction is associated with improved (coordinated) ventricular function. This advantage is reduced if the PR interval is prolonged. Daily checks are undertaken for pacing threshold, sensing threshold, capture, underlying rhythm, and pacemaker function. Heart block beyond 48 hours warrants referral to electrophysiologist for consideration of permanent pacing [5].

Mechanical support

Patients who fail to wean from cardiopulmonary bypass or develop cardiogenic shock in the post-operative period, refractory to volume loading and inotropes, may be considered for mechanical support. The simplest form is the intra-aortic balloon pump; this is a specialized arterial catheter with a helium filled balloon that is usually inserted percutaneously into the femoral artery. The balloon inflates during diastole, increasing coronary perfusion, and deflates prior to systole, thereby decreasing ventricular afterload and creating a modest improvement in systemic perfusion. If more significant ventricular assistance and circulatory support is required then this can be provided by either veno-arterial extracorporeal membrane oxygenation (VA-ECMO) or a ventricular assist device (VAD). Early institution can improve survival, but should only be undertaken if the underlying cause is thought to be reversible or the patient is a candidate for bridge to transplantation. Complications of mechanical support include bleeding, infection, and vascular compromise.

Respiratory management

Causes of respiratory dysfunction are listed in Box 368.2. Lung volumes are reduced following sternotomy, due to altered chest wall mechanics, effusions, and pain. Radiological evidence of atelectasis occurs in nearly all those in whom an internal mammary artery is harvested and in a majority of other patients. It is caused by surgical compression, pain, drowsiness, pleural effusions, and inadequate expectoration. Management includes sitting upright, incentive spirometry, physiotherapy, continuous positive airway pressure or bi-phasic positive airway pressure. Pneumonia and acute lung injury occur in cardiac surgical patients with similar manifestations as non-cardiac patients. Diagnosis and management follow similar principles.

Central nervous system management

The spectrum of neurological injury following cardiac surgery encompasses stroke (irreversible cerebral injury), reversible ischaemic neurological deficit (RIND), cognitive dysfunction, and delirium.

Pathophysiological mechanisms vary:

- **Global injury**: prolonged hypoperfusion.
- **Watershed injury**: regions supplied by terminal branches of cerebral arteries e.g. parietotemporal cortices.
- **Focal injury**: arterial occlusion by emboli.
- **Diffuse –microfocal injury (wide micro-embolism)**: probably occurs in the majority of cases.

Diagnosis includes clinical criteria (National Institutes of Health Stroke Index) [6] and CT or MRI imaging. The mainstay of therapy involves supportive measures, such as maintaining cerebral perfusion and arterial blood pressure, treating hyperthermia and hyperglycaemia, supportive treatment of raised intracranial pressure, antibiotics, anticoagulants, physical therapy, and rehabilitation. Acute thrombolysis is generally contraindicated in the immediate post-operative period, even in proven thromboembolism, due to the risks of massive haemorrhage.

Box 368.2 Causes of respiratory dysfunction after cardiac surgery

Sternotomy-related lung mechanical alterations

- Atelectasis.
- Pleural effusion.
- Acute lung injury/inflammatory response to CPB.
- Pneumonia.
- Pneumothorax.

Renal management

Cardiac surgery associated acute kidney injury is common and is an independent predictor of mortality. Renal dysfunction is categorised according to severity, incorporating degree of oliguria, percentage decrease in glomerular filtration rate/rise in creatinine, and persistence of dysfunction over time.

Management is supportive with the emphasis primarily on attempted prevention of injury. A variety of pharmacological protection strategies have been attempted including vasodilators, dopamine agonists, diuretics and antioxidants. To date none have proved efficacious. Approximately 1% of patients require renal replacement therapy with a 50% peri-operative mortality [7]. Approaches aimed at prevention are outlined in Box 368.3.

Haematological management

Post-operative bleeding is common after cardiac surgery and is attributable to:

- Surgical bleeding.
- Residual heparinization.
- Fibrinolysis or cardiopulmonary bypass (CPB) induced coagulopathy/impairment of platelet function.
- Pre-operative anti-platelet agents.

Management includes investigation of the cause, administration of drugs and blood products, and surgical intervention. In addition to routine coagulation screening, thromboelastography (TEG) is useful as it provides a quick, point of care assessment of whole blood haemostasis. Platelet function testing or platelet mapping are also available as point of care technologies, and are useful in patients on anti-platelet agents.

Specific management:

- Haemodynamic control.
- Protamine.
- Normothermia.
- Antifibrinolytics.
- **Blood component therapy**:
  - *Platelets*—if low platelet count, narrow TEG maximum amplitude, recent anti-platelet drug administration.
  - *Fresh frozen plasma/prothrombin complex concentrate*—significant depletion of clotting factors is uncommon.
- **Surgical exploration**: significant losses (more than 400 mL blood loss in less than 4 hours) require surgical exploration (2–5% of patients).

Box 368.3 Prevention of renal dysfunction after cardiac surgery

- Normovolaemia, optimize cardiac output, and arterial blood pressure.
- Avoid nephrotoxic agents.
- Maintain glycaemic control.
- Maintain flow/pressure during CPB.
- Avoid excessive haemodilution.
- Haemofiltration during CPB.

Infection management

Sternal wound infection is an uncommon, but potentially devastating complication. Deep sternal wound infection occurs in 2% [8]. It is more common with diabetes, internal mammary grafts, cardiopulmonary bypass, and obesity. In a study of 9500 patients, coagulase negative staphylococci were isolated in 46%, *Staphylococcus aureus* in 26% and Gram-negative bacteria in 18% [9]. Antimicrobial sensitivities often differ from patients' normal flora (suggesting infection is initiated from the peri-operative environment). 90% of coagulase negative staphyloccoal infections are resistant to flucoxacillin [10].

Management includes:

- Local dressings.
- Antimicrobials.
- Debridement and irrigation.
- Radical debridement in the presence of mediastinitis.

Plastic surgery is usually necessary for chest wall reconstruction. Vacuum dressings have greatly simplified the treatment of wound dehiscence and sternal breakdown if conservative treatment is favoured.

Thoracic surgery

The last decade has seen a dramatic increase in thoracic surgical activity with a 60% increase in operations. Improvements in operative mortality have led to surgery being undertaken in higher-risk patients [11]. This has significant implications for post-operative care.

General management principles

Admission to an intensive care unit is usually required for continued ventilatory assistance or invasive monitoring and haemodynamic support. The following principles should be applied to promote recovery.

Early tracheal extubation

Intubation and positive pressure ventilation increase the risk of persistent air leakage, bronchopleural fistula, pulmonary infection, and acute respiratory distress syndrome (ARDS). Immediate tracheal extubation should be planned in all patients unless significant complications preclude it.

Restriction of intravenous fluids

Positive fluid balance is a risk factor for the development of post-resection ARDS [12]. A restrictive approach to fluid administration is recommended and in general patients should receive no more than of 20 mL/kg of fluid in the first 24 hours after surgery. Vasopressors may be required to maintain adequate perfusion pressure, particularly when epidural analgesia is used.

Effective analgesia

Pain causes shallow breathing and poor cough resulting in retention of secretions, atelectasis and respiratory failure. Other adverse effects include myocardial ischaemia, arrhythmia and development of chronic pain. Traditionally, thoracic epidural has been considered the most effective form of pain relief; however, it causes complications including hypotension, which can lead to inappropriate fluid loading. Paravertebral block is a good alternative as it can provide comparable analgesia with fewer side effects [13].

Early mobilization and physiotherapy

Deep breathing, incentive spirometry, chest physiotherapy, and early mobilization have been recommended to minimize post-operative complications. Evidence to support the effectiveness of these interventions is limited, although benefit may be seen if used in combination and delivered by specialized therapists [14].

Early drain removal

Early removal reduces pain and facilitates mobilisation. The majority of surgeons leave the drains *in situ* until fluid output is less than 250mL/day. Following pneumonectomy some place a drain, and clamp and open it once per hour. Suction is never applied. Others do not place a drain and instead aspirate air from the pleural space. The key element is to ensure is that the mediastinum is midline on the post-operative chest radiograph.

Respiratory management

Respiratory complications include sputum retention, atelectasis, pneumonia, re-expansion pulmonary oedema, and ARDS, all of which can lead to respiratory failure. Non-invasive ventilation (NIV) can be used to improve gas exchange and avoid re-intubation. However, absence of initial response or presence of cardiac co-morbidity predict failure and a high risk of mortality. If re-intubation is required then it should be undertaken early and a protective ventilatory strategy used to reduce the risk of ventilator-induced lung injury. If a prolonged period of ventilation is expected, consideration should be given to tracheostomy. In circumstances of severe respiratory failure, where recovery of residual lung function is anticipated, extracorporeal support can be considered to provide gas exchange temporarily and facilitate protective ventilation. This is rarely associated with survival.

Alveolopleural fistula (APF) is a common surgical complication following thoracic surgery and results in an air leak that is defined as persistent if it continues beyond 7 days. It is due to the development of an abnormal communication between the pleural space and pulmonary parenchyma, distal to a segmental bronchus. Positive pressure ventilation increases the air leak, so steps should be taken to minimize transpulmonary pressure in order to reduce fistula flow and encourage healing. Mechanical ventilation strategies include use of volume control ventilation, reduction of inspiratory pressure, tidal volumes, respiratory rate, positive end expiratory pressure, and inspiratory times. Most air leaks will settle spontaneously over a few days, although if they are persistent, management strategies include:

- Occlusion or pressurization of the chest tube.
- Lung isolation and independent lung ventilation.
- High frequency ventilation
- Repair of the fistula.

Bronchopleural fistula (BPF) is a serious complication with a high mortality, particularly in those who have undergone pneumonectomy. It is distinguished from an APF as an abnormal communication between the pleural space and lobar or segmental bronchi. The main hazards are contamination of the remaining lung and tension pneumothorax. Immediate management involves positioning the patient with the affected side down and isolating the good lung using a double lumen endotracheal tube (bronchial lumen to the good side) under direct bronchoscopic guidance. If a chest tube is not in situ then spontaneous ventilation should be maintained until one is inserted. After intubation, peak airway pressures should be minimized. Broad spectrum antibiotics are indicated. Surgical management involves immediate closure or wide open drainage.

Lobar torsion is a rare complication that may prove fatal if not recognized. It represents a rotation of the bronchovascular pedicle with resultant airway obstruction and vascular compromise. Bronchoscopy is diagnostic and emergency re-exploration is required.

Cardiovascular management

Cardiovascular complications include peri-operative myocardial infarction (MI), arrhythmia, and right ventricular failure. Non-fatal peri-operative MI occurs in 1–5% of patients. Antiplatelet therapy is limited by the risk of surgical bleeding. Atrial fibrillation is the most common arrhythmia. Initial management should focus on a rhythm-control strategy. Use of amiodarone is contentious, particularly following pneumonectomy, due to the risk of pulmonary toxicity. Consideration should be given to anticoagulation. Right ventricular failure can occur after lung resection due to reduction in the pulmonary vascular bed, which acutely increases afterload. Basic principles of management include maintenance of systemic perfusion pressure, optimization of cardiac inotropy and reduction in right-ventricular afterload using pulmonary vasodilators, such as epoprostenol or phosphodiesterase inhibitors.

Cardiac herniation is a rare and catastrophic complication of pneumonectomy that occurs when the heart herniates into the hemithorax through a defect in the pericardium. The chest drain should be taken off suction immediately and the patient transferred to surgery in the lateral decubitus position with the operated side uppermost.

Renal management

Acute kidney injury (AKI) is estimated to occur in 1–8% of patients following lung resection, and is associated with cardiopulmonary complications and prolonged hospitalization. No relationship has been demonstrated between intra-operative fluid restriction or crystalloid balance in the first 24 hours following surgery. Recovery usually occurs and management is supportive.

Haematological management

Post-operative bleeding after pulmonary resection is uncommon, but may require urgent re-exploration. Chest tube drainage of greater than 100 mL/hour for more than 2 hours is cause for concern. Patients require fluid resuscitation and, if present, coagulopathy should be corrected.

Infection management

Infection is a relatively frequent complication after thoracic surgery, most commonly pneumonia, empyema, and surgical site. Antibiotic selection should take into consideration that patients may have suffered multiple episodes of pre-operative respiratory tract infection and have chronic airway colonisation with resistant organisms.

References

1. British Heart Foundation. (2012). *Coronary Heart Disease Statistics*. Birmingham: British Heart Foundation.

2. Bertrand X. (2013). The future of cardiac surgery: find opportunity in change. *European Journal of Cardiothoracic Surgery*, **43**(1), 253–4.
3. Januzzi JL. (2009). Troponin testing after cardiac surgery. *HSR Proceedings in Intensive Care and Cardiovascular Anesthesia*, **1**(3), 22–32.
4. Shah PM. (2003). Hypertrophic cardiomyopathy and diastolic dysfunction. *Journal of the American College of Cardiology*, **42**(2), 286–7.
5. Kim MH, Deeb GM, Eagle KA, et al. (2001). Complete atrioventricular block after valvular heart surgery and the timing of pacemaker implantation. *American Journal of Cardiology*, **87**, 649–51.
6. National Institute of Neurological Disorders and Stroke (NINDS). (2003). NIH Stroke Scale. Available at: http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf
7. Leacche MM, Winkelmayer WC, Paul S, et al. (2006). Predicting survival in patients requiring renal replacement therapy after cardiac surgery. *Annals of Thoracic Surgery*, **81**, 1385–92.
8. Kubota H, Miyata H, Motomura N, et al. (2013). Deep sternal wound infection after cardiac surgery. *Journal of Cardiothoracic Surgery*, **8**, 132.
9. Gardlund Bitkover CY, and Vaage J. (2002). Postoperative mediastinitis in cardiac surgery—microbiology and pathogenesis. *European Journal of Cardiothoracic Surgery*, **21**(5), 825–30.
10. Mossad SB, Serkey JM, Longworth DL, et al. (1997). Coagulase-negative staphylococcal sternal wound infections after open heart operations. *Annals of Thoracic Surgery*, **63**(2), 395–401.
11. Society for Thoracic Surgery in Great Britain and Ireland (2011). Second National Thoracic Surgery Activity and Outcomes Report. Liverpool: STSGBI. Available at: http://www.scts.org/_userfiles/resources/634558869917493937_Thoracic_2011_FINAL.pdf
12. Moller Am, Pedersen T, Svendsen PE, and Englquist A. (2002). Perioperative risk factors in elective pneumonectomy: the impact of excess fluid balance. *European Journal of Anaesthesiology*, **19**, 57–62.
13. Elsayed H, McKevith J, McShane J, and Scawn N. (2012). Thoracic epidural or paravertebral catheter for analgesia after lung resection: is the outcome different? *Journal of Cardiothoracic and Vascular Anesthesia*, **26**(1), 78–82.
14. Varela G, Novoa NM, Agostini P, and Ballesteros E. (2011). Chest physiotherapy in lung resection patients: state of the art. *Seminars in Thoracic and Cardiovascular Surgery*, **23**(4), 297–306.

CHAPTER 369

Intensive care management after neurosurgery

Kamalakkannan Subhas and Martin Smith

Key points

- Close monitoring is required in the first 6–12 hours following neurosurgery as deterioration in clinical status is usually the first sign of a potentially fatal complication.
- Cardiovascular and respiratory disturbances adversely affect the injured or 'at risk' brain, and meticulous blood pressure control and prevention of hypoxia are key aspects of management.
- A moderate target (7.0–10 mmol/L) for glycaemic control is recommended, avoiding hypoglycaemia and large swings in blood glucose concentration.
- Pain, nausea, and vomiting are the most common complications after neurosurgery, and a multimodal approach to pain management and anti-emesis is recommended.
- Disturbances of sodium and water homeostasis can lead to serious complications and a structured approach to diagnosis and management minimizes adverse outcomes.

Introduction

The main focus of the post-operative management of neurosurgical patients is the prevention, prompt detection, and management of surgical complications, and other factors that put the brain or spinal cord at risk. This relies on frequent clinical examination and monitoring, and optimization of systemic and cerebral physiology [1]. The majority of patients do not require complex monitoring or intervention beyond the first 12 hours after elective surgery, although prolonged intensive care unit management may be required for those who develop complications, or after acute brain injury.

Monitoring

Besides the close monitoring and assessment of cardiac and respiratory functions, frequent neurological monitoring is essential because deterioration in clinical status is usually the first sign of a potentially fatal complication after neurosurgery [2]. The Glasgow coma scale (GCS) provides a standardized method for evaluating a patient's global neurological status by recording best eye opening, motor and verbal responses to physical and verbal stimuli. Although not designed for this purpose, the GCS is widely used to monitor the level of consciousness after neurosurgery. More recently, a new coma score, the Full Outline of UnResponsiveness (FOUR) score, has been introduced to address some of the shortcomings of the GCS by incorporating brainstem reflexes and respiration [2]. Localizing signs such as pupil responses and limb weaknesses should also be recorded. A reduction in conscious level or the development of new localizing signs should prompt an urgent CT scan to identify a surgically remedial cause.

Serial clinical assessment performed by an experienced nurse is the simplest and most effective neurological monitor, but clinical evaluation is unable to detect changes in sedated patients. Multimodal intracranial monitoring, including measurement of intracranial pressure (ICP), cerebral oxygenation, cerebral blood flow, and brain tissue biochemistry, has a key role in guiding individualized management strategies after acute brain injury, but the indications for monitoring after elective neurosurgery are less well defined [3].

Emergence from anaesthesia and extubation

Rapid awakening after general anaesthesia permits early clinical assessment, but extubation should only be considered in a fully awake, normothermic, and haemodynamically stable patient with no new neurological deficit [4]. Pre-existing impairment of neurological status is no longer considered an absolute contraindication to early post-operative extubation [5]. Approximately 10% of neurosurgical patients require post-operative ventilation and sedation to allow stabilization of intracranial and systemic variables (Box 369.1). Sedation and analgesia should be titrated to allow frequent neurological examination, while preserving haemodynamic stability. Propofol is a widely-used sedative agent in neurosurgical patients and, in association with ultra-short acting opioids, allows reliable clinical assessment within a few minutes of stopping the infusion [6]. An ICP monitor should be placed if prolonged sedation is required [3].

Airway complications

Macroglossia and airway swelling secondary to venous obstruction may occur during prolonged posterior fossa or craniocervical junction surgery in the prone position, and post-operative oedema or haematoma can cause acute airway obstruction after anterior cervical spine or carotid surgery. Where there is potential for airway compromise in this way, the presence of a leak around

Box 369.1 Indications for post-operative ventilation and sedation after neurosurgery

Neurosurgical factors

- Resection of large tumour with midline shift.
- Intra-operative brain swelling.
- Large intra-operative blood loss.
- Cranial nerve damage.
- Long-lasting surgery.
- Seizures during emergence.
- Pre-operative reduced conscious level.

Systemic factors

- Cardiovascular instability.
- Hypothermia (temperature <35°C).
- Respiratory insufficiency.
- Coagulopathy.
- Severe metabolic disturbance.
- Comorbidities, particularly severe cardiac and respiratory disease.

the endotracheal tube and an adequate swallow must be confirmed prior to extubation. Re-intubation is likely to be technically demanding so skilled personnel and appropriate equipment should be immediately available.

Blood pressure management

Both hypertension and hypotension can adversely affect the injured or 'at risk' brain [1] and meticulous blood pressure control is essential in the early post-operative period. Cardiovascular disturbances may be related to neurogenic effects (such as direct brainstem and neurohormonal effects), emergence from anaesthesia, and concurrent drug therapy for medical comorbidities. After elective neurosurgery systolic blood pressure is generally maintained between 120–150 mmHg, although more specific targets are relevant in certain conditions [7].

Hypertension

Hypertension is common after intracranial neurosurgery and may cause complications, such as intracranial bleeding and cerebral oedema, or be a consequence of them [8]. Treatable causes such as pain, full bladder, or shivering should be excluded before administration of anti-hypertensive agents. To reduce blood pressure, drugs such as labetalol and esmolol are preferred, whereas calcium-channel blockers, nitrates, and sodium nitroprusside should be avoided because they are cerebral vasodilators and may increase ICP [7].

Hypotension

Hypotension is less common than hypertension and may occur because of hypovolaemia (particularly if osmotic diuretics have been administered during surgery) and brain injury-related neurogenic peripheral vasodilatation or stunned myocardium syndrome. Even short periods of hypotension can compromise cerebral or spinal cord perfusion, and should be treated aggressively, initially by fluid challenges. Euvolaemia and normal serum osmolality are the fluid resuscitation goals after neurosurgery, with some evidence that aggressive fluid resuscitation strategies may be detrimental to the injured brain. Intravascular volume should be maintained with isotonic crystalloids, and 0.9% saline is a justified choice despite a lack of evidence of superiority. Hypo-osmolar and glucose-containing solutions should be avoided [9].

If pharmacological blood pressure augmentation is required vasopressors, such as phenylephrine, metaraminol, and noradrenaline, are the most appropriate first choice since they are associated with increases in cerebral blood flow (CBF) [7]. Patients with previous cardiac disease or neurogenic myocardial failure may require additional inotropic support.

Blood pressure control in specific situations

Blood pressure control requires special attention in certain post-operative situations.

Emergence hypertension

Emergence from anaesthesia is associated with systemic hypertension in 70–90% of patients after cranial neurosurgery and may cause cerebral hyperaemia and raised ICP (4). The short-acting cardioselective β-blocker esmolol is useful in managing emergence hypertension.

Post-operative intracranial haemorrhage

Systolic blood pressure > 200 mmHg is a major risk factor for intracranial haemorrhage after intracranial neurosurgery and should be treated aggressively. The risks associated with lower levels of hypertension are less clear [10].

Cerebral hyperaemia

The cerebral hyperperfusion syndrome (CHS) occurs in 3% to 12% of patients after treatment of intracranial atherosclerotic or carotid disease. An acute rise in CBF occurs because some parts of the cerebral vasculature remain paretic and unable to constrict in response to higher flow in areas that were previously accustomed to low intravascular pressures because of restricted flow. In severe cases, CHS is associated with cerebral haemorrhage, severe brain swelling and death. Arterial blood pressure should be aggressively reduced if CHS develops, and a target systolic pressure between 90 and 140 mmHg has been recommended [11].

Respiratory management

Neurosurgical patients commonly develop respiratory complications. Brainstem compression by post-operative haematoma or hydrocephalus can cause respiratory arrhythmias and hypoventilation, and reduced level of consciousness, poor bulbar function, and lack of mobility increase the risk of pulmonary aspiration and infection. Neurogenic pulmonary oedema develops in up to 50% of patients with severe brain injury and may present acutely in the post-operative period.

There is no specific evidence to guide arterial blood gas targets after neurosurgery, but the prevention of hypoxia and maintenance of normocapnoea are paramount [5]. Protective ventilation strategies minimize the risk of ventilator-induce lung injury, but can

conflict with brain-directed strategies in some patients; therapy may thus be a compromise determined on a case-by-case basis [12].

Glycaemic control

Hyperglycaemia is common because of the stress response to surgery and the use of corticosteroids to reduce peri-tumoural oedema. High blood glucose is detrimental to the injured or 'at risk' brain and associated with a higher rate of infectious complications, but the optimal glucose level in neurosurgical patients is uncertain [13]. 'Tight' glycaemic control increases the risk of hypoglycaemia and has not been shown to improve outcome after acute brain injury [14]. A moderate target for glycaemic control is thus recommended, aiming to maintain blood glucose levels between 7.0 and 10 mmol/L, and avoiding hypoglycaemia and large swings in glucose [13].

Fever and infectious complications

Wound infection rates after craniotomy are low (< 4%), but increased substantially by repeated surgery. Untreated wound infections can lead to meningitis, cerebrititis, or brain abscess. Intraventricular catheters are complicated by infection in up to 11% of cases, with the risk of infection increasing after 5 days. Antibiotic impregnated or silver-coated ventricular catheters reduce the overall infection risk. Pneumonia is the most common infective complication after neurosurgery because of the increased risk of pulmonary aspiration in patients with reduced conscious level or poor bullbar function.

Fever, leukocytosis, and elevated CRP may be related to a post-operative or brain injury-related inflammatory response, but should always prompt investigation for an infective cause. Pharmacological methods of maintaining normothermia, such as paracetamol, are used routinely; physical cooling methods may have a role in some patients, although shivering must be avoided [15].

Pain control and sedation

Up to 80% of patients experience moderate to severe pain that can persist for several days after craniotomy [16]. Adequate analgesia not only ensures patient comfort, but also avoids pain-related hypertension. A multimodal approach to pain management, incorporating local anaesthetic wound infiltration, paracetamol, and opioids is recommended. Codeine and tramadol are still frequently used after intracranial neurosurgery, but morphine provides superior analgesia and has a good safety profile [17]. The use of NSAIDs remains controversial because of the perceived risks of intracranial bleeding and impaired bone healing after spinal surgery. Local anaesthetic nerve blocks are effective in reducing the incidence of chronic pain, but do not modify acute pain [16]. The pre-operative administration of gabapentin may improve pain control in the first 48 hours after neurosurgery in selected patients.

Post-operative nausea and vomiting is one of the most frequent complications after neurosurgery. Vomiting, which is highly unpleasant and may also result in hypertension and raised ICP, occurs in approximately 40% of patients. Multimodal treatment with ondansetron, dexamethasone and droperidol is recommended [18].

Sodium disturbances

Disturbances of sodium and water homeostasis are common after neurosurgery and can lead to serious complications and adverse outcomes [19].

Hyponatraemia

Hyponatraemia may occur because of administration of hypotonic fluids in the presence of high levels of antidiuretic hormone (ADH) in the peri-operative period. Other causes after intracranial neurosurgery and brain injury include the syndrome of inappropriate ADH secretion (SIADH) and the cerebral salt wasting syndrome (CSWS). An expectant and supportive treatment strategy is best in asymptomatic patients since the sodium disturbance is often transient and self-limiting. Prompt treatment is indicated in those with acute symptomatic hyponatraemia in order to minimize the risk of neurological complications and death. Electrolyte-free water restriction forms the mainstay of treatment of SIADH, but may be contraindicated in the early post-operative period, and after brain injury, where euvolaemia is essential to maintain cerebral perfusion. Pharmacological treatment is an option in resistant cases; democlocycline inhibits the renal responses of ADH, and ADH-receptor antagonists, such as conivaptan, inhibit the binding of ADH to renal receptors. The primary treatment of CSWS is volume and sodium resuscitation. 0.9% saline is generally indicated although, in acute symptomatic hyponatraemia, hypertonic saline is recommended.

Hypernatraemia

Hypernatraemia can be related to the use of sodium-containing osmotic diuretics such as mannitol, or the development of cranial diabetes insipidus (CDI), which is particularly common after pituitary surgery and severe acute brain injury. The aims of the management of CDI are two-fold—replacement and retention of water, and replacement of ADH. In conscious patients, free access to water may be all that is required as the CDI is often self-limiting. In unconscious patients enteral water should be administered via a gastric tube, guided by accurate assessment of volume status. If urine output continues > 250 mL/hour, synthetic ADH, in the form of small titrated doses of 1-deamnio-8-D-arginine vasopressin (desmopressin), should be administered.

Deep vein thrombosis prophylaxis

Neurosurgical patients are at high risk of venous thromboembolic disease. Combined mechanical and pharmacological prophylaxis is more effective than a single modality. Sequential pneumatic calf compression devices and graduated compression stockings should be continued postoperatively until the patient is ambulating. Low molecular weight heparin is safe after the first post-operative day.

Specific neurosurgical considerations

Post-operative complications occur in up to 27% of neurosurgical patients overall, with major complications leading to poor outcome and death occurring in 3–7% [4].

Immediate post-operative haematoma

Most post-operative intracranial haematomas occur within the first 6 hours after craniotomy. Risk factors include the pre-operative use of antiplatelet agents, including aspirin, peri-operative coagulopathy and excision of large vascular meningiomas and arteriovenous malformations. Decreased level of consciousness, new pupillary abnormalities or other focal signs are the presenting clinical

features, emphasizing the importance of close monitoring in the early post-operative period.

Intracranial hypertension

Intracranial hypertension (ICP > 20 mmHg) is common after elective supratentorial surgery but the implications of modest and relatively short-lived rises in ICP, some of which may be related to emergence hypertension, are unclear since few patients have an associated clinical deterioration [4]. More persistent and severe intracranial hypertension may be related to the development of a post-operative haematoma, or cerebral oedema. Reduction in conscious level, with or without focal signs, should prompt an urgent CT scan, but treatment of raised ICP should be started immediately if the patient shows signs of brainstem dysfunction and imminent herniation.

Seizures and status epilepticus

Seizures occur in almost 20% of patients after intracranial neurosurgery, usually within the first 48 hours [2]. The presence of clinical seizures is rarely in doubt, but non-convulsive seizures are more difficult to diagnose. Seizures should be considered in patients with reduced consciousness, or those who fail to wake after surgery. An EEG should be performed when other causes, such as intracranial bleeding, have been excluded.

Post-operative seizures must be brought rapidly under control because of the risks of secondary cerebral damage and/or progression to status epilepticus. A benzodiazepine such as lorazepam is effective and, in a critical care environment, small doses of propofol are a useful alternative. Recurrent seizures require the introduction of long-acting anticonvulsant agents. Levetiracetam has a better safety profile than established agents such as phenytoin, but there is currently no evidence to support the choice of one drug over another. Many patients continue to receive prophylactic anticonvulsants prior to craniotomy, but there is little evidence to support this practice [20], and they should be discontinued within the first post-operative week in those who do not have seizures.

References

1. El Beheiry H. (2012). Protecting the brain during neurosurgical procedures: strategies that can work. *Current Opinion in Anesthesiology*, **25**, 548–55.
2. Pfister D, Strebel SP, and Steiner LA. (2007). Postoperative management of adult central neurosurgical patients: systemic and neuro-monitoring. *Best Practice Research in Clinical Anaesthesiology*, **21**, 449–63.
3. Kirkman M and Smith M. (2012). Multimodal intracranial monitoring: implications for clinical practice. *Anesthesiology Clinic*, **30**, 269–87.
4. Bruder NJ. (2002). Awakening management after neurosurgery for intracranial tumours. *Current Opinion in Anesthesiology*, **15**, 477–82.
5. Rozet I and Domino KB. (2007). Respiratory care. *Best Practice Research in Clinical Anaesthesiology*, **21**, 465–82.
6. Hutchens MP, Memtsoudis S, and Sadovnikoff N. (2006). Propofol for sedation in neuro-intensive care. *Neurocritical Care*, **4**, 54–62.
7. Rose JC and Mayer SA. (2004). Optimizing blood pressure in neurological emergencies. *Neurocritical Care*, **1**, 287–99.
8. Schubert A. (2007). Cardiovascular therapy of neurosurgical patients. *Best Practice Research in Clinical Anaesthesiology*, **21**, 483–96.
9. Van Aken HK, Kampmeier TG, Ertmer C, and Westphal M. (2012). Fluid resuscitation in patients with traumatic brain injury: what is a SAFE approach? *Current Opinion in Anaesthesiology*, **25**, 563–5.
10. Basali A, Mascha EJ, Kalfas I, and Schubert A. (2000). Relation between perioperative hypertension and intracranial hemorrhage after craniotomy. *Anesthesiology*, **93**, 48–54.
11. Reddy U and Smith M. (2012). Anesthetic management of endovascular procedures for cerebrovascular atherosclerosis. *Current Opinion in Anaesthesiology*, **25**, 486–92.
12. Young N, Rhodes JK, Mascia L, and Andrews PJ. (2010). Ventilatory strategies for patients with acute brain injury. *Current Opinion in Critical Care*, **16**, 45–52.
13. Godoy DA, Di NM, Biestro A, and Lenhardt R. (2012). Perioperative glucose control in neurosurgical patients. *Anesthesiology Research and Practice*, 690362.
14. Zafar SN, Iqbal A, Farez MF, Kamatkar S, and de Moya MA. (2011). Intensive insulin therapy in brain injury: a meta-analysis. *Journal of Neurotrauma*, **28**(7), 1307–17.
15. Polderman KH. (2008). Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet*, **371**, 1955–69.
16. Flexman AM, Ng JL, and Gelb AW. (2010). Acute and chronic pain following craniotomy. *Current Opinion in Anaesthesiology*, **23**, 551–7.
17. Gottschalk A and Yaster M. (2009). The perioperative management of pain from intracranial surgery. *Neurocritical Care*, **10**, 387–402.
18. Eberhart LH, Morin AM, Kranke P, Missaghi NB, Durieux ME, and Himmelseher S. (2007). Prevention and control of postoperative nausea and vomiting in post-craniotomy patients. *Best Practice Research in Clinical Anaesthesiology*, **21**, 575–93.
19. Tisdall M, Crocker M, Watkiss J, and Smith M. (2006). Disturbances of sodium in critically ill adult neurologic patients: a clinical review. *Journal of Neurosurgical Anesthesiology*, **18**, 57–63.
20. Klimek M and Dammers R. (2010). Antiepileptic drug therapy in the perioperative course of neurosurgical patients. *Current Opinion in Anaesthesiology*, **23**, 564–7.

CHAPTER 370

Intensive care management after vascular surgery

Alexander Timothy Dewhurst and Brigitta Brandner

Key points

- Vascular patients have multiple co-morbidities.
- Serious post-operative complications, such as myocardial infarction, cerebrovascular accident, acute renal failure, and mesenteric ischaemia contribute to mortality.
- Recent developments in endovascular stent technology allow the treatment of high risk patients.
- The post-operative management of high risk vascular patients should be multidisciplinary with early involvement of intensive care staff.
- The long-term outcome and cost benefit of endovascular versus open surgical procedures are yet to be established.

Introduction

Vascular patients often have multiple co-morbidities and are at risk of major complications. Their management strategy requires a multidisciplinary approach with defined clinical pathways. Vascular emergencies require immediate resuscitation and transfer to a tertiary cardiovascular centre.

Epidemiology

The prevalence of peripheral arterial disease (PAD) is in the range of 12–14% of the population with 20% of over 70s being affected [1]. Abdominal aortic aneurysm (AAA) occurs in 9% of over 65s. It predominates in males in the ratio of 5:1 [2]. The prevalence of thoracic aortic disease (aneurysm and dissection) is in the order of 16 per 100,000 per year [3].

Types of vascular surgery

Emergencies

Increasing numbers of Stanford Type B descending aortic dissections are now being treated with endovascular stents [4,5]. Pre-operative blood pressure control to reduce the risk of further dissection or rupture may require admission to an intensive care unit (ICU). Arterial cannulation and intravenous infusion of a β-blocker or vasodilator are required to control blood pressure. The systolic pressure should be kept below 140 mmHg. It is important to ensure adequate analgesia. A left-sided haemothorax is common and may compromise respiratory function depending on its size. Surgeons prefer not to decompress the haemothorax because of its splinting effect on the aorta. If transfer to a tertiary centre is required for treatment, good communication is essential.

Traumatic transection of the descending thoracic aorta can present after rapid deceleration injuries. Most with complete transection do not survive. Partial transection or contained rupture may present for urgent vascular stenting. In 80% of cases the site of transection occurs just distal to the origin of the left subclavian artery near the attachment of the ligamentum arteriosum. Resuscitation and stabilization of blood pressure are paramount. There is weak evidence that endovascular stenting provides better morbidity and mortality (9 versus 19%) over open surgical repair. The mortality for medical therapy alone is 46% [6].

Ruptured or leaking AAA present with the clinical triad of abdominal or back pain, a pulsatile abdominal mass, and hypotension. It carries a high mortality of 40–70%. Surgical referral is urgent. Treatment in high volume centres reduces mortality so patients may require resuscitation in the emergency department and transfer to a tertiary centre [7]. Restricting intravenous volume resuscitation (permissive hypotension) during the acute phase of resuscitation reduces the degree of bleeding, haemodilution and coagulopathy. Emergency AAA repairs are admitted to intensive care post-operatively. Patients are often mechanically ventilated, and may be hypothermic, acidotic, and coagulopathic.

Critical limb ischaemia occurs in 1–2% of patients with PAD. Patients have a severely painful, white pulseless limb and require urgent surgery to revascularize the limb. Treatment includes embolectomy, angioplasty, stents, or bypass procedures. Post-operatively patients can develop compartment syndrome, rhabdomyolysis, and renal failure. Their vascular grafts may fail with further limb ischaemia and the possibility a non-viable limb requiring amputation. At 1 year a quarter will have required an amputation and a quarter will have died from a cardiovascular cause [8].

Elective cases

ICU admission of elective vascular cases should be considered for the following operations:

- Intervention for PAD in the high risk patient.
- Carotid endarterectomy in selected patients.
- Open aortic surgery including aorto-bifemoral by-pass surgery.
- Infrarenal endovascular aneurysm repair in high risk patients.

- Fenestrated endovascular aneurysm repair.
- Thoracic endovascular aneurysm repair (TEVAR).
- Hybrid procedures

Lower limb PAD

Patients with significant concurrent coronary artery disease (CAD), aortic stenosis, cardiac failure, cerebrovascular disease (CVD) or renal impairment will require high dependency unit admission after surgery for invasive monitoring.

Open surgical repair of AAA

AAA is defined as an aortic diameter of greater than 3 cm. At 5.5 cm it is recommended that AAA be repaired to reduce the risk of rupture. The choice of open surgical repair or endovascular stent depends on the patient's risk factors and the anatomy of the aneurysm [9]. In patients with low to medium risk, repair by open surgical technique is appropriate.

Patients who return to intensive care following an elective AAA repair are expected to be extubated. Thoracic epidural analgesia has advantages over opioid based pain relief in improving respiratory function and quality of pain relief.

Open surgical repair of thoraco-abdominal aortic aneurysm

Open surgical repair of thoraco-abdominal aortic aneurysm (TAAA) is a high-risk procedure. It requires the patient to be placed in the right lateral position. A thoraco-abdominal incision is performed through the diaphragm exposing the descending aorta. Left lung deflation is required for surgical exposure and a spinal cerebrospinal fluid (CSF) drain is inserted to provide spinal cord protection. The aorta is clamped above and below the aneurysm leading to central hypertension and distal hypotension. Clamping the proximal aorta results in a sudden increase in left heart afterload and can lead to acute left ventricular failure. Partial left heart by-pass is used to offload the left ventricle and provide distal perfusion.

ICU care is complex and involves the management of acute lung injury, myocardial failure, cerebral haemorrhage, spinal cord ischaemia, mesenteric ischaemia, and renal failure.

Endovascular repair of aortic disease

Endovascular stenting of the aorta can be performed throughout the length of the aorta including the iliac arteries. In extensive thoraco-abdominal disease the entire descending aorta may be stented with fenestration and stenting of renal and mesenteric vessels. These cases may involve complex hybrid procedures where various vessels are bypassed with vascular grafts. Patients are at risk of similar complications seen in open procedures, although the reported rates of mortality and complications are lower [9]. However, patients who are deemed unfit for open surgical repair or general anaesthesia, and who undergo endovascular repair, have significant early mortality and morbidity [10].

Carotid endarterectomy

The benefit of carotid endarterectomy compared to medical treatment has been demonstrated [11,12]. Patients presenting for surgery should have a recent carotid duplex ultrasound scan and a CT scan of the brain. The criteria for carotid stenosis grading should be based on published guidelines and the decision to proceed to surgery depends on the degree of stenosis and presence of symptoms [13].

A few patients require ICU, depending on their co-morbidities and severity of neurological symptoms if they have suffered a stroke or transient ischaemic attack (TIA).

Hyperperfusion syndrome (HPS) occurs as a result of disordered cerebrovascular autoregulation. It is characterized by ipsilateral headache, hypertension, seizures, and focal neurological deficit. It is most common in patients who have had a high-grade stenosis corrected and have more than doubled their cerebral perfusion compared with baseline. This can occur up to 5 days after surgery. Patients should be admitted to a high-dependency unit for control of their blood pressure and neurological observation.

Regular assessment of the surgical wound should be performed as post-operative haemorrhage maybe dramatic and the resulting haematoma can rapidly compromise the airway. Tracheal re-intubation maybe difficult because of airway distortion and urgent surgical decompression of the haematoma maybe required before re-intubation is possible. A difficult airway trolley should be available.

Common co-morbidities in vascular patients

Cardiovascular

Between 30 and 60% of vascular patients have underlying coronary artery disease [14]. Ischaemia maybe silent and often occurs in the post-operative period.

Many patients will be taking aspirin and other anti-platelet agents. Stopping these agents places the patient at risk of in-stent thrombosis and myocardial infarction.

Respiratory

Smoking-related lung disease is common in vascular patients. Patients with a productive cough and poor pulmonary reserve are at risk of post-operative respiratory failure. Post-operatively patients may need prolonged respiratory support with either non-invasive or invasive techniques. Bronchoscopy maybe required in patients with severe sputum retention.

Renal

Vascular surgery to major vessels, particularly to the aorta, is complicated by renal dysfunction in 10–25% cases.

Risk factors for renal dysfunction are:

- Pre-existing renal impairment.
- Intraoperative ischaemia.
- Nephrotoxic agents (particularly contrast medium).
- Embolization of atherosclerotic debris.
- Pro-inflammatory response.
- Genetic predisposition.

There are no pharmacological agents that prevent renal dysfunction. Maintenance of hydration and adequate renal perfusion pressure are important in preserving function.

Cerebrovascular disease

Microvascular disease of the cerebral circulation is common in elderly vascular patients. Underlying occult cognitive deficit may

be revealed in the post-operative period. Confusion and delirium may complicate and delay recovery.

Specific management issues relating to vascular patients

Spinal cord ischaemia

Spinal cord ischaemia or infarction occurs after open surgical repair of TAAA (8–28%) and TEVAR (4–7%) [15].

The risk factors are:

- Aneurysm extent.
- Open surgical repair.
- Failure to re-implant spinal arteries.
- Emergency operation.
- Prior distal aortic operation.
- Cross-clamp time.
- Severe peripheral vascular disease.
- Anaemia.
- Hypotension.

Manoeuvres aimed at reducing spinal cord dysfunction include reduction of ischaemic time, increasing cord tolerance to ischaemia, increased spinal cord perfusion, and monitoring cord function. There are no pharmacological agents that prevent or treat spinal cord ischaemia.

Late onset spinal cord dysfunction can present in high-risk patients who become hypotensive or severely anaemic. There are reports that increasing spinal cord perfusion can reverse this dysfunction [16]. Augmentation of blood pressure using vasopressors in combination with lumbar CSF drainage may increase spinal cord perfusion [17,18]. It is important to ensure cardiac output and haemoglobin levels are adequate.

Lumbar drains maybe used in patients who are going to receive partial or full anticoagulation. The complications associated with the technique include headache, persistent CSF leak, catheter fracture, meningitis, and direct nerve injury. In addition, intracranial hypotension, subdural haematoma, intracranial haemorrhage, and spinal haematoma have been reported.

Mesenteric ischaemia

Acute intestinal ischaemia is life threatening. Occlusive mesenteric ischaemia can occur from embolism or thrombosis. Non-occlusive mesenteric ischaemia may occur in low cardiac output states when vasopressors are being used or with vasospasm after revascularization. Intestinal ischaemia should be suspected in patients who develop abdominal pain following transaortic catheter procedures, after a new arrhythmia or recent myocardial infarction.

Patients present with severe abdominal pain, out of proportion to the physical signs. Blood tests reveal leucocytosis, lactic acidosis, and raised amylase in 50% of cases. Plain abdominal X-ray may show dilated bowel loops. CT scan with contrast may demonstrate ischaemia and is often requested by surgical teams. However, in non-occlusive ischaemia it may provide a false negative result and consideration should be given to the risk of contrast nephropathy. Mesenteric arteriography is the definitive investigation. An expedient laparotomy by a surgeon capable of resection of or revascularization of viable ischaemic bowel maybe life saving.

Anticoagulation

During surgery, partial or full anticoagulation maybe required with unfractionated heparin. Thomboprophylaxis is required post-operatively and is commonly provided by the use of low molecular weight heparin (LMWH).

During open vascular surgery and endovascular stenting, with or without cardiopulmonary bypass, heparin will be administrated to prevent thrombotic complications.

Neuro-axial anaesthesia and lumbar CSF drains are often employed during vascular surgery. The main concern with the use of neuro-axial blockade and lumbar CSF drains is the risk of spinal or epidural haematoma formation in patients receiving anticoagulants. Guidelines on the use of regional anaesthesia in patients receiving antithrombotic agents have been published, and these should be followed for both the insertion and removal of catheters [19].

To summarize, the recommendations are as follows:

- Catheters should not be inserted or removed within 10–12 hours of a dose of LMWH or heparin.
- LMWH or heparin should not be given until 1–2 hours after catheter insertion or removal.
- In the event of a bloody tap consider postponing surgery.
- Consider insertion of catheter day before surgery.
- Patients should be monitored neurologically post-operatively.
- Early radiological investigation if neurological symptoms occur.

Analgesia

Thoracic epidural analgesia results in significantly lower pain scores in the first three post-operative days and reduces the duration mechanical ventilation, cardiovascular complications, acute respiratory failure, and gastrointestinal complications [20]. Non-steroidal anti-inflammatory drugs are often contraindicated due to comorbidities and the increased risk of renal failure, secondary to the procedure or the use of contrast during endovascular procedures. Paracetamol reduces opioid requirements. The choice of opioid depends on the patient's comorbidities and often the side effects are the limiting factor to control pain. Neuropathic pain relief can be of benefit particular in severe ischaemic and post-amputation pain.

References

1. Shammas NW. (2007). Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. *Vascular Health and Risk Management*, **3**(2), 229–34.
2. Steckmeier B. (2001). Epidemiologie der Aortenerkrankung: Aneurysma, Dissektion, Verschluss. [Epidemiology of aortic disease: aneurysm, dissection, occlusion.] *Der Radiologe*, **41**(8), 624–32.
3. Olsson C, Thelin S, Stahle E, Ekbom A, and Granath F. (2006). Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. *Circulation*, **114**(24), 2611–18.
4. Lombardi JV, Cambria RP, Nienaber CA, et al. (2012). Prospective multicenter clinical trial (STABLE) on the endovascular treatment of complicated type B aortic dissection using a composite device design. *Journal of Vascular Surgery*, **55**(3), 629–40 e2.

5. Nienaber CA, Rousseau H, Eggebrecht H, et al. (2009). Randomized comparison of strategies for type B aortic dissection: the INvestigation of STEnt Grafts in Aortic Dissection (INSTEAD) trial. *Circulation*, **120**(25), 2519–28.
6. Murad MH, Rizvi AZ, Malgor R, et al. (2011).Comparative effectiveness of the treatments for thoracic aortic transection [corrected]. *Journal of Vascular Surgery*, **53**(1), 193–9 e1–21.
7. Finks JF, Osborne NH, and Birkmeyer JD. (2011). Trends in hospital volume and operative mortality for high-risk surgery. *New England Journal of Medicine*, **364**(22), 2128–37.
8. Weitz JI, Byrne J, Clagett GP, et al. (1996). Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation*, **94**(11), 3026–49.
9. Hirsch AT, Haskal ZJ, Hertzer NR, et al. (2006). ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Journal of the American College of Cardiology*, **47**(6), 1239–312.
10. Buth J, van Marrewijk CJ, Harris PL, Hop WC, Riambau V, and Laheij RJ. (2002). Outcome of endovascular abdominal aortic aneurysm repair in patients with conditions considered unfit for an open procedure: a report on the EUROSTAR experience. *Journal of Vascular Surgery*, **35**(2), 211–21.
11. (1991). MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. *Lancet*, **337**(8752), 1235–43.
12. North American Symptomatic Carotid Endarterectomy Trial Collaborators. (1991). Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *New England Journal of Medicine*, **325**(7), 445–53.
13. Oates CP, Naylor AR, Hartshorne T, et al. (2009). Joint recommendations for reporting carotid ultrasound investigations in the United Kingdom. *European Journal of Vascular and Endovascular Surgery*, **37**(3), 251–61.
14. McCann RL and Clements FM. (1989). Silent myocardial ischemia in patients undergoing peripheral vascular surgery: incidence and association with perioperative cardiac morbidity and mortality. *Journal of Vascular Surgery*, **9**(4), 583–7.
15. Greenberg RK, Lu Q, Roselli EE, et al. (2008). Contemporary analysis of descending thoracic and thoracoabdominal aneurysm repair: a comparison of endovascular and open techniques. *Circulation*, **118**(8), 808–17.
16. Cheung AT, Weiss SJ, McGarvey ML, et al. (2002). Interventions for reversing delayed-onset postoperative paraplegia after thoracic aortic reconstruction. *Annals of Thoracic Surgery*, **74**(2), 413–19; discussion 20–1.
17. Khan SN and Stansby G. (2004). Cerebrospinal fluid drainage for thoracic and thoracoabdominal aortic aneurysm surgery. *Cochrane Database of Systematic Reviews* (1), CD003635.
18. Cina CS, Abouzahr L, Arena GO, Lagana A, Devereaux PJ, and Farrokhyar F. (2004). Cerebrospinal fluid drainage to prevent paraplegia during thoracic and thoracoabdominal aortic aneurysm surgery: a systematic review and meta-analysis. *Journal of Vascular Surgery*, **40**(1), 36–44.
19. Gogarten W, Vandermeulen EP, Van Aken H, Kozek S, Llau JV, and Samama CM. (2010). Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. *European Journal of Anaesthesiology*, **27**, 16.
20. Nishimori M, Ballantyne JC, and Low JH. (2006). Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. *Cochrane Database of Systematic Reviews* (3), CD005059.

CHAPTER 371

Intensive care management in hepatic and other abdominal organ transplantation

Ivonne M. Daly and Ali Al-Khafaji

Key points

- Outcome is determined by the pre-operative physiology, quality of the donated organ, and intra-operative events.
- An understanding the physiology of end-stage liver disease is critical to post-operative management.
- The intensivist must anticipate, rather than respond to problems in these patients with reduced physiologic reserve.
- Infection, not rejection, is the most common cause of mortality after transplant. The goal is a fine balance between prevention of rejection and avoidance of infection.
- Attention to additive nephrotoxicities of medications is critical to management after transplant.

Introduction

The transplanted organ needs good oxygen delivery, microvascular flow, clearance of toxins and balance of electrolytes, and immune suppression that balances risks of rejection and infection to recover from the insults of ischaemia and reperfusion. Each abdominal organ failure causes medical problems that persist for days to months after transplant and require special management.

Care of the recipient

Cardiovascular

Cardiovascular complications are the leading cause of death with a functioning allograft among renal, hepatic, and pancreatic allograft recipients, and may account for 30% of post-transplant mortality [1]. Intra-operative events, including volume shifts, massive bleeding, and post-perfusion syndrome, can negatively affect the heart. When the organ is reperfused, acidosis, hyperkalaemia, cytokine release from the new liver, and hypothermia, both from the implanted organ and from infusions of chilled blood can lead to haemodynamic instability. Most patients will require volume resuscitation and, possibly, vasopressor support during the first few hours after transplant. Inotropes and vasopressors are initiated if haemodynamic values are still inadequate after adequate volume resuscitation.

Hypertension can be related to steroids and other immunosuppressants or, in kidney transplant patients, to the underlying disease. Labetalol or hydralazine are appropriate first line agents for treatment of hypertension. Atrial fibrillation should be treated with β-blockers or amiodarone. Calcium channel blockers should be used with caution since they affect tacrolimus metabolism.

For orthotopic liver (OLT) and multivisceral transplant patients, an understanding of cirrhotic cardiomyopathy is essential. Patients with end-stage liver disease (ESLD) have a hyperdynamic circulation with increased cardiac output and decreased peripheral vascular resistance. Many also have diastolic dysfunction and prolongation of the QTc interval [2,3]. In up to 50% of cirrhotic patients, the myocardium is less responsive to catecholamines—in these patients, the increase in cardiac output expected with sepsis, bleeding, or surgery may not occur. Congestive heart failure may suddenly develop after transplant, when vasopressors are initiated or in states of volume overload [4]. Right heart failure can lead to congestion and dysfunction of the allograft. Cirrhotic cardiomyopathy may be reversible after OLT, but the natural history of requires further investigation [3].

It is difficult to recommend specific fluid for resuscitation, although albumin improves long-term renal function in hepatorenal syndrome [5]. Vasopressors are frequently required to improve distributive shock and restore organ perfusion. In patients who develop cardiovascular collapse, an urgent echocardiogram is required to exclude cardiac tamponade related to extension of the surgical incision.

Pulmonary

The primary goal of respiratory management is adequate oxygen delivery without the use of excessive pressure or volume. Kidney and pancreas transplants are usually extubated in the operating room (OR), but liver transplants, small intestine, and multivisceral transplants are usually returned to the ICU intubated. When indicators of graft function are promising, patients with normal lung function may be extubated within hours of surgery. Due to impaired drug metabolism, short-acting analgesics are preferred.

Hepatopulmonary syndrome (HPS) and porto-pulmonary hypertension (PPHTN) are two distinct pulmonary problems that occur in patients with ESLD.

HPS is defined by the presence of hypoxia due to ventilation—perfusion mismatch, intrapulmonary shunting, pulmonary vasodilation, and limitation of oxygen diffusion in patients with ESLD

and portal hypertension. Liver transplantation remains the definitive treatment and most HPS resolve within 1 year after transplantation [6,7].

PPHTN is pulmonary arterial hypertension due to increased pulmonary vascular resistance in the presence of portal hypertension and a pulmonary artery wedge pressure <15 mmHg. Vasoactive substances that are metabolized in the liver travel to the pulmonary circulation via portosystemic shunts causing vasoconstriction. Mean pulmonary artery pressure >45 mmHg increases the risk of graft failure due to venous congestion and right ventricular dysfunction. Pulmonary artery pressures can improve after liver transplantation [6].

The risk of ventilator associated pneumonia is very high due to malnutrition, muscle weakness, and immune suppression.

Renal

Most patients will have some degree of renal injury after non-renal organ transplant. Haemodynamic instability, haemorrhage, inferior vena cava clamping, and peri-operative hyperglycaemia are associated with AKI and worsening of pre-existing renal dysfunction. Many have impaired renal function prior to transplantation; predictably, these patients have worse outcomes.

The use of large volumes of citrated blood products can cause ionized hypocalcaemia and mild metabolic alkalosis. Hypophosphataemia occurs during liver regeneration, when a partial allograft is used. In the setting of renal insufficiency after transplant, the main indications for renal replacement therapy are severe electrolyte imbalance, metabolic acidosis, and volume overload impairing oxygenation and congesting the allograft. Continuous renal replacement therapy is better tolerated than intermittent dialysis.

Blood levels of calcineurin inhibitors must be monitored to limit their contribution to renal dysfunction. Induction protocols that delay initiation of calcineurin inhibitor do not improve renal outcomes (class 2C evidence) [8]. Medications that reduce systemic blood pressure (angiotensin-converting enzyme inhibitors,) reduce glomerular perfusion (non-steroidal anti-inflammatory drugs,) or are directly nephrotoxic (aminoglycosides, amphotericin) should be avoided.

In hepatorenal syndrome (HRS), renal vasoconstriction occurs in the presence of splanchic vasodilatation. This results in activation of the renin-angiotensin-aldosterone system causing fluid retention and massive ascites. Although OLT is the definitive treatment for HRS, some patients will require long-term renal replacement therapy and eventually kidney transplantation.

Endocrine

Adrenal insufficiency occurs in some patients with chronic illness and can become more common in the post-operative period due to the use of steroids. Hyperglycaemia is common due to the stress of surgery and the use of steroids during induction. Many patients require insulin after transplant. After pancreas transplant, 'resting' the pancreas with a low dose insulin infusion aimed at maintaining blood glucose between 4.5 and 7.8 mmol/L is associated with improved islet cell function [9].

Haematological

Patients are at increased risk of bleeding and thrombotic complications immediately after transplant. Tachycardia, hypotension associated with falling haemoglobin, or significant bloody drainage from the surgical drains or the incision should prompt notification of the transplant team for possible re-exploration, especially if the bleeding persist despite coagulation correction.

After transplant, patients are prone to deep vein thrombosis (DVT) and thrombotic complications of the vascular anastomoses. Correction of coagulopathy or thrombocytopenia should be done in consultation with the transplant team. Correction of coagulopathy increases the risk of thrombosis, and, in the case of OLT, masks graft dysfunction. Many advocate replacing platelets only if the count is below 20×10^9/L or if there is active bleeding. Because the pancreas is a low-flow organ, it is at particularly high risk of thrombotic complications. Sequential compression devices and possibly heparin are used for DVT prophylaxis.

Patients with ESLD have disordered coagulation that places them at increased risk of both bleeding and thrombosis. As the liver allograft recovers, it begins to make procoagulant factors II, VII, IX, and X before making anticoagulant factors Protein C, S, and anti-thrombin III. Thrombocytopenia can persist for up to 2 weeks after OLT due to hypersplenism, consumption, and sequestration by the allograft.

Infection

Maintaining immune suppression to prevent rejection of the allograft while minimizing infection is a fine balance. Infection is the most common cause of mortality and morbidity in the first month after transplant [10]. Small intestine, multivisceral, and pancreas transplants [11] have the highest risk of infection due to intestinal anastomoses and increased gut permeability that occurs in states of rejection. In OLT patients, a hepatojejunostomy increases the risk of infection relative to a bile duct-to-bile duct anastomosis. Infections at the surgical site are also potentiated by prolonged surgery, extensive dissection, and massive blood transfusion.

Infections with antibiotic resistant organisms and fungal infections are common. In the setting of unresolved infection, limiting immunosuppression should be considered in consultation with the transplant team.

Regimens for prophylaxis against opportunistic infection vary. All patients receive prophylaxis against *Pneumocystis jiroveci pneumonia* and cytomegalovirus (CMV) (class 1A evidence). CMV is an immunomodulating virus—patients with active CMV disease have a higher incidence of bacterial and fungal infections and a higher incidence of chronic rejection. Kidney transplant patients receive CMV prophylaxis with valganciclovir for 6 months. Antifungal prophylaxis is indicated in cases with difficult dissection, massive transfusions, bile leaks, retransplants, patients with preoperative renal failure or fulminant hepatic failure (class 1A evidence). *Aspergillus* infections affect 1% of transplant recipients with 60% mortality [10]. Treatment should be early with an echinocandin and voriconazole. Kidney transplant patients also have a high incidence of *Clostridium difficile* infections, and routinely receive prophylaxis against this organism.

Nutrition

Many patients presenting for abdominal organ transplant have nutritional deficiencies that increase the risk of post-operative infections and respiratory complications. Protein catabolism is markedly increased after transplant. In liver and multivisceral transplant patients, drainage of ascites, and pleural effusions predisposes to protein malnutrition. Intestinal transplant patients are particularly malnourished.

Small volume tube feeds can be started within 12–24 hours of a transplant that does not involve an enteric anastomosis (class 1c evidence) [12]. OLT and pancreatic transplant patients with bile duct- or pancreatic duct-to-intestine anastomoses are fed 5 days later. In intestinal transplant patients, parenteral nutrition is resumed normally on post-operative day 1 and enteral feeding is started if the ostomy is healthy, non-oedematous, the first small intestine mucosal biopsy does not show findings compatible with rejection, and signs of intestinal function are evident. An elementary enteral formula is usually started on post-operative day 7. Oral intake is started if the patient tolerates full enteral feeding without a nasogastric tube.

Neurological

Calcineurin inhibitors, steroids, and electrolyte imbalance can alter mental status. Analgesia and sedation may be challenging in intestinal transplant patients, because many have chronic pain and narcotic tolerance from multiple abdominal surgeries. Delirium is common and often multifactorial, particularly after OLT. In these patients, clearance of sedatives and analgesics may be limited. Hepatic encephalopathy may persist from the pre-operative state, or arise in the setting of primary transplant non-function. Flumazenil can improve mental status related to liver failure and can help identify the cause of mental status changes. A comatose patient warrants an electroencephalogram to rule out status epilepticus.

Care of the allograft

All transplanted organs are at risk of surgical complications including bleeding, vascular thrombosis, and anastomotic leaks. Doppler ultrasound may be used to assess vascular patency. Transplants with enteric anastomoses are prone to leakage of intestinal contents. OLT recipients may have bile leaks, and kidney transplant recipients may have lymphoceles, haematomas, and leaks of urine from the uretero-bladder anastomosis. All transplants may suffer impaired function due to factors associated with the donor, harvest and ischaemia time.

Graft function can be impaired by haemodynamic instability, the use of vasopressors, hypoxaemia, and electrolyte imbalance in the donor prior to harvest. Infections in the donor at the time of harvest necessitate appropriate antibiotic therapy in the recipient. Duration of hypoxia before harvest is important in donors after cardiac death. Macrosteatosis and fibrosis are associated with delayed graft function in OLT. Delayed graft function and reperfusion injury also correlate with the organ's cold ischaemia time and donor's age.

Organs are at increased risk of delayed graft function and primary non-function when harvested from less than ideal donors [13]. Some grafts with delayed function recover, but delayed function is commonly associated with increased mortality.

Immune suppression and risk of rejection

After transplant, the need for immune suppression is usually lifelong, and serious side effects accumulate over time. The mechanism of action, uses, and side effects of commonly used immune suppressive agents are described in Table 371.1 [14]. When life-threatening infections occur after transplant, a decrease in immune suppression should be considered.

Acute cellular rejection (ACR) is mediated by T cells and can occur as early as a few days after transplant. ACR can be asymptomatic, but can present with fever, right upper quadrant/back pain, and tenderness over the allograft. OLT recipients will have elevated transaminases; kidney transplant recipients will also have an increase in creatinine; pancreas transplant recipients will have increased glucose; intestinal transplant recipients will have an increase in stomal output. Episodes of ACR are treated with corticosteroids, an increase in baseline immunosuppression, or if severe, T cell depletion therapy. Antibody-mediated hyperacute rejection is a very rare entity due to advances in tissue typing.

Liver

The most sensitive early markers of adequate liver function are normalization of the prothrombin time. The prothrombin time is elevated in liver failure and quickly returns to normal once factor V is produced by hepatocytes, usually within hours of implantation. Adequate allograft function is also indicated by resolution of acidosis and clearance of lactate. Transaminases peak during the first 24–48 hours with normalization after 72 hours. Delayed graft function manifests with rising transaminases, bilirubin, and prothrombin time. Rising bilirubin and transaminases in a previously healthy graft should trigger a liver ultrasound to exclude vascular thrombosis, stenosis, and biliary leaks. A biopsy to exclude ACR sometimes is done.

The hepatic artery is the most common site of thrombotic complications. Hepatic artery thrombosis occurs in 2–5% of OLT and is a major cause of allograft loss if revascularization is not accomplished urgently. Hepatic artery thrombosis manifests with dramatic elevation of aspartate transaminase and alanine transaminase that are typically in the thousands.

Several risk factors have been reported for early hepatic artery thrombosis including retransplantation, use of arterial conduits, prolonged operation and cold ischaemic times, low recipient weight, severe rejection, variant arterial anatomy, and low volume transplantation centres. Thrombosis rates are higher after split-liver and living-related transplants, because of the smaller calibre of vessels and the complex arterial reconstruction required. Prompt re-exploration with thrombectomy and revision of the anastomoses is indicated if the diagnosis is made early. If hepatic necrosis is extensive, a retransplant may be indicated.

Primary non-function (PNF) is a devastating complication seen in less than 5% transplants, with mortality > 80% without a retransplant. The cause of PNF is unknown, but several donor factors like advanced age, increased fat content of the donor liver, longer donor hospital stay before organ procurement, prolonged cold ischaemia (>18 hours), and reduced-sized grafts may predict its development. Unfortunately, no medical treatment is effective for PNF. If a retransplant is to influence outcome, it must be done before multi-organ failure develops.

Kidney

Patients are not usually critically ill after a kidney transplant, but may be admitted to the ICU if comorbidities complicate care. Patients with peripheral vascular disease are at increased the risk of embolic events and may require ICU monitoring.

Urine output is replaced with hypotonic fluid to avoid over-administration of glucose and to match the dilute urine that is produced by the allograft. Oliguria in the setting of adequate intravascular volume suggests acute tubular necrosis or reperfusion injury, delayed graft function, acute cellular rejection, ureteral/

Table 371.1 Immune suppressive agents

Name	Mechanism of action	Uses and cautions	Side effects
Tacrolimus	◆ Calcineurin inhibitor ◆ Inhibits IL-2 production	◆ Mainstay of most regimens ◆ Monitor blood levels	Seizures, hyperkalaemia, nephrotoxicity, hyperglycaemia, focal neurological deficits, tremor, hypertension
Ciclosporin	Similar to tacrolimus	◆ Used when tacrolimus is not available ◆ Associated with a higher incidence rejection compared with tacrolimus (class 1a evidence) ◆ Monitor blood levels	Seizures, gingival hyperplasia, hirsutism, hyperkalaemia, hepatotoxicity, nephrotoxicity, gastroparesis
Glucocorticoids	Broad anti-inflammatory effects		Hypertension, psychosis, hyperglycaemia, adrenal suppression, osteoporosis, pancreatitis, electrolyte abnormalities, peptic ulcers, myopathy
Mycophenolate mofetil	Inhibits purine synthesis, limiting lymphocyte proliferation and function	◆ Used for steroid resistant ACR and in renal sparing protocols ◆ Increases risk of CMV complications	Hypertension, hyperkalaemia, bone marrow suppression, impaired wound healing, GI effects
Sirolimus	Inhibits response to IL-2 by inhibiting cell cycle enzyme	◆ Used in combination with tacrolimus in steroid-free and renal sparing regimens ◆ Causes delayed wound healing	Wound dehiscence, bone marrow suppression, hyperlipidaemia, fever, gastro-intestinal effects
Basiliximab Daclizumab	Antibody the alpha subunit of IL-2 receptors	Induction therapy	Fever, hypotension, increased incidence of opportunistic infections
Alemtuzumab	Anti-CD-52 antibody on mature lymphocytes	Induction therapy	Associated with infusion bronchospasm, pulmonary oedema, ARDS, hypotension, arrhythmias
Antithymocyte globulin	Antibody to T-cells generated in rabbit or horse	◆ Induction for prevention of graft versus host disease ◆ Treatment of steroid-resistant ACR	Symptoms of cytokine release Increased risk of post-transplant lymphoproliferative disorder
Muromonab-CD3 (OKT3)	◆ Monoclonal antibody to CD3 ◆ Activates t-cells before inducing apoptosis	Treatment of steroid-resistant ACR	Symptoms of cytokine release

Data from Perry I and Neuberger J, 'Immunosuppression: towards a logical approach in liver transplantation', *Clinical & Experimental Immunology*, 2005, **139**(1), pp. 2–10.

bladder anastomotic leak, or seroma compromising the flow of blood or urine. Oliguria should prompt irrigation of the urinary catheter. If oliguria persists despite adequate vascular volume and haemodynamics ultrasound should be used to assess vascular patency, to rule out anastomic leaks and compression by a fluid collection. Thrombosis at the arterial or venous anastomosis is suspected with abrupt cessation of urine production [13].

Delayed graft function requiring dialysis in the post-operative period does not necessarily portend a need for retransplant. The transplanted kidney can spontaneously recover after several weeks/months.

Pancreas

Patients are at high risk for thrombosis at the anastomotic site, since the pancreas is a relatively low-flow organ. Pancreatic venous drainage to the portal system is accomplished with an interposition graft, which adds to the risk of thrombosis. Manipulation of the organ during harvest is associated with pancreatitis after transplant. Post-operative pancreatitis occurs in 16% of pancreas recipients.

The duodenal stump associated with the pancreatic duct may be attached to the bladder, which allows monitoring of urinary amylase as an indicator of rejection, but results in significant loss of bicarbonate into the urine. The native pancreas is left in situ to provide exocrine function. When the stump is attached to the intestine, exocrine function of the transplanted pancreas is preserved, and bicarbonate is reabsorbed by the intestine. Patients are also at high risk from enterocutaneous fistulae from the poorly vascularized duodenal stump [9,11].

Hyperglycaemia is the hallmark of rejection of an isolated pancreas transplant. Abdominal pain and tenderness over the pancreas allograft is a late sign and is often indicative of an allograft that has already thrombosed. In a combined kidney/pancreas transplant, graft tenderness, and elevated creatinine signal rejection.

Small Intestine and mulitvisceral transplant

A multivisceral transplant refers to an en-bloc allograft that includes liver, stomach, duodenum, pancreas, small intestine, and, variably, spleen, kidney, and or right colon. Patients are admitted to the ICU after MVT due to the stress and fluid load of the very long surgery and due to the need for delayed abdominal closure. These transplant recipients are at high risk of enteric leaks. Aorto-enteric fistula from unrecognized enteric leak close to aortic graft is the most feared complication.

The intestinal graft contains copious lymph tissue, so immune suppression can be challenging. In these patients, rejection is associated with loss of barrier function with translocation of bacteria or lipopolysaccharide into the bloodstream. Rejection after intestinal transplant is heralded by stomal output that becomes bloody or increases in volume; however, this may not be apparent in the immediate post-operative period. Surveillance mucosal biopsies are done twice weekly through the ileostomy during the first few weeks. Abdominal pain is a late sign of rejection and may denote a thrombosed allograft [15].

Conclusion

Peri-operative care of the transplant patient can be extremely rewarding. Transplant recipients can have dysfunction of almost every organ system, yet most have the potential to recover fully. In the immediate post-operative period, intensivists must anticipate problems related to the disordered physiology that exists before transplant. The intensivist should consider the needs of the allograft, as well as the needs of the patient as a whole. Graft function is related to the quality of the donated organ and surgical technique. Meticulous attention to the level of immune suppression and the risk of infection is critical to ensure the best possible outcome.

References

1. Findlay JY, Wen D, and Mandell MS. (2010). Cardiac risk evaluation for abdominal transplantation. *Current Opinion in Organ Transplantation*, **15**(3), 363–7.
2. Mohamed R, Forsey PR, Davies MK, and Neuberger JM. (1996). Effect of liver transplantation on QT interval prolongation and autonomic dysfunction in end-stage liver disease. *Hepatology*, **23**(5), 1128–34.
3. Myers RP and Lee SS. (2000). Cirrhotic cardiomyopathy and liver transplantation. *Liver Transplantation*, **4**(Suppl. 1), S44–52.
4. Sawant P, Vashishtha C, and Nasa M. (2011). Management of cardiopulmonary complications of cirrhosis. *International Journal of Hepatology*, 280569.
5. Davenport A, Ahmad J, Al-Khafaji A, Kellum JA, Genyk YS, and Nadim MK. (2012). Medical management of hepatorenal syndrome. *Nephrology Dialysis and Transplantation*, **27**(1), 34–41.
6. Swanson KL, Wiesner RH, and Krowka MJ. (2005). Natural history of hepatopulmonary syndrome: Impact of liver transplantation. *Hepatology*, **41**(5), 1122–9.
7. Al-Khafaji A and Huang DT. (2011). Critical care management of patients with end-stage liver disease. *Critical Care Medicine*, **39**(5), 1157–66.
8. Flechner SM, Kobashigawa J, and Klintmalm G. (2008). Calcineurin inhibitor-sparing regimens in solid organ transplantation: focus on improving renal function and nephrotoxicity. *Clinical Transplantation*, **22**(1), 1–15.
9. Sutherland DE, Gruessner RW, and Dunn DL. (2001). Lessons learned from more than 1,000 pancreas at a single institution. *Annals of Surgery*, **233**(4), 463–501.
10. Fishman JA. (2007). Infection in solid-organ transplant recipients. *New England Journal of Medicine*, **357**(25), 2601–14.
11. Scalea JR and Cooper ML. (2012). Current concepts in the simultaneous transplantation of kidney and pancreas. *Journal of Intensive Care Medicine*, **27**(4), 199–206.
12. Sanchez AJ and Aranda-Michel J. (2006). Nutrition for the liver transplant patient. *Liver Transplantation*, **12**(9), 1310–16.
13. Cameron AM, Ghobrial RM, Yersiz H, et al. (2005). Optimal utilization of donor grafts with extended criteria: a single-center experience in over 1000 liver transplants. *Annals of Surgery*, **243**(6), 748–53.
14. Perry I and Neuberger J. (2005). Immunosuppression: towards a logical approach in liver transplantation. *Clinical and Experimental Immunology*, **139**(1), 2–10.
15. Abu-Elmagd K, Costa G, Bond G, et al. (2009). Evolution of the immunosuppressive strategies for the intestinal and multi visceral recipients with special reference to allograft immunity and achievement of partial tolerance. *Transplant International*, **22**(2), 96–109.

CHAPTER 372

Intensive care management in cardiac transplantation

Keshava Rajagopal and Bartley P. Griffith

Key points

- Cardiac transplant recipients are both surgically and medically complex.
- Appropriate recipient selection, donor selection, and technically well-performed operations are critical contributors to the best outcomes.
- Low cardiac output syndrome following heart transplantation has numerous pre-, intra-, and post-operative outcomes, and is the most important peri-operative morbid complication contributing to patient mortality.
- Achievement and maintenance of optimal allograft function is mandatory in the heart transplant recipient.
- Other important peri-operative issues in the heart transplant recipient relate to invasive mechanical ventilation—oxygenation/ventilation and its relationship to the pulmonary circulation, blood product transfusion, and immunosuppression strategies.

Donor organ management

After identifying a suitable cardiac transplantation donor (Box 372.1), the donor heart is procured. The donor is systemically anticoagulated, and a catheter for administration of preservation solution is placed in the ascending aorta. The superior vena cava is ligated. The heart is unloaded of volume by exsanguination. The ascending thoracic aorta is cross-clamped, and hypothermic preservation solution, of which several types exist, is administered antegrade via the ascending aorta into the coronary arteries. The heart is cooled topically with ice. After the preservation solution has been administered, the heart is excised, leaving adequate lengths of ascending aorta, left atrium, main pulmonary artery, and both vena cavae. It is placed in a cold storage container for transportation.

Transplant procedure

The recipient is systemically anticoagulated with heparin for cardiopulmonary bypass (CPB). The ascending aorta is directly cannulated, or another systemic artery is cannulated. Both cavae or branches of the superior/inferior vena cava are cannulated. CPB is initiated, typically with mild systemic hypothermia (32–34°C). The ascending aorta is cross-clamped and the native heart is excised. The donor heart is then implanted. The left atrial anastomosis is performed first, since it is most posterior. A left ventricular vent catheter is placed to allow for left-sided cardiac de-airing. Next, the ascending aortic anastomosis is performed. At the completion of this anastomosis, an ascending aortic vent/antegrade cardioplegia catheter is placed to facilitate both left-sided cardiac de-airing, and delivery of a dose of warm blood cardioplegia that may be administered antegrade via the ascending aorta. During this time, a bolus dose of steroid (methylprednisolone) is administered intravenously. The aortic cross-clamp is released, thereby reperfusing the heart. Cardiac allograft ischaemic time is minimized by using this approach of performing the left-sided cardiac anastomoses and releasing the aortic cross-clamp. The heart is defibrillated if necessary. The main pulmonary arterial anastomosis is constructed next, followed by the caval anastomoses (in the more commonly performed bicaval technique; classic bi-atrial technique utilizes a right atrial anastomosis as opposed to individual caval anastomoses). Ventricular and atrial epicardial pacing wires are placed, pacing initiated if needed, pharmacological inotropic/vasoactive support is initiated, invasive mechanical ventilation is resumed at full levels, and CPB is eventually discontinued. Heparin anticoagulation is reversed with protamine, decannulation accomplished, and the procedure concluded.

Peri-operative management

Cardiovascular system

Cardiac allograft function is the most important determinant of outcome after heart transplantation. Ventricular and/or valvular dysfunction may be left ventricular (LV), biventricular (BiV), or right ventricular (RV); these may manifest intra-operatively or early in the post-operative period, and have a variety of aetiologies (Box 372.2).

Technical complications may result in allograft dysfunction. An undersized donor aorta anastomosed to a relatively larger recipient aorta may result in dilatation of the sinotubular junction of the allograft and aortic valve regurgitation [1]. Coronary arterial compromise and myocardial ischaemia may result from injury to the left circumflex coronary artery (or coronary sinus) during creation of the left atrial anastomosis. The mitral valve may also be distorted by the left atrial anastomosis, causing mitral valve regurgitation [2], particularly if an excessively shortened left atrial cuff is prepared. The main pulmonary artery is often short if lungs are procured from the donor, and pulmonary valve regurgitation may result due to imperfections in the anastomosis. More commonly, the main

Box 372.1 Standard donor criteria for cardiac transplantation

- Adequate donor organ size (<20% size mismatch between donor and recipient).
- Donor age <65 years.
- Anticipated organ ischaemic time <4 hours.
- Good donor biventricular function (ejection fraction >55%, pulmonary artery occlusion pressure <18 mmHg, central venous pressure <12 mmHg) on no or low levels of inotropic support, assessed non-invasively and/or invasively via right-sided cardiac catheterization.
- Absence of important coronary arterial disease (when specifically assessed based upon risk factors) or structural heart disease (e.g. valvular heart disease).
- Major blood group (ABO) compatibility.
- Absence of extracranial malignancy, or no evidence of disease >5 years after treatment.
- Absence of bloodstream infection.

Box 372.2 Aetiologies of allograft dysfunction following heart transplantation

- Technical (i.e. anastomotic) complications.
- Intracoronary arterial air embolization.
- Hyperacute rejection.
- **Acute rejection**: cellular, humoral.
- **Primary graft dysfunction**: ischaemia/reperfusion injury.

pulmonary artery is excessively long resulting in twisting or kinking of the main pulmonary artery [3]. Superior vena caval anastomotic stenosis is relatively common and may manifest late after transplantation [4]. Finally, the inferior vena cava is often short if the liver is obtained from the donor, and this can result in impingement of the coronary sinus after creation of the inferior vena caval anastomosis; the results of this may be catastrophic, with impaired cardiac venous drainage and myocardial oedema [5].

LV and/or RV dysfunction can occur due to coronary arterial air embolization that typically manifests with ST changes on ECG, or less commonly, with ventricular arrhythmias. This is usually a transient problem, and can be treated by increasing the systemic arterial pressure, and intra-operatively, also by ascending aortic venting and/or coronary sinus retroperfusion. Intra-operative allograft failure may rarely occur due to hyperacute rejection, mediated by pre-existing donor-specific antibodies [typically against donor major histocompatibility complex (MHC) molecules] in the recipient [6]. This complication rarely occurs in the modern era because of screening assessments of panel-reactive anti-MHC antibodies (PRA) and antibodies against MHC Class I chain A (MICA) in recipients, and virtual and/or prospective cross-matching for pre-sensitized recipients. Acute cellular rejection (ACR) is much more common, may occur early in the post-operative period, and can afflict any of the cardiac chambers [7]. Consequently, LV/BiV/RV dysfunction—systolic and/or diastolic—may be present; arrhythmias, more commonly supraventricular, may occur as well. Transjugular venous endomyocardial biopsy makes the diagnosis of acute rejection.

Primary graft dysfunction (PGD), is thought to be a consequence of ischaemia-reperfusion injury [8]. PGD may also manifest with LV/BiV/RV dysfunction, but most commonly presents with RV-predominant dysfunction. Although the RV may be more tolerant of ischemia-reperfusion injury than the LV due to the lower afterload and requisite oxygen consumption, the incidence of RV ischemia-reperfusion injury is greater than that for the LV due to inferior RV myocardial protection [9] in the procured cardiac allograft. The RV is also less tolerant of and more often exposed than the LV to 'afterload mismatch.' Afterload mismatch refers to an elevation in ventricular afterload relative to contractility, and is essentially secondary systolic ventricular dysfunction [10]. The RV has lower contractility and acute contractile reserve than the LV. Moreover, while pulmonary vascular resistance is generally much lower than systemic vascular resistance (and, consequently, under these normal circumstances, RV and LV outputs are matched since ventricular contractility is matched to afterload), patients with end-stage heart disease often have chronically elevated pulmonary vascular resistance. This may be further increased acutely during the transplantation procedure, particularly due to the effects of CPB.

Pharmacological support of cardiac allograft function is utilized routinely in the peri-transplant period. Inotropic support using monoamines/catecholamines that are agonists for the β-adrenergic receptors [11] (dobutamine, dopamine, adrenaline, isoprenaline, noradrenaline) is instituted empirically, even with normal biventricular systolic function, due to positive chronotropic effects that can be beneficial in the early peri-operative period—when the denervated allograft often displays chronotropic dysfunction. Of these inotropes, isoprenaline is the most potent chronotrope, and is frequently used beyond the early peri-operative period to maintain an adequate heart rate. Afterload reduction of both the LV and RV, but particularly for the RV, is beneficial and often necessary. The cAMP phosphodiesterase inhibitors (e.g. milrinone) are especially useful because of mixed positive inotropic and arteriolar vasodilatory properties [12]. Selective pulmonary vasodilators, such as inhaled nitric oxide or epoprostenol are employed frequently, particularly in the setting of pre-existing systemic vasodilatation [13]. Importantly, intentional augmentation of LV afterload may be useful in the treatment of isolated RV dysfunction; this is due to systolic ventricular interdependence (enhanced rightward motion of the interventricular septum), and increased right coronary arterial blood flow [14]. Finally, keeping the chest open is routine in the treatment of peri-operative RV dysfunction.

Uncommonly, allograft dysfunction may be so severe that mechanical circulatory support must be instituted (Table 372.1). LV dysfunction refractory to inotropic/vasoactive support may respond to intra-aortic balloon counterpulsation (IABP). In addition, although little evidence suggests that IABPs are useful in the treatment of RV dysfunction, right coronary arterial blood flow is enhanced, and this may prevent RV ischaemia in the setting of RV distension and dysfunction. Severe ventricular dysfunction, which most commonly afflicts the RV, may be treated using short-term ventricular assist device (VAD) support of the affected

Table 372.1 Mechanical cardiopulmonary support strategies

Failing Component	V-A ECMO	BiVAD + V-V ECMO	LVAD + V-V ECMO	BiVAD	LVAD	V-V ECMO + RVAD	V-V ECMO	RVAD
LV	+	+	+	+	+	–	–	–
LV + Lungs	+	+	+	–	–	–	–	–
LV + RV	+	+	–	+	–	–	–	–
LV + Lungs + RV	+	+	–	–	–	–	–	–
Lungs	+	+	+	–	–	+	+	–
Lungs + RV	+	+	–	–	–	+	–	–
RV	+	+	–	+	–	+	–	+

+, denotes feasibility of strategy; –, denotes lack of feasibility of strategy.

ventricle(s), most commonly using extracorporeal devices [15]. Severe peri-transplant cardiorespiratory failure is generally treated using systemic veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO); V-A ECMO essentially functions as CPB, is also easily instituted using existing CPB cannulae when in the operating room, and supports both ventricles as well as the lungs [16].

Cardiac tamponade may occur after any cardiac surgical procedure, and is common when excessive antecedent bleeding occurs. Transthoracic echocardiography may identify the presence of a pericardial effusion, with respirophasic transmitral flow variation, RV diastolic collapse, and inferior vena cava distension consistent with tamponade physiology. Pulmonary arterial catheters are routinely used in heart transplant recipients peri-operatively; tamponade is suggested by diastolic equalization of the pulmonary artery occlusion and central venous pressures, and this is the most sensitive diagnostic sign for post-cardiac surgical tamponade [17]. However, both non-invasive and invasive assessments for tamponade are frequently inaccurate; consequently, a high index of suspicion must be present. Late tamponade may occur beyond 1 week post-transplant, and often is associated with the first endomyocardial biopsy. Its presentation is frequently insidious and non-specific, with general malaise, dyspnoea, mild systemic arterial hypotension, and rising creatinine. When suspected or diagnosed, emergent mediastinal re-exploration is mandatory.

Pulmonary system

Intra-operatively, invasive mechanical ventilation is used, but is typically discontinued for the CPB portion of most cardiac surgical procedures. However, pulmonary atelectasis occurs, and this may elevate the pulmonary vascular resistance [18], thereby exacerbating RV afterload mismatch that may manifest when preparing to separate from CPB. Consequently, maintenance of modest levels of invasive mechanical ventilatory support may be beneficial (e.g. respiratory rate of 10 breaths/minute, tidal volume 4–6 mL/kg, positive end-expiratory pressure of 5). Full mechanical ventilator support is reinstituted when preparing to wean and separate from CPB.

Since important pulmonary disease is a contraindication to isolated heart transplantation, heart transplant recipients typically do not have important peri-transplant pulmonary dysfunction. The principal exception to this is high-LA pressure pulmonary oedema secondary to allograft LV dysfunction, the management of which has been discussed. However, low-pressure pulmonary oedema can be due to pro-inflammatory effects of CPB that increase alveolocapillary membrane permeability, and transfusion-related acute lung injury—also characterized by increased alveolocapillary membrane permeability. Prolonged invasive mechanical ventilation using lung-protective strategies is implemented in such circumstances, and systemic veno-venous (V-V) ECMO may be necessary in rare cases of isolated respiratory failure (i.e. in the absence of cardiac failure) following heart transplantation.

Haematological/immunological system

Peri-operative blood product transfusion is minimized, with target haemoglobin levels determined in the context of the adequacy of O_2 delivery, assessed by mixed venous O_2 saturation; transfusion of platelets, fresh frozen plasma, etc., is based upon clinical assessment of coagulopathy in the context of laboratory coagulation measures. Patients who are chronically anticoagulated with warfarin are usually administered vitamin K prior to transplantation, and intra-operatively, the CPB circuit can be primed using plasma. All cases using CPB require intra-operative anticoagulation, almost always using heparin. Heparin is reversed using protamine after weaning from CPB is complete. Post-operatively, serial assessments of haemoglobin, platelet count, and coagulation measures are obtained; transfusion criteria are the same as those used intra-operatively. Factor complex concentrates and/or recombinant coagulation factors may be useful as well.

Transplant recipients receive a bolus dose of steroid, typically methylprednisolone (1 g intravenously). This is administered prior to graft reperfusion, i.e. after aortic cross-clamp release. Subsequently, a steroid taper is initiated, and most transplant recipients are maintained on low-dose glucocorticoid. The remainder of the immunosuppressant regimen is comprised of an antiproliferative agent (mycophenolate mofetil or azathioprine) and a calcineurin antagonist (tacrolimus or ciclosporin).

Recipients with high PRA levels ('sensitized') are at high risk for acute graft rejection; this is largely mitigated by the standard usage of flow-cytometric 'virtual' cross-matching, and in cases of a local organ donor from whom blood may be obtained prior to transplantation, cytotoxicity assay actual cross-matching [19]. In patients who have a positive post-operative cross-match, or more broadly those with an elevated PRA, induction immunosuppression therapy may be utilized [20]. A variety of induction agents exist, which are most commonly polyclonal antisera (e.g.

T cell-depleting anti-thymocyte globulin), monoclonal antibodies (e.g. T cell depleting muromonab anti-CD3, anti-IL2Rα basiliximab, B cell-depleting rituximab, anti-CD52 alemtuzumab), or immunoglobulin fusion (e.g. CTLA4-Ig belatacept). These agents are used in an attempt to reduce the rates of acute cellular and humoral rejection. Finally, recipient antibodies can be depleted in the peri-transplant period using plasmapheresis. If acute rejection is identified peri-operatively, higher doses of steroids, antiproliferative agents, and calcineurin antagonists are used. Induction immunosuppressant agents are also often used to treat acute rejection, with the choice of agent determined by the type of rejection: cellular versus humoral.

Other

Heart failure is a common pre-renal aetiology of renal dysfunction, and consequently, pre-transplant renal dysfunction may be present in the recipient. Renal failure following cardiac surgery is poorly understood, and may occur as a consequence of several factors—most importantly intra-operative hypotension of any aetiology, including pre-operative low renal blood flow, and the effects of CPB on renal blood flow. Calcineurin antagonists are noteworthy as nephrotoxic agents unique to transplant recipients. Induction immunosuppression and withholding calcineurin antagonists in the early post-transplant period are thought to attenuate peri-transplant renal dysfunction. Thus, pretransplant renal insufficiency is a common indication for usage of induction immunosuppressants.

Infectious complications early after heart transplantation are unusual, but in the long-term, are the leading causes of heart transplant recipient mortality. Broad spectrum antibiotics are generally used in the early perioperative course, but are generally discontinued within 48–72 hours post-transplant.

References

1. Miralles A. (1994). Aortic mismatch in heart transplantation: readaptation. *Annals of Thoracic Surgery*, **64**(4), 1188–90.
2. De Simone R, Lange R, Sack FU, Mehmanesh H, and Hagl S. (1994). Atrioventricular valve insufficiency and atrial geometry in orthotopic heart transplantation. *Cardiologia*, **39**(5), 325–34.
3. Gieraerts R, Schertz C, and Ghignone M. (1989). Right ventricular failure after heart transplantation caused by a kink in the pulmonary artery anastomosis. *Journal of Cardiothoracic Anesthesia*, **3**(4), 470–2.
4. Sze DY, Robbins RC, Semba CP, Razavi MK, and Dake MD. (1998). Superior vena cava syndrome after heart transplantation: percutaneous treatment of a complication of bicaval anastomoses. *Journal of Thoracic ad Cardiovascular Surgery*, **116**(2), 253–61.
5. Urbanova D. (1989). Coronary sinus thrombosis in patients after heart transplantation. *Cor Vasa*, **31**(3), 231–7.
6. Duquesnoy RJ, Cramer DV. (1990). Immunologic mechanisms of cardiac transplant rejection. *Cardiovascular Clinic* **20**(2), 87–103.
7. Barry WH. (1994). Mechanisms of immune-mediate myocyte injury. *Circulation*, **89**(5), 2421–32.
8. Lima B, Rajagopal K, Petersen RP, et al. (2006). Marginal cardiac allografts do not have increased primary graft dysfunction in alternate list transplantation. *Circulation*, **114**(1 Suppl.), I27–32.
9. Christakis GT, Weisel RD, Mickle DA, et al. (1990). Right ventricular function and metabolism. *Circulation*, **82**(5 Suppl.), IV332–40.
10. Ross J., Jr. (1976). Afterload mismatch and preload reserve: a conceptual framework for the analysis of ventricular function. *Progress in Cardiovascular Diseases*, **18**(4), 255–64.
11. Rajagopal S, Rajagopal K, and Lefkowitz RJ. (2010). Teaching old receptors new tricks: biasing seven-transmembrane receptors. *Nature Reviews Drug Discovery*, **9**(5), 373–86.
12. Colucci WS, Wright RF, and Braunwald E. (1986). New positive inotropic agents in the treatment of congestive heart failure. Mechanism of action and recent clinical developments. 2. *New England Journal of Medicine*, **314**(6), 349–58.
13. Oz MC and Ardehali A. (2004). Collective review: perioperative uses of inhaled nitric oxide in adults. *Heart Surgery Forum*, **7**(6), E584–9.
14. Park CH, Nishimura K, Kitano M, Okamoto Y, and Ban T. (1994). Right ventricular performance is impaired by full assist of left heart bypass. Analysis of right ventricular performance against change in afterload in heart failure models. *ASAIO Journal*, **40**(3), M303–8.
15. Yerebakan C, Buz S, Huebler M, Weng Y, Lehmkuhl H, and Hetzer R. (2008). Right ventricular failure following heart transplantation—recovery after extended mechanical support. *Journal of Cardiovascular Surgery*, **23**(5), 578–80.
16. Kittleson MM, Patel JK, Moriguchi JD, et al. (2011). Heart transplant recipients supported with extracorporeal membrane oxygenation: outcomes from a single-center experience. *Journal of Heart and Lung Transplantation*, **30**(11), 1250–6.
17. Chuttani K, Tischler MD, Pandian NG, Lee RT, and Mohanty PK. (1994). Diagnosis of cardiac tamponade after cardiac surgery: relative value of clinical, echocardiographic, and hemodynamic signs. *American Heart Journal*, **127**(4 Pt 1), 913–18.
18. Duggan M and Kavanagh BP. (2007). Atelectasis in the perioperative patient. *Current Opinion in Anaesthesiology*, **20**(1), 37–42.
19. Mehra MR, Uber PA, Uber WE, Scott RL, and Park MH. (2003). Allosensitization in heart transplantation: implications and management strategies. *Current Opinion in Cardiology*, **18**(2), 153–8.
20. Aliabadi A, Grömmer M, and Zuckermann A. (2011). Is induction therapy still needed in heart transplantation? *Current Opinion in Organ Transplantation*, **16**(5), 536–42.

CHAPTER 373

Intensive care management in lung transplantation

Keshava Rajagopal and Bartley P. Griffith

Key points

- Lung transplant recipients are both surgically and medically complex.
- Appropriate recipient selection, donor selection, and technically well-performed operations are critical contributors to the best outcomes.
- Acute respiratory failure following lung transplantation has numerous pre-operative, intra-operative, and post-operative outcomes, and is the most important peri-operative morbid complication contributing to patient mortality.
- Achievement and maintenance of optimal allograft function is mandatory in the lung transplant recipient.
- Other important peri-operative issues in the lung transplant recipient relate to cardiac function—particularly of the right ventricle, blood product transfusion, and immunosuppression strategies.

Donor organ management

After identifying a suitable lung transplantation donor (Box 373.1), the donor lung(s) is/are procured. Inspiratory and expiratory mechanics are assessed based on clinical (inspiratory lung expansion and expiratory lung recoil) and mechanical ventilatory (airways resistance, lung compliance) parameters. Valsalva recruitment manoeuvres are performed as needed, taking care not to use excessive ventilator pressures (peak inspiratory pressure >40 cmH_2O) or cause lung hyperinflation. Selective pulmonary venous blood gas sampling permits assessment of the gas exchange functions of each lung (and the upper and lower lung zones within a lung), and is essential when single lung transplantation is to be undertaken.

The donor is systemically anticoagulated, and a cannula for administration of preservation solution is placed in the main pulmonary artery and directed towards the pulmonary valve. During procurement prostaglandin E_1 is administered into the main pulmonary artery [1]. The lung preservation solution—of which several types exist, is administered via the main pulmonary artery after left atrial venting and each pleural space is packed with ice. The former main pulmonary arterial cannula is used to individually cannulate and administer preservation solution retrograde via the pulmonary veins. This serves to flush out material within the pulmonary circulation. The lungs are excised en bloc, leaving adequate lengths of pulmonary artery, left atrium, and trachea. The excised lungs are placed in a cold storage container for transportation.

Transplant procedure

The incision and surgical approach are determined based upon whether single or bilateral lung transplantation is to be undertaken. CPB or V-A ECMO are selectively utilized under the following circumstances: (1) severe right ventriclular (RV) dysfunction or elevation of the pulmonary vascular resistance—pulmonary arterial clamping is poorly tolerated in these situations, and/or (2) severe hypoxemia or hypercapnia—since single lung ventilation and sequential lung transplantation are poorly tolerated in these situations. Under the second set of circumstances, V-V ECMO may be utilized. [When CPB is utilized for bilateral or right lung transplantation, the patient is systemically anticoagulated with heparin, and the ascending aorta and right atrium can be cannulated; central systemic venous cannulation for left lung transplantation is challenging, and typically, femoral arterial and venous cannulation are utilized.] Selective single lung ventilation is initiated, and the contralateral native lung is excised. In this process, the pulmonary artery and veins supplying the excised lung are controlled; a modest dose of heparin (e.g. a 50–100 unit/kg bolus dose administered prior to implantation of each lung, in contrast to a 300 unit/kg dose for cardiopulmonary bypass (CPB)) is administered. The ipsilateral pulmonary artery is clamped as proximally as possible, while the ipsilateral pulmonary venous confluence/portion of left atrium is dissected out and clamped. The appropriate donor lung is brought to the field. The mainstem bronchial anastomosis is created first. Next, the pulmonary arterial anastomosis is created. The pulmonary venous/left atrial anastomosis is created last. Prior to tying the anastomotic suture line, a bolus dose of steroids is administered intravenously; the pulmonary arterial clamp is partially released, allowing for antegrade de-airing, and the left atrial clamp is released, facilitating retrograde de-airing. The anastomotic suture line is then tied. The allograft is ventilated. Controlled reperfusion of the lung is undertaken to prevent over perfusion of the allograft and facilitate free radical washout, releasing the pulmonary arterial clamp in graded fashion; this is thought to mitigate ischemia-reperfusion injury. Once this process is completed, selective ventilation of the lung allograft is performed. The second native lung is then excised as described. Implantation of the second lung allograft is performed as described. Bilateral invasive mechanical ventilation is re-initiated, and when relevant, weaning and separation from CPB

Box 373.1 Standard donor criteria for lung transplantation

- Adequate donor organ size (assessed radiographically).
- Donor age <65 years.
- Anticipated organ ischaemic time <8 hours.
- Good donor pulmonary function (PIP <30 cmH_2O with tidal volume >6 cm^3/kg—static compliance >25 cm^3/cmH_2O, PaO_2 >300 on FIO_2 100% and PEEP 5 cmH_2O).
- Absence of important chronic pulmonary disease (e.g. asthma requiring mechanical ventilation, chronic obstructive pulmonary disease, restrictive lung disease, pulmonary vascular disease, etc.).
- Absence of major radiographic abnormalities thought to be irreversible (e.g. pulmonary nodules suggestive of malignancy).
- Bronchoscopic assessment without secretions that cannot be cleared.
- Major blood group (ABO) compatibility.
- Absence of extracranial malignancy, or no evidence of disease >5 years after treatment.
- Absence of bloodstream infection.

performed. Anticoagulation is reversed, decannulation accomplished when CPB has been used, and the procedure concluded. The dual lumen endotracheal tube is exchanged for a single lumen tube, and flexible fibreoptic bronchoscopy is performed to examine both bronchial anastomoses and evacuate intrapulmonary blood/secretions.

Peri-operative management

Cardiovascular system

Patients undergoing lung transplantation are excluded from having important and irreparable cardiac disease. Uncommonly, concomitant cardiac operations (e.g. coronary artery bypass grafting, valve repair/replacement) may be undertaken in otherwise low-risk recipients [2]. Excluding cases of concomitant cardiac surgery, cardiac dysfunction may occur following lung transplantation. Isolated left ventricle (LV) dysfunction is uncommon, even when CPB is used, since lung transplantation is performed under conditions of normal coronary arterial blood flow and myocardial perfusion. Clamping the left-sided pulmonary veins for left lung transplantation can injure the left circumflex coronary artery that may, in turn, result in LV lateral wall ischemia and dysfunction. Intraoperative transoesophageal echocardiography may identify this, and repositioning the clamp resolves the problem.

More commonly, RV dysfunction may occur following lung transplantation. This is because of pre-existing chronic cor pulmonale in some lung transplant recipients that may not improve immediately after lung transplantation due to acutely elevated allograft pulmonary vascular resistance. Elevated pulmonary vascular resistance may be due to lung ischemia-reperfusion injury, or the effects of CPB (**3**). Afterload reduction of the RV is beneficial and often necessary. The cAMP phosphodiesterase inhibitors (e.g. milrinone) are especially useful because of mixed positive inotropic and arteriolar vasodilatory properties [4]. Importantly, intentional augmentation of LV afterload may be useful in the treatment of isolated RV dysfunction; this is due to systolic ventricular interdependence (enhanced rightward motion of the interventricular septum), and increased right coronary arterial blood flow [5]. Inhaled pulmonary vasodilators are particularly useful in the lung transplant recipient, as they enhance ventilation–perfusion matching. Consequently, inhaled nitric oxide and/or epoprostenol are used liberally in peri-operative lung transplant recipients [6].

Pulmonary system

Lung allograft function is the most important determinant of outcome after lung transplantation. Respiratory failure after lung transplantation has several possible aetiologies, which are reviewed later and summarized in Box 373.2.

Technical complications of lung transplantation may involve the bronchial, pulmonary arterial, and/or pulmonary venous anastomoses. Bronchial anastomotic complications are by far the most common, and historically have had profound negative impact on lung transplantation outcomes [7]. Anastomotic dehiscence, which manifests in the acute peri-operative setting (although not necessarily evident on intra-operative completion bronchoscopy), is a catastrophic complication mandating emergent re-operation. For this reason, daily surveillance bronchoscopy is essential in the peri-operative lung transplant recipient, particularly when invasively mechanically ventilated. Imperfections in the pulmonary arterial anastomosis, as well as kinking due to excessive donor/recipient pulmonary arterial length, may cause pulmonary arterial stenosis, or even less commonly, thrombosis. This increases the vascular resistance of the allograft, impairing perfusion and ventilation–perfusion matching. Intra-operative transoesophageal echocardiography can identify anastomotic stenosis, although not reliably. Passage of the pulmonary arterial catheter beyond the arterial anastomosis can directly determine whether a resistive pressure drop, i.e. anastomotic stenosis, is present. This can be performed intra-operatively under echocardiographic guidance, or in the intensive care unit under fluoroscopic guidance; catheter passage across the anastomosis should not be performed without image guidance, as anastomotic disruption and lethal haemorrhage can occur. In addition, peri-operative ventilation-perfusion scanning, which is performed routinely, may identify impaired graft blood flow [8], consistent with a haemodynamically important pulmonary arterial stenosis, although impaired allograft perfusion is not specific for a pulmonary arterial stenosis. Imperfections in the left atrial anastomosis can also cause stenosis. This causes increased resistance to pulmonary venous drainage and elevations in pulmonary venous and capillary pressure. Allograft pulmonary oedema

Box 373.2 Aetiologies of allograft dysfunction following lung transplantation

- Technical (i.e. anastomotic) complications.
- Hyperacute rejection.
- **Acute rejection**: cellular, humoral.
- **Primary graft dysfunction**: ischaemia/reperfusion injury.
- Pneumonia.

can occur with disastrous sequelae [9]. Fortunately, intra-operative echocardiography evaluates the pulmonary veins well, due to their posterior location. Transoesophageal echocardiography or magnetic resonance imaging can be used post-operatively. Revision of the left atrial anastomosis is necessary if evidence of stenosis is present.

As is the case in heart transplantation, hyperacute lung allograft rejection is nearly non-existent in the modern era due to current screening strategies. However, acute rejection in the early peri-operative period is more common than in heart transplantation [10]. Rejection may manifest with impaired lung mechanics, hypercapnia, and hypoxaemia clinically, often in the setting of new or worsening infiltrates on chest imaging. Bronchoscopy with biopsy is the essential diagnostic test to evaluate allograft rejection [10]. Treatment of rejection similar to that for acute cardiac allograft rejection.

Primary graft dysfunction (PGD) complicates up to 20% of lung transplant operations. Hypoxaemia, with or without hypercapnia, is present, usually with radiographic evidence of pulmonary oedema. In some patients, this can be managed non-invasively. However, the majority of patients require prolonged invasive mechanical ventilation. Lung-protective (i.e. employing low tidal volumes and ventilator pressures) mechanical ventilatory strategies are used. If hypoxaemia and hypercapnia persist, while treating with lung-protective invasive mechanical ventilation, higher level ventilator support is avoided. Most lung transplant surgeons advocate a strategy of extracorporeal lung support in this setting; since co-existent cardiac dysfunction is usually not present, V-V ECMO is usually sufficient [12].

Haematological/immunological system

Peri-operative blood product transfusion is minimized, with target haemoglobin levels determined in the context of the adequacy of O_2 delivery, assessed by mixed venous O_2 saturation; transfusion of platelets, fresh frozen plasma, etc., is based upon the clinical assessment of coagulopathy in the context of laboratory coagulation measures. Transfusion-related acute lung injury is a particular concern following lung transplantation, because of the sensitivity of the previously ischaemic and newly-reperfused allograft to noxious stimuli that elevate the already increased alveolocapillary membrane permeability, and the absence of normal lymphatic drainage in the allograft. Consequently, blood product transfusion is strictly controlled following lung transplantation.

Immunosuppression for lung transplantation is similar to that used for cardiac transplantation. Specifically, most recipients are treated using a combination of steroids, antiproliferative agents, and interleukin-2 synthesis-suppressing (thus impairing T cell-mediated immune responses) calcineurin antagonists [13]. Similar criteria for induction immunosuppressant usage are used for heart and lung transplantation: positive cross-match, high rejection risk (e.g. elevated panel reactive antibody (PRA)), and renal insufficiency. Plasmapheresis is also a useful adjunct in recipients with positive cross-match or high donor-specific antibody titers; novel anti-plasma cell proteasome inhibitors have similar utility. An important difference between heart and lung transplantation, however, is the absolute incidence of acute and chronic graft rejection. Rejection is more common after lung transplantation than heart transplantation, and in the long-term (bronchiolitis obliterans syndrome (BOS)) [14], is the most important reason for poorer outcomes after lung transplantation in comparison with transplantation of other solid organs.

Other

Lung transplant recipients generally do not have impaired cardiac output or renovascular disease. Peri-transplant renal insufficiency is usually a consequence of intentional volume restriction to avoid allograft oedema and pleural effusions, and nephrotoxic medications. Fluid restriction is maintained in the lung transplant recipient, even at the expense of moderate renal dysfunction. Nephrotoxic medications are minimized, and peri-operative renal insufficiency usually resolves. Calcineurin antagonists are noteworthy as nephrotoxic agents unique to transplant recipients. Induction immunosuppression and withholding calcineurin antagonists in the early post-transplant period is thought to attenuate peri-transplant renal dysfunction. Thus, pre-transplant renal insufficiency is a common indication for usage of induction immunosuppressants.

Infectious complications are extremely common following lung transplantation, due to colonization of the recipient (particularly in infectious lung diseases) and transmission of donor-derived infection [15]. Broad spectrum antibacterial, antifungal, and even antiviral drugs are instituted and maintained in the majority of lung transplant recipients. Frequent bronchoscopy is thought to be important in protection from graft pneumonia, although little evidence exists to support this practice.

Gastrointestinal complications are also very common in lung transplant recipients. Pre-existing gastro-oesophageal reflux disease contributes to native lung disease, and in the absence of surgical treatment, contributes to impaired long-term allograft survival [16]. In addition, the lung transplantation operation may incur injury to the vagus nerve(s) and/or the recurrent laryngeal nerves, which cause impaired gastric emptying and airway protection, respectively. Aspiration-induced lung injury is thus a major contributor to the development of long-term allograft dysfunction [17]. For this reason, when possible, patients with gastro-oesophageal reflux disease undergo surgical fundoplication—usually post-lung transplant. In addition, many lung transplant surgeons advocate liberal usage of gastrojejunostomy tubes (gastric port for medication administration, jejunostomy port for continuous feeding) and maintenance of nil by mouth status early after lung transplantation.

References

1. de Perrot M, Fischer S, Liu M, et al. (2001). Prostaglandin E1 protects lung transplants from ischemia-reperfusion injury: a shift from pro- to anti-inflammatory cytokines. *Transplantation*, **72**(9), 1505–12.
2. Parekh K, Meyers BF, Patterson GA, et al. (2005). Outcome of lung transplantation for patients requiring concomitant cardiac surgery. *Journal of Thoracic Cardiovascular Surgery*, **130**(3), 859–63.
3. Fullerton DA, McIntyre RC Jr, Mitchell MB, Campbell DN, and Grover FL. (1995). Lung transplantation with cardiopulmonary bypass exaggerates pulmonary vasomotor dysfunction in the transplanted lung. *Journal of Thoracic Cardiovascular Surgery*, **109**(2), 212–16.
4. Colucci WS, Wright RF, and Braunwald E. (1986). New positive inotropic agents in the treatment of congestive heart failure. Mechanism of action and recent clinical developments. *New England Journal of Medicine*, **314**(6), 349–58.
5. Oz MC and Ardehali A. (2004). Collective review: perioperative uses of inhaled nitric oxide in adults. *Heart Surgery Forum*, **7**(6), E584–9.
6. Khan TA, Schnickel G, Ross D, et al. (2009). A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled

prostacyclin in heart transplant and lung transplant recipients. *Journal of Thoracic Cardiovascular Surgery*, **138**(6), 1417–24.
7. FitzSullivan E, Gries CJ, Phelan P, et al. (2011). Reduction in airway complications after lung transplantation with novel anastomotic technique. *Annals of Thoracic Surgery*, **92**(1), 309–15.
8. Patterson GA, Maurer JR, Williams TJ, Cardoso PG, Scavuzzo M, and Todd TR. (1991). Comparison of outcomes of double and single lung transplantation for obstructive lung disease. The Toronto Lung Transplant Group. *Journal of Thoracic Cardiovascular Surgery*, **101**(4), 623–31.
9. Griffith BP, Magee MJ, Gonzalez IF, et al. (1994). Anastomotic pitfalls in lung transplantation. *Journal of Thoracic Cardiovascular Surgery*, **107**(3), 743–53.
10. Onsager DR, Canver CC, Jahania MS, et al. (1999). Efficacy of tacrolimus in the treatment of refractory rejection in heart and lung transplant recipients. *Journal of Heart and Lung Transplantation*, **18**(5), 448–55.
11. Wahidi MM and Ernst A. (2004). The role of bronchoscopy in the management of lung transplant recipients. *Respiratory Care Clinics of North America*, **10**(4), 549–62.
12. Hartwig MG, Appel JZ 3rd, Cantu E 3rd, et al. (2005). Improved results treating lung allograft failure with venovenous extracorporeal membrane oxygenation. *Annals of Thoracic Surgery*, **80**(5), 1872–9.
13. Bush EL and Lin SS. (2006). Lung transplantation: advances in immunosuppression. *Thoracic Surgery Clinic*, **16**(4), 421–33.
14. Todd JL and Palmer SM. (2011). Bronchiolitis obliterans syndrome: the final frontier for lung transplantation. *Chest*, **140**(2), 502–8.
15. Rajagopal K, Watkins AC, Gibber M, et al. (2013). Reoperative lung transplantation for donor-derived pulmonary mucormycosis. *Annals of Thoracic Surgery*, **98**(1), 327–9.
16. Cantu E 3rd, Appel JZ 3rd, Hartwig MG, et al. (2004). J. Maxwell Chamberlain Memorial Paper. Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. *Annals of Thoracic Surgery*, **78**(4), 1142–51.
17. Hartwig MG and Davis RD. (2012). Gastroesophageal reflux disease-induced **aspiration** injury following lung transplantation. *Current Opinion in Organ Transplantation*, **17**(5), 474–8.

PART 20.2

Oncological intensive care

CHAPTER 374

ICU selection and outcome of patients with haematological malignancy

William M. Townsend and Emma C. Morris

Key points

- The concept that patients with haematological malignancies should not be considered for intensive care admission is outdated and inappropriate.
- There are no absolute contraindications to intensive care unit (ICU) admission in this patient cohort.
- It is important to promptly identify patients who may benefit from ICU admission, ideally prior to the development of organ failure.
- Close liaison between the critical care and haematology teams is vital.
- Formal review of the appropriateness of continued intervention in critically unwell haematology patients should be performed on a regular basis.

Introduction

The admission of patients with haematological malignancy and, in particular, recipients of haematopoietic stem cell transplants (HSCT) to the intensive care unit (ICU) has been the subject of much controversy and conjecture. The poor survival previously observed in many units led some to question the validity of continuing to admit such patients to the ICU. However, over recent years, evidence of improved outcomes, in combination with better treatments and longer survival for many of these malignancies, has challenged the notion that such patients should be denied admission. An underlying diagnosis of a haematological malignancy is no longer considered a contraindication to ICU admission. Nevertheless, it is recognized that providing critical care to this patient population presents particular challenges.

This chapter details the commonest reasons for ICU admission in patients with haematological malignancy and reviews their outcome. Important aspects relevant to their critical care are highlighted.

The scale of the problem

The number of ICU admissions of patients with haematological malignancy depends on the size and activity of the local haematology and oncology departments. In tertiary referral centres managing large numbers of such patients and performing allogeneic HSCTs, a high proportion of ICU admissions will be from this cohort, placing a significant burden on the critical care department. In the UK, 1.5% of all ICU admissions involve patients with haematological malignancy [1].

The prevalence of haematological malignancies is increasing worldwide due in part to the ageing population (with the exception of acute lymphoblastic leukaemia and Hodgkin lymphoma, which peaks in childhood or young adulthood, respectively), and longer survival secondary to improved therapies. HSCT is increasingly utilized as a potentially curative procedure for a wide range of haematological malignancies; between 2005 and 2012 the number of allogeneic HSCTs in Europe increased by 37% [2]. It is likely that the number of ICU admissions will continue to increase.

Reasons for ICU admission

Patients with haematological malignancy can become critically unwell due to the underlying disease itself, as a consequence of cytotoxic chemotherapy, or following HSCT. The commonest reasons for ICU admission are discussed in the following section.

Disease

Acute leukaemia

Patients with acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) often present with a short history of days to weeks. Approximately 10% of patients with newly-diagnosed acute leukaemia require ICU admission due to consequences of leukostasis, cytopenias, sepsis, or haemorrhage (which may be due to thrombocytopenia or disseminated intravascular coagulation (DIC)) [3]. Rapid identification and treatment of early complications, initiation of appropriate supportive care and commencement of definitive induction chemotherapy are all important aspects of care.

For patients admitted with newly-diagnosed acute leukaemia, the course of the critical illness is influenced by the untreated leukaemia. Timely treatment of the underlying malignancy will have implications for long-term outcome, so it is important to consider initiating chemotherapy on the ICU alongside critical care support and interventions (see Box 374.1) [4].

Box 374.1 Overview of AML and ALL

Acute leukaemias

Acute leukaemias are life-threatening malignancies characterized by rapid and uncontrolled proliferation and accumulation of blasts in the bone marrow with subsequent failure of normal haematopoiesis.

The prognosis and clinical course are highly variable. Children with ALL have an excellent prognosis with cure rates >80%, while survival in adults is <50%. The prognosis of AML depends on specific cytogenetic and molecular characteristics, as well as patient-related factors, in particular age. Patients <60 years with good prognostic factors have a 60–70% chance of cure, whereas older patients with adverse cytogenetics have a very poor prognosis.

The current challenges in acute leukaemia are in predicting and preventing relapse in those with poor risk disease, and improving the survival of elderly patients.

Acute promyelocytic leukaemia (APML)

APML is a sub-type of AML that requires special mention because of its association with severe DIC causing significant morbidity and mortality due to intracerebral and pulmonary haemorrhage. Patients with APML are often critically unwell at diagnosis, but it has a very good long-term prognosis with survival rates of 70–80%, largely due to the efficacy of treatment with all **trans**-retinoic acid (ATRA).

Full supportive care for these patients is warranted with meticulous attention to correction of coagulopathy often requiring large volumes of blood products [16].

Chronic myeloid leukaemia (CML)

This typically develops insidiously, but can present in an acute phase with a marked leukocytosis. Few patients with CML require ICU admission due to the underlying disease, although leukostasis, hyperviscosity, organ infiltration, and complications of cytopenias can all lead to acute deterioration. Treatment and prognosis have been revolutionized by the use of tyrosine kinase inhibitors [5].

Chronic lymphocytic leukaemia (CLL)

This indolent malignancy predominantly affects the elderly. Chronic disease-related immune suppression, hypogammaglobulinaemia, or severe immune-mediated cytopenias may cause decompensation and the need for ICU input.

Lymphoma

Although most patients with Hodgkin or non-Hodgkin lymphoma are managed as outpatients, critical illness can occur, typically due to bulky lymphadenopathy causing organ compromise. This is seen most commonly in the highly proliferative non-Hodgkin lymphomas (NHL), such as diffuse large B cell lymphoma (the commonest type) and Burkitt lymphoma. Large mediastinal masses, commonest in Hodgkin lymphoma and primary mediastinal diffuse large B cell lymphoma may cause superior vena cava or airway obstruction requiring ICU input. Critical illness may also be due to lymphomatous organ infiltration of the central nervous system (CNS) or gastrointestinal tract. CNS infiltration, which may be primary or secondary, can lead to a reduced conscious level and seizures. Involvement of the gastrointestinal tract, occurring most commonly in mantle cell lymphoma, marginal zone lymphomas, Burkitt lymphoma, and some T cell lymphomas, can cause obstruction or perforation at the time of presentation or after starting chemotherapy. Lymphoid masses typically reduce rapidly in size following initiation of treatment and surgical intervention is rarely required, but ICU support may be necessary until organ compromise has resolved. Patients with bulky disease are at risk of tumour lysis syndrome and acute renal failure after initiation of chemotherapy (see Box 374.2).

Multiple myeloma

Myeloma has a median age of presentation of 65–70 years and is characterized by bone marrow infiltration, lytic bone lesions with pathological fractures, paraproteinaemia, and renal failure. Electrolyte disturbance (hypercalcaemia), hyperviscosity due to paraproteinaemia and renal failure may all precipitate ICU referral.

Treatment

Infections

The most frequent treatment-related reason for ICU admission is infection. Myelosuppression following cytotoxic chemotherapy or after HSCT, prolonged impairment of adaptive immunity,

Box 374.2 Lymphomas: classification, prognosis, and treatment

Hodgkin lymphoma

The incidence peaks at 30 years. Presentation is commonly with lymphadenopathy, often mediastinal, and constitutional 'B' symptoms—night sweats, fever, and weight loss. Treatment of early stage disease is with combination chemotherapy and radiotherapy with excellent cure rates and long-term survival >90%. Advanced stage disease treated with chemotherapy alone has a 5-year survival of 80–90%. In the relapsed setting, autologous HSCT is typically used in second remission with good success [17].

Non-Hodgkin lymphoma

NHL comprises a heterogeneous group of malignancies, which can be broadly divided into low- and high-grade. Low grade NHLs usually respond well to chemotherapy in combination with monoclonal antibody treatment, although relapses are inevitable with subsequent remissions of sequentially shorter duration. Follicular lymphoma, the commonest low grade NHL, has a median survival of approximately 12 years with current treatments.

High-grade NHLs progress rapidly and often present with large volume lymphadenopathy. The commonest subtypes are diffuse large B cell lymphoma (DLBCL) and Burkitt lymphoma. Current treatment is with combination chemotherapy and anti-CD-20 monoclonal antibody. Prognosis depends on several factors including stage of disease, performance status and age. Good risk patients have a 5-year survival >75%, while poor risk disease has a 5-year survival of approximately 25%. The risk of relapse in DLBCL patients achieving remission with first line therapy is 30–40% [18].

breakdown of the mucosal barriers to infection, long duration of hospital admissions, frequent use of broad-spectrum antibiotics, and the placement of in-dwelling central venous catheters all place these patients at high-risk of potentially life-threatening infection. Despite clinical evidence of sepsis, blood cultures are only positive in 25–30% of cases of febrile neutropenia. With a prolonged duration and severity of immunosuppression, the risk of infection increases, as does the range of likely pathogens with atypical bacterial infections, fungal infections, and viral reactivation, especially herpes viridae, becoming increasingly common. Routine antifungal prophylaxis in high-risk patients and monitoring for cytomegalovirus (CMV) reactivation after allogeneic HSCT are essential components of supportive care.

Fluid overload and electrolyte imbalance

Patients undergoing intensive chemotherapy and HSCT frequently receive large volumes of intravenous fluid in the form of crystalloids, drugs, and blood products. The combined volume can cause pulmonary oedema and, occasionally, the need for ICU support especially in patients with cardiac co-morbidities. Severe electrolyte imbalance is also commonly experienced and can lead to arrhythmias.

Tumour lysis syndrome

Rapid lysis of tumour cells leads to release of cellular contents that are catabolized to insoluble uric acid. This can cause tumour lysis syndrome (TLS), which comprises rapid-onset renal failure and electrolyte imbalance (hyperkalaemia, hyperphosphataemia, and hypocalcaemia). TLS occurs most commonly following initiation of treatment for acute leukaemia or high-grade lymphomas where there is a large tumour burden. Significant tumour lysis can also be precipitated by corticosteroids in the treatment of lymphoma.

ICU admission post-HSCT

There is considerable variation in the reported rates of ICU admission after HSCT. This may be due to differences in local practice and whether reports differentiate between autologous and allogeneic HSCT. Overall, 15.7% of patients undergoing HSCT worldwide are admitted to ICU, although up to 40% of allogeneic HSCT recipients will require admission due to complications [6]. Fewer admissions have been reported after reduced intensity (RI) conditioning regimens than after myeloablative HSCT.

In the conditioning and pre-engraftment periods, the reasons for ICU admission include sepsis (bacterial, fungal, or viral), respiratory failure, fluid overload, cardiac dysfunction, arrhythmias, capillary leak syndrome, diffuse alveolar haemorrhage, hepatic veno-occlusive disease, mucositis, and gastrointestinal haemorrhage. Chronic complications of allogeneic HSCT, such as chronic graft versus host disease, viral reactivation, and prolonged suppression of both humoral and adaptive immune systems can precipitate ICU admission long after the transplant procedure (see Box 374.3) [7].

Box 374.3 Haematopoietic Stem Cell Transplantation: important differences in type of HSCT

Autologous HSCT

Most commonly used in consolidating the treatment of multiple myeloma or relapsed lymphoma. After conditioning chemotherapy, previously collected autologous haematopoietic stem cells (HSCs) are reinfused after thawing. The period of profound cytopenias is typically 8–12 days and is frequently accompanied by mucositis and neutropenic sepsis. Following recovery of peripheral blood counts, most patients experience rapid recovery with fewer long-term sequelae than after allogeneic HSCT.

Allogeneic HSCT

Allogeneic HSCT offers a chance of cure for many patients with haematological malignancy. The HSC source is either a human leukocyte antigen (HLA)-matched **sibling** donor, or an HLA-matched **unrelated donor**. **Umbilical** cord and **haploidentical** HSCTs are employed where no suitable sibling or unrelated donor can be identified. HSCs are harvested either from the bone marrow or collected by leukapheresis after mobilization into the peripheral blood with G-CSF. Conditioning can be either myeloablative or RI. RI transplants have lower levels of acute toxicity and have allowed allogeneic HSCTs to be offered to older patients. Although RI conditioning regimens are less toxic than myeloablative regimens, the prolonged immunosuppression required to permit engraftment of the donor HSCs leads to more late effects, particularly infections and/or graft versus host disease.

Patient outcomes

A retrospective analysis of data from the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme database in the UK revealed that the ICU and hospital mortality of 7689 patients with haematological malignancy (including HSCT recipients) was 43.1 and 59.2%, respectively [1]. This is supported by a number of single-centre observation studies reporting similar rates of survival in recent years. The ICU mortality for patients who have undergone HSCT is reported to be 65%, although this underestimates the mortality for allogeneic HSCT recipients, as much of the published literature does not distinguish between autologous and allogeneic HSCT [6]. These survival outcomes represent a dramatic improvement from earlier studies that reported ICU mortality rates of 80–95%; indeed, some recent single-centre studies have demonstrated improved outcomes over time [8–10].

Predicting outcomes

Several studies have investigated whether outcome can be correlated with patient characteristics or clinical variables.

Age

Age is an important risk factor for long-term survival. It features in the prognostic scores used in AML, Hodgkins lymphoma (HL), and NHL, but a clear association of increasing age with short-term ICU survival has not been demonstrated.

Disease status

For patients admitted to ICU with a new presentation of an untreated malignancy, the short-term outcome is unrelated to characteristics of the underlying disease. However, long-term survival after ICU discharge can be anticipated to be inferior in patients with relapsed, refractory or poor risk disease [11].

Neutropenia

The effect of neutropenia on ICU outcome is unclear; some studies report an adverse association, while others fail to identify it as an independent adverse risk factor. Growth factors such as granulocyte colony-stimulating factor (G-CSF) shorten the period of neutropenia. Although widely administered to neutropenic patients in ICU, no survival benefit has yet been demonstrated.

Infection

Superior outcomes have been reported for patients in whom bacterial sepsis is identified as the cause of admission, reflecting the reversibility of the critical illness [12].

Organ failure

Organ failure has been consistently demonstrated to be the single most important indicator of ICU survival, with an increasing number of organ failures associated with a worse outcome. From the ICNARC database, patients with one, three, and five organ failures had ICU mortality rates of 50, 84, and 98% respectively [1].

Respiratory failure

Respiratory failure and the subsequent need for invasive mechanical ventilation is an important predictor of ICU outcome, especially in HSCT recipients; short-term survival in allogeneic HSCT recipients is reported to be 60–80% when ventilation is not required compared with 18–26% in ventilated patients [7,13]. A longer duration of ventilation and the severity of hypoxaemia prior to intubation have been associated with an adverse prognosis among ventilated patients with haematological malignancy. Non-invasive ventilation has been investigated in hypoxaemic haematology patients; while its use was initially reported to be associated with better outcomes and lower rates of intubation than oxygen therapy alone, recent trials have yielded less clear-cut results [14].

Type of HSCT

Due to the lack of distinction in the literature, it is difficult to draw firm conclusions about the impact of different types of HSCT on ICU outcome. The survival rate of patients admitted after autologous HSCT is superior to allogeneic HSCT recipients; furthermore, despite having an older median age, recipients of reduced intensity (RI) allogenic HSCT have superior ICU outcomes compared with myeloablative allograft recipients [15]. Most published series have failed to identify the stem cell source, whether from peripheral blood or bone marrow, and sibling or unrelated donor, as an independent predictor of ICU outcome.

Predictive scores

The Acute Physiology and Chronic Health Evaluation (APACHE) and serial organ failure (SOFA) scores remain predictive of ICU mortality in patients with haematological malignancies, but have been found to be poorly calibrated and underestimate mortality [1]. Organ failure scores may more accurately predict ICU mortality if reassessed at day 5 of ICU admission, although this does not aid prospective identification of patients suitable for ICU admission. Although many single-centre studies have identified combinations of risk factors that predict outcome, there are no predictive scoring systems specific to patients with haematological malignancy or to recipients of HSCTs that have been validated in prospective multi-centre studies.

Long-term outcomes

It is important to consider not only the immediate outcome, but also the long-term prognosis. Treatments are improving with the prospect of cure for more patients than ever before. In studies assessing the long-term survival of patients with haematological malignancy admitted to intensive care, the 6-month survival was approximately 20%, while for those allogeneic HSCT recipients who survived ICU admission, the subsequent 1- and 5-year survival was 61 and 51%, respectively [15]. This impressive long-term survival should serve to support the argument for admission of such patients to critical care.

Reasons for improved outcomes

There are many possible reasons for the improvements in outcome, including better supportive care on the haematology ward, e.g. antifungal prophylaxis, monitoring, and pre-emptive treatment for CMV reactivation, prompt initiation of treatment for sepsis, and better selection of which patients are most suitable for ICU admission. It is also likely that early identification of critically-ill patients using physiological track and trigger systems, and early warning scores, input from critical care outreach teams, and early ICU transfer prior to the development of organ failure has had a beneficial impact on outcome. Finally, the treatments for haematological malignancy are continuing to improve and this, too, will have an impact on long-term survival.

Admission policies, and withholding or withdrawing care

Determining precise admission policies and providing recommendations to identify patients unsuitable for ICU admission remains controversial. The improved long-term survival for haematological malignancy per se, and the improved ICU outcomes for these patients suggest that the same criteria used in patients with non-malignant conditions should be applied when determining the appropriateness of ICU admission. In most instances, it is appropriate to admit critically unwell patients to the ICU, although the appropriateness of ongoing treatment must be formally reviewed on a regular basis. When patients are identified on the ward as being unlikely to benefit from ICU admission, due to either refractory disease with no further possible lines of treatment, or due to frailty, a pre-emptive decision not to admit in the event of critical illness should be considered and, where possible, discussed with patients and their relatives. Close liaison between the ICU and haematology teams is essential, as is communication with the patient and their relatives.

References

1. Hampshire PA, Welch CA, McCrossan LA, Francis K, and Harrison DA. (2009). Admission factors associated with hospital mortality in patients with haematological malignancy admitted to UK adult, general critical care units: a secondary analysis of the ICNARC Case Mix Programme Database. *Critical Care*, **13**, R137.
2. Passweg JR, Baldomero H, Gratwohl A, et al., for the European Group for Blood and Marrow Transplantation (EBMT). (2012). The EBMT activity survey: 1990–2010. *Bone Marrow Transplant*, **47**, 906–23.

3. Schellongowski P, Staudinger T, Kundi M, et al. (2011). Prognostic factors for intensive care unit admission, intensive care outcome, and post-intensive care survival in patients with *de novo* acute myeloid leukemia: a single center experience. *Haematologica*, **96**, 231–7.
4. Darmon M, Thiery G, Ciroldi M, et al. (2005). Intensive care in patients with newly diagnosed malignancies and a need for cancer chemotherapy. *Critical Care Medicine*, **33**, 2488–93.
5. O'Brien SG, Guilhot F, Larson RA, et al., for the IRIS investigators. (2003). Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *New England Journal of Medicine*, **348**, 994–1004.
6. Afessa B and Azoulay, E. (2010). Critical care of the hematopoietic stem cell transplant recipient. *Critical Care Clinics*, **26**, 133–50.
7. Naeem N, Reed MD, Creger RJ, Youngner SJ, and Lazarus HM. (2006). Transfer of the hematopoietic stem cell transplant patient to the intensive care unit: does it really matter? *Bone Marrow Transplant*, **37**, 119–33.
8. Legrand M, Max A, Peigne V, et al. (2012). Survival in neutropenic patients with severe sepsis or septic shock. *Critical Care Medicine*, **40**, 43–9.
9. Rubenfeld, GD and Crawford SW. (1996). Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: a case for evidence-based guidelines. *Annals of Internal Medicine*, **125**, 625–33.
10. Faber-Langendoen K, Caplan AL, and McGlave PB. (1993). Survival of adult bone marrow transplant patients receiving mechanical ventilation: a case for restricted use. *Bone Marrow Transplant*, **12**, 501–7.
11. Massion PB, Dive AM, Doyen C, et al. (2002). Prognosis of hematologic malignancies does not predict intensive care unit mortality. *Critical Care Medicine*, **30**, 2260–70.
12. Depuydt P, Kerre T, Noens L, et al. (2011). Outcome in critically ill patients with allogeneic BM or peripheral haematopoietic SCT: a single-centre experience. *Bone Marrow Transplant*, **46**, 1–6.
13. Pène F, Aubron C, Azoulay E, et al. (2006). Outcome of critically ill allogeneic hematopoietic stem-cell transplantation recipients: a reappraisal of indications for organ failure supports. *Journal of Clinical Oncology*, **24**, 643–9.
14. Hilbert G, Gruson D, Vargas F, et al. (2001). Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *New England Journal of Medicine*, **344**, 481–7.
15. Townsend W, Holroyd A, Pearce R, et al. (2013). Improved intensive care unit survival for critically ill allogeneic haematopoietic stem cell transplant recipients following reduced intensity conditioning. *British Journal of Haematology*, **161**, 578–86.
16. Milligan DW, Grimwade D, Cullis JO, et al., for the British Committee for Standards in Haematology. (2006). Guidelines on the management of acute myeloid leukaemia in adults. *British Journal of Haematology*, **135**, 450–74.
17. Townsend W and Linch D. (2012). Hodgkin's lymphoma in adults. *Lancet*, **380**, 836–47.
18. Shankland KR, Armitage JO, and Hancock BW. (2012). Non-Hodgkin lymphoma. *Lancet*, **380**, 848–57.

CHAPTER 375

Management of the bone marrow transplant recipient in ICU

Andrew Retter

Key points

- Bone marrow transplant recipients are amongst the most complicated patient's admitted to intensive care. They should always be managed jointly with a haematologist specifically trained in their management.
- There are two types of bone marrow transplant. An autologous transplant is where the patient's own cells are returned to them and an allogeneic transplant where the patient receives donor stem cells.
- Only allogeneic bone marrow transplants can develop graft-versus-host disease.
- All transplant recipients are heavily immunosuppressed and are inherently vulnerable to atypical infections presenting in an unusual manner. There must always be a low threshold to consider infection and a low threshold for investigation and empirical treatment.
- Cytomegalovirus (CMV) viral loads should be checked twice weekly in allograft recipients. CMV viral loads do not need to be routinely checked in patients who have received an autologous transplant.

Introduction

In recent decades outcomes of patients with haematological malignancies have progressively improved due to a better understanding of the underlying disease, increased intensity of chemotherapy regimens, and advances in supportive care. Despite these gains, a proportion of patients will relapse and chemotherapy alone will not provide a cure. Bone marrow transplants (BMT) enable escalation of therapy to treat patients with relapsed disease or those who are at a particularly high risk of relapse. BMT recipients are amongst the sickest and most complicated patients admitted to critical care. Their admission is usually precipitated by a complication directly related to their transplant or underlying disease.

Leukaemia and other cancers consist of hierarchies of cells at various levels of differentiation. Tumours arise from malignant stem cells, which themselves are derived from mutations occurring in normal stem cells [1]. Normal and malignant stem cells repair DNA efficiently, resist apoptosis, and have several mechanisms to excrete toxic drugs [2,3]. Therefore, although chemotherapy can destroy a tumour almost completely, tumour stem cells can survive and cause relapse. BMT allows potential cure of patients at high risk of relapse, or whose underlying disease has been relatively resistant to initial treatment.

There are two types of BMT. The first and simplest form, **autologous bone marrow transplant**, involves collection of stem cells from the patient and their return at a later time. As the patient's own stem cells are returned there is no risk of graft-versus-host disease (GvHD). The second type, **allogeneic BMT**, involves transfusion of donor stem cells to a patient. The key therapeutic mechanism in is the introduction of immunologically active cells from the donor. These cells have the potential to recognize the patient's malignant stem cells and eliminate them [4]. This graft-versus-leukaemic effect reduces the risk of relapse. It is most effective at treating slow-growing cancers. Graft-versus-host disease only occurs in allogeneic BMTs. As with solid organ transplantation, immunosuppression is an essential component of allogeneic transplants to prevent rejection of the donor stem cells (see Fig. 375.1).

Allogeneic BMT can be either myeloablative or non-myeloablative. Initial models regarded allogeneic BMT as a means of escalating the intensity of chemotherapy administered. Transplantation was seen as an 'antidote' to otherwise lethal conditioning. It was thought essential to clear the bone marrow to create space for the new stem cells to repopulate. These concepts are now recognized as over-simplistic. Conditioning serves two purposes:

- It helps to eradicate residual disease.
- It provides immunosuppression allowing engraftment of the transplanted stem cells [5].

The appeal of reduced intensity conditioning (RIC) is that it removes many of the limitations associated with high-dose regimens, so older patients are now eligible for transplantation as are those with underlying medical problems. There has been a progressive tendency to move towards RIC in all but the youngest of patients over the last decade. Treatment complications vary between conditioning regimens and the individual indications for each transplant. Allogeneic BMT provides improved survival,

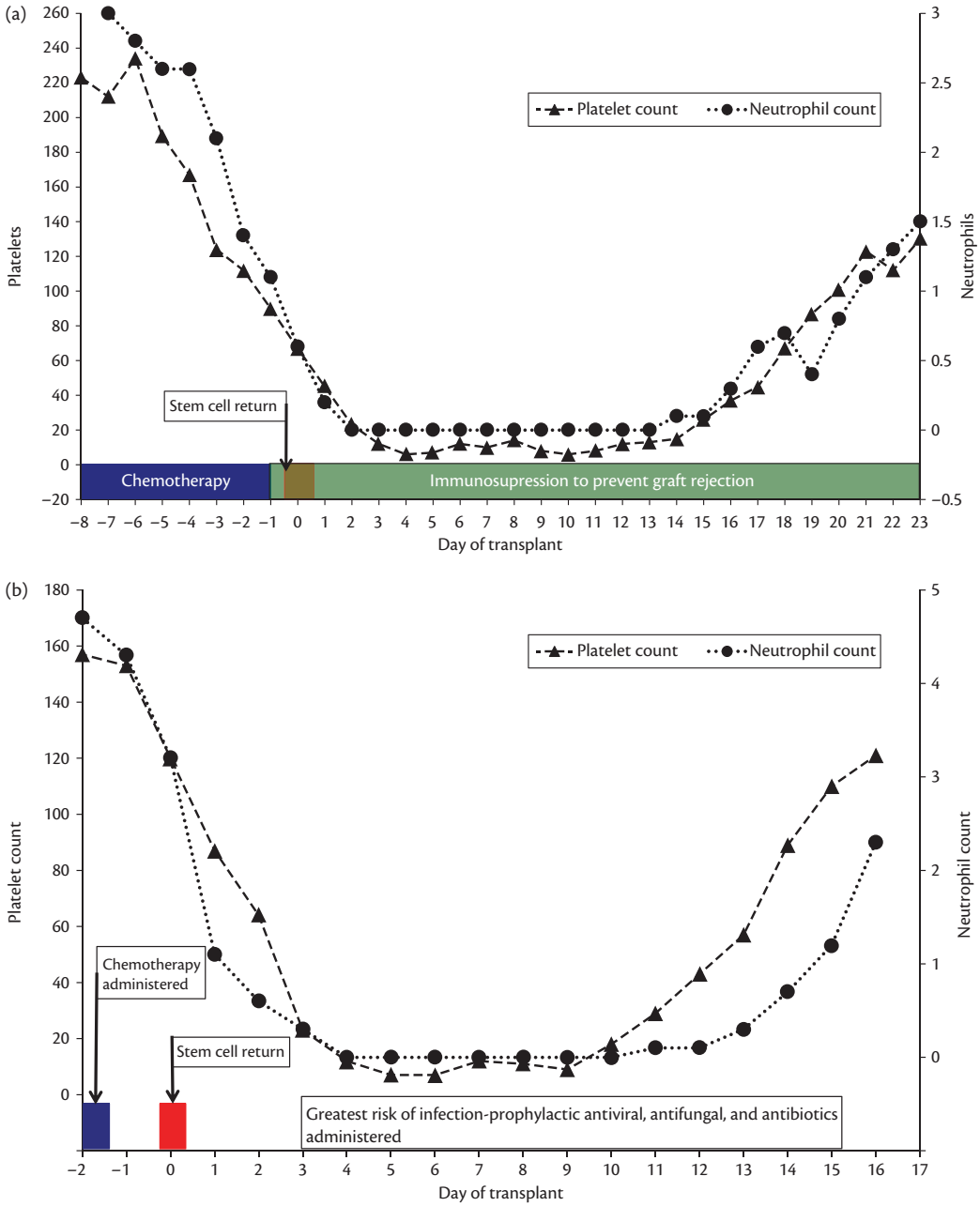


Fig. 375.1 The two graphs depict the fall and recovery of a typical patient undergoing a bone marrow transplant. (a) Pattern of myelosupression and treatment in an allogenic patient. illustrating the greater intensity of chemotherapy in allogenic bone marrow transplants and highlighting the need for immunosuppression in the post-transplant period. (b) Pattern of myelosupression and treatment in an autologous bone marrow transplant.

however it is associated with substantial short- and long-term morbidity and mortality. Around 40% of allogeneic BMT patients will be admitted to intensive care [6].

A summary of the management of BMT patients is given in Table 375.1.

Toxicities associated with bone marrow transplant

The toxic effects of BMT increase with age, particularly in those over 50 years old, and it is generally precluded in patients over 65 years. Complications after transplantation are usually classed as either early (<100 days) or late (>100 days). Early complications of transplantation include infections, (bacterial, fungal, herpes simplex virus, and cytomegalovirus), haemorrhage related to severe thrombocytopenia, acute graft-versus-host disease, haemorrhagic cystitis, interstitial pneumonitis, veno-occlusive disease, and cardiac failure. Late complications include infections (classically encapsulated bacterial and viral, especially varicella zoster virus) chronic graft-versus-host disease, chronic pulmonary disease, autoimmune disease, infertility, and secondary malignancies. The management of specific infectious complications requires a high

Table 375.1 Check list for the management of bone marrow transplant patients

1	Review transplant protocol—is any more chemotherapy required?
2	Ensure GvHD prophylaxis and immunosuppression prescribed
3	Measure ciclosporin level and confirm therapeutic range
4	Determine timing for CMV surveillance
5	Confirm blood product support with haematology and inform local blood bank to ensure provision of irradiated blood products

level of vigilance, and should be managed in conjunction with microbiologists and haematologists. Given the immunocompromised state of BMT patients, prolonged antimicrobial courses are almost always given. The most common non-infectious complications are discussed in the next section.

Graft-versus-host disease

GvHD remains a major complication and cause of mortality. The incidence of acute GvHD is between 10-80% [7]. Diagnosis is based on clinical findings. Any organ system can be affected, most commonly skin, gastrointestinal tract, and liver. The grading system is summarized in Table 375.2. The most severe forms can cause toxic epidermal necrolysis, fulminant hepatic failure, intestinal failure or severe respiratory failure. The grade of acute GvHD correlates with overall survival with transplant-related mortality of grades III and IV reported as 65 and 90%, respectively.

Every patient should be examined daily for GvHD. Initial management involves optimization of their ciclosporin level (target 200–250 μg/L). Patients with grade 3–4 GvHD also require 2 mg/kg methylprednisolone. Topical steroids are given for skin GvHD and oral non-absorbable steroids for gut GvHD. If these fail, a large number of second line agents are available, although none has been shown to be particularly successful when compared with another. The mortality of severe refractory GvHD is very high. These patients are extremely challenging to manage; their care should be coordinated with a dedicated haematologist specialized in managing BMT recipients.

Veno-occlusive disease (or sinusoidal obstructive syndrome)

Veno-occlusive disease (VOD) usually occurs within the first 14 days post-BMT. There is a toxic insult to the hepatic sinusoidal endothelium (presumably as a side-effect of treatment). Endothelial cells desquamate and occlude the microvascular lamina producing a pro-inflammatory response and collagen deposition in hepatic venules leading to liver failure. The diagnosis is difficult to make as the differential includes severe sepsis, acute GvHD, haemolysis, and cholestasis related to medication. Patients complain of right upper quadrant pain and there is a progressive hyperbilirubinaemia with fluid retention and weight gain. Management is supportive. Care must be taken to exclude the differential diagnoses, and to correct any fluid or electrolyte imbalance. Defibrotide, a mixture of single-stranded phosphodiester nucleotides, stimulates plasminogen activator inhibitor, and may help to ameliorate VOD and improve outcome [8].

Ciclosporin toxicity

Ciclosporin is the most commonly used agent for GvHD prophylaxis, although similar principles apply to other immunosuppressive agents, such as mycophenolate mofetil, tacrolimus, or sirolimus. Careful attention must be paid to an allogeneic BMT patient's ciclosporin level when they are admitted. Their condition may mandate the use of intravenous ciclosporin. Plasma levels should be assessed twice weekly to ensure that no large unanticipated deviation from target levels occurs. Low levels can lead to severe GvHD or possible rejection of the donor graft, whereas high levels can cause hypertension, renal toxicity, tremors, seizures, and thrombotic micro-angiopathy. Levels should not be taken from a central line through which ciclosporin has been given as the drug binds to the catheter lumen and can give falsely high, inaccurate results.

Infections associated with bone marrow transplantation

Patients undergoing bone marrow transplantation have compromised innate, cell-mediated, and humoral immunity. This

Table 375.2 Consensus criteria for grading acute GvHD

Stage	Skin	Liver (bilirubin)	Gut
1	Rash <25% BSA[α]	35–50 μmol/L	Persistent nausea, diarrhoea <0.5 L/day
2	Rash 25–50% BSA	51–102	Diarrhoea 1–1.5 L/day
3	Rash >50% BSA	103–255	Diarrhoea >1.5 L/day
4	Generalised erythroderma	>255	Severe abdominal pain or ileus

BSA[α], total body surface area (calculated using the 'rule of 9's).

leads to a high risk of infection, in particular atypical infections. Infections are considered as either pretransplant, pre-engraftment (days 0–20), post-engraftment (days 20–100 post-transplant), and late (>100 days post-transplant). Most commonly, pre- and post-engraftment infections are seen in the ICU. Typically, the first infection seen in the pre-engraftment stage is a bacterial infection; however, respiratory symptoms should raise the possibility of an opportunistic fungal infection, in particular *Aspergillus, Cryptococcus*, or *Candida*.

Fungal infections in bone marrow transplant recipients

The incidence of invasive fungal infection depends on the type of transplant. They are proven in 6% of HSCT recipients. In one series, 90% of patients who developed invasive aspergillosis died [9]. The most common organisms are *Candida* and *Aspergillus*. Neutropenia $\leq 0.5 \times 10^9$/L for >10 days is the most significant risk factor. Patients with chronic GvHD are also at increased risk. Clinical features suggestive of invasive fungal infection include a progressive upper respiratory tract infection, maxillary swelling and tenderness, peri-orbital swelling, palatal necrosis, and popular or nodular skin necrosis. To confirm the diagnosis, hyphae must be detected from a histological or cytological specimen, or a mould should be grown. Depending on the patient's symptoms it is appropriate to consider broncho-alveolar lavage, urine culture, CSF analysis, or tissue biopsy. Clinical features consistent with a lower respiratory tract infection require investigation with an urgent high resolution CT scan with 1-mm slices taken at 1-cm intervals. The 'halo' and air crescent sign, and cavitation are consistent with fungal infection. If empirical treatment is required, local guidelines should be followed. The key principle is to minimize the toxicity associated with antifungal therapy. The British Society of Clinical Haematology Guidelines recommends either liposomal amphotericin or caspofungin as initial therapy [10].

Cytomegalovirus surveillance, prophylaxis, and treatment

Cytomegalovirus (CMV) is a herpes virus which has the ability to remain latent within the body for prolonged periods. Reactivation of the virus is a major concern, and a cause of significant morbidity and mortality in allogeneic BMT recipients. Complications include retinitis, pneumonitis, and colitis. Once established, these are difficult to treat and require prolonged therapy so patients should receive prophylaxis with acyclovir 800 mg tds. Early pre-emptive treatment of viral reactivation can prevent progression to CMV-related organ impairment and failure. All allograft patients should have blood taken twice a week in the early post-transplant period. Occasionally, the level is seen to rise and fall without intervention. Two progressive increments in the CMV level, or a viral load >5000 copies, will require an escalation from prophylaxis to formal treatment. The first line agent is ganciclovir, but this can be myelosuppressive so treatment may need to be switched to foscarnet. Treatment should be continued for a minimum of 2 weeks and only ceased when two consecutive tests confirm that the viral load is undetectable. The risk of recurrent viraemia is high once a patient has reactivated CMV. Any patient with a suspicion of CMV disease should be started on therapy while awaiting the results of the CMV viral load.

Blood product support in bone marrow transplant recipients

Patients undergoing BMT require extensive blood product support. They are at risk of transfusion-associated graft versus host disease. Red cell antigens are not major histocompatibility antigens and haemopoietic stem cell components may be transplanted between red cell antigen (ABO) disparate donors. This can lead to confusion as to the patient's blood group. All bone marrow transplant patients admitted to critical care should have their blood group tested and any special transfusion requirements confirmed with their transplant team and the blood transfusion services. This is particularly important if the patient is admitted to a hospital in which they have not been previously treated. As a general principle the haemoglobin should be maintained above 7 g/dL and platelet count above 10×10^9/L. Platelet transfusion thresholds will be higher if the patient is bleeding or has severe sepsis.

Transfusion-associated GvHD (TA-GvHD) is rare, but almost universally fatal. It occurs when viable white blood cells are transfused from donor to recipient. These white cells detect a disparity with the donor human lymphocyte antigen type and mount a cell-mediated immune response. The features resemble acute GvHD and typically manifest between 10 and 14 days after the transfusion. Irradiation of blood components renders the white cells non-viable and prevents the development of TA-GvHD. All BMT recipients should receive irradiated blood products from at least 14 days prior to transplantation. Irradiation is only required for cellular blood products, which include red blood cells, platelets, and granulocytes. Fresh frozen plasma and cryoprecipitate do not need to be irradiated.

CMV-negative blood components

Recently published position statement by the advisory committee on the safety of blood tissue and organs suggest it is no longer necessary to give BMT recipients CMV-negative products as leukodepletion effectively removes the virus [11]. However, cellular blood components have the potential to transmit CMV and, historically, it was a cause of high morbidity and mortality in BMT patients. Transplant units are currently developing local policies in view of this guidance.

Management of tunnelled venous (Hickman®) lines

Tunnelled venous lines are central to the management of BMT patients. They provide a secure route for administration of chemotherapy, and permit regular administration of blood products and antibiotic support. However, data relating to their safety are lacking. There remains significant concern over the ability to sterilize an infected tunnelled line and the potential for it to act as a sanctuary site for bacteria. Studies of colonized CVP lines suggest that, despite treatment with high-dose antibiotics and the use of antibiotic locks, colonization persists in 35–40% of cases. This constitutes a high risk in BMT recipients who are severely immunosuppressed. Therefore, any such patient admitted to the

ICU with septic shock should have their tunnelled line removed as soon as is practical. The use of antibiotic locks is not recommended and they should not be used to try to 'save-a-line'. Most patients will require administration of a pool of platelets to elevate the platelet count >50 × 10^9/L prior to removal of a tunnelled line. The use of lidocaine with adrenaline is helpful in reducing blood loss when removing the line.

Outcomes for BMT recipients admitted to the ICU

The mortality from severe sepsis in haematology patients is significantly higher than age- and APACHE II-matched controls. ICU survival rates ranging from 17 to 48.3% have been reported [12]. The mortality of BMT patients receiving mechanical ventilation is approximately 90%, but only 78% for those who require renal replacement therapy [13]. These figures do not mean that ICU admission is futile; indeed, mortality rates are improving, although this is generally based on small single-centre studies only. Patients can be managed on non-invasive ventilation and this is associated with improved outcomes. No specific alterations are required for the initiation of ventilation or renal replacement therapy in BMT patients and standard ICU practice with lung-protective ventilation should be followed.

In view of the high mortality, it is important that open and realistic discussions regarding the probable outcome of patients admitted to the ICU are conducted soon after admission with the patient and their family. Ideally, this should be led by a senior intensivist and haematologist. Early referral to palliative care may be appropriate.

References

1. Bonnet D and Dick JE. (1997). Human acute myeloid leukaemia is organised as a hierarchy that originates from a primitive hematopoietic cell. *Nature Medicine*, **3**, 730–7.
2. Dean M, Fojo T, and Bates S. (2005) Tumour stem cells and drug resistance. *Nature Reviews Cancer*, **367**, 645–8.
3. Copelan EA. (2006). Hematopoietic stem-cell transplantation. *New England Journal of Medicine*, **354**, 1813–26.
4. Bleakley M and Riddell S. (2004). Molecules and mechanisms of the graft-versus-leukaemia effect. *Nature Reviews Cancer*, **4**, 371–80.
5. Antin JH. (2007). Reduced-intensity stem cell transplantation. *Hematology: American Society of Hematology Education Program*, 47–54.
6. Horak DA and Forman SJ. (2001). Critical care of the hematopoietic stem cell patient. *Critical Care Clinics*, **17**(3), 671–95.
7. Dignan FL, Clark A, Amrolia P, et al. (2012). Diagnosis and management of acute graft-versus-host disease. *British Journal of Haematology*, **158**(1), 30–45.
8. Benimetskaya L, Wu S, Voskresenskiy AM, et al. (2008). Angiogenesis alteration by defibrotide: implications for its mechanism of action in severe hepatic veno-occlusive disease. *Blood*, **112**(10), 4343–52.
9. Walsh TJ, Finberg RW, Arndt C, et al. (1999). Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *New England Journal of Medicine*, **340**(10), 764–71.
10. Prentice A, Glasmacher A, Hobson R, et al. (2008). Guidelines on the management of invasive fungal infection during therapy for haematological malignancy. Available at: http://www.bcshguidelines.com/documents/fungal_infection_bcsh_2008.pdf (accessed 3 September 2015).
11. Advisory Committee on the Safety of Blood, Tissue and Organs (SaBTO). Cytomegalovirus tested blood components. Position Statement. Available at: www.gov.uk/government/uploads/system/uploads/attachment_data/file/215125/dh_133086.pdf
12. Benoit DD, Depuydt PO, Peleman RA, et al. (2005). Documented and clinically suspected bacterial infection precipitating intensive care unit admission in patients with hematological malignancies: impact on outcome. *Intensive Care Medicine*, **31**(7), 934–42.
13. Pene F, Aubron C, Azoulay E, et al. (2006). Outcome of critically ill allogeneic hematopoietic stem-cell transplantation recipients: a reappraisal of indications for organ failure supports. *Journal of Clinical Oncology*, **24**(4), 643–9.

CHAPTER 376

Management of oncological complications in the ICU

Niall S. MacCallum

Key points

- Cancer pain is complex and requires multidisciplinary management.
- Cytotoxic therapies can induce toxicity in all major organ systems.
- Management of complications include cessation of cytotoxic therapy and supportive care.
- There are very few proven prevention/treatment strategies.
- Intensivist knowledge of individual cytotoxic therapy allows a better understanding of likely compromised organ systems and physiological reserve.

Introduction

Cancer incidence continues to rise year on year; more than one in three people will be diagnosed with cancer during their lifetime. UK data from 2010 cites prostate, breast, lung, and colorectal cancers as the most common (see Table 376.1).

Complications can be due to treatment (surgery, radio-, chemo-, endocrine, and biological therapy) or disease. Those relevant to critical care are discussed here with the exception of neutropenic sepsis and bone marrow transplant/graft versus host disease that are discussed elsewhere.

Complications

Pain

The aetiology of cancer-related pain is complex and varied. The World Health Organization analgesic ladder has limitations in this context so more comprehensive models have been developed that utilize a mechanism-based multimodal approach [1].

Management should be multidisciplinary, often led by specialists in pain medicine and palliative care, but should also include psychologists and therapists. Accurate assessment is required. Opioids remain the backbone of management, and are used in combination with other agents, e.g. non-steroidal anti-inflammatory agents, anti-epileptics, sodium channel blockers, interventional procedures, and other therapies that treat or palliate cancers.

Management of post-operative pain in cancer patients on high-dose opioids remains challenging. Understanding of the pharmacokinetics of analgesic agents should underpin a detailed management plan to avoid inadequate analgesia, the development of withdrawal symptoms (more likely following an extended period of strong opioid use) or tolerance. Baseline provision of opioids should continue, with supplemental short-acting opioids and non-steroidal anti-inflammatory agents, paracetamol, clonidine, and local anaesthetic infiltration as these have opioid 'sparing effects'. Regional and neuro-axial blocks are recommended where appropriate though further data are needed to ascertain whether these techniques affect disease recurrence.

Chemotherapeutic complications: pancytopenia

Neutropenia

Although definitions vary, a neutrophil count below 0.5×10^9 cells/L is generally accepted. Causative factors are cytotoxic chemotherapy and/or sepsis. The neutrophil count reaches a nadir at 5–7 days for most chemotherapeutic regimens, and can take >2 weeks to recover. Granulocyte-colony stimulating factors (G-CSF) and the cytotoxic regimen affect both the degree and duration of neutropenia. The former is most commonly used in conjunction with 'high-risk regimens', but practice varies widely. The UK National Institute of Clinical Excellence does not advise starting G-CSF unless part of a chemotherapeutic regimen [2].

Anaemia

There is no evidence that critically-ill cancer patients should be subject to higher transfusion thresholds than the currently accepted practice of a haemoglobin level of 70 g/L [3]. Peri-operative blood transfusions not only worsen short-term surgical outcomes, but may also lead to an increased risk of cancer recurrence [4].

Thrombocytopenia

Platelet transfusion thresholds of $10–20 \times 10^9$/L are based on studies demonstrating little or no increased risk of bleeding, but a substantial reduction in the use of platelet transfusions. It is common practice to raise this threshold (e.g. to 50×10^9/L) in the presence of deranged coagulation or active bleeding, and preceding interventions [5].

Methotrexate

Bone marrow suppression can be a dose-limiting side effect of therapy, but is usually more prevalent in low-dose regimens (e.g. for managing rheumatoid arthritis), rather than the high-dose regimens used for malignant disease. Administration of folinic acid to bypass the metabolic block induced by methotrexate avoids host-induced toxicity without diminishing anti-tumour activity.

Table 376.1 Commonest cancers in the United Kingdom in 2010 represented as percentage of all cancers excluding non-melanoma skin cancer

Commonest cancers in the United Kingdom in 2010	Percentage of all cancers excluding non-melanoma skin cancer
Breast	15.4
Lung	12.9
Prostate	12.6
Colorectal	12.5
Malignant melanoma	3.9
Non-Hodgkin lymphoma	3.8
Bladder	3.2
Renal	3.0
Oesophageal	2.6
Pancreatic	2.6
Uterine	2.6
Leukemia	2.5
Gastric	2.2
Ovarian	2.2
Oral	2.0
Central nervous system	1.5
Melanoma	1.4
Hepatic	1.3
Cervical	0.9
Thyroid	0.8

Data from www.cancerresearch.org.uk

Mechanisms whereby reduced folate rescues normal, but not malignant cells are incompletely understood.

Chemotherapeutic complications: cardiac toxicity

The increasing age and cardiac co-morbidities of patients receiving chemotherapy is likely to cause more adverse events, the spectrum of which is expanding following the recognition of additive cardiac toxicities of chemotherapeutic agents and the increased use of targeted 'biological' therapies [6].

Anthracyclines

Doxorubicin and other anthracyclines may cause cardiomyocyte and interstitial injury via oxidative stress and the induction of apoptosis. Acute clinical manifestations include atrial fibrillation, heart failure, myocarditis, and myocardial infarction. Chronic manifestations are due to dose-dependent cumulative toxicity leading to diastolic and systolic dysfunction. Factors increasing the risk of cardiac toxicity include age, combinations of cyclophosphamide, taxanes, or trastuzumab, and mediastinal irradiation. Delayed late toxicity manifest as left ventricular dysfunction is reported in 5–10% of patients in remission. Strategies for prevention of cardiac toxicity have largely lacked success. There may be a role for prolonging the duration of administration. While cardiovascular drugs show promise in animal models, these have either not been translated into human use or sufficiently investigated. Antioxidant drugs have not shown efficacy in humans with the exception of dexrazoxane, an iron-chelating compound, which led to lower reductions in left ventricular ejection fraction.

Alkylating agents

High-dose cyclophosphamide (e.g. as induction therapy for bone marrow transplantation) is linked to acute heart failure and often associated with pericardial effusion. Mechanism may be related to glutathione redox cycling. Pathological findings include necrosis, endothelial injury, microvascular thrombi, and ischaemia. If patients survive the acute episode, the left ventricular dysfunction is reversible. Cisplatin can result in hypertension, myocardial ischaemia and left ventricular dysfunction.

Antimetabolites

The risk of cardiac toxicity (myocardial ischaemia, acute heart failure, hypotension, ventricular arrhythmias) with agents such as fluorouracil and capecitabine is increased in patients with cardiac co-morbidity or associated risk factors. Acute coronary syndromes can occur despite normal coronary angiography. Pharmacological interventions to prevent recurrent ischaemia have not proved to be effective.

Microtubule inhibitors

Paclitaxel and docetaxel may cause bradycardia, ventricular arrhythmias, myocardial ischaemia and left ventricular dysfunction. They also potentiate anthracycline cardiotoxicity.

Targeted therapies

Monoclonal antibodies and tyrosine kinase inhibitors are associated with left ventricular dysfunction, which is often transient. The mechanism of action is purported to be via target genes. The incidence is increased with age, pre-existing cardiac disease, and combination radio- or chemotherapy, particularly with anthracyclines where sequential therapy is advocated.

Management should be placed in the context of improved cure rates for many cancers. Clinically significant cardiac toxicity occurs in up to 10% of patients. Evaluation should be performed prior to administering chemotherapy to identify patients at increased risk. They should be closely monitored, preferably in collaboration with a cardiologist. Routine investigations include electrocardiograms and cardiac imaging. Troponin levels may assist in risk assessment, but the role of other biomarkers (e.g. B-type natriuretic peptide) is less clear. Critical care management is supportive. Follow-up should occur at regular intervals and for a longer duration in those who develop cardiac toxicity. Early initiation of angiotensin-converting enzyme inhibitors and β-adrenergic receptor blockade has shown promise for long-term recovery of left ventricular dysfunction.

Chemotherapeutic complications: pulmonary toxicity

Toxicity post-exposure to chemotherapeutic agents occurs in 20% of patients. The wide spectra of pulmonary manifestations and important differential diagnoses (infection, disease progression, interstitial lung disease, pulmonary oedema, and non-chemotherapeutic drug effects) continue to pose challenges. Furthermore, lack of clear diagnostic criteria lead to a diagnosis based on exposure and exclusion of other aetiologies. Many adverse drug reactions are idiosyncratic and unpredictable. Pathogenesis is poorly understood, with direct cytotoxicity being the most likely mechanism. Pre-existing lung disease, increasing age, smoking (e.g. with bleomycin), previous radiotherapy, cumulative dose (e.g. nitrosourea) and/or specific combinations of chemotherapeutic agents (e.g. gemcitabine and paclitaxel) are associated with increased risk.

Oxygen therapy is well recognized to increase pulmonary toxicity in certain circumstances, e.g. with bleomycin or mitomycin. There is also an increased prevalence of pulmonary infection attributable to certain chemotherapeutic agents [7,8].

Investigation often reveals a reduction in transfer factor and a restrictive pattern on pulmonary function testing. Radiographic patterns include reticular or nodular markings, ground glass opacities, consolidation, and pleural effusions. Broncho-alveolar lavage fluid leukocyte counts are usually elevated, but have no diagnostic specificity. Generic management includes balancing the risk-benefit of discontinuation of therapy and supportive care. Steroid therapy (after exclusion of infective aetiology) may have a role. However, evidence remains largely observational. Specific chemotherapeutic agents are discussed in the following section and others are listed in Table 376.2.

Antimetabolites

The folic acid analog methotrexate induces pulmonary toxicity in <10% of patients. Incidence varies with indication, co-administration of cytotoxic agents, and pulmonary co-morbidities. Hypersensitivity pneumonitis is most prevalent, but organizing pneumonia, interstitial pneumonia, non-cardiogenic pulmonary oedema, pulmonary fibrosis, and pleural effusions also occur. Suggested mechanisms include hypersensitivity reactions and direct toxic effects. Lymphoproliferative disease may appear during, and regress following, methotrexate therapy. Diminished immune surveillance and Epstein–Barr virus infection may also be implicated.

Cytotoxic antibiotics

Bleomycin causes severe pulmonary fibrosis in up to 10% of patients and, less commonly, organizing pneumonia and hypersensitivity pneumonitis. Toxicity is cumulative dose (≥400 units) dependent. Risk factors include renal dysfunction, exposure to high oxygen levels, radiation therapy, age >40 years, and smoking. Mechanisms include oxidative damage, augmentation of inflammatory mediators, (pulmonary) deficiency in the inactivating enzyme and genetic factors. Additional management includes titration of inspired oxygen to target lower oxygen saturation (SaO_2 88–92%).

Mitomycin induces a breadth of pulmonary toxicity in ~10%, particularly at higher doses (>20 mg/m^2), including bronchospasm, acute lung injury, interstitial pneumonitis, pulmonary hypertension, thrombotic micro-angiopathy, and pleural disease. Risk factors include co-administration of cytotoxic agents (e.g. vinca alkaloids) and high FiO_2 (>0.5). Thrombotic micro-angiopathy has similar characteristics to thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, and is associated with acute lung injury, cumulative dose exposure, and certain drugs (e.g. fluorouracil). Pathology varies depending on the type of injury. Additional management includes plasma exchange for thrombotic micro-angiography and titration of inspired oxygen to lower oxygen saturation targets (SaO_2 88–92%).

Table 376.2 Chemotherapeutic agent induced pulmonary toxicity

Agent	Toxicity	Notes
Alkylating agent: Busulfan Chlorambucil Cyclophosphamide Fosfamide Melphalan Oxaliplatin	◆ Acute lung injury ◆ Chronic interstitial fibrosis ◆ Alveolar haemorrhage ◆ Chronic interstitial pneumonitis ◆ Pneumonitis (acute and chronic) ◆ Interstitial pneumonia, methemoglobinaemia ◆ Pneumonitis, bronchospasm ◆ Interstitial and/or eosinophilic/cryptogenic organizing pneumonia, alveolar haemorrhage	Used prior to haematopoietic stem cell transplantation **Acute**: cessation and steroid therapy result in complete resolution **Chronic**: poorly responsive to steroids **Risk factors**: radiotherapy, oxygen therapy, co-administration of cytotoxic agents that cause pulmonary toxicity Limited evidence for steroids β-adrenergic agents Limited evidence for steroids
Angiogenesis inhibitor: thalidomide	Thromboembolic disease, non-thromboembolic pulmonary hypertension, interstial fibrosis, lymphocytic alveolitis, eosinphilic pneumonia, organizing pneumonia	
Antibiotic: doxorubicin	Interstitial and/or organizing pneumonia	
Antimetabolite: Cytarabine Fludarabine Gemcitabine	◆ Non-cardiogenic pulmonary oedema ◆ Interstitial pneumonitis ◆ Interstitial pneumonitis, non-cardiogenic pulmonary oedema, alveolar haemorrhage, pleural effusion, eosinophillic pneumonia	Cessation and steroid therapy results in resolution Cessation and steroid therapy results in amelioration. Potent radiosensitizer **Risk factors**: co-administration (bleomycin, paclitaxel), pre-existing pulmonary fibrosis
Camptothecin: irinotecan	Fibrosis, pleural effusions	Limited evidence for steroids
Nitrosourea: carmustine	Pulmonary fibrosis (acute and late onset)	Limited evidence for steroids **Risk factors**: cumulative dose, co-administration with cyclophosphamide
Proteasome inhibitors: Bortezomib, carfilzomib	Severe dyspnoea	Limited evidence for steroids **Reported**: interstitial lung disease, pulmonary hypertension

Microtubule inhibitors

Taxanes (paclitaxel and docetaxel) induce a spectrum of pulmonary toxicity in <5%, including interstitial pneumonitis and capillary leak syndrome, the former via an immune-mediated delayed hypersensitivity reaction. Capillary leak syndrome subsequent to docetaxel administration can lead to non-cardiogenic pulmonary oedema and effusions. Risk factors include dose, associated use of growth factors, pre-existing lung disease, co-administration with cytotoxic agents (e.g. gemcitabine) and radiotherapy. Steroid administration has some evidence of benefit in capillary leak syndrome.

Targeted therapies

Molecularly-targeted anti-cancer therapy is increasingly utilized and associated with pulmonary toxicity. Rituximab (B-cell depleting anti-CD20 monoclonal antibody) is increasingly used in critical care settings: dyspnoea and bronchospasm are common. Interstitial pneumonia occurs in <10% and is more likely to occur with co-administration of other cytotoxic agents. Rituximab-associated acute lung injury has a mortality of 30% [9].

Chemotherapeutic complications: renal toxicity

Chemotherapeutic agents are associated with electrolyte disorders, development of acute kidney injury, urate nephropathy, renal calculi, or bladder toxicity [10,11]. Intra-vascular volume depletion, concomitant non-chemotherapeutic nephrotoxic drugs (e.g. aminoglycosides), obstructive uropathy secondary to underlying tumour, and idiopathic renal disease related to other co-morbidities are potential risk factors for renal dysfunction. Chemotherapeutic agents can affect the glomerulus, tubules, interstitium, or microvasculature of the kidney. Most chemotherapeutic agents have significant renal clearance.

Platinum analogues

Mechanisms contributing to renal dysfunction include tubular epithelial cell toxicity (necrosis and apoptosis), microvascular vasoconstriction, and increased expression of pro-inflammatory mediators. Toxicity is manifest as renal dysfunction (up to 50% of patients), but salt wasting, a Fanconi-like syndrome and anaemia (through erythropoietin deficiency) are also reported. The incidence of renal impairment depends on the dose and frequency of administration, and increases with subsequent courses. In combination with bleomycin or gemcitabine, cisplatin is associated with a thrombotic micro-angiopathy-induced renal dysfunction. Renal dysfunction can be prevented with lower doses of cisplatin in combination with intravenous isotonic crystalloid. Carboplatin is less nephrotoxic than cisplatin.

Alkylating agents

Cyclophosphamide and ifosfamide toxicity is manifest as haemorrhagic cystitis or hyponatremia (via an increased effect of anti-diuretic hormone). Hyponatraemia normally resolves after discontinuing the chemotherapeutic agent. Therapies to prevent haemorrhagic cystitis include hyperhydration, bladder irrigation, and mesna (2-mercaptoethane sodium sulfonate). Mesna is protective during oxazaphosphorine therapy, but must be present in the bladder at the time of chemotherapy administration. Ifosfamide is more likely to cause nephrotoxicity than cyclophosphamide.

Antimetabolite

High-dose methotrexate can reversibly decrease glomerular filtration and cause tubular injury by precipitation. Dehydrated patients or those who excrete acidic urine are at greatest risk. An adequate diuresis and urinary alkalinization (urinary pH >7) minimizes the risk of precipitation. However, despite wide use, benefits remain unproven. Methotrexate toxicity can be treated with glucarpidase generating an inactive metabolite.

Nitrosoureas

Prolonged therapy carmustine can induce interstitial nephritis, although underlying mechanisms are poorly understood. Melphalan is associated with inappropriate anti-diuretic hormone secretion.

Cytotoxic antibiotics

Mitomycin toxicity is manifest as renal failure and micro-angiopathic haemolytic anaemia. It is related to cumulative dose, and most likely due to endothelial injury.

Tumour lysis syndrome

Tumour lysis syndrome (TLS) occurs after initiating cytotoxic therapy, most commonly for high-grade lymphomas (e.g. Burkitt's) and acute lymphoblastic leukaemia, but also for other tumour types with a high proliferative rate, large tumour burden, or increased sensitivity to cytotoxic therapy [12]. Prerenal failure, pre-existing renal abnormalities and hyperuricaemia are contributory factors. Clinical TLS is defined by the presence of laboratory TLS (≥2 of hyperuricaemia, hyperphosphataemia, hyperkalaemia, hypocalcaemia) and ≥1 of a 50% increase above the normal range of serum creatinine, cardiac arrhythmia/sudden death, or seizure. Clinical TLS significantly increases morbidity, treatment-related complications, and the risk of death.

Substantial tumour cell lysis releases large amounts of intracellular potassium, phosphate and nucleic acids, the latter leading to hyperuricaemia via enzymatic degradation by xanthine oxidase and secondary hypocalcaemia. Increased uric acid excretion can result in uric acid precipitation in renal tubules, a decrease in renal blood flow, impaired autoregulation and inflammation, culminating in acute kidney injury (AKI). Hyperphosphataemia causes calcium phosphate deposition in the renal tubules, also leading to AKI.

Hyperuricaemia and hyperphosphataemia also enhance precipitation of uric acid and calcium phosphate crystals in each other's presence.

Uric acid is poorly soluble in water, particularly in an acidic environment (distal tubules and collecting system) leading to crystal deposition and acute uric acid nephropathy. Hypouricaemic agents (e.g. allopurinol, rasburicase) have significantly reduced the risk. Nephrocalcinosis is now the major cause of AKI in TLS. Calcium phosphate deposition in the heart may lead to cardiac arrhythmias.

Allopurinol competitively inhibits xanthine oxidase, thereby increasing hypoxanthine levels and blocking uric acid production. Hypoxanthine is more water-soluble than uric acid. However, allopurinol will also increase xanthine excretion, and this may precipitate in the renal tubules, paradoxically inducing an AKI and/or xanthine calculi.

Urate oxidase, which oxidizes uric acid to the significantly more soluble allantoin, is not present in humans. Rasburicase, an exogenous urate oxidase, markedly reduces uric acid levels within hours.

Rasburicase is contraindicated in glucose-6-phosphate dehydrogenase deficiency as it can cause methemoglobinaemia and haemolytic anaemia.

The hallmark of management is prevention. This can be based on a (disease-specific) risk stratification [13] and may include:

- **Fluid hydration**: aggressive fluid therapy (to minimize crystal precipitation) targeting a urine output of 2 mL/kg/hour; diuretic therapy may be supplementary in the absence of hypovolaemia or obstructive uropathy.
- **Urinary alkalinization**: not recommended in the absence of metabolic acidosis and may promote calcium phosphate deposition. It is not needed for patients receiving rasburicase.
- **Hypouricaemic agents**: in principle, rasburicase is recommended for high-risk patients, and rasburicase or allopurinol for intermediate risk cases. With regard to rasburicase treatment, G6PD deficiency should be excluded, uric acid levels should be monitored, and allopurinol administered if only a single dose has been used.

Chemotherapeutic complications: hepatic toxicity

Chemotherapy-induced hepatotoxicity can be direct or may potentiate pre-existing liver disease [14]. Altered hepatic drug metabolism may potentiate toxicity. Mechanisms are varied and include hepatocellular injury, inflammation, cholestasis, endothelial damage, and thrombosis. Hepatic sinusoidal obstruction syndrome is caused by non-thrombotic obliteration (fibrin deposition) of small intrahepatic veins, leading to obstruction and centrilobular hepatocellular necrosis; it occurs most commonly following haematopoietic stem cell transplantation and may be drug-induced (e.g. dacarbazine, dactinomycin, azathioprine).

Clinical presentations range from deranged biochemical indices to fulminant hepatocellular failure. Management is supportive with withdrawal of the likely agent. Distinction between chemotherapy-induced hepatotoxicity and other aetiologies of hepatic failure, such as tumour progression and exacerbation of co-existing liver disease can be challenging. Imaging may be helpful.

Chemotherapeutic complications: neurotoxicity

Chemotherapeutic agents can be directly neurotoxic or act indirectly via metabolic, vascular or autoimmune paths. Chemotherapy-induced peripheral neuropathy (CIPN) is the most common problem. Differential diagnoses include metastatic disease, paraneoplastic syndromes and co-existing neurological dysfunction. Risk factors include dose, duration, and co-administration of neurotoxic agents (e.g. platinum analogs) [15].

CIPN is frequently associated with treatment for breast or colon cancer. Sensory neuropathy is more common than motor, while autonomic neuropathy is uncommon except with vincristine. Management includes agent cessation or dose and/or duration adjustment. Many neuroprotective agents aimed at preventing or treating neuropathy have been tried, however, the evidence base remains weak.

Platinum analogs are commonly associated with neurotoxicity. Cisplatin is associated primarily with peripheral neuropathy and ototoxicity. The risk of neuropathy is cumulative dose-dependent and recovery often incomplete. Ototoxicity is manifest as high-frequency sensorineural hearing loss; concomitant cranial radiotherapy is synergistic. Other chemotherapeutic agents and associated neurotoxicity are listed in Table 376.3.

Chemotherapeutic complications: nausea and emesis

Chemotherapy-induced nausea and vomiting can be extremely distressing and challenging to treat. Three types of emesis have been defined:

- Acute, occurring within the first 24 hours after chemotherapy.
- Delayed, after 24 hours, more difficult to manage with anti-emetics, frequently associated with platinum analogs.
- Anticipatory, a conditioned response in those with severe symptoms from previous chemotherapy.

Table 376.3 Chemotherapeutic agent-induced neurotoxicity

Agent	Toxicity	Notes
Dihydrofolate reductase inhibitor: methotrexate	◆ Aseptic meningitis ◆ Transverse myelopathy ◆ Encephalopathy ◆ Leukoencephalopathy	Typically following intrathecal administration, indistinguishable from other aseptic meningitides More common with concurrent radiotherapy More frequent with high dose therapy
Cyclophosphamide analog: ifosfamide	Encephalopathy	Greater risk with renal dysfunction
Platinum analogues: oxaliplatin	◆ Acute neurosensory complex ◆ Sensory neuropathy	Cumulative dose-dependent
Proteasome inhibitors: bortezomib	Painful sensory neuropathy	
Taxanes, anti-microtubule agents: paclitaxel, docetaxel	Sensory neuropathy	Cumulative dose dependent
Thalidomide	◆ Peripheral neuropathy (sensory and motor) ◆ Somnolence ◆ Autonomic neuropathy	Dose dependent and cumulative
Vinca alkaloids: vincristine	◆ Axonal neuropathy ◆ Autonomic neuropathy ◆ Focal mononeurothy	Dose-related severity

Mechanisms are many, complex, and incompletely understood. Afferent inputs include the chemoreceptor trigger zone and the gastrointestinal tract (vagus and splanchnic nerves) triggering efferent signals from the brainstem (vomiting centre). Many neurotransmitters (e.g. dopamine, serotonin, substance P) are implicated as their antagonists demonstrate clinical benefit. Some chemotherapeutics interact directly with the chemoreceptor trigger zone, while others initiate release of neurotransmitters through direct cytotoxic effects on intestinal cells.

The principle of management is prevention. Chemotherapeutic regimens are categorized on the probability of inducing emesis [16]. Anti-emetics with the highest therapeutic index: 5-hydroxytryptamine (5-HT3) receptor antagonists, glucocorticoids and neurokinin-1 (NK1) receptor antagonists (e.g. aprepitant) form the mainstay of treatment and are synergistic. 5-HT3 antagonists have a lesser role in delayed emesis. The anti-emetic properties of glucocorticoids are probably a class effect; dexamethasone is most evaluated and commonly used. Other agents (e.g. prochlorperazine, metoclopramide, cannabinoids, olanzapine) are reserved for specific situations or when first-line agents prove refractory. Complementary therapies (e.g. supplemental ginger, acupuncture) play a modest role.

Miscellaneous chemotherapeutic complications

Chemotherapeutic regimens can affect mucous membranes, skin, hair, and nails through various mechanisms. Differential diagnoses include cutaneous adverse non-cytotoxic drug reactions, pre-existing conditions, infection, graft-versus-host disease, metastatic disease, paraneoplastic phenomena, and cutaneous manifestations of the underlying cancer.

Musculoskeletal toxicity is reported, most commonly manifest as arthralgia and/or myalgia, but also arthritis, scleroderma, Raynaud's phenomenon, osteonecrosis, and elevated creatine kinase.

Radiotherapy complications

Radiation therapy can induce interstitial fibrosis in both heart and lung [17]. In radiation-associated cardiotoxicity there is narrowing of blood vessels with endothelial cell damage. The ratio of capillaries to myocytes is reduced, leading to necrosis and fibrosis. This can be manifest clinically as coronary artery disease, or valvular, myocardial, and conduction system fibrosis. Risk factors include total radiation dose, fractional dose, exposure of heart, and concomitant cardiotoxic agents. Patients with breast cancer or Hodgkin's lymphoma are at risk of developing cardiac toxicity.

Radiation-induced lung injury is more likely in patients with genetic susceptibility. Pro-inflammatory mediators are upregulated following irradiation with direct cytotoxic effects, inflammation, and fibrosis. Transforming growth factor-β, and platelet-derived growth factor induce fibroblast collagen deposition and fibroblast growth factor. Risk factors include the volume of lung irradiated, radiation dose, concurrent chemotherapy (e.g. bleomycin), and induction chemotherapy. Clinically, apparent radiation pneumonitis occurs in up to 10–15% of breast and lung cancer patients, with radiological abnormalities present in up to two-thirds. Diagnosis is based on correlation between onset of symptoms and timing of radiation, imaging, pulmonary function tests and bronchoscopy. Glucocorticoids may play a role in modulating disease, but prospective evidence is lacking [18].

Gut toxicity can occur when the gastrointestinal tract is exposed to radiation therapy. Effects can be early (e.g. nausea and diarrhoea) or late (e.g. ulceration, stricture formation and obstruction, malnutrition). The mechanism of action is a direct cytotoxic effect on the epithelial layer leading to mucosal thinning, inflammation, and fibrosis. Risk factors include radiation dose, concurrent chemotherapy, and vasculopathy. Management is symptomatic and includes endoscopic dilation for strictures.

Radiotherapy is also directly hepatotoxic. Injury is worsened with addition of chemotherapeutic agents (e.g. vincristine) that are also associated with radiation 'recall' injury. Radiation hepatitis is manifest by veno-occlusive disease progressing to fibrosis, cirrhosis, and hepatic failure.

Thromboembolic disease

Thromboembolic disease is a common cause of mortality and morbidity in cancer patients who have a 6-fold increased risk compared with the normal population. When adjusted for prevalence, the most common malignancies associated with thrombosis are pancreatic, ovarian, and central nervous system cancers. Low molecular weight heparin may be superior to oral anticoagulation [19].

References

1. British Pain Society. (2010). Management of acute pain in cancer patients. In: Cancer Pain Management, pp. 91–95. London: British Pain Society; 2010; Available from: https://www.britishpainsociety.org/static/uploads/resources/files/book_cancer_pain.pdf.
2. NICE. (2012). Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. London: National Collaborating Centre for Cancer for National Institute of Clinical Excellence.
3. Hebert PC, Wells G, Blajchman MA, et al. (1999). A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *New England Journal of Medicine*, **340**, 409–17.
4. Al-Refaie WB, Parsons HM, Markin A, Abrams J, and Habermann EB. (2012). Blood transfusion and cancer surgery outcomes: a continued reason for concern. *Surgery*, **152**, 344–54.
5. Goodnough LT, Levy JH, and Murphy MF. (2013). Concepts of blood transfusion in adults. *Lancet*, **381**, 1845–54.
6. Monsuez JJ, Charniot JC, Vignat N, and Artigou JY. (2010). Cardiac side-effects of cancer chemotherapy. *International Journal of Cardiology*, **144**, 3–15.
7. Limper AH. (2004). Chemotherapy-induced lung disease. *Clinical Chest Medicine*, **25**, 53–64.
8. Sadowska AM, Specenier P, Germonpre P, and Peeters M. (2013). Antineoplastic therapy-induced pulmonary toxicity. *Expert Reviews in Anticancer Therapy*, **13**, 997–1006.
9. Bitzan M, Anselmo M, and Carpineta L. (2009). Rituximab (B-cell depleting antibody) associated lung injury (RALI): a pediatric case and systematic review of the literature. *Pediatric Pulmonology*, **44**, 922–34.
10. Perazella MA. (2012). Onco-nephrology: renal toxicities of chemotherapeutic agents. *Clinical Journal of the American Society for Nephrology*, **7**, 1713–21.
11. Lam AQ and Humphreys BD. (2012). Onco-nephrology: AKI in the cancer patient. *Clinical Journal of the American Society for Nephrology*, **7**, 1692–700.
12. Howard SC, Jones DP, and Pui CH. (2011). The tumor lysis syndrome. *New England Journal of Medicine*, **364**, 1844–54.
13. Cairo MS, Coiffier B, Reiter A, and Younes A. (2010). Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *British Journal of Haematology*, **149**, 578–86.

14. McWhirter D, Kitteringham N, Jones RP, Malik H, Park K, and Palmer D. (2013). Chemotherapy induced hepatotoxicity in metastatic colorectal cancer: a review of mechanisms and outcomes. *Critical Reviews in Oncology/Hematology*, **88**, 404–15.
15. Schiff D, Wen PY, and van den Bent MJ. (2009). Neurological adverse effects caused by cytotoxic and targeted therapies. *Nature Reviews in Clinical Oncology*, **6**, 596–603.
16. Basch E, Prestrud AA, Hesketh PJ, et al. (2011). Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology*, **29**, 4189–98.
17. Krasin MJ, Constine LS, Friedman DL, and Marks LB. (2010). Radiation-related treatment effects across the age spectrum: differences and similarities or what the old and young can learn from each other. *Seminars in Radiation Oncology*, **20**, 21–9.
18. Westbury CB and Yarnold JR. (2012). Radiation fibrosis—current clinical and therapeutic perspectives. *Clinical Oncology*, **24**, 657–72.
19. Barsam SJ, Patel R, and Arya R. (2013). Anticoagulation for prevention and treatment of cancer-related venous thromboembolism. *British Journal of Haematology*, **161**, 764–77.

SECTION 21

Recovery from critical illness

PART 21.1

In-hospital recovery from critical illness

CHAPTER 377

Chronic critical illness

Catherine L. Hough

Key points

- Chronic critical illness (CCI) is common, with estimated point prevalence of over 100,000 patients in the United States, and expectations for a rapid rise.
- CCI encompasses much more than the respiratory system, with effects on metabolism, skin, brain, and neuromuscular function.
- During CCI, patients have a high burden of symptoms and impaired capacity to communicate their needs.
- Mortality and quality of life are generally poor, but highly variable, with one-year mortality over 50% and most survivors suffering permanent cognitive impairment and functional dependence.
- Caring for the chronically critically ill is a substantial burden both to patients' families, and to the health care system as a whole.

Introduction

For most patients in the intensive care unit (ICU), change happens quickly. However, there are patients—collectively termed the 'chronically critically ill'—who neither quickly resolve organ failures nor die, remaining dependent on mechanical ventilation and other life-sustaining therapies for weeks, months, or more. This chapter will discuss chronic critical illness (CCI), beginning with definitions and epidemiology. Clinical features and outcomes will be presented, as will the impact of CCI on family members and the health care system.

Definitions

As a state where a critically ill patient is no longer dying or recovering, CCI is easiest to recognize late, or in hindsight. Definitions generally focus on duration of critical illness of mechanical ventilation, ranging from ≥48 hours to ≥4 weeks of ventilator support. A consensus definition of prolonged mechanical ventilation, the condition most commonly associated with CCI, is ≥21 days of mechanical ventilation [1]. Since administrative data typically do not include precise duration of mechanical ventilation, alternative definitions have been developed for health services research using tracheotomy in combination with either ≥96 hours of mechanical ventilation or ICU length of stay ≥21 days [2]. Tracheotomy is an appealing marker of CCI; it is reliably coded in administrative data and represents both a commitment to ongoing life support as well as an expectation of need for ongoing ventilator support. However, utilization of tracheotomy is highly variable; inclusion in the definition may markedly underestimate CCI incidence. A pragmatic definition of CCI for clinical use suggests at least 10 days of mechanical ventilation with no expectation for imminent death or ventilator liberation [3].

Epidemiology

The incidence of critical illness is increasing in the United States, with an estimated 2.7 hospitalizations involving mechanical ventilation for each 1000 people each year, for a total of nearly 800,000 hospitalizations [4]. The number of patients receiving ≥96 hours of mechanical ventilation is also increasing, including nearly 40% of all patients receiving ventilation. The incidence of CCI is also rising, occurring in 4–10% of ICU admissions in the United States and United Kingdom [3]. In North Carolina, the incidence of CCI nearly tripled between 1993 and 2004 [5].

It may be challenging to identify a patient who will go on to develop CCI early in the course of acute illness. A 'typical' CCI patient initially looks like most critically-ill patients: aged 50–70 years, with pneumonia or sepsis, afflicted with several pre-morbid conditions, and severely ill. Certain factors are independently associated with CCI [6], duration of ventilation [7] or ICU stay [8]: ICU admission diagnoses (pneumonia, acute respiratory distress syndrome, aortic dissection/rupture, head injury, and intracranial haemorrhage); patient factors (age, prior functional status); and physiological variables (severity of illness scores, tachypnoea, hypoxaemia). However, models to predict CCI or even readiness for ventilator liberation, perform poorly [9].

Clinical features

Most CCI patients have respiratory failure requiring prolonged mechanical ventilation. A smaller proportion may require ongoing life support for other organ failures (e.g. vasopressor support, renal replacement therapy). In addition, the syndrome of CCI is marked by profound multisystem dysfunction. Acute brain dysfunction, in the form of coma and delirium, is common in CCI. Neuromuscular dysfunction (including atrophy, critical illness myopathy and neuropathy) is omnipresent in CCI and likely plays an important role in ventilator weaning. There are changes in body composition (including loss of lean muscle mass, increased fat, and anasarca) and complex neuroendocrine changes, with loss of pulsatile secretion of anterior pituitary hormones due to decreased hypothalamic stimulation [3].

Characteristic metabolic changes occur in CCI, including protein catabolism, hypoalbuminaemia, stress hyperglycaemia, and

bone hyper-resorption [10]. Cardiac dysfunction may accompany acute critical illness, exacerbated by baroreceptor dysfunction and deconditioning. Patients are at risk for infectious complications, due to loss of barriers, altered immune function, and exposure to multi-drug resistant organisms. Treatment factors, including immobility, fluid overload, under- or over-feeding, ventilator-associated lung injury, phlebotomy and transfusion, and heavy use of sedatives, may play important roles in occurrence and outcome of CCI.

CCI is marked by high levels of symptom distress. In one study of fifty CCI patients on mechanical ventilation, difficulty with communication was nearly universally endorsed, and was highly and frequently distressing for patients [11]. All 16 symptoms assessed were endorsed by at least half of the patients surveyed, and half of all patients rated their lack of energy, dry mouth, hunger, thirst, worry, sadness, and nervousness as moderate to severe.

Treatment

There is little empiric evidence to guide the care of CCI, either for specific processes of care, or for venues or models of care delivery. As CCI is typified by multisystem involvement, care should be integrated and interdisciplinary. Liberation from ventilation is a crucial component; observational studies have suggested that protocolized weaning by non-physician care providers is associated with marked reductions in weaning time [12]. Recently, a randomized controlled trial in a long-term acute care hospital (LTACH) demonstrated that a protocol of tracheotomy collar trials may be superior to pressure support [13]. Many questions remain about the 'best' approach to ventilator weaning in CCI. Similarly, there is little to help identify patients who may benefit from tracheotomy placement, and ideal timing remains uncertain [9].

A significant task in the care of CCI is prevention of complications. Processes of care that prevent infection (e.g. hand washing, isolation, avoidance of unnecessary antibiotics, and limiting catheter use) and skin breakdown require vigilance. There are important roles for nutritionists (e.g. prioritizing enteral feeds, targeting protein and caloric intake) despite minimal empiric evidence [10]. Early integration of rehabilitation therapies can help maintain focus on functional recovery. Equally important is palliative care to help address and alleviate symptom distress, to continue to re-explore goals of care, to enhance communication, and to plan for transitions in care beyond the acute care environment. Families are frequently ill informed about expected outcomes, including survival, functional impairment, and caregiving needs, with a high degree of discordance between anticipated and actual outcomes [3].

Outcomes

Understanding expected outcomes and matching care to patient values is especially important in CCI, given the cost, duration, and high symptom burden. Outcomes after CCI are variable, and may be magnified by heterogeneity of definition and cohort. For example, defining CCI by placement of tracheotomy for prolonged mechanical ventilation or by LTACH admission may identify a cohort with better outcomes since clinicians may select these treatments in patients with better anticipated survival.

Among ventilator-dependent patients with CCI, 30–54% of patients achieve ventilator liberation and discharge from acute care hospital [14]. Unfortunately, the risk of death remains high. One year survival ranges from 31–52% across definitions of CCI [14]. Initial discharge home is rare; multiple re-admissions and transfers between institutional settings are common after CCI [15]. Survivors have a high burden of functional impairment and dependence; studies have consistently shown that less than 12% of one-year survivors are capable of independent living. Survivors have persistent deficits in physical function, but many are too impaired to participate in follow-up, leading to an underestimate of physical impairment [3]. While outcomes are poor for most with CCI, there is considerably variability in likelihood and quality of survivorship. Patient factors, such as age, number of residual organ failures, and inciting factor for CCI, can identify patients at highest and lowest risk of death [16]. High quality care of the patient and caregiver requires recognizing likely outcome, discussing with family, and guiding care accordingly.

Impact on informal caregivers and the health care system

The cost of CCI is high, as experienced by patients, families, and the health care system. Studies of families show a high degree of depression and post-traumatic stress symptoms that may be long-lasting [17]. Family members report deterioration of their own physical health. The financial impact may be significant, from loss of work and medical costs, even among insured. Notably, negative effects on physical and mental health are seen in families who provide care at home as well as those using institutional care. Improving family outcomes is an important target of research in care of CCI, with studies underway of strategies to decrease distress.

CCI is a significant—and growing—challenge for the health care system. Accounting for less than 10% of all mechanically-ventilated patients, CCI patients use up to 40% of ICU beds and critical care resources. It has been estimated that overall health care costs of CCI surpassed 20 billion dollars in 2009 [2], and are continuing to rise. Cost-effectiveness is widely variable, given the broad range of expected outcomes, and is heavily driven by age. Since costs are most substantial early in the hospital course, early recognition of patients who are unlikely to gain value from prolonged mechanical ventilation and offering alternative goals of care is critically important.

Creating alternative models and venues of acute care delivery is important as well. In the United States, use of LTACHs after critical illness is rising rapidly [18], with increasing admissions among Medicare beneficiaries of 38.1 to 99.7 per 100,000 from 1997 to 2006. An increasing proportion of LTACH patients received mechanical ventilation over this period of time (16.4–29.8%). Despite suggestion that LTACH utilization may be an avenue to decrease costs and increase value of care to the CCI, a recent study of over 200,000 Medicare beneficiaries with CCI demonstrated that while LTACH care is associated with equivalent survival to short term acute care with decreased costs, payments are higher among LTACH patients due to an elevated cost-to-charge ratio [19]. Novel health care delivery approaches and venues may improve the future of care of CCI.

References

1. MacIntyre NR, Epstein SK, Carson S, et al. (2005). Management of patients requiring prolonged mechanical ventilation: report of a NAMDRC consensus conference. *Chest*, **128**(6), 3937–54.

2. Cox CE, Carson SS, Govert JA, Chelluri L, and Sanders GD. (2007). An economic evaluation of prolonged mechanical ventilation. *Critical Care Medicine*, **35**(8), 1918–27.
3. Nelson JE, Cox CE, Hope AA, and Carson SS. (2010). Chronic critical illness. *American Journal of Respiratory Critical Care Medicine*, **182**(4), 446–54.
4. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, and Kahn JM. (2010). The epidemiology of mechanical ventilation use in the United States. *Critical Care Medicine*, **38**(10), 1947–53.
5. Cox CE, Carson SS, Holmes GM, Howard A, and Carey TS. (2004). Increase in tracheostomy for prolonged mechanical ventilation in North Carolina, 1993–2002. *Critical Care Medicine*, **32**(11), 2219–26.
6. Estenssoro E, Reina R, Canales HS, et al. (2006). The distinct clinical profile of chronically critically ill patients: a cohort study. *Critical Care*, **10**(3), R89.
7. Seneff MG, Zimmerman JE, Knaus WA, Wagner DP, and Draper EA. (1996). Predicting the duration of mechanical ventilation. The importance of disease and patient characteristics. *Chest*, **110**(2), 469–79.
8. Zimmerman JE, Kramer AA, McNair DS, Malila FM, and Shaffer VL. (2006). Intensive care unit length of stay: benchmarking based on Acute Physiology and Chronic Health Evaluation (APACHE) IV. *Critical Care Medicine*, 3**4**(10), 2517–29.
9. Young D, Harrison DA, Cuthbertson BH, Rowan K, and TracMan C. (2013). Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial. *Journal of the American Medical Association*, **309**(20), 2121–9.
10. Schulman RC and Mechanick JI. (2012). Metabolic and nutrition support in the chronic critical illness syndrome. *Respiratory Care*, **57**(6), 958–77; discussion 77–78.
11. Nelson JE, Meier DE, Litke A, Natale DA, Siegel RE, and Morrison RS. (2004). The symptom burden of chronic critical illness. Critical Care Medicine, **32**(7), 1527–34.
12. Scheinhorn DJ, Chao DC, Stearn-Hassenpflug M, LaBree LD, and Heltsley DJ. (1997). Post-ICU mechanical ventilation: treatment of 1,123 patients at a regional weaning center. *Chest*, **111**(6), 1654–9.
13. Jubran A, Grant BJ, Duffner LA, et al. (2013). Effect of pressure support vs unassisted breathing through a tracheostomy collar on weaning duration in patients requiring prolonged mechanical ventilation: a randomized trial. *Journal of the American Medical Association*, **309**(7), 671–77.
14. Carson SS. (2012). Definitions and epidemiology of the chronically critically ill. *Respiratory Care*, **57**(6), 848–56; discussion 56–58.
15. Unroe M, Kahn JM, Carson SS, et al. (2010). One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. *Annuals of Internal Medicine*, **153**(3), 167–75.
16. Carson SS, Kahn JM, Hough CL, et al. (2012). A multicenter mortality prediction model for patients receiving prolonged mechanical ventilation. Critical Care Medicine, **40**(4), 1171–76.
17. Douglas SL and Daly BJ. (2003). Caregivers of long-term ventilator patients: physical and psychological outcomes. *Chest*, **123**(4), 1073–81.
18. Kahn JM, Benson NM, Appleby D, Carson SS, and Iwashyna TJ. (2010). Long-term acute care hospital utilization after critical illness. *Journal of the American Medical Association*, **303**(22), 2253–9.
19. Kahn JM, Werner RM, David G, Ten Have TR, Benson NM, and Asch DA. (2013). Effectiveness of long-term acute care hospitalization in elderly patients with chronic critical illness. *Medical care*, **51**(1), 4–10.

CHAPTER 378

Promoting physical recovery in critical illness

Gregory A. Schmidt and Kevin Doerschug

Key points

- ICU acquired weakness starts within the first day of critical care.
- Muscle dysfunction can cripple skeletal muscles, but also the diaphragm.
- Early ICU interventions can change long-term outcomes.
- Muscles should be stimulated: posture, physical therapy, minimal sedation, and active mobilization.
- Think liberation from the burdens of critical illness rather than protection of the sick.

Introduction

Many patients survive critical illness only to suffer profound debility, dependence on others for activities of daily living (ADLs), or inability to work. For example, survivors of the acute respiratory distress syndrome (ARDS) are often not limited by persistent decrements in lung function, but rather from neuromuscular weakness that interferes with daily activities and persists years after the critical illness subsides [1]. Intensive care unit (ICU)-acquired weakness (ICU-AW) is identified in roughly one-in-four survivors after one week of mechanical ventilation. Advancements in survival from critical illness coupled with a rise in the incidence of conditions like severe sepsis combine to produce a huge burden of post-ICU incapacity. Yet evidence is accumulating that these long-term ravages can be modified by clinicians' actions in the first week of critical illness. This chapter explores the factors that exacerbate muscle loss and strategies to preserve strength and function. We conclude with specific recommendations for building and nurturing a team to facilitate mobilization and recovery of even the sickest patients.

Pathophysiology of ICU-acquired weakness

A complete discussion of the mechanisms of ICU-AW is beyond the scope of this chapter. However, a brief review of pathophysiology and contributing factors will help practitioners understand how to promote physical recovery more effectively. Early electrophysiological studies of this syndrome identified axonal degeneration consistent with acute polyneuropathy in the setting of sepsis. Subsequent research revealed myopathy, as demonstrated by myosin loss in skeletal muscle, also contributes to ICU-AW. Two aspects of the time-course of ICU-AW are remarkable:

- Muscle is lost as early as the first day of critical illness [2].
- Weakness may persist for years [1].

Both accelerated muscle proteolysis as well as decreased muscle protein synthesis contribute to sepsis induced myopathy [3,4]. Importantly, muscle catabolism is opposed when muscles are actively contracting. In parallel, perhaps the greatest causal factor of ICU-AW is muscular silence, a hypothesis that may explain the contributory role of sedatives, neuromuscular blocking drugs, controlled mechanical ventilation, and bed rest. Exercise induces the production of transcription factors that ameliorate stress-induced atrophy.

Promoting recovery

There is ample evidence that the details of care provided in the ICU can be related to longer-term neuromuscular outcomes.

Avoiding harm

Knowledge of the factors associated with muscle weakness suggests several approaches to avoid compounding the effects of critical illness with iatrogenic harm. Ventilator settings that lead to fully passive mechanical ventilation are best avoided. While there may be some patients who are so ill that any activity provokes life-threatening oxyhaemoglobin desaturation or ventilator dyssynchrony, most patients should have settings adjusted so as to encourage inspiratory muscle activation. This is more an issue of choosing appropriate goals for ventilation, rather than selecting a particular mode, since even high levels of pressure-support are sufficient to produce diaphragm dysfunction. One approach is to gradually reduce the level of ventilatory support until the patient is making regular, but unlaboured and synchronized, inspiratory efforts, regardless of the arterial partial pressure of carbon dioxide.

In a randomized, controlled trial of ARDS, cis-atracurium infusion was associated with reduced mortality, decreased systemic inflammation, and a trend toward **less** ICU-AW [5]. One hypothesis for this is that patient-ventilator dyssynchrony resulted in excessive tidal volumes, which in turn lead to systemic inflammation, and that this was averted through short-term therapeutic paralysis. Clearly more work is needed to fully understand and guide neuromuscular blockade during critical illness. Until definitive work is

complete, many practitioners continue to avoid generalized use of these agents.

Most patients receiving mechanical ventilation receive sedative and analgesic medications aimed at improving patient-ventilator synchrony and relieving discomfort. Intravenous sedation serves to decrease patient movement: continuous sedative infusions may silence muscle to an extent resembling pharmacologic paralysis. Several trials have examined methods to decrease the impact of sedation during mechanical ventilation, with daily interruption of continuous sedative infusions [6] representing the most common strategy. Such practices decrease time on the ventilator and allow for more purposeful movement while on the ventilator, thus avoiding the muscle disuse that perpetuates ICU-AW. In addition to increasing patient movements, less sedation also facilitates more meaningful participation in physical therapy. Many of the interventions aimed to prevent complications and promote physical recovery have been gathered in the 'ABCDE' bundle:

> A = Awakening; B = Breathing trials coordinated; C = Choice of sedatives and analgesics; D = Delirium monitoring; and E = Early mobility and exercise [7].

Clinicians have historically viewed the active patient as an accident waiting to happen. Sedatives are often prescribed to keep the patient motionless in a misguided effort to maintain homeostasis. Caregivers hesitate to allow patient movement, fearing that this will impede ventilation or circulation, or dislodge supportive devices. Increasing evidence suggests that this fully supportive care does not maintain homeostasis, but rather allows for neuromuscular atrophy.

This attitude of over-protecting the fragile patient (as opposed to liberating them from noxious interventions) is seen also when seeking to 'wean' patients from mechanical ventilation. Clinicians are often slow to recognize that their patient no longer needs the ventilator. Protocols that initiate daily spontaneous breathing trials without the requirement of physician orders lead to more rapid extubation than those that require physician input [8]. These spontaneous breathing trials are more likely to lead to extubation when paired with daily awakening trials, and also reduce mortality [9]. While the effect of these practices on ICU-AW have not been specifically evaluated, it seems reasonable to assume that an awake and extubated patient is better prepared for physical recovery than one who remains tethered to the ventilator.

Many other devices have consequences for patient mobility. For example, it is easier to imagine walking with a critically-ill patient bearing a subclavian, rather than femoral, central venous catheter. Yet decisions regarding catheter site selection are usually dominated by concerns regarding anatomy, infection, bleeding, and thrombosis, rather than whether a given site will impede physical therapy. Similar issues surround the timing of tracheostomy or the pros and cons of inserting an arterial cannula. A remarkable example is the shift in philosophy surrounding extracorporeal life support. Historically, patients with catastrophic respiratory failure undergoing extracorporeal therapies have been deeply sedated, respecting the catastrophic cost of cannula disconnection. Now, there is increased recognition that, while alternative therapies (such as high frequency ventilation or lung-protective ventilation) generally preclude mobilization, extracorporeal support can potentially free the patient from sedation and even from the ventilator entirely, making physical therapy realistic and practical [10].

Thus, a crucial component of promoting physical recovery is to establish a culture of awareness surrounding the mobility impact of medical decisions. It is essential that caregivers recognize when patients can be freed of both drugs and devices and to institute protocols for sedative interruption, daily spontaneous breathing, and removal of invasive devices.

Early mobilization to promote recovery

Immobility leads to myopathy and weakness, thus mobility seems a reasonable defence against ICU-AW. Interestingly, even movements that don't require active muscle contraction are helpful. One study of continuous passive range of motion for nine hours daily during mechanical ventilation with neuromuscular blockade revealed that this simple intervention, applied unilaterally to a leg, prevented the muscle protein losses seen in the untreated leg [11].

A survey of physical therapy involvement in ICU patients revealed that few hospitals appear to emphasize this intervention [12]. Most require a specific physician consultation to initiate physical therapy, and only 10% of hospitals have established criteria to initiate physical therapy in the ICU. In summary, there is a significant spectrum of physical therapy utilization even in ICUs where it is available.

A few groups have sought to evaluate more aggressive physical therapy than that commonly provided during critical illness. In one study, 103 subjects that required mechanical ventilation for more than 4 days were prospectively enrolled for intervention [13]. A team that included a physical therapist, respiratory therapist, nurse, and critical care technician delivered therapy twice daily. Therapy was initiated when the subject was awake and free of catecholamine drips, the fraction of inspired oxygen was less than 60%, and PEEP no higher than 10 cm H_2O. During sessions, subjects progressed as tolerated from sitting on bed without support to sitting in chair, to ambulation. The study recorded 1449 activity events, nearly 600 of which included intubated patients. In sessions that involved subjects with an endotracheal tube, nearly half included ambulation. Importantly, no accidental extubations occurred, and other adverse events occurred in fewer than 1% of sessions. This study is reassuring that ambulating intubated patients can be safe and feasible. Although this is considered a landmark study, its implications are limited by the lack of a comparison group to evaluate efficacy. Further, this study enrolled subjects that had already received 4 days of mechanical ventilation and thus may have already suffered significant loss of strength.

A subsequent study addressed these limitations in a before-and-after study design as they implemented a standardized early mobility therapy protocol in seven ICUs [14]. With implementation of the early mobility protocol within 48 hours of intubation, physical therapy was initiated in 91% of patients compared with just 13% in the control arm. The early mobility protocol was also associated with significant decreases in ICU and hospital length of stay.

The first randomized, controlled, multicentred study of early mobility enrolled subjects within 72 hours of intubation, and specifically timed mobilization sessions to coincide with daily sedative interruptions [15]. Subjects in the intervention arm initiated physical therapy within 2 days of intubation, while the median time from intubation to first therapy session in the control arm was 7.4 days. The primary outcome was the rate of return to independent functional status at hospital discharge and the intervention was

significantly superior to standard care. This intervention also lead to more ventilator-free days and a shorter duration of delirium. Intervention subjects achieved important milestones previously thought unattainable during mechanical ventilation: 43% transferred to chair and 24% were able to walk—some as far as 30 m.

Barriers to mobilizing the critically ill

The evidence to support early mobilization is compelling, and continues to mount, yet widespread adoption of early mobilization remains heterogeneous. This failure of the medical community to fully embrace aggressive recovery programs in critical illness likely stems from some combination of fear of patient decompensation or injury and a persistent culture that lacks urgency to liberate patients from critical illness. Fortunately, these barriers are surmountable and these are addressed in the following section.

Safety of early ICU mobilization

The rigorous studies of early mobilization all demonstrate tremendous safety with the protocols implemented. Teams generally consist of at least three clinicians including physical therapist, nurse, and a third team member who can assist with patient stability. Additional safety comes from persistent, but careful progression through a mobility protocol that identifies suboptimal physiology that may limit the next step. One such progression, adapted from Schweickert [15], is shown in Table 378.1. During ambulation, a wheelchair pushed by a clinician provides additional safety by allowing quick access to a resting position should the patient develop fatigue or distress.

It is worth emphasizing that very ill patients still tolerate active physical therapy. For example, in one trial the first day of physical therapy averaged 1.5 days following intubation; therapy was provided on 89% of ventilator days; and in 23% of sessions patients were being treated for shock with vasoactive drug infusions [16]. Published ICU mobility protocols imbed stop criteria that temporarily defer initiation of a session, or halt sessions already in progress. Rather, the haemodynamic responses to mobility were monitored, and therapy halted or discontinued if significant changes occurred. Remarkably, only 4% of sessions were terminated for safety concerns [16]. With these measures in place, the initial trials of early ICU mobilization report few adverse events. The most commonly reported were periods of patient-ventilator asynchrony. Falls to knees without injury did not occur in two studies [14,15], but occurred rarely in another [13]. Accidental extubations were not seen in these early studies.

Table 378.1 Progression of ICU mobilization

Step 1 Unconscious patients	Passive range of motion, all limbs	
Step 2 Interactive patients	Active assisted and active independent ROM in supine position	Upright bed position, up to 30 minutes bd, temporally separated from ROM
Step 3 Absence of orthostasis	Upright sitting with, then without, support	Activities of daily living
Step 4 Able to sit without support	Sit-to-stand, up to 10 repetitions	Transfer from bed to chair
Step 5 Able to stand	Pre-gait exercises	Ambulation

Adapted from *The Lancet*, **373**(9678), Schweickert WD et al., 'Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial', pp. 1874–82. Copyright © 2009, with permission from Elsevier.

When implementing a new mobility culture, the champions should anticipate some resistance from clinicians unconvinced of safety. At times, such resistance arises from physicians, primary care clinicians, bedside nurses, and even family members. Leadership should invest in identifying those who support mobilization to encourage their support, but also work with sceptics to provide education and listen to concerns.

The risks of early mobilization, although rare, are immediate, obvious, and potentially catastrophic. In contrast, the benefits are delayed 2–3 weeks [15] and may never be witnessed by the intensive care team, leading some clinicians to 'first do no harm'. Furthermore, when occasional (but, ultimately, predictable with some frequency) adverse events complicate mobilization, there is a risk that an emotional, short-term-oriented response can threaten an entire mobility programme. ICU leadership must emphasize the foundation for mobilization; acknowledge prospectively that rare patients may be harmed; and be prepared to defend the mobility team if their role is questioned. In the event of a complication, a 'just culture' approach is encouraged, rather than finger-pointing.

With increasing recognition of the benefits of early mobilization patients, many institutions have developed ICU mobilization teams. Given the past trend of prolonged deep sedation during critical illness, any progress toward mobilization should be applauded. Merely awakening and participating in active range of motion is progress when it follows a culture of deep sedation and 'protective support'; nevertheless, this clearly falls short of ambulating 30 m while intubated. Thus, caregivers should not consider these early activity milestones as endpoints of ICU therapy. Critical illness is a degenerating disease. Without progress, further injury—in this discussion, weakness—will come. In a progressive culture of early ICU mobility, the caregivers should strive for progress, not simply supportive maintenance. This progressive culture represents a paradigm shift from past practices of excluding patients considered too sick to mobilize to a notion that the most severely-ill patients have the greatest needs for mobilization.

In addition to changing the culture of physical recovery in the ICU, critical care practitioners must work with caregivers beyond the ICU to ensure that recovery continues. In fact, at one institution, more than half of the patients that were able to walk in the ICU had a decrease in activity level on the first full ward day [17]. The reasons for this decrease in activity level were not examined in the study. However, it seems likely that an urgency to liberate the patients from the effects of critical illness was not sufficiently engrained in the culture beyond the ICU walls.

Adjuncts to early mobilization

With increasing attention to early promotion of physical recovery from critical illness, caregivers have applied novel equipment to this quest. Cycle ergometry, with passive or increasingly active motion, increases functional status at the time of ICU discharge [18]. Ergonomic lifting devices can support patients, further increasing safety and effectiveness of ICU ambulation (see Fig. 378.1). Many ICU bed manufacturers now make units specifically designed to facilitate upright posture and transfer to standing positions. As the

acceptance of ICU mobilization increases, equipment to aid the ambulation of critically-ill patients is becoming widely available.

If the beneficial impact of mobilization follows from provoking muscles to contract, perhaps neuromuscular electrical stimulation (NMES) could play a role, especially in patients who cannot otherwise be mobilized. NMES forces muscular contraction without requiring patient effort, so may be applicable for deeply sedated patients. NMES has been shown to preserve muscle mass during critical illness and prevent ICU-acquired weakness [19]. These results have not been seen consistently, however [20]. Conflicting results may represent differences in NMES methodology or other factors and thus further studies of NMES in critical illness are needed.

Conclusion

Many critically-ill patients will survive the acute crisis with limiting neuromuscular debility. Early interventions to reduce sedation, speed liberation from the ventilator, and enhance early physical therapy can improve long-term functional outcomes significantly. A team approach, engaged leadership, and administrative support are essential components for successful implementation.

Acknowledgements

Text credit for ABCDE mnemonic: Reproduced from Morandi A et al., 'Sedation, delirium, and mechanical ventilation: the 'ABCDE' approach', Current Opinion in Critical Care, 17, 1, pp. 43–49, Copyright © 2011 Wolters Kluwer Health Ltd, with permission.

Fig. 378.1 ICU mobility. An ICU mobility team assists a patient in respiratory failure. This team utilizes a specialized lifting device and harness that provides additional support and safety against falls.

References

1. Herridge MS, Tansey CM, Matte A, et al. (2011). Functional disability 5 years after acute respiratory distress syndrome. *New England Journal of Medicine*, **364**(14), 1293–304.
2. Levine S, Nguyen T, Taylor N, et al. (2008). Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *New England Journal of Medicine*, **358**(13), 1327–35.
3. Callahan LA and Supinski GS. (2009). Sepsis-induced myopathy. *Critical Care Medicine*, **37**(Suppl.10), S354–67.
4. Witt NJ, Zochodne DW, Bolton CF, et al. (1991). Peripheral nerve function in sepsis and multiple organ failure. *Chest*, **99**(1), 176–84.
5. Papazian L, Forel JM, Gacouin A, et al. (2010). Neuromuscular blockers in early acute respiratory distress syndrome. *New England Journal of Medicine*, **363**(12), 1107–16.
6. Kress JP, Pohlman AS, O'Connor MF, Hall JB. (2000). Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New England Journal in Medicine*, **342**(20), 1471–7.
7. Morandi A, Brummel NE, and Ely EW. (2011). Sedation, delirium and mechanical ventilation: the 'ABCDE' approach. *Current Opinion in Critical Care*, **17**(1), 43–49.
8. Ely EW, Bennett PA, Bowton DL, Murphy SM, Florance AM, and Haponik EF. (1999). Large scale implementation of a respiratory therapist-driven protocol for ventilator weaning. *American Journal of Respiratory Critical Care Medicine*, **159**(2), 439–46.
9. Girard TD, Kress JP, Fuchs BD, et al. (2008). Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*, **371**(9607), 126–34.
10. Turner DA, Cheifetz IM, Rehder KJ, et al. (2011). Active rehabilitation and physical therapy during extracorporeal membrane oxygenation while awaiting lung transplantation: a practical approach. *Critical Care Medicine*, **39**(12), 2593–8.
11. Griffiths RD, Palmer TE, Helliwell T, MacLennan P, and MacMillan RR. (1995). Effect of passive stretching on the wasting of muscle in the critically ill. *Nutrition*, **11**(5), 428–32.
12. Hodgin KE, Nordon-Craft A, McFann KK, Mealer ML, and Moss M. (2009). Physical therapy utilization in intensive care units: results from a national survey. *Critical Care Medicine*, **37**(2), 561–6; quiz 6–8.
13. Bailey P, Thomsen GE, Spuhler VJ, et al. (2007). Early activity is feasible and safe in respiratory failure patients. *Critical Care Medicine*, **35**(1), 139–45.
14. Morris PE, Goad A, Thompson C, et al. (2008). Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Critical Care Medicine*, **36**(8), 2238–43.
15. Schweickert WD, Pohlman MC, Pohlman AS, et al. (2009). Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*, **373**(9678), 1874–82.
16. Pohlman MC, Schweickert WD, Pohlman AS, et al. (2010). Feasibility of physical and occupational therapy beginning from initiation of mechanical ventilation. *Critical Care Medicine*, **38**(11), 2089–94.
17. Hopkins RO, Miller RR, 3rd, Rodriguez L, Spuhler V, and Thomsen GE. (2012). Physical therapy on the wards after early physical activity and mobility in the intensive care unit. *Physical Therapy*, **92**(12), 1518–23.
18. Burtin C, Clerckx B, Robbeets C, et al. (2009). Early exercise in critically ill patients enhances short-term functional recovery. *Critical Care Medicine*, **37**(9), 2499–505.
19. Routsi C, Gerovasili V, Vasileiadis I, et al. (2010). Electrical muscle stimulation prevents critical illness polyneuromyopathy: a randomized parallel intervention trial. *Critical Care*, **14**(2), R74.
20. Poulsen JB, Moller K, Jensen CV, Weisdorf S, Kehlet H, and Perner A. (2011). Effect of transcutaneous electrical muscle stimulation on muscle volume in patients with septic shock. *Critical Care Medicine*, **39**(3), 456–61.

CHAPTER 379

Promoting renal recovery in critical illness

Nattachai Srisawat and John A. Kellum

Key points

- Renal recovery post-acute kidney injury (AKI) can be classified as complete or partial recovery (chronic kidney disease (CKD)), based on the degree of renal function that returns.
- Evidence demonstrates that AKI can progress to CKD, and end stage renal disease (ESRD).
- There is no patient survival or renal recovery advantage for high intensity renal replacement therapy.
- Potential predictors of renal recovery include both of conventional markers (clinical variables, urine output, etc.) and novel biomarkers (pNGAL, uNGAL, uHGF, uCystatin C, pIL-6, pIL-8, pIL-10, pIL-18, pMIF, pTNFR-I, pDR-5, uIGFBP-7, uTIMP-2).
- Serum creatinine might not be a good marker for renal function due to the decreasing of muscle mass after the severe illness and other confounding factors.

Introduction

How to facilitate renal recovery is a key question in the management of acute kidney injury (AKI). Two large randomized controlled trials, the Acute renal failure Trial Network (ATN) study [1] and the Randomized Evaluation of Normal versus Augmented Level Renal Replacement Therapy (RENAL) study [2] have shown a significant number of AKI patients who failed to return to baseline renal function following an episode of AKI. Importantly, the rate of recovery was 3-fold different across these two trials suggesting that risk of non-recovery is variable and perhaps affected by treatment. This chapter explores the definition, mechanism, epidemiology, and outcome predictors of renal recovery with the goal of improving AKI outcomes.

How to define renal recovery?

First of all, an understanding of the definition of renal recovery is needed. In 2004, the Acute Dialysis Quality Initiative (ADQI) [3] proposed the following definition of renal recovery: 'complete renal recovery' was defined as return to pre-morbid renal function, and 'partial renal recovery' was defined as an improvement in **R**isk **I**njury **F**ailure **L**oss **E**nd stage renal disease (RIFLE) classification (R, I, or F) and not requiring long-term renal replacement therapy (RRT), but failing to return to baseline renal function'. Non-recovery was therefore defined as persistent requirement of RRT, or no change in RIFLE score during hospitalization. Since baseline renal function is hard to quantify precisely, most authors operationalize a return to baseline as a return to within 150% of baseline serum creatinine. Most of the studies evaluating AKI recovery have studied only patients receiving RRT. Therefore, renal recovery can be defined more simply as patients who are alive and dialysis-free. However, patients who die after coming off dialysis might also be considered as 'AKI non-recovery' and it is sometimes difficult to assess whether a patient dying after AKI has truly recovered renal function. The optimal duration of follow-up for patients with AKI needs to be defined. The consensus from the second ADQI conference suggests using from 60 to 90 days of follow-up for the evaluation of all-cause mortality.

Which parameter should be assessed to define renal function after renal recovery? Serum creatinine might not be a good marker to use due to the decreasing of muscle mass after the severe illness and other confounding factors. Therefore, the measurement of glomerular filtration rate by radioisotope clearance might be an alternative.

Partial recovery after AKI is particularly important because most of these patients will have, by definition, chronic kidney disease (CKD). If they did not have CKD prior to AKI, then this will be new onset CKD. We need to better understand what happens to these patients. Do they ultimately recover? Do they progress as other patients with CKD?

In summary, renal recovery can be defined as complete or partial recovery based on returning of renal function, while non-recovery generally includes patients who do not survive or who require chronic dialysis (Fig. 379.1).

Mechanisms of renal recovery and repair

The pathobiology of AKI appears to involve a complex interplay between tubular injury, renal haemodynamics, and inflammation (Fig. 379.2). Surviving renal proximal tubular epithelial cells (RPTCs) play a major role in the repair process and appear to follow a program which shares a number of similarities with the series of events observed during kidney development. RPTCs first appear to undergo dedifferentiation (i.e. loss of apical-basal polarity, lack of tight junctions, accompany with a decrease in the expression of epithelial cell marker and an increase in the expression of mesenchymal cell or fibroblast markers), and then proliferation. When the cell population has expanded sufficiently to physically replenish

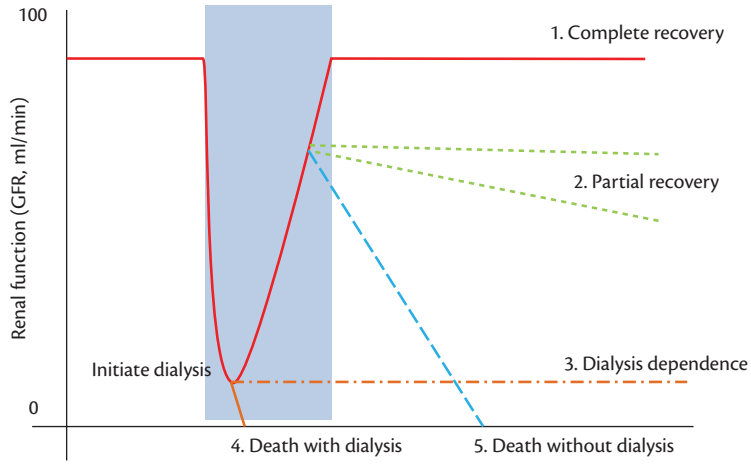


Fig. 379.1 Schematic showing the natural history of AKI. Patients who developed AKI may experience. (1) Complete recovery. (2) Partial recovery with progressive to CKD. (3) Development of ESRD (dialysis dependence). (4) Death with dialysis dependence. (5) Death without dialysis.
Data from Cerdá J et al., 'Epidemiology of acute kidney injury', *Clinical Journal of the American Society of Nephrology*, 2008, **3**(3), pp. 881–6.

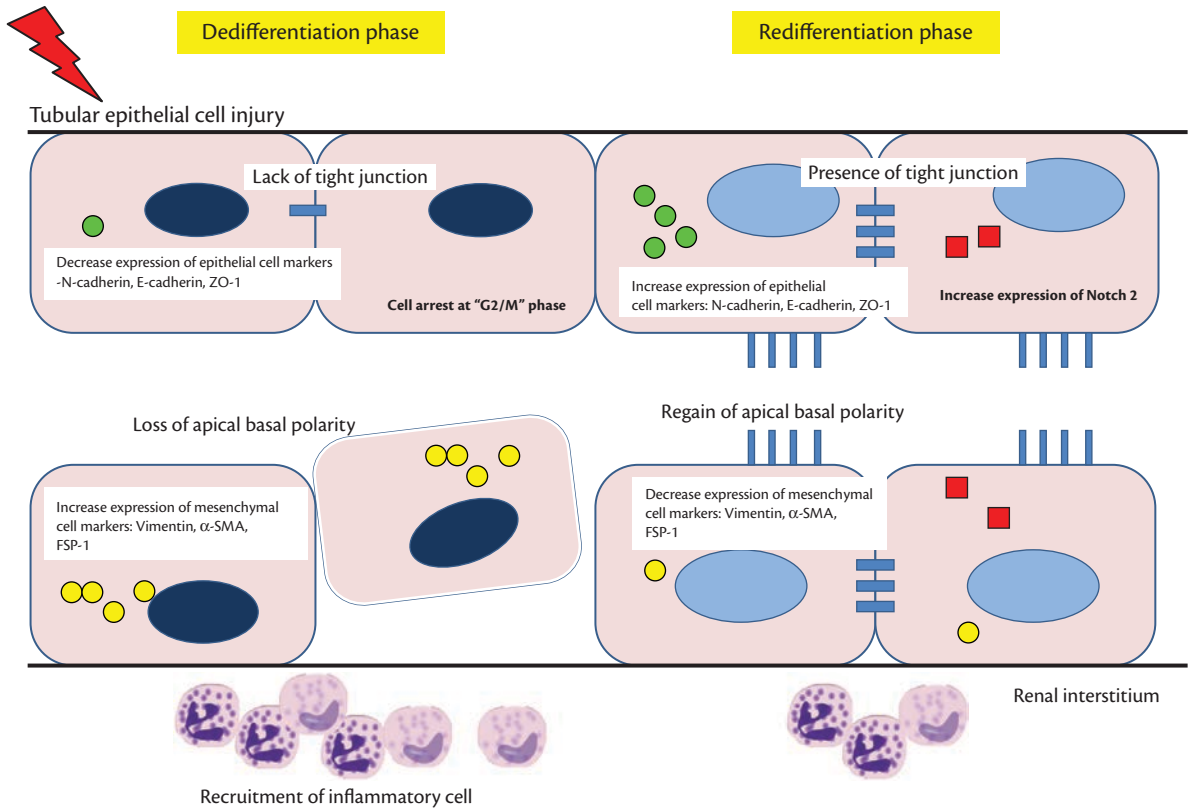


Fig. 379.2 Process of renal recovery after acute insult to tubular epithelial cells.
N-cadherin: neural-cadherin; E-cadherin: epithelial-cadherin; ZO-1, zona occludens-1; α-SMA, α-smooth muscle actin; FSP-1. fibroblast specific protein-1.

sloughed epithelium, cells undergo a redifferentiation process characterized by a decrease in mesenchymal cell markers and increase in epithelial cell markers to finally restore the physiologic function of RPTCs [4].

A number of growth factors such as the hepatocyte growth factor (HGF), epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), bone morphogenic protein-7 (BMP-7), and the transforming growth factor-β (TGF-β) help renal repair by interaction with the transmembrane receptors of the tubular epithelial cells. Ultimately, the renal repair process requires redifferentiation of transformed renal epithelial cell function to restore tubular morphology [5].

Various other mechanisms have been implicated in controlling the repair process [6], many of which could be exploited as diagnostic or therapeutic targets. Recently, a cell-cell communication mechanism that regulates development, tissue homeostasis and

repair has been identified to play a potential role in repair and regeneration after AKI—known as Notch [7]. Generally absent in the mature kidney, Notch is reactivated after AKI, and could be responsible for cellular differentiation, proliferation, and repair [8]. This notion is supported by studies from various laboratories independently observing a linkage between increased expression of Notch2 and its target Hes1, and increased proliferation renal tubular epithelial cells in the setting of various insults [9].

Another important mechanism is cell-cycle regulation. When epithelial cells, including those lining the proximal tubule become injured or even stressed, they may deviate from normal cell-cycle progression. Cells that become 'arrested' at G2/M may adopt a pro-inflammatory phenotype that is also pro-fibrotic [10]. There may also be a therapeutic value in blocking the initiation of G2/M arrest, or using of various agents to stimulate cell-cycle progression [11].

Epidemiology of renal recovery

Studies of AKI outcome have been heterogeneous in terms of patient populations, aetiologies of AKI, outcomes, and duration of follow-up. We can divide the studies into two major groups based on study population. First, studies have focused on patients who receive RRT, and considered renal recovery as dialysis independence. Almost all studies of this type have been conducted in the ICU setting. AKI outcomes from the major clinical trials show mortality rates ranged from 35 to 60% [1,2]. Unfortunately, these trials did not necessarily report how many patients died while still receiving RRT. The renal recovery rate among survivors of severe AKI (dialysis independence) varied from 75 to 90%. However, these statistics hide the fact that survival following severe AKI is poor and more patients die following discharge than enter chronic dialysis (Fig. 379.3).

Secondly, studies have focused on AKI more broadly and have performed long term follow up (more than 2 years). Most of these studies have included AKI across all severity groups, not only severe AKI. Outcomes usually included mortality, CKD and end-stage renal disease (ESRD) rates (per 100 person-years). The major obstacle to drawing conclusions from these studies as to the relationship between AKI and CKD or ESRD is the presence of various confounders that can affect long-term outcomes after AKI (Fig. 379.4).

Clinical predictors of recovery

One set of current tools for predicting renal recovery is the clinical severity scores. Uchino et al. [12] tested two general illness severity scores (APACHE II and SOFA), and four AKI-specific severity scores in 1742 patients as part of the BEST Kidney Study. Unfortunately, none of these scoring systems tested had a high level of discrimination or calibration to predict outcome for AKI patients. Thus, although not specifically tested, it seems unlikely that any of the current severity scores can provide good prediction for renal recovery. We still need a study that is directly designed to identify the factors associated with renal recovery.

Urine output is one of the conventional and oldest known biomarkers. Although oliguria is a common event in the ICU and urine flow is one of the diagnostic and staging criteria for AKI, only a few studies have focused on the role of urine output as a prognostic renal biomarker. A recent study by Macedo and colleagues [13] found olgiuric patients without change in serum creatinine have an increased mortality, increased dialysis requirements, and longer lengths of ICU and hospital stay than patient without AKI. Subsequent analysis data from the BEST kidney study [14] found that the urine output had area under the receiver operating characteristics curve (AUC-ROC) for successful discontinuation of CRRT was 0.85, although it fell to 0.67 when diuretics were used.

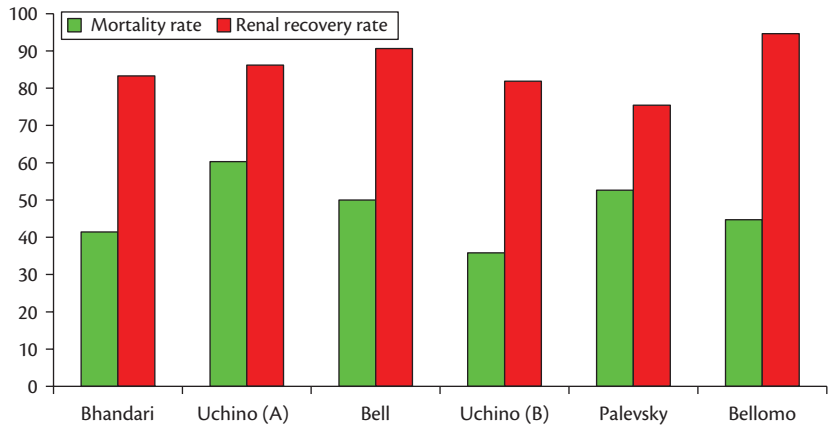


Fig. 379.3 Summary of hospital mortality and renal recovery (dialysis independence) in survivors from severe AKI (including only studies with more than 1000 patients). Data from: Bhandari S and Turney JH, 'Survivors of acute renal failure who do not recover renal function', *Quarterly Journal of Medicine*, 1996, **89**, pp. 415–21; Uchino S et al., 'Acute renal failure in critically-ill patients: a multinational, multicenter study', *Journal of the American Medical Association*, 2005, **294**, pp. 813–18; Bell M et al., 'Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure', *Intensive Care Medicine*, 2007, **33**, pp. 773–780; Uhino S et al., 'Continuous renal replacement therapy: a worldwide practice survey. The beginning and ending supportive therapy for the kidney (B. E. S. T. kidney) investigators', *Intensive Care Medicine*, 2007, **33**, pp. 1563–70; Palevsky PM et al., 'Intensity of renal support in critically-ill patients with acute kidney injury', *New England Journal of Medicine*, 2008, **359**, pp. 7–20; and Bellomo R et al., 'RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients', *New England Journal of Medicine*, 2009, **361**, pp. 1627–38.

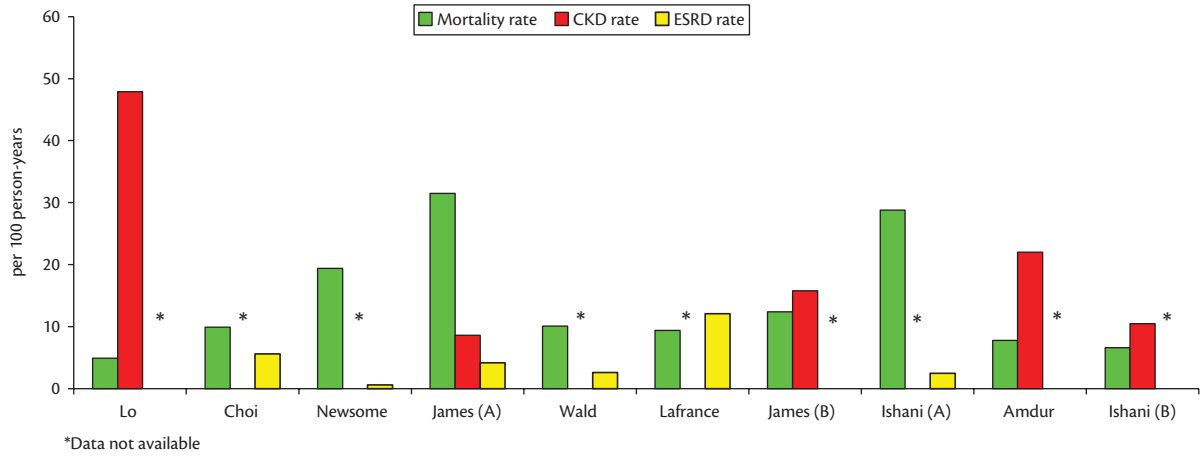


Fig. 379.4 Summary of long-term AKI outcomes (mortality, chronic kidney disease (CKD), and end stage renal disease (ESRD). Rate are shown as 100 person-years from AKI. Only studies with more than 1000 patients were included.

Data from: Lo LJ et al., 'Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease', *Kidney International*, 2009, **76**, pp. 893–9; Choi AI et al., 'Long-term clinical consequences of acute kidney injury in the HIV-infected', *Kidney International*, 2010, **78**, pp. 478–85; Newsome BB et al., 'Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction', *Archives of Internal Medicine*, 2008, **168**, pp. 609–16; James MT et al., 'Acute kidney injury following coronary angiography is associated with a long-term decline in kidney function', *Kidney International*, 2010, **78**, pp. 803–9; Wald R et al., 'University of Toronto Acute Kidney Injury Research Group. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis', *Journal of the American Medical Association*, 2009, **302**, pp. 1179–85; James MT et al., 'Alberta Kidney Disease Network. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study', *Lancet*, 2010, **376**, pp. 2096–103; Ishani A et al., 'Acute kidney injury increases risk of ESRD among elderly', *Journal of the American Society of Nephrology*, 2009, **20**, pp. 223–8; Amdur RL et al., 'Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis', *Kidney International*, 2009, **76**, pp. 1089–97; and Ishani A et al., 'The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death', *Archives of Internal Medicine*, 2011, **171**, pp. 226–33.

Novel biomarkers for recovery

Based on the physiology of renal recovery, a number of biomarkers have the potential to predict renal recovery. Neutrophil Gelatinase-Associated Lipocalin (NGAL) has been extensively studied in the field of AKI. In the late phase of AKI, NGAL is believed to play a role as a growth and differentiation factor for restoring tubular epithelial function with the assistance of siderophore-iron complexes. However, most of the previous studies have tested plasma/urine NGAL as a marker for early diagnosis of AKI, and only a few studies which have examined plasma/urine NGAL as a prognosticate marker of clinical outcome.

We examined plasma of patients on the first day of which they experienced severe AKI (defined as RIFLE-F) [15]. The elevated pNGAL levels were associated with renal non-recovery. Although the absolute predictive value of pNGAL alone was only fair (AUC 0.74). These data are most notable for two reasons. First, because AKI can cause CKD and ESRD, decisions regarding long-term care (for example, use of dialysis, vascular access, and follow-up) are often made in a piecemeal approach. If objective metrics coupled with clinical assessment can improve prognostic accuracy, a better informed decision can be made for survivors of AKI. Secondly, the association between pNGAL and renal non-recovery suggests that renal injury is ongoing, and even if a patient is undergoing dialysis, therapies directed at mitigating ongoing injury may have a role in AKI treatment.

We also conducted the **Bio**logical **Mark**ers of Recovery for the Kidney (BioMarK) study as an ancillary to the ATN study [16]. Urine samples were collected on days 1, 7, and 14 from 76 patients who developed AKI and required renal support. We explored whether levels of uNGAL, uHGF, uCystatin C, uIL-18, uNGAL/MMP-9, and urine creatinine could predict subsequent renal recovery. Patients who recovered had higher uCystatin C on day 1 and lower uHGF on day 7 and 14. For predicting recovery, decreasing uNGAL and uHGF in the first 14 days was associated with greater odds of renal recovery.

Using the BioMarK cohort, 11 plasma inflammatory and apoptosis markers on renal recovery, and mortality in 817 critically-ill subjects receiving RRT [17] was also examined.

The study found that increased concentrations of plasma IL-8, IL-18 and TNFR-I were independently associated with slower renal recovery [adjusted hazard ratio (AHR) range for all markers, 0.70–0.87]. Higher concentrations of IL-6, IL-8, IL-10 and IL-18; MIF; TNFR-I and DR-5 were associated with mortality. In an analysis of multiple markers simultaneously, increased IL-8 and TNFR-I were associated with slower recovery, and increased IL-8; MIF and TNFR-I were associated with mortality [17].

Finally, markers of cell-cycle arrest have recently been shown to predict human AKI [18,19]. Insulin-like growth factor-binding protein (IGFBP)-7 and tissue inhibitor of metalloproteinase (TIMP)-2 are both linked to cell cycle arrest during the very early phases of cell injury. In response to cell stress IGFBP7 and TIMP2 are expressed in the tubular cells. IGFBP7 directly increases the expression of p53, p21, and TIMP2 stimulates p27 expression. These effects are conducted in an autocrine and paracrine manner and the p proteins in turn, block the effect of the cyclin dependent protein kinase complexes (CyclD-CDK4 and CyclE-CDK2) on the cell cycle promotion, thereby resulting in transient cell cycle arrest. It is likely that this effect is protective when temporary and helps avoid injured cells from dividing, which can result in apoptosis of both daughter cells. However, prolonged cell cycle arrest may lead to maladaptive repair and fibrosis. Supporting this, Kashani et al. using a large cohort of critically-ill patients at risk for AKI, found that a urinary [TIMP-2]·[IGFBP7] value above 2.0 was associated

with almost a four-fold increased risk of major adverse kidney events at 30 days [17].

Strategies to facilitate renal recovery

Mode of renal replacement therapy and renal recovery

ATN [1] and RENAL [2], have provided high-quality data to help understanding of the impact of RRT on renal recovery. Unfortunately, there appears to be no patient survival or renal recovery advantage for high intensity RRT. At day 28, survivors in the RENAL study demonstrated a 13.3% rate of RRT dependence, compared with 45.2% in the ATN study. At day 60, 24.6% of survivors in the ATN study were still receiving RRT. Table 379.1 shows a direct comparison of the two trials. Overall, the cohorts were closely matched and yet survival to day 60 and recovery of renal function (off dialysis) by day 28 was substantially better in RENAL.

Much has been made of the earlier start of treatment in RENAL compared with ATN in terms of time from ICU admission (2.1 versus 6.7 days), yet the BUN at the start of therapy (another surrogate for timing) was nearly identical. Another difference between the two trials that could have accounted for the differences in outcomes was the exclusive use of CRRT as the initial mode of RRT in RENAL compared with a strategy that allocated patients to CRRT only if they were haemodynamically unstable (on vasopressor therapy) in ATN.

Fluid balance and renal recovery

There is an emerging body of evidence that the consequences of fluid overload, in excess of 5–10% of bodyweight, in critically-ill patients are significant with worsening organ dysfunction and mortality [20]. Fluid overload increases the risk of intra-abdominal compartment syndrome and increase renal venous pressure. Renal interstitial oedema can lead to decrease glomerular filtration, distorted tissue architecture, and impaired tissue perfusion.

Bouchard et al. [20] analysed the data from The **P**rogram to **I**mprove **C**are in **A**cute **R**enal **D**isease (PICARD). They found patients with fluid overload experienced significantly higher mortality within 60 days of enrolment. Among dialysed patients, survivors had significantly lower fluid accumulation when dialysis was initiated compared w4ith non-survivors after adjustments for dialysis modality and severity of illness. The adjusted odds ratio for death associated with fluid overload at dialysis initiation was 2.07 (95% CI 1.27–3.37).

Table 379.1 Comparison of the RENAL and ATN studies

	RENAL	ATN
Age (years)	64.5	59.6
Male (%)	946 (64.6%)	793 (70.6%)
Baseline eGFR ≤ 60 mL/min*	473 (58%)	361 (41.6%)
Mechanical ventilation	1082 (73.9%)	905 (80.5%)
Severe sepsis	723 (49.3%)	708 (63%)
Oliguria	874 (59.7%)	877 (78%)
Time in ICU prior to randomization (days)	2.1	6.7
BUN at start of RRT (mg/dL)	65.8	66.3
Alive at Day 60	57.5%†	47.4%
Dialysis independence at Day 28 (survivors only)	86.7%	54.8%

*% Based on number with known baseline.

†Kaplan–Meier estimate (55.3% were alive at 90 days).

Data from; VA/NIH Acute Renal Failure Trial Network, Palevsky PM et al., 'Intensity of renal support in critically ill patients with acute kidney injury', *New England Journal of Medicine*, 2008, **359**(1), pp. 7–20; and RENAL Replacement Therapy Study Investigators, Bellomo R et al., 'Intensity of continuous renal-replacement therapy in critically ill patients', *New England Journal of Medicine*, 2009, **361**(17), pp. 1627–38.

Conclusion

Increasing evidence demonstrates that AKI may result in important long-term adverse outcomes. Therefore, methods to identify which patients are likely to develop this complication are urgently needed as are treatments to mitigate this risk. Biomarkers may also be useful in predicting renal recovery and may therefore play an important role in disease management.

References

1. VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, et al. (2008). Intensity of renal support in critically ill patients with acute kidney injury. *New England Journal of Medicine*, **359**(1), 7–20.
2. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, et al. (2009). Intensity of continuous renal-replacement therapy in critically ill patients. *New England Journal of Medicine*, **361**(17), 1627–38.
3. Bellomo R, Ronco C, Kellum JA, Mehta RL, and Palevsky P. (2004). Acute Dialysis Quality Initiative workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Critical Care*, **8**(4), R204–12.
4. Shibe S and Cantley LG. (2008). Epithelial-mesenchymal-epithelial cycling in kidney repair. *Current Opinions on Nephrology and Hypertension*, **17**, 379–85.
5. Liu KD and Brakeman PR. (2008). Renal repair and recovery. *Critical Care Medicine*, **36**, S187–92.
6. Singbartl K and Kellum JA. (2012). AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. *Kidney International*, **81**,819–25.
7. Sirin Y and Susztak K. (2012). Notch in the kidney: development and disease. *Journal of Pathology*, **226**, 394–403.
8. McCright B. (2003). Notch signaling in kidney development. *Current Opinions in Nephrology and Hypertension*, **12**, 5–10.
9. Kobayashi T, Terada Y, Kuwana H, et al. (2008). Expression and function of the Delta-1/Notch-2/Hes-1 pathway during experimental acute kidney injury. *Kidney International*, **73**(11), 1240–50.
10. Yang L, Besschetnova TY, Brooks CR, Shah JV, and Bonventre JV. (2010). Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. *National Medicine*, **16**(5), 535–43.
11. Cianciolo C, Skrypnyk NI, Brilli LL, et al. (2013). Histone deacetylase inhibitor enhances recovery after AKI. *Journal of American Society Nephrology*, **24**(6), 943–53.
12. Uchino S, Bellomo R, Morimatsu H, et al. (2005). External validation of severity scoring systems for acute renal failure using a multinational database. *Critical Care Medicine*, **33**, 1961–7.
13. Macedo E, Malhotra R, Bouchard J, Wynn SK, and Mehta RL. (2011). Oliguria is an early predictor of higher mortality in critically ill patients. *Kidney International*, **80**(7), 760–7.

14. Uchino S, Bellomo R, Morimatsu H, et al. (2009). Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. *Critical Care Medicine*, **37**(9), 2576–82.
15. Srisawat N, Murugan R, Lee M, et al. (2011). Genetic and Inflammatory Markers of Sepsis (GenIMS) Study Investigators. Plasma neutrophil gelatinase-associated lipocalin predicts recovery from acute kidney injury following community-acquired pneumonia. *Kidney International*, **80**(5), 545–52.
16. Srisawat N, Wen X, Lee M, Kong L, Elder M, Carter M, et al. (2011). Urinary biomarkers and renal recovery in critically ill patients with renal support. *Clinical Journal of American Society Nephrology*, **6**(8), 1815–23.
17. Murugan R, Wen X, Shah N, et al., for the Biological Markers for Recovery of Kidney (BioMaRK) Study Investigators. (2014). Plasma inflammatory and apoptosis markers are associated with dialysis dependence and death among critically ill patients receiving renal replacement therapy. *Nephrology Dialysis Transplantation*, **29**(10), 1854–64.
18. Kashani K, Al-Khafaji A, Ardiles T, et al. (2013). Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Critical Care*, **17**(1), R25.
19. Bihorac A, Chawla LS, Shaw AD, et al. (2014). Validation of Cell-Cycle Arrest Biomarkers for Acute Kidney Injury Using Clinical Adjudication. *American Journal of Respiratory Critical Care Medicine*, **189**(8), 932–9.
20. Bouchard J, Soroko SB, Chertow GM, et al. (2009). Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney International*, **76**(4), 422–7.

CHAPTER 380

Recovering from critical illness in hospital

Saxon Ridley

Key points

- Between 10% and 27% of patients survive intensive care unit (ICU), but die before hospital discharge. Some of these deaths may be avoidable.
- Complications and adverse events after ICU increase patient discomfort, hospital length of stay and costs.
- Such complications can be mitigated by attention to detail before and after ICU discharge.
- Processes and delivery of care are more important than specific treatment intervention.
- Comprehensive communication and handover at discharge is probably the most important element in ensuring smooth transition to the general ward.

Introduction

Discharge from the intensive care unit (ICU) is only the start of the patient's convalescence. Adverse events including mortality and complications can occur on the general ward before hospital discharge. Ward mortality after intensive care ranges between 10 and 27% [1,2]. Clinical deterioration on the general ward leads to increased lengths of stay, costs, and longer patient recovery. If serious, such relapses may prompt re-admission to intensive care. Post ICU mortality, clinical deterioration on the ward, and ICU re-admission are dependent upon events before or after ICU discharge.

Patient morbidity after ICU discharge

Classification

The problems besetting patients following discharge to the general ward may be classified in at least three ways.

Post-intensive care syndrome

Because of the wide range of problems that may affect critical illness survivors, Needham et al. [3] proposed that the term 'Post Intensive Care Syndrome' should be used. The syndrome may affect both the patient and their family; the problems fall into three categories:

- Mental health (e.g. anxiety, depression and post-traumatic stress disorder (PTSD)).
- Cognitive impairment (causing decreased executive function, poor memory, attention defects, and reduced mental processing).
- Physical impairment (due to alterations in pulmonary and neuromuscular function).

Organ system classification

While any organ dysfunction can potentially slow a patient's recovery, the most relevant organ systems for the survivors of ICU are pulmonary, neuromuscular, physical function, psychiatric, and cognitive.

Pulmonary

Reductions in lung volumes, compliance and diffusion capacity will occur after acute lung injury and the adult respiratory distress syndrome (ARDS). Fortunately these are usually mild and in the longer term (i.e. after hospital discharge) recover. However, while on the general ward inadequate respiratory reserve combined with laryngeal dysfunction will predispose to pulmonary infections. Decreased diffusion capacity is inversely related to the duration of mechanical ventilation [4].

Neuromuscular

Critical illness polyneuropathy and/or myopathy may develop in up to 50% of ICU patients with sepsis, multiple organ failure, or prolonged mechanical ventilation [5]. This may severely disable patients by impeding walking or respiratory capacity after ICU discharge. Abnormalities within the axon, neuromuscular junction and muscle have all been implicated and may be caused by inflammatory axonal injury, muscle breakdown, sodium channel dysfunction, and failure of mitochondrial energy production. Predisposing factors on ICU include hyperglycaemia, systemic inflammatory response syndrome, sepsis, and multiple organ failure [5,6].

Physical function

Virtually all ICU survivors suffer some degree of physical dysfunction in the first week after discharge from ICU. A cohort of previously healthy ARDS survivors had a 40% decrease in their activities of daily living (ADLs) 28 days after ICU discharge [7]. Specific ICU related risk factors for physical impairment include exposure to systemic corticosteroids, new ICU acquired illnesses, and slow resolution of lung injury in the ICU.

Psychiatric

General ICU survivors suffer a median 28% (range 8%–57%) prevalence of clinically significant depressive symptoms in studies using a validated questionnaire [8]. Patient risk factors include pre ICU psychiatric symptoms, younger age, poorer education, and being female. ICU-related risk factors include poor recall of the ICU stay, traumatic or delusional ICU memories, and level of ICU sedation.

Cognitive

Duration of ICU delirium has been associated with cognitive impairment at 1 year [9]. Brain atrophy has been observed on

magnetic resonance images (MRIs) of critically ill patients with delirium, but it is unclear whether atrophy is a risk factor for, or an effect of, a common neurological insult. Potential ICU related risk factors include hypoglycaemia, hypoxemia, hypotension, and sedation.

Pathological classification

Post ICU problems can be classified by relating the adverse event to the original ICU admission diagnosis:

- Same pathology or disease process precipitates the clinical deterioration (e.g. another exacerbation of acute pancreatitis).
- New, but related pathology (e.g. enterocutaneous fistula following bowel resection, atrial fibrillation following an oesophagogastrectomy).
- New and unrelated pathology (e.g. pulmonary embolism, cardiovascular accident, chest infection following abdominal surgery).
- Exacerbation of pre-existing co-morbidities (e.g. chronic renal failure or chronic obstructive pulmonary disease).

Avoidance and amelioration

While some post-ICU complications are unavoidable, many may be prevented by ensuring a smooth transition from ICU to the general ward. Processes rather than specific interventions are more important.

Prior to ICU discharge

- **Minimizing the impact of the general supportive measures**: avoiding hyperglycaemia, without implementing tight glucose control, may reduce critical illness polyneuropathy and/or myopathy. Although corticosteroids and neuromuscular blocking agents are not consistently associated with critical illness polyneuropathy and/or myopathy, these drugs are best used only when necessary. Lighter sedation or daily breaks may prevent PTSD [10]. Screening for and treating delirium (e.g. reducing benzodiazepine use) and preventing hypoglycaemia may help preserve cognitive function and offset psychiatric problems.
- **Completion of critical care**: with the higher nurse to patient ratio on ICU, advanced treatments such as tracheostomy care and renal replacement therapy can be safely applied. There is conflicting evidence as to whether decannulation prior to ICU discharge adversely affects mortality. However, tracheostomies are commonly associated with prolonged length of ICU stay and hence complications of critical illness. If possible, it may be safer for the patient to be decannulated on ICU. Although patients with tracheostomy may be stable medically, their nursing requirements may not be met on a busy general ward.
- **Rehabilitation**: prior to discharge or as early as possible, a short clinical assessment to determine the patient's risk of developing physical and non-physical morbidity should be performed [11]. The reassessment should pay particular attention to:
  - *Physical, sensory and communication problems*—e.g. unable to get out of bed independently or mobilize over short distances, obvious significant physical or neurological injury, lack of cognitive functioning to continue exercise independently, requiring ≥ 35% oxygen, presence of pre-morbid respiratory or mobility problems.
  - *Underlying factors*—e.g. as pre-existing psychological or psychiatric issues (e.g. substance abuse, low-self-esteem, poor or low self-image and/or body image issues, relationship difficulties including those with the family and/or carer).
  - *Symptoms that have developed during the critical care stay*—e.g. delusions, intrusive memories, anxiety, panic episodes, nightmares, flashbacks, or depression.

Early rehabilitation on the ICU improves short-term physical function [12]. However, timing is important as rehabilitation is most effective when started as early as possible (i.e. before ICU or hospital discharge).

At ICU discharge

- **Effective communication**: a fundamental component of safe transition to the ward is effective communication between the critical care team and ward team. A formal structured handover of care will ensure that nothing is omitted and should include [11]:
  - Summary of critical care stay, including diagnosis and treatment.
  - Monitoring and investigation plan.
  - Plan for ongoing treatment, including drugs, nutrition, and therapies, infection status and any agreed limitations of treatment (e.g. Do Not Resuscitate (DNR) orders).
  - Physical and rehabilitation needs.
  - Psychological and emotional needs.
  - Specific communication or language needs.
  - Quantifying prognosis in general terms including whether the patient is suitable for re-admission to ICU, usefully reinforces the underlying expectations of outcome.
- **Timing**: increased pressure for ICU beds may result in premature discharge of patients, who may then be at an increased risk of adverse events. Night-time discharges to the general ward are associated with higher hospital mortality, independent of illness severity or discharge Therapeutic Intervention Scoring System scores [13]. Also weekends may predispose to excess discharges so that patient load is adjusted to ICU capacity. Patients discharged in the early weekend (00:00 Friday to 23:59 Saturday) had a greater risk of dying (24.6% versus 17.7%) and re-admission to ICU (17.5% versus 10.1%) [14].

After ICU discharge

- **Location**: for some recovering ICU patients, their requirements for on-going care are too great to be safely managed on the general ward. Under such circumstances stepping down to an intermediate care area (e.g. High Dependency Care Unit in the UK) can provide a useful bridge to prevent adverse outcomes that may have otherwise occurred. Such intermediate care areas are most useful in countries where the provision of critical care beds (measured in terms of ICU bed numbers per 100,000 population) is relatively poor, such as the UK. Intermediate care areas are ideally suited to monitoring patients and managing single organ failure. They can ensure that the ICU survivor continues on a positive course. For example, cardiac surgical re-admissions before cohorting in a step down unit over a 1 year period ranged from 6.7 to 8.9%. After six months of cohorting such patients, the re-admission rate fell to 4% [15].
- **Follow-up**: critical care outreach services (in the UK), rapid response teams (in the USA) and medical emergency teams (in

Australia) aim to improve the management of acutely deteriorating patients on the hospital ward. Part of their role is to oversee the progress of patients recently discharged from ICU. Critical care outreach services reduce deaths, cardiac arrests, hospital length of stay, ICU length of stay and cost [16]. Outreach services may also facilitate ICU re-admission where appropriate. Compared with contemporaneous patients admitted to the same ICU, critical care outreach visits were associated with a significantly higher re-admission rate (risk ratio 1.43) [17].

Re-admission to ICU

Importance

Re-admission to intensive care in the same hospital admission is a measure of critical care quality. Re-admission is demoralizing for patient and family, associated with clinical deterioration and an increase in hospital mortality. Furthermore re-admission denies critical care resources to other patients and will increase costs.

Re-admission rate

Re-admission rates vary depending upon case mix, delivery of care and local resources. Prior to 2000, re-admission rates were reported at 5–16% [18]. However, more recent figures suggest that the re-admission rates may be lower at 4.6% (6024/129674 UK patients [1] and 3632/79090 Canadian patients [19]).

Risk factors

Factors present on ICU that are significantly associated with subsequent re-admission are [18]:

- Weakness (e.g. previous cerebrovascular accident (CVA), deficit from Guillain–Barré or critical illness weakness).
- History of respiratory or cardiac disease.
- Colonization with a resistant organism.
- History of depression.
- Age >65 years.

The reasons for re-admission were most commonly impairments of organ systems:

- Respiratory (39%).
- Cardiovascular (18%).
- Neurological (15%).
- Gastrointestinal (11%).
- Metabolic (8%).
- Septic (7%).
- Haematological (5%).

Outcome

The mortality of re-admitted patients is higher than that of patients who experience a single ICU admission. The patient's physiological reserve has been degraded during the first ICU admission and the patients are less fit to survive a second episode of critical illness. The decision to re-admit a patient is an evaluation of the patient's ability to mount a satisfactory response against new pathophysiological insults. Causes of death on the ward are usually nosocomial infections (mainly respiratory), relapse of primary illness (e.g. stroke, cancer, heart failure) and progressive global deterioration.

Minimizing re-admissions

Avoiding complications and adverse events after ICU discharge will reduce ICU re-admissions. One of the most useful tasks around ICU discharge is to formally record the patient's prognosis including whether ICU re-admission is warranted should a relapse occur. Between 13% and 16% patients have DNR orders established during the ICU stay [19]. Outreach teams can help facilitate discussions about DNR orders so that ICU re-admission at the point of, or shortly after, cardiac arrests is avoided.

Conclusion

Preventing complications and adverse events after ICU discharge is dependent upon processes and delivery of care rather than specific therapeutic interventions. There are simple measures that can be taken on ICU (e.g. initiating rehabilitation, completing critical care by avoiding premature discharges) to improve the patient's chances of a smooth convalescence. Probably the most important aspect of safe transfer to the general ward is comprehensive handover of the patient's care to the receiving team. Continued follow-up by the critical care services will supplement communication and improve timely decision making.

References

1. Harrison DA, Brady AR, and Rowan K. (2004). Case mix, outcome and length of stay for admissions to adult, general critical care units in England, Wales and Northern Ireland: the Intensive Care National Audit & Research Centre Case Mix Programme Database. *Critical Care*, **8**, R99–111.
2. Williams TA, Dobb GJ, Finn JC, et al. (2008). Determinants of long-term survival after intensive care. *Critical Care Medicine*, **36**, 1523–30.
3. Needham DM, Davidson J, Cohen H, et al. (2012). Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Critical Care Medicine*, **40**, 502–9.
4. Schelling G, Stoll C, Vogelmeier C, et al. (2000). Pulmonary function and health-related quality of life in a sample of long-term survivors of the acute respiratory distress syndrome. *Intensive Care Medicine*, **26**, 1304–11.
5. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, and Needham DM. (2007). Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Medicine*, **33**, 1876–91.
6. Hermans G, De Jonghe B, Bruyninckx F, and Van den Berghe G. (2009). Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *Cochrane Database System Reviews*, **1**, CD006832.
7. Angus DC, Clermont G, Linde-Zwirble WT, et al. (2006). Healthcare costs and long-term outcomes after acute respiratory distress syndrome: a phase III trial of inhaled nitric oxide. *Critical Care Medicine*, **34**, 2883–90.
8. Davydow DS, Gifford JM, Desai SV, Bienvenu OJ, and Needham DM. (2009). Depression in general intensive care unit survivors: a systematic review. *Intensive Care Medicine*, **35**, 796–809.
9. Girard TD, Jackson JC, Pandharipande PP, et al. (2010). Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Critical Care Medicine*, **38**, 1513–20.
10. Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, and Hall JB. (2003). The long-term psychological effects of daily sedative interruption on critically ill patients. *American Journal of Respiratory Critical Care Medicine*, **168**, 1457–61.
11. National Institute for Health and Clinical Excellence. (2009). Rehabilitation after critical illness, NICE Clinical Guideline 83.

Available at: https://www.nice.org.uk/guidance/cg83 (accessed 25 May 2014).
12. Needham DM, Korupolu R, Zanni JM, et al. (2010). Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Archives of Physical Medical Rehabilitation*, **91**, 536–42.
13. Beck DJ, McQuillan P, and Smith GB. (2002). Waiting for the break of dawn? The effects of discharge time, discharge TISS scores and discharge facility on hospital mortality after intensive care. *Intensive Care Medicine*, **28**, 1287–93.
14. Obel N, Schierbeck J, Pedersen L, et al. (2007). Mortality after discharge from the intensive care unit during the early weekend period: a population-based cohort study in Denmark. *Acta Anaesthesiologica Scandinavia*, **51**, 1225–30.
15. Cepero KA. (2010). CS71 Impact of cardiac surgical step-down on critical care readmissions. *Critical Care Nurse*, **30**, e18.
16. Devita MA, Bellomo R, Hillman K, et al. (2006). Findings of the first consensus conference on medical emergency teams. *Critical Care Medicine*, **34**, 2463–78.
17. Harrison DA, Gao H, Welch CA, and Rowan KM. (2010). The effects of critical care outreach services before and after critical care: a matched-cohort analysis. *Journal of Critical Care*, **25**, 196–204.
18. Paratz J, Thomas P, and Adsett J. (2005). Re-admission to intensive care: identification of risk factors. *Physiotherapy Research International*, **10**, 154–63.
19. Priestap FA and Martin CM. (2006). Impact of intensive care unit discharge time on patient outcome. *Critical Care Medicine*, **34**, 2946–51.

PART 21.2

Complications of critical illness

CHAPTER 381

Physical consequences of critical illness

Margaret S. Herridge and Jane Batt

Key points

- Functional dependencies and decreased health-related quality of life are important consequences of critical illness and are related to Intensive Care Unit acquired weakness (ICU-AW) and a broad range of physical disabilities.
- Physical morbidities may not be reversible.
- Functional limitations may vary by age group, ICU length of stay, and burden of comorbid illness.
- ICU-AW is likely related to upregulation of the ubiquitin proteasome pathway with differential repair of muscle and nerve injury across different risk groups.
- Family caregivers also experience psychological morbidity and are important risk modifiers of patient outcome over time.

Background

Critical illness causes decrements in physical and neuropsychological function, incurs increased health care utilization and cost, and compromises the mental health of family caregivers [1–4]. Disability may not be remediable and may lead to a change in disposition secondary to acquired functional dependencies.

Physical health and outcome measures after critical illness

The evolution of our understanding of physical disability after critical care has progressed from an emphasis on early cardiopulmonary physiological outcomes to generic health-related quality of life (HRQoL). Early data reported significant decrements in physical function without elucidation of major contributing factors. More recent data support the link between ICU-AW and physical functioning captured as the physical component score of the SF-36 and modified by neurocognitive dysfunction and mood disturbances [1-4]. Currently, there is an emphasis on functional independence as a key patient- and family-centred outcome and how this informs HRQoL across patients of different age and underlying health.

Health-related quality of life

HRQoL is a cornerstone of the outcomes literature, but it is also intensely personal and may have important limitations in its ability to inform the nuances of rehabilitation programs.

The ARDS outcomes literature is intriguing because of the relatively homogenous nature of its outcomes compared with other groups of critically ill patients. In 1994, McHugh and her colleagues reported on pulmonary function and HRQoL using the Sickness Impact Profile (SIP). SIP scores rose in the first 3 months and only slightly thereafter and patients' pulmonary symptoms were only modestly associated with overall disability [5]. Weinert et al also reported functional impairment in their lung injury survivors with important decrements in role-physical and physical function domains of the SF-36 [6]. Davidson and investigators evaluated differences in health-related quality of life in ARDS survivors and comparably ill controls using the SF-36 and a pulmonary disease specific measure (St. Georges Respiratory Questionnaire (SGRQ)). Like other reports, all domains of the SF-36 were reduced, with the largest reduction in the role-physical domain. Although ARDS survivors scored worse on the SGRQ compared to other critically ill patients, it was uncertain whether this was lung-related or due to other extrapulmonary contributors [7].

Another HRQoL measure, the quality of health and well-being (QWB), was employed by Angus and colleagues [8] to measure quality-adjusted survival in ARDS survivors in the first year after hospital discharge. The mean QWB scores for their ARDS cohort was lower than a control population of patients with cystic fibrosis and when scores were disaggregated, the most common complaints were musculoskeletal and constitutional. Orme and colleagues [9] evaluated HRQoL and pulmonary function outcomes in ARDS patients treated with higher tidal volume versus lower tidal volume ventilation strategies. Similar to other studies, each group reported important reductions in physical functioning and although minor pulmonary function abnormalities were recorded and correlated with decreased HRQoL, the relative importance of the pulmonary contribution to the reported disability was unclear.

Long-term functional disability

Impaired physical function is reported in many papers over many years by a variety of investigators. These findings are also clearly persistent. Davidson reported these outcomes at 23 months after critical illness [7] and Herridge et al have noted persistent physical limitation at 2 and again at 5 years after ICU discharge [1] Physical dysfunction, partially or completely attributed to ICU-AW, may contribute to the reported reduction in the physical component score (PCS) of the SF-36.

In survivors of sepsis and critical illness, Iwashyna and others noted a persistent and incremental reduction in function compared to premorbid status. Using a study sample of older patients (median age 77), they reported the acquisition of 1.57 new limitations (CI 0.99–2.15) for those who had no limitations prior to their episode of critical illness and for those with some antecedent disability further decrements were noted. Physical decline persisted for at least 8 years after the episode of sepsis and clearly represented a pivotal decline in the patients' independent function [3].

Recently, Unroe and coworkers reported on new and persisting morbidity after chronic critical illness [2]. Patients had a mean age of 55, were unemployed, retired or disabled at the time of recruitment and had at least 2 comorbid illnesses. Only 9% of this cohort was alive and living independently at one year and negative risk prognosticators included more comorbid disease, older age, and discharge to a post-acute care facility. The mean cost per patient was $306,135 (SD, $285,467) for an estimated $3.5 million per independently functioning survivor at 1 year.

Neuromuscular dysfunction

The concept of a continuum of weakness has been borne out by recent work. Muscle injury begins within hours of the initiation of mechanical ventilation [10], is demonstrable with bedside testing at one week after ICU admission using the MRC scoring system [11] and persists with limitation for years after ICU discharge.

ICU-AW is ubiquitous in severe lung injury and complex critical illnesses and contributes to poor long-term function. A Round Table Conference developed a classification framework for ICU-AW [12] where ICU-AW is comprised of a nerve or muscle lesion or a combination of each.

Critical illness polyneuropathy

In 1984, Bolton and colleagues first described Critical Illness Polyneuropathy (CIP) in 5 critically ill patients requiring prolonged mechanical ventilation [13]. Patients had a primary axonopathy on electrophysiological testing with clinical manifestations of a mixed sensorimotor neuropathy. CIP occurs in a variable proportion of longer stay ICU patients (40%–100%) and primarily affects the limb and respiratory muscles. Limb involvement is symmetrical, and affects lower extremity, proximal muscle groups preferentially.

Aetiology and pathophysiology

SIRS and sepsis

CIP is associated with microcirculatory derrangement and axonal injury and occurs commonly in sepsis. Recent work demonstrates increased E-selectin on the endoneurial and epineurial vessels of peripheral nerves in septic patients with evidence of mediation by pro-inflammatory cytokines such as TNF-α and IL-1 [14].

Hyperglycaemia

Hyperglycaemia is an important risk factor for ICU-AW. Van den Berghe and others reported that tight glycaemic control in a surgical population reduced CIP, from 51.9% in control subjects to 28.7% among insulin treated patients [15]. The pathophysiology of tight glycaemic control and neuroprotection is unclear, but emerging insights include a protective effect on mitochondria and the deleterious effect of oxidant injury and apoptosis. Deranged nitric oxide may also play a role. Asymmetric dimethylarginine inhibits nitric oxide production and is an independent predictor of mortality in critically ill patients. Siroen et al showed recently that insulin modulates levels of asymmetric dimethylarginine and this may be an additional pathway by which insulin improves this outcome. Insulin may play a key role by inhibiting pro-inflammatory transcription factors that hasten neuroregeneration in critical illness [16].

Pharmacological agents

It is unclear whether we can implicate specific drug exposures in the pathogenesis of ICU-AW. Early reports of treatment in status asthmaticus suggested a link between neuromuscular dysfunction and the use of neuromuscular blockers and systemic corticosteroids. However, these concerns have not been borne out by recent reviews. Reports linking aminoglycoside, vasopressor, and renal replacement therapy use with neuromuscular dysfunction are confounded by the coexistence of sepsis or SIRS and inability to establish a causal link. In a recent randomized controlled study by Papazian et al, early exposure to 48 hours of paralytic therapy in patients with severe ARDS did not confer additional risk for weakness in the ICU survivors as assessed by the Medical Research Council score assessing strength [17].

Critical illness myopathy

The incidence of Critical Illness Myopathy (CIM) varies between 48 to 96% based on muscle biopsy and includes critical illness myopathy, acute quadriplegic myopathy, thick filament myopathy and necrotizing myopathy. It is characterized most commonly by a diffuse, non-necrotizing myopathy associated with fatty degeneration of muscle fibres, atrophy, and fibrosis. Patients are paretic and unable to wean and the clinical presentation may be indistinguishable from CIP. Only muscle biopsy can differentiate between these lesions.

Selective loss of myosin filaments in association with corticosteroid or neuromuscular blocker exposure and immobility is characteristic of thick filament myopathy. This may be a precursor to acute necrotizing myopathy since this form of CIM may progress to myonecrosis. Acute necrotizing myopathy is characterized by extensive myonecrosis with vacuolization and phagocytosis of muscle fibres and occurs with multiple organ dysfunction.

The pathophysiology of CIM involves derranged membrane excitability, inflammation, and catabolism evidenced by an observed increase in urinary nitrogen loss. There is evidence for the upregulation of the calpain and ubiquitin proteolytic pathways and this occurs in concert with an increase in apoptosis.

Inactivity in critically ill patients propagates inflammatory mediators that cause the following: protein loss in differentiated muscle cells; promotion of oxidative injury and disruption of insulin receptor signalling leading to impairment of myofibril growth and repair [18]. IL-1, IL-6 and TNF- μ have pro-inflammatory properties, augment proteolysis and have been implicated in muscle degradation, loss of muscle mass, and decrease in strength. IL-10 may play a role in mediating apoptosis and myocyte proteolysis through the inhibition of pro-inflammatory mediators. There is also evidence of muscle membrane inexcitability related to inactivation of sodium channels at the resting potential (sodium channelopathy). Allen and colleagues recently reported altered muscle-fibre excitability and muscle membrane dysfunction as the primary abnormality in CIM.

Clinical phenotypes in critical illness and the spectrum of disability

Recent cohort studies and administrative datasets suggest that heterogeneous disability after critical illness may be organized into discrete aetiologically neutral clinical phenotypes with different risks and recovery trajectories over weeks and months after critical illness.

Ubiquitous injury

The imbalance between protein synthesis and protein degradation appears to be universal in critical illness. Proteolysis in diaphragm and muscles of the axial skeleton occur within hours of mechanical ventilation and appear ubiquitous. Levine and colleagues [10], in their landmark work, noted that patients from very diverse clinical groupings had similar muscle injury related to upregulation of the ubiquitin-proteosome pathway. In further studies, these same investigators reported important decreases in myosin heavy chains and atrophic AKT-FOXO signalling play pivotal roles in myofibre atrophy and decreased diaphragm force generation. Other investigators have highlighted the induction of autophagy and mitochondrial dysfunction in human muscle as nonspecific contributors to muscle injury. These important observations support the hypothesis that muscle injury is not specifically linked to underlying disease or aetiology.

Differential repair

Muscle injury may be inevitable, but repair appears variable across patient groups with most recovery occurring by 6 to 12 months after critical illness [1]. The observation of variable outcome reinforces the construct of a spectrum of disability related to age, comorbidities and duration of ICU stay. The current literature supports these as key determinants of functional independence and HRQoL [1-4]. It is possible that these simple patient and clinical characteristics may act as proxies for nerve and muscle reserve and/or organ injury that predated the critical illness.

Additional physical morbidity

ICU-AW and neuropsychological dysfunction represent major disabilities. However, many other physical consequences of critical illness, although less frequent, may also affect physical HRQoL. These have been evaluated most comprehensively in ARDS survivors and include pulmonary dysfunction, entrapment neuropathy, late tracheal stenosis, heterotopic ossification, and cosmetic changes that have been linked to emotional outcomes, social isolation, and sexual dysfunction (Fig. 381.1) [1].

Pulmonary function abnormalities

The lung is a very resilient organ after severe ARDS. Most survivors have normal or near normal pulmonary function and when there are impairments, these are typically mild restrictive changes and a mild associated reduction in diffusion capacity [1,5,9]. Orme et al reported abnormal pulmonary function associated with decreased health-related quality of life one year following hospital discharge [9] and Neff and colleagues reviewed 30 studies that evaluated pulmonary function in ARDS survivors [19] and found important variability in the proportion of patients with obstructive (0%–33%) and restrictive (0%–50%) defects and compromised diffusion capacity (33%–82%). Herridge and collaborators showed normal to near normal pulmonary function achieved by 6 months to one-year after ICU discharge with continued stability over the 5-year study period. Evaluation of detailed chest imaging in these patients also showed minimal structural change to the pulmonary parenchyma at 5 years after ICU discharge [1,20]. Population heterogeneity may account for this broad spectrum of

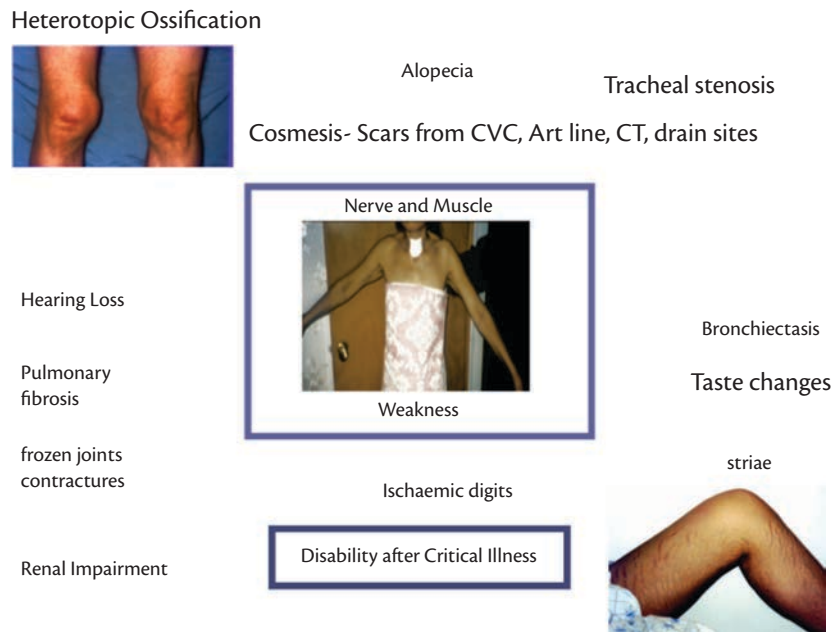


Fig. 381.1 The spectrum of disability after an episode of critical illness. ICU Acquired weakness is the central physical morbidity but other, less frequent issues are also noted here.

Courtesy of Margaret Herridge.

pulmonary dysfunction and specifically to evolving definitions or severity of ARDS, different ventilatory strategies, prior lung disease or smoking.

Entrapment neuropathy and joint contractures

The prevalence of peroneal and ulnar nerve palsies was six percent in the Toronto ARDS Outcomes study [1]. A small proportion of patients were affected, but when these nerve palsies occurred, they represented an often devastating injury with a prolonged recovery. In some cases, these injuries precluded the patients' ability to return to their original work. Contractures also contribute importantly to impaired long-term rehabilitation after critical illness.

Heterotopic ossification

Heterotopic Ossification (HO) is the deposition of para-articular ectopic bone and is associated with polytrauma, burns, pancreatitis, and ARDS and in the context of paralysis and prolonged immobilization. The prevalence of HO in the Toronto ARDS cohort was 5% and all patients had large joint involvement with the subsequent development of functional dependencies [1]. Survivors of critical illness should be evaluated for this since it may be modifiable with surgical debridement.

Cosmesis

Critical illness transforms the patient's physical appearance and some patients suffer enormous emotional distress from their altered appearance which leads to social isolation and sexual dysfunction. Examples include scars from complex wound infections, occipital (Fig. 381.2) or sacral ulcers related to immobility, laparotomy, chest tube, central line, arterial line and tracheostomy insertion, burns, striae from volume overload, and facial scars from prolonged non-invasive mask ventilation.

Caregiver and family burden in critical illness

Critical illness affects the entire family and caregivers represent important risk modifiers for patient outcome. Recent data show most ICU survivors who required long-term mechanical ventilation still required the assistance of a family caregiver one year after their critical illness. Current published evidence suggests that the provision of complex care after critical illness may have a negative effect on caregivers, and may jeopardize their HRQoL outcomes. Caregivers may also be at risk for post-traumatic stress disorder emotional distress, burden, depression, and anxiety.

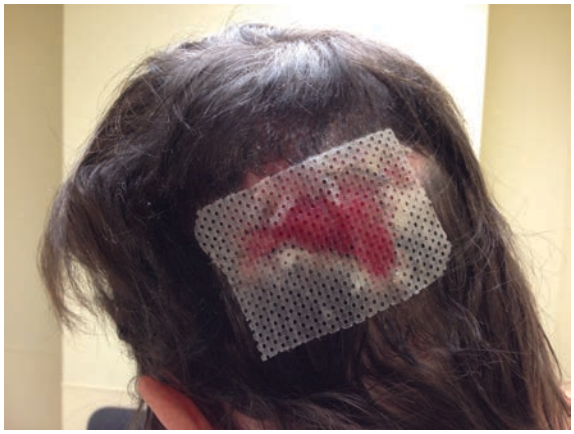


Fig. 381.2 Persistent occipital bed sore in survivor of complex critical illness 1 year after ICU discharge.
Courtesy of RECOVER program.

Conclusion

Patients sustain important disability after critical illness, regardless of inciting aetiology. ICU-AW is the most prevalent physical sequela and many would argue is ubiquitous. Emerging literature would suggest that there are different risk phenotypes based on age, burden of comorbid illness and duration of ICU stay and within these groups, there may be differential injury and repair of muscle and nerve injury. This observation may have important implications for risk stratification and the development of rehabilitation models that are better tailored to individual need and outcome trajectory. Family caregivers develop significant mood disorders and since they are important risk modifiers of outcome, need to be integrated into family-centred post ICU care and follow-up programs.

References

1. Herridge MS, Tansey CM, Matte A, et al. (2011). Functional disability 5 years after acute respiratory distress syndrome. *New England Journal of Medicine*, **364**(14), 1293–304.
2. Unroe M, Kahn JM, Carson SS, et al. (2010). One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. *Annuals of Internal Medicine*, **153**(3), 167–75.
3. Iwashyna TJ, Ely EW, Smith DM, and Langa KM. (2010). Long-term cognitive impairment and functional disability among survivors of severe sepsis. *Journal of the American Medical Association*, **304**(16), 1787–94.
4. Pandharipande PP, Girard TD, Jackson JC et al. (2013). Long-term cognitive impairment after critical illness. *New England Journal of Medicine*, **369**(14), 1306–16.
5. McHugh LG, Milberg JA, Whitcomb ME, Schoene RB, Maunder RJ, and Hudson LD. (1994). Recovery of function in survivors of the acute respiratory distress syndrome. *American Journal of Respiratory Critical Care Medicine*, **150**(1), 90–4.
6. Weinert CR, Gross CR, Kangas JR, Bury CL, and Marinelli WA. (1997). Health-related quality of life after acute lung injury. *American Journal of Respiratory Critical Care Medicine*, **156**(4,Pt 1), 1120
7. Davidson TA, Caldwell ES, Curtis JR, Hudson LD, and Steinberg KP. (1999). Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. *Journal of the American Medical Association*, **281**(4), 354–60.
8. Angus DC, Musthafa AA, Clermont G, et al. (2001). Quality-adjusted survival in the first year after the acute respiratory distress syndrome. *American Journal of Respiratory Critical Care Medicine*, **163**(6), 1389–94.
9. Orme J, Jr., Romney JS, Hopkins RO, et al. (2003). Pulmonary function and health-related quality of life in survivors of acute respiratory distress syndrome. *American Journal of Respiratory Critical Care Medicine*, **167**(5), 690–4.
10. Levine S, Nguyen T, Taylor N, et al. (2008). Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *New England Journal of Medicine*, **358**(13), 1327–35.
11. De Jonghe B, Sharshar T, Lefaucheur JP, et al. (2002). Paresis acquired in the intensive care unit: a prospective multicenter study. *Journal of the American Medical Association*, **288**(22), 2859–67.
12. Stevens RD, Marshall SA, Cornblath DR, et al. (2009). A framework for diagnosing and classifying intensive care unit-acquired weakness. *Critical Care Medicine*, **37**(10), S299-S308.
13. Bolton CF, Gilbert JJ, Hahn AF, and Sibbald WJ. (1984). Polyneuropathy in critically ill patients 1. *Journal of Neurological Neurosurgery Psychiatry*, **47**(11), 1223–31.

14. Fenzi F, Latronico N, Refatti N, and Rizzuto N. (2003). Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders. *Acta Neuropathology* (*Berlin*), **106**(1), 75–82.
15. Van den BG, Wouters P, Weekers F, et al. (2001). Intensive insulin therapy in the critically ill patients. *New England Journal of Medicine*, **345**(19), 1359–67.
16. Siroen MP, van Leeuwen PA, Nijveldt RJ, Teerlink T, Wouters PJ, and van den BG. (2005). Modulation of asymmetric dimethylarginine in critically ill patients receiving intensive insulin treatment: a possible explanation of reduced morbidity and mortality? *Critical Care Medicine*, **33**(3), 504–10.
17. Papazian L, Forel JM, Gacouin A, et al. (2010). Neuromuscular blockers in early acute respiratory distress syndrome. *New England Journal of Medicine*, **363**(12), 1107–16.
18. Winkelman C. (2004). Inactivity and inflammation: selected cytokines as biologic mediators in muscle dysfunction during critical illness 1. *AACN Clinical Issues*, **15**(1), 74–82.
19. Neff TA, Stocker R, Frey HR, Stein S, and Russi EW. (2003). Long-term assessment of lung function in survivors of severe ARDS. *Chest*, **123**(3), 845–53.
20. Wilcox ME and Herridge MS. (2010). Long-term outcomes in patients surviving acute respiratory distress syndrome. *Seminar on Respiratory Critical Care Medicine*, **31**(1), 55–65.

CHAPTER 382

Neurocognitive impairment after critical illness

Ramona O. Hopkins and James C. Jackson

Key points

- Neurocognitive impairment after critical illness is highly prevalent, occurring in up to 60% of patients.
- Neurocognitive impairment after critical illness is persistent, with evidence suggesting that it is likely permanent in some cases.
- Neurocognitive impairment after critical illness is often diffuse and affects multiple domains of functioning including memory, attention, and executive functioning.
- A number of mechanisms of injury and associated risk factors for neurocognitive impairment have been identified including inflammation and hypoxia.
- The development of interventions to improve neurocognitive impairment is a high priority both during and after critical illness and specific interventions are beginning to show promise in reducing such impairment.

Introduction

In the past several decades the number of survivors of critical illness has increased, at least in part due to a sustained and concerted effort by the critical care community to improve survival. A large number of studies over the past 20 years indicate surviving critical illness is not benign, as many survivors will develop long-term physical, neurocognitive, and psychiatric morbidities that adversely impact functional and quality of life outcomes. A recent systematic review of ~25 prospective investigations in critically-ill cohorts, including populations of medical, surgical, sepsis, and acute respiratory distress syndrome (ARDS) patients found a high prevalence of neurocognitive impairments months to years after hospital discharge [1–3]. Fig. 382.1 shows prevalence in neurocognitive impairments in representative studies in several critically-ill populations. Most neurocognitive outcome studies to date are small single centre cohort studies, but similar findings of severe and persistent neurocognitive impairment were recently reported in a large single centre study [4] and a large prospective multi-centre cohort study [5].

Onset of neurocognitive impairments

Several longitudinal cohort studies in older adults that assessed cognitive function before and after critical illness indicate that the onset of neurocognitive impairments occurs after intensive care unit (ICU) admission [2,3]. In older sepsis patients from the Health and Retirement Study in which neurocognitive function was assessed before and after sepsis, moderate to severe new neurocognitive impairment and new functional limitations were associated with severe sepsis [2]. The new neurocognitive impairments and functional limitations remained present years after ICU discharge (measured 1, 2, and 3 years after hospital discharge) and were severe enough that they resulted in increased utilization of caregiver support, increased admission to a nursing home, and depression in these patients. A study in elderly Medicare beneficiaries found critical illness was associated with development of dementia after accounting for risk factors [3]. During the three year follow-up period, new diagnosis of dementia occurred in 17.8% of the sepsis survivors. Independent risk factors for dementia included factors associated with critical illness including severe sepsis or infection, renal replacement therapy, and neurologic dysfunction. Importantly, older age increased the dementia prevalence in individuals who were 85 years or older (33%), which is almost double the rate of the group as a whole [3]. Not only are the neurocognitive impairments new, but as the data from the previously mentioned studies suggest, the impairments are severe and adversely impact patients' functional abilities [2,3] in a manner that is significantly limiting, as is characteristically observed in dementia. For example, the severity of the cognitive impairments is similar to the severity of impairment in individuals with mild Alzheimer's disease or moderate traumatic brain injury [4]. Thus, one adverse consequence of critical illness is development of new severe neurocognitive impairments.

Neurocognitive impairments occur not just in older individuals, but are prevalent across all age ranges in adults, highlighting the fact that cognitive deficits in survivors of critical illness are not a function of advanced age. Data from a recent study found 34% of patients' age <49 years had cognitive impairments at 12 months a rate that was similar to older patients (50–64 years and >65 years) and cognitive impairments were common even in those without significant medical comorbidity [4]. A recent systematic review found the prevalence of neurocognitive impairment was 11–62% of critically-ill patients in studies that used standard neuropsychological tests [1]. In the five studies that administered only cognitive screening tests or questionnaires to assess neurocognitive function, the prevalence of cognitive impairment was somewhat lower—ranging from 11 to 56%. While these rates are broadly similar, the authors note 'in general studies with

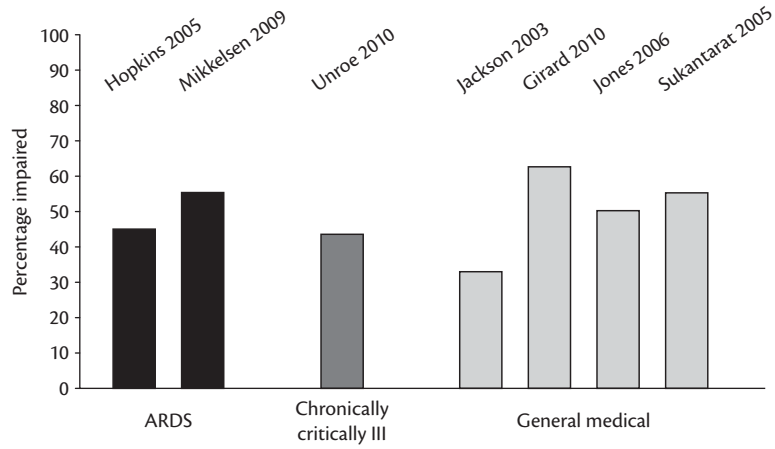


Fig. 382.1 Neurocognitive impairment rates across ICU populations [6,7,16].
Data from various sources (see references); Mikkelsen ME et al., 'Cognitive, mood and quality of life impairments in a select population of ARDS survivors', *Respirology*, 2009, **14**(1), pp. 76–82; Sukantarat KT et al., 'Prolonged cognitive dysfunction in survivors of critical illness', *Anaesthesia*, 2005, **60**(9), pp. 847–53; Jackson JC et al., 'Six-month neuropsychological outcome of medical intensive care unit patients', *Critical Care Medicine*, 2003, **31**(4), pp. 1226–34; and Unroe M et al., 'One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study', *Annals of Internal Medicine*, 2010, **153**(3), pp. 167–75.

extensive neuropsychological testing reported a higher incidence of neurocognitive impairment than those with screening test data.' Neurocognitive impairments persist months to years, but few studies have followed patients beyond three years, a possible weakness of current research. Neurocognitive impairments are reported in multiple cognitive domains including memory, attention, language, executive function (broadly defined as decision making, ability to organize, prioritize, and manage time), processing speed, and visuospatial function [1]. The most frequently assessed neurocognitive domain was memory followed by executive function. Impairments in memory and executive function often lead to functional impairments. Assessments of executive function in ARDS survivors found nearly 1 in 2 ARDS survivors (48%) demonstrated impairment in executive function [6]. For example, an investigation of 30 ICU survivors employed a novel problem solving and planning task and found 87% of survivors had significant executive function deficits one week after discharge and the deficit persisted in half of all patients up to 2 months later [7]. Data to date suggest neurocognitive impairments are new, prevalent, persistent, affect multiple neurocognitive domains, and are sufficiently severe to impact functional ability.

Trajectories of neurocognitive outcome

Questions remain regarding the nature of neurocognitive changes following critical illness including whether impairments are stable or prone to change over time—reflecting either improvement or decline (for an example of possible trajectories of change using hypothetical follow-up times, refer to Fig. 382.2). Evidence to date offers support for the view that in the early period after critical illness, individuals typically demonstrate significant improvement over a span of several months before they plateau and reach what for many is a new baseline [1,4]. For some, this new baseline reflects a level of cognitive ability which is at or only slightly below their pre-ICU level and which may reflect largely 'normal' functioning. Alternatively, for others, this new baseline may reflect significant and chronic cognitive impairment which, while potentially less severe than was demonstrated in the immediate period after

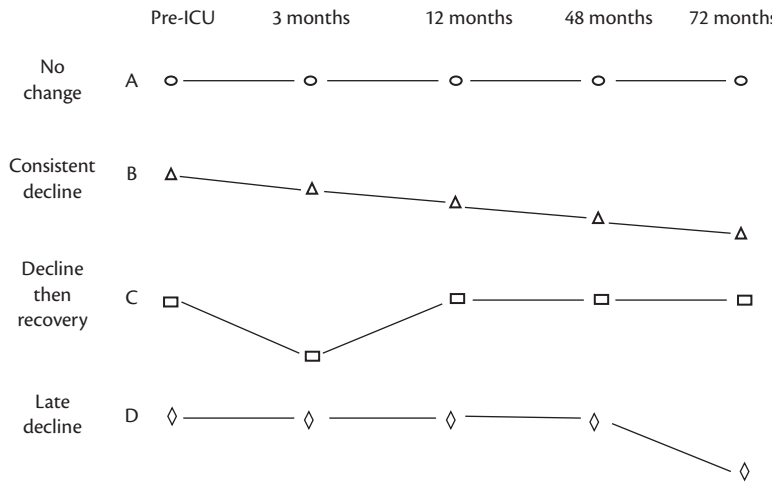


Fig. 382.2 Potential neurocognitive outcome trajectories.

hospital discharge, is substantially below their pre-ICU baseline and what is required for effective daily functioning. In a subset of patients, there may be additional decline over time, likely due to the effects of increased age, other risk factors such as comorbid disease (e.g. cardiovascular disease), or the existence of undiagnosed mild cognitive impairment or preclinical dementia at the time of ICU hospitalization. It may be that individuals with pre-existing conditions such as mild cognitive impairment experience an unusually rapid transition to dementia (including Alzheimer's disease) and that this accelerated neurocognitive decline may be fostered by the effects of critical illness—notably factors such inflammation and hypoxia (discussed later), both of which have been implicated in animal models in the development of Alzheimer's disease [8,9]. In these patients, it is potentially misleading to think of a 'new baseline' because, unlike their counterparts, their neurocognitive function never plateaus, but rather persistently declines over time.

Mechanisms and risk factors of neurocognitive impairment

There is growing, but limited information regarding mechanisms of neurocognitive impairment following critical illness, which are likely heterogeneous and interact with patient risk factors such as comorbid diseases or older age and factors associated with critical illness (e.g. inflammation, cytokine activation, hypoxia), its consequences (e.g. delirium, glucose dysregulation), or interventions (e.g. sedative use). Potential pathways to neurocognitive decline and associated mechanisms and risk factors are portrayed via Fig. 382.3. Mechanisms of brain injury include hypoxia [6,10], hypotension [6], glucose dysregulation [11,12], and inflammation and cytokine activated immune system deregulation [13,14]. These mechanisms likely interact with risk factors such as older age, delirium, and sedative use. In the case of delirium and sedatives, it is unclear whether these are risk factors on pathway to neurocognitive impairment (and, as such, may amplify the effects of key mechanisms) or whether they are directly injurious to the brain [15]. A study by Girard et al., found delirium duration was associated with worse neurocognitive functioning after adjusting for age, education, pre-existing cognitive functioning, illness severity, sepsis, and others, highlighting the potential long-term adverse consequences of delirium on neurocognitive functioning [16]. A study by Jackson et al. which analysed data from the Awakening and Breathing Controlled Trial, subjects in the intervention arm who received both spontaneous awakening trials and spontaneous breathing trials had better neurocognitive functioning at 3 month follow-up, though this effect dissipated at 12 month follow-up [17]. The Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU (BRAIN-ICU) survivors study found a longer duration of delirium was independently associated with cognitive impairment (global cognition and executive function scores) at both 3 and 12 months [4]. These data suggest that external factors such as sedation may be limited to the short-term, and may have little or no bearing on long-term neurocognitive outcomes. Alternatively, factors such as delirium may have both short- and long-term effects, and could be an early expression of a brain injury, with neurocognitive impairment being the long-term expression of this acute brain dysfunction. A comprehensive discussion of mechanisms and risk factors is beyond the scope of this review and has been addressed elsewhere [18].

ICU and post-ICU interventions

In an ideal world, it would be possible to eliminate or modify risk factors contributing to neurocognitive impairment in survivors of critical illness although, as a practical matter, this is extremely difficult and has not been currently achieved. As such, it may be important to develop and implement interventions that could partially prevent or ameliorate cognitive deficits both in the ICU and after. In an in-patient context, various approaches to fluid management and to nutrition have been employed to improve ICU survivor and long-term outcomes. The Adult Respiratory Distress Cognitive Outcomes Study (ACOS), which measured long-term outcomes in survivors of the Fluid and Catheter Treatment Trial (FACTT), found a liberal fluid management strategy was associated with

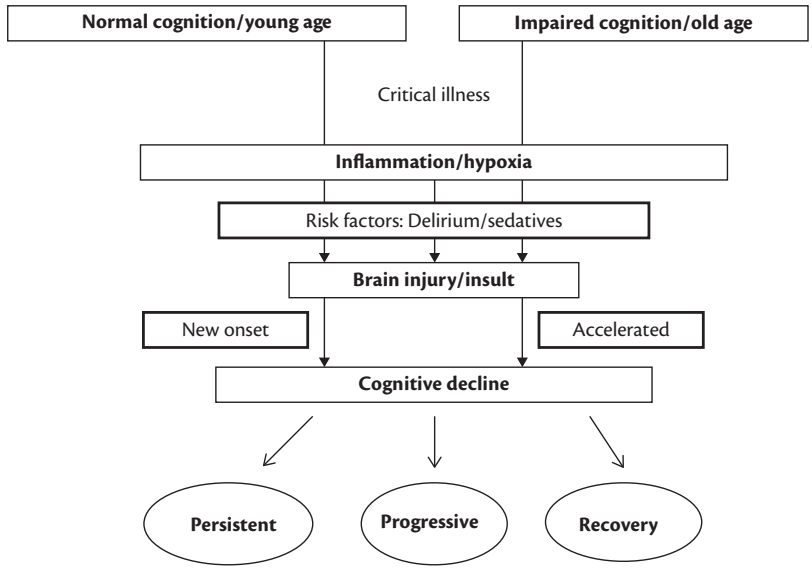


Figure 382.3 Potential pathways of neurocognitive outcome following critical illness

better cognitive outcomes [10]. However, there were significant limitations of the ACOS study, including low consent rate, attrition, and missing data, which temper these findings. In the ALTOS study which assessed one year outcomes in patients with acute lung injury who were enrolled in the EDEN randomized trial that compared full energy enteral feeding vs. low energy permissive underfeeding in ICU patients, there was no difference in neurocognitive outcomes between the treatment arms at six months or one year [5]. Taken together, these studies provide little guidance regarding the efficacy of ICU related interventions that may prevent or ameliorate neurocognitive impairments.

In addition to in-hospital interventions, efforts are increasingly focusing on post-ICU rehabilitation which has taken a variety of forms—including physical and cognitive rehabilitation as a way of positively impacting post-ICU neurocognitive functioning. In a small randomized study that assessed the effects of six weeks of physical rehabilitation in ICU survivors with prolonged mechanical ventilation found a 20% improvement in the cognitive component of the functional independence measure (FIM) score, a widely used metric in rehabilitation medicine, in the treatment group and a decline of 32% in the control group [19]. In a randomized trial in medical and surgical ICU survivors who received a protocolized rehabilitation program that included in-home physical and cognitive rehabilitation targeting executive dysfunction [20]. While very small and clearly preliminary in nature, the study by Jackson et al., demonstrated that patients in the intervention group had better neurocognitive and overall daily functioning than their counterparts. These interventions, both pilot studies with small sample sizes, appear to improve—although not eliminate—deficits and they may be promising, though their results should be replicated in larger more definitive investigations.

Conclusion

A large and growing body of evidence demonstrates that neurocognitive impairment is a common and persistent morbidity in survivors of critical illness and one associated with adverse functional outcomes. Neurocognitive impairments has been shown to occur in up to 60% of individuals, are reported across ICU populations, and affect specific neuropsychological domains including memory, attention, and executive functioning related areas. Mechanisms that undergird the development of this impairment are not yet well described though a number of factors are implicated including hypoxia and inflammation which are notable among numerous others as are risk factors such as delirium. Relatively little attention has been paid to interventions to reduce or ameliorate these impairments, though efforts aimed at patients after hospital discharge appear to be relatively more promising (to this point) than those occurring in an inpatient context. Neurocognitive impairment—whether new or worsening—is a substantial burden for patients and their families and carries with it significant public health consequences which until recently have been largely underestimated or unrecognized. A pressing need exists to direct clinical and research related resources to this problem.

References

1. Wolters AE, Slooter AJ, van der Kooi AW, and van Dijk D. (2013). Cognitive impairment after intensive care unit admission: a systematic review. *Intensive Care Medicine*, **39**(3), 376–86.
2. Iwashyna TJ, Ely EW, Smith DM, and Langa KM. (2010). Long-term cognitive impairment and functional disability among survivors of severe sepsis. *Journal of the American Medical Association*, **304**(16), 1787–94.
3. Guerra C, Linde-Zwirble WT, and Wunsch H. (2012). Risk factors for dementia after critical illness in elderly medicare beneficiaries. *Critical Care*, **16**(6), R233.
4. Pandharipande PP, Girard TD, Jackson JC, et al. (2013). BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. *New England Journal of Medicine*, **369**(14), 1306–16.
5. Needham DM, Dinglas VD, Bienvenu OJ, et al. (2013). One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. *British Medical Journal*, **346**, f1532.
6. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, and Orme JF, Jr. (2005). Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *American Journal of Respiratory Critical Care Medicine*, **171**(4), 340–7.
7. Jones C, Griffiths RD, Slater T, Benjamin KS, and Wilson S. (2006). Significant cognitive dysfunction in non-delirious patients identified during and persisting following critical illness. *Intensive Care Medicine*, **32**(6), 923–6.
8. Zetterberg H, Mörtberg E, Song L, et al. (2011). Hypoxia due to cardiac arrest induces a time-dependent increase in serum amyloid β levels in humans. *PloS One*, **6**(12), e28263.
9. Wilson CJ, Finch CE, and Cohen HJ. (2002). Cytokines and cognition: the case for a head to toe inflammatory paradigm. *Journal of the American Geriatrics Society*, **50**, 2041–56.
10. Mikkelsen ME, Christie JD, Lanken PN, et al. (2012). The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *American Journal of Respiratory Critical Care Medicine*, **185**(12), 1307–15.
11. Hopkins RO, Suchyta MR, Snow GL, Jephson A, Weaver LK, and Orme JF. (2010). Blood glucose dysregulation and cognitive outcome in ARDS survivors. *Brain Injury*, **24**(12), 1478–84.
12. Duning T, van den Heuvel I, Dickmann A, et al. (2010). Hypoglycemia aggravates critical illness-induced neurocognitive dysfunction. *Diabetes Care*, **33**(3), 639–44.
13. McGrane S, Girard TD, Thompson JL, et al. (2011). Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. *Critical Care*, **15**(2), R78.
14. Holmes C, Cunningham C, Zotova E, et al. (2009). Systemic inflammation and disease progression in Alzheimer disease. *Neurology*, **73**(10), 768–74.
15. Jackson JC, Gordon SM, Hart RP, Hopkins RO, and Ely EW. (2004). The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychology Reviews*, **14**(2), 87–98.
16. Girard TD, Jackson JC, Pandharipande PP, et al. (2010). Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Critical Care Medicine*, **38**(7), 1513–20.
17. Jackson JC, Girard TD, Gordon SM, et al. (2010). Long-Term Cognitive and Psychological Outcomes in the Awakening and Breathing Controlled Trial. *American Journal of Respiratory Critical Care Medicine*, **182**(2), 183–91.
18. Hopkins RO, Ely EW, and Jackson JC. (2007). The role of future longitudinal studies in ICU survivors: understanding determinants and pathophysiology of brain dysfunction. *Current Opinions on Critical Care*, **13**(5), 497–502.
19. Chiang LL, Wang LY, Wu CP, Wu HD, and Wu YT. (2006). Effects of physical training on functional status in patients with prolonged mechanical ventilation. *Physical Therapy*, **86**(9), 1271–81.
20. Jackson JC, Ely EW, Morey MC, et al. (2012). Cognitive and physical rehabilitation of intensive care unit survivors: results of the RETURN randomized controlled pilot investigation. *Critical Care Medicine*, **40**(4), 1088–97.

CHAPTER 383

Affective and mood disorders after critical illness

Daniel W. Klyce and James C. Jackson

Key points

- Clinically significant depressive symptoms occur in approximately a third of survivors of critical illness (more in certain sub-populations) and persist over time.
- In survivors of critical illness, symptoms of depression and symptoms of ongoing physical illness often mimic each other, making it difficult to arrive at a proper diagnosis.
- Pre-existing depression and physical debility predict symptoms of depression in survivors of critical illness after discharge, but the contributions of 'in hospital' factors to outcomes is less clear.
- Interventions focused on addressing depressive symptoms in critically ill patients both in and out of the hospital are promising, but largely unstudied.
- The integration of the disciplines of psychology and psychiatry into the treatment of survivors of critical illness is an important goal and should be pursued.

Introduction

Patients who survive critical illness or injury to be discharged from intensive care units (ICUs) are often faced with an arduous course of recovery and rehabilitation. Beyond the potential risk of negative physical health outcomes, a growing body of evidence indicates that these patients are also at risk for significantly poorer mental health outcomes and health related quality of life. Commonly observed psychological sequelae of critical care included generalized anxiety, symptoms of post-traumatic stress, impaired neurocognitive functioning, and affective or mood impairment. Although still relatively small in scope, research related to psychological and neuropsychological outcomes has bourgeoned in the last decade. Within this area of research, post-ICU depressive disorders have emerged as an early focus of study. This section will review the following topics related to post-ICU affective disorders—prevalence rates, assessment and identification, risk factors, empirical support for early interventions, and important questions for future research.

Scope of the problem

In their systematic review, Davydow et al. [1] reported a 28% median point-prevalence rate of clinically significant symptoms of depression. Furthermore, they reported the prevalence of depressive disorders diagnosed by a clinician 2 months post-discharge at 33%. In a related review of depression among survivors of acute respiratory distress syndrome (ARDS), Davydow et al. [2] reported a point prevalence range of 17–43%, with a median of 28%. Similarly, Jackson et al. [3] cited evidence that depression is observed among 25–50% of ICU survivors and that symptoms of depression may continue to be observed at rates much higher in than the general population (i.e. up to 58% [4]) 2 years post-ICU discharge.

Although these reviews provide much-needed information about the prevalence of post-ICU affective impairment, they also identify multiple methodological limitations related to defining the scope of the problem. A pervasive problem in research involving ICU survivors is attrition, often with more than half of the original sample lost to follow-up—despite considerable effort invested in retention over time. Consequently, even methodologically strong studies often are based on less than desirable sample sizes with little data available to characterize the portion of the original sample lost to follow-up. Relatedly, information about long-term psychological outcomes is scantly available. Most studies have been restricted to follow-up periods of one year or less, complicating efforts to understand the persistence of affective impairment in the years post-ICU discharge. Finally, identification of significant symptoms of depression is overwhelmingly limited to screening instruments, and 'clinical significance' has been defined variously by research using different criterion guidelines.

Assessment and identification

The clinical syndromes included in the family of mood disorders are characterized by affective, cognitive, and somatic disturbances. The significant overlap between physiological symptoms of depression and an organic condition that may be associated with critical care can complicate the accurate diagnoses of a mood disorder in this population. Physiological symptoms of a major depressive episode (i.e. changes in sleep patterns, psychomotor agitation or retardation, fatigue or loss of energy, significant changes in weight, and changes in appetite) are readily observable criteria that can also be associated with a variety of medical conditions. In the context of current diagnostic and classification systems, particular care should be taken to make an accurate differential diagnoses between a depressive disorder and Mood Disorder Due to a General Medical Condition. In making this distinction, the clinician seeks to establish that the 'mood disturbance is aetiologically related to the general medical condition through a physiological mechanism (DSM-IV-TR [5])'.

In samples of critically-ill patients and survivors of ICU admissions, a thorough assessment is required to distinguish between mood disturbances that are physiological consequents of a general medical condition and depressive disorders that are *secondary to* a major illness or injury (e.g. secondary to physical limitations, social isolation/stigma, hopelessness related to prognosis, lost productivity, etc.). As indicated by the DSM [5], it is often instructive in the process of making a differential diagnosis to compare the course of the mood disturbance with that of the illness and to identify any patient factors not often associated with the common course of specific depressive disorders (e.g. typical age of onset, gender, etc.). The obvious implication of a misdiagnosis is the application of a psychological intervention when, in fact, the depressive mood symptoms are physiologically related to a medical syndrome; in this instance, medical remediation of the underlying organic condition is the primary course of treatment.

Optimally, such distinctions can be made by clinical interviews conducted by mental health professionals integrated into recovery/rehabilitation programs. Formal interviews—such as the Structured Clinical Interview for DSM-IV [5] (SCID)—provide the framework for a thorough investigation of clinical symptoms and facilitate differential diagnoses, however, they can often require one to two hours of a patient's and clinician's time. If a thorough interview is not possible, due to time constraints or patient comfort, there are several screening instruments that have demonstrated good reliability and criterion validity. These include the Beck Depression Inventory-II (BDI-II), the Brief Symptom Inventory-30 (BSI-30), the Center for Epidemiological Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), the Hamilton Rating Scale for Depression (HRSD), and the Hospital Anxiety and Depression Scale (HADS). Each of these instruments allows clinicians to assess various affective, cognitive, and somatic aspects of depressive symptoms. These instruments provide a cross-sectional assessment of current or recent mood functioning; however, more thorough questioning may be necessary to determine the course of the mood disturbance in order to diagnose a specific clinical syndrome. Furthermore, these instruments may not fully assess the differential impact of physical limitations versus psychological disturbances on social and occupational functioning.

Risk factors

Risk factors related to post-ICU depression are commonly grouped into (1) pre-injury/illness psychosocial variables, (2) ICU treatment/illness variables, and (3) post-ICU/recovery variables (e.g. Davydow, et al. [1]). Two reviews—Davydow and colleagues' [1] systematic review and Jackson and colleagues' [3] overview—represent important efforts to identify these risk factors, and have been supported by a small collection of empirical studies published between 2009 and 2012 [6–9].

The background characteristics that patients 'bring with them' to the ICU are often difficult to assess, given that measuring pre-morbid psychological or physical functioning requires retrospective collection of data from patients or their surrogates. Even so, Davydow et al. [1] found evidence to suggest that depressed mood and poor physical functioning in the month preceding ICU admission predicted symptoms of depression at follow-up and post-discharge. Inconsistent findings related to gender have been reported, however, when an effect has been observed, female gender is more predictive of depression than male gender. In addition to premorbid depression and anxiety, Jackson et al. [3] cited evidence supporting higher body mass indices as a predictor of post-ICU depression. Finally, Tøien et al. [8] reported that being unemployed pre-ICU admission predicted depression at 12-month follow-up.

Several ICU-treatment variables have been associated with post-ICU affective impairment. In their review, Jackson et al. [3] reported evidence that longer ICU stays and longer duration of mechanical ventilation were associated with depression; Adhikari, et al. [8] reported similar findings among ARDS patients, showing that these two variables predicted higher BDI-II scores at follow-up. Jackson et al. [3] also identified studies implicating the number of days on sedatives, mean ICU benzodiazepine dosage, and maximum organ failure scores as predictors of affective dysfunction. Notably, in their systematic review, Davydow et al. [1] concluded that ICU length of stay and the duration of sedation had no appreciable impact on depression post-discharge. Furthermore, patient subjective perception of the ICU experience appears to play a role. Rattray et al. [7] reported that patient recall of frightening experiences in the ICU at discharge predicted higher rates of depression, as did poor recall for the ICU experience and dissatisfaction with quality of care. Finally, Kiekkas et al. [6], in a review of psychological distress and delusional memories following critical care, cited evidence supporting a link between delusional memories of the ICU and higher rates of post-discharge depression.

Davydow et al. [1], presented several findings related to post-ICU predictors of depression. An obvious finding that enjoys consistent report is that post-ICU indicators of psychological dysfunction are associated with other comorbid conditions and dysfunction at subsequent follow-ups. For instance, post-ICU symptoms of anxiety and post-traumatic stress are associated with cross-sectional elevated rates of depression. In one of the few long-term follow-up studies, Adhikari et al. [9], showed that elevated symptoms of depression among ARDS patients at 2-year follow-up predicted elevated (and relatively stable) rates of depression at 5-year follow-up; they also noted that slower recovery of organ functioning was predictive of depression. As reviewed by Davydown et al. [1], Weinert and Meller [10] found that poorer physical functioning also played a role. Specifically, a decline in physical function between two and six months post-discharge predicted higher rates of depression at six months; however, a decline in functioning between discharge and two months did not. Finally, Jackson et al. [11], reported that cognitive impairment at 6 months post-discharge was significantly associated with higher symptoms of depression (see Box 383.1).

Early intervention

Although there is growing urgency to provide services targeting early emergence of psychological disturbances during ICU treatment and post-discharge, few empirically supported programs have been developed specifically for this population. Peris et al. [12] developed an ICU programme based on the participation of clinical psychologists in intra-ICU treatment. Psychologists and trained staff offered a variety of services to patients at bedside and to family members involved in the patient's care. Bedside, clinical psychologists were involved in providing psychoeducational services, promoting stress management and coping strategies, and counselling; on average, patients had five or six encounters with psychology staff. Psychologists were also involved in supporting family

Box 383.1 Risk factors having moderate to strong associations with post-ICU depressive symptoms

Strong support

- Use of anti-depressant medications pre-injury/illness.
- Retrospective report of depressed mood pre-ICU admission.
- Poor physical functioning prior to ICU admission.
- Mean benzodiazepine dosage during ICU treatment.
- Cognitive impairment at discharged and follow-ups.
- Recall of stressful memories or nightmares from ICU experience.
- Symptoms of other psychiatric disorders (e.g. anxiety) at discharge and follow-up.
- Quality of physical and mental health post-ICU.

Moderate/inconsistent support

- Female gender.
- Unemployment status pre-injury/illness.
- Longer length of hospital stay.
- Longer duration of mechanical ventilation.
- ICU treatment specialty (e.g. medical versus trauma ICU).
- Daily sedative interruption.
- Satisfaction with hospital care/treatment.
- Changes in physical functioning post-discharge.

members' decision-making processes and their bedside interactions with patients. Patients who were admitted subsequent to the implementation of this service evidenced less negative psychological outcomes 12 months post-discharge than did patients admitted prior to the implementation of this service. Patients participating in the clinical psychologist intervention showed lower rates of depression (6.5 versus 12.8%), anxiety (8.9 versus 17.4%), and symptoms of post-traumatic stress (21.1 versus 57%); these patients also endorsed significantly higher subjective ratings of quality of life than the control group. Notably, the annual cost associated with the Clinical Psychology Service at Careggi Florence University Hospital (Florence, Italy) is €30,000.

Beyond psychological interventions delivered during critical care, Jones et al. [13], demonstrated the potential of psychological services integrated into rehabilitation and recovery programs. In a multi-site, randomized control trial involving patients admitted to ICUs, Jones et al. [13] tested the benefit associated with a rehabilitation program to promote positive physical and psychological outcomes after critical illness. All patients were visited on units, had three follow-up telephone calls, and were offered clinic appointments at 8 and 24 weeks post-discharge. Patients in the intervention group were provided a rehabilitation manual to self-implement during the at-home recovery. The manual detailed a 6-week rehabilitation package that targeted psychological, psychosocial, and physical problems. Patients who used the rehabilitation manual evidenced significantly improved physical functioning at 8 and 24 weeks post-discharge as compared with the control group. Although not statistically significant, the intervention group also evidenced lower rates of depression (12 versus 25%).

These promising results emphasize the importance of involving psychology services or allied disciplines in ICU treatment and post-discharge recovery. What is particularly encouraging about these results is evidence to suggest that post-ICU mood or affective disorders are tractable and that they might be influenced by relatively low-key interventions such as a self-guided rehabilitation program manual. Given the potential for symptoms of depression to interfere with patient adherence to recovery care or rehabilitation programmes, early intervention programmes like these may prove beneficial to facilitating physical recovery and minimizing the costs associated with rehabilitation and delayed return to productivity.

Future research

The risks and benefits associated with administering antidepressant medications during and post-ICU care are important areas for future research. In his review of treatments for psychiatric conditions developing after critical care, Weinert [14] cited inconsistent evidence supporting the safety and efficacy of administering antidepressants to ICU survivors. Weinert also reviewed evidenced from allied disciplines (i.e. from biopsychology studies) suggesting that psychopharmacological interventions administered in the ICU could protect neural pathways and other brain structures often implicated in the development of post-ICU depression. Given the potential for antidepressants to facilitate faster recovery and increased participation in rehabilitation, Weinert's call for new research focused on confirming results from previous clinical trials is renewed here.

Beyond the effectiveness of psychopharmacological interventions, models for the effective delivery of rehabilitation/recovery services more generally should be the focus of new research efforts. One candidate system that has enjoyed recent critical review [15,16] is post-ICU follow-up clinics. These clinics, where they do exist, may provide services such as primary care, physical and/or cognitive rehabilitation, and psychological treatment. In their 2006 survey of ICU follow-up clinics in the UK, Griffiths et al. [17] found that 'clinical psychology' was the discipline with which these clinics most frequently had prenegotiated referral arrangements. Given the identified need for psychological services, evaluations of critical care follow-up clinic programmes should focus on the effective ways that mental health professionals may be incorporated in such interdisciplinary treatment teams. In addition to identifying the long-term needs of ICU survivors, these clinics could provide an appropriate context to establish empirical support for the differences between affective disorders in this population versus other physically ill or injured patients.

References

1. Davydow DS, Gifford JM, Desai SV, Bienvenu OJ, and Needham DM. (2009). Depression in general intensive care unit survivors: a systematic review. *Intensive Care Medicine*, **35**(5), 796–809.
2. Davydow DS, Desai SV, Needham DM, and Bienvenu OJ. (2008). Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. *Psychosomology Medicine*, **70**(4), 512–19.
3. Jackson JC, Mitchell N, and Hopkins RO. (2009). Cognitive functioning, mental health, and quality of life in ICU survivors: an overview. *Critical Care Clinic*, **25**(3), 615–28.

4. Cheung AM, Tansey CM, Tomlinson G, et al. (2006). Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **174**, 538–44.
5. American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. Washington, DC: APA.
6. Kiekkas P, Theodorakopoulou G, Spyratos F, and Baltopoulos GI. (2010). Psychological distress and delusional memories after critical care: a literature review. *International Nurse Review*, **57**(3), 288–96. [Review.]
7. Rattray J, Crocker C, Jones M, and Connaghan J. (2010). Patients' perceptions of and emotional outcome after intensive care: results from a multicentre study. *Nurse Critical Care*, **15**(2), 86–93.
8. Tøien K, Myhren H, Bredal IS, Skogstad L, Sandvik L, and Ekeberg Ø. (2010). Psychological distress after severe trauma: a prospective 1-year follow-up study of a trauma intensive care unit population. *Journal of Trauma*, **69**(6), 1552–59.
9. Adhikari NK, Tansey CM, McAndrews MP, et al. (2011). Self-reported depressive symptoms and memory complaints in survivors five years after ARDS. *Chest*, **140**(6), 1484–93.
10. Weinert C and MellerW (2006). Epidemiology of depression and antidepressant therapy after acute respiratory failure. *Psychosomatics*, **47**, 339-407.
11. Jackson JC, Hart RP, Gordon SM, et al. (2003). Six-month neuropsychological outcome of medical intensive care unit patients. *Critical Care Medicine*, **31**(4), 1226–34.
12. Peris A, Bonizzoli M, Iozzelli D, et al. (2011). Early intra-intensive care unit psychological intervention promotes recovery from post traumatic stress disorders, anxiety and depression symptoms in critically ill patients. *Critical Care*, **15**(1), R41.
13. Jones C, Skirrow P, Griffiths RD, et al. (2003). Rehabilitation after critical illness: A randomized, controlled trial. *Critical Care Medicine*, **31**(10), 2456–61.
14. Weinert C. (2005). Epidemiology and treatment of psychiatric conditions that develop after critical care. *Current Opinions In Critical Care*, **11**, 376–80.
15. Williams TA and Leslive GD. (2008). Beyond the walls: A review of ICU clinics and their impact on patient outcomes after leaving hospital. *Australian Critical Care*, **21**, 6–17.
16. Rattray J and Crocker C. (2007). The intensive care follow-up clinic: Current provision and future direction? *Nursing in Critical Care*, **1**(1), 1–3.
17. Griffiths JA, Barber VS, Cuthbertson BH, and Young JD. (2006). A national survey of intensive care follow-up clinics. *Anaesthesia*, **61**, 950–5.

PART 21.3

Out-of-hospital support after critical illness

CHAPTER 384

Long-term weaning centres in critical care

Jeremy M. Kahn

Key points

- Successful liberation from prolonged mechanical ventilation requires an inter-disciplinary care team and consistent application of evidence based practice.
- Dedicated weaning centres may facilitate liberation of mechanical ventilation by concentrating this expertise in a low acuity environment.
- The evidence that weaning centres improve outcomes is limited, but available data suggest that they may provide equivalent care to intensive care units (ICU) at a lower cost.
- The availability of weaning centres may have unintended spillover effects to acute care hospitals that influence how they manage patients with chronic critical illness (CCI).
- Future research should determine which types of patients will most benefit from admission to a dedicated weaning centre and how to organize and manage these facilities to best improve outcomes.

The role of care setting in ventilator weaning

Acute respiratory failure requiring invasive mechanical ventilation is one of the most common reasons for intensive care unit (ICU) admission [1]. Common causes of acute respiratory failure include pneumonia, congestive heart failure, acute exacerbations of chronic respiratory disease, and post-operative respiratory insufficiency. In addition to treating the underlying illness causing respiratory failure, ICU practitioners must consider the use of key evidence-based practices that might facilitate weaning from mechanical ventilation, including daily spontaneous breathing trials, avoidance of continuous intravenous sedation, and early mobilization of the ventilated patient [2]. Liberation becomes even more complex in the subset of patients requiring prolonged mechanical ventilation. Additional considerations in these patients include the timing of tracheostomy, the use of a protocolized approach to liberation, and, in patients with very poor prognoses, decisions surrounding potentially placing limits on the use of life-sustaining therapy [3].

Weaning patients in this manner, especially those patients requiring prolonged mechanical ventilation, requires extensive expertise about pulmonary physiology, an experienced interdisciplinary care team and a rigorous, often protocolized approach to discontinuing ventilator support [4,5]. Historically this care was provided solely in the ICU of an acute care hospital. However, given the complexity of the process, it is increasingly being provided in dedicated weaning centres [6]. Dedicated weaning centres differ from acute care ICUs in they primarily admit patients directly from acute care hospitals and typically admit only longer term ventilated patients, allowing them to focus on the special needs of this population. Thus, dedicated weaning centres offer a novel and potentially beneficial care setting for these unique and high-risk patients.

Types of weaning centres

There are two major types of dedicated weaning centres: long-term acute care hospitals (LTACHs) that provide care to many types of patients with chronic critical illness (CCI) including those without ventilator dependence, and hospitals that only care for patients receiving prolonged mechanical ventilation.

Long-term acute care hospitals

The major type of dedicated weaning centre in the United States is specialized hospitals that care for a variety of patients with CCI. Called LTACHs, these hospitals are governed by special regulations set forth by the United States Centers for Medicare & Medicaid Services. LTACHs are defined not by the types of patients they care for, but by their average length of stay, which by rule must exceed 25 days. This means that they not only provided dedicated weaning services to patients receiving prolonged mechanical ventilation, but also provide other types of acute care for patients who are sick enough to be hospitalized, but do not require all the services of an acute care hospital [7].

LTACHs are generally smaller than most general acute care hospitals, with fewer beds and fewer annual admissions [8]. This lower case load allow LTACHs to focus on more holistic aspects of care, including the nutritional, rehabilitation, and social planning needs of this population. Many if not all of the patients admitted to an LTACH for ventilator weaning have already undergone tracheostomy and placement of a feeding tube [9]. LTACHs vary in their ability to respond to severe physiological decomposition, which can happen during the weaning process. Some LTACHs have ICUs on site, while others have to transfer these patients back to an acute care hospital.

LTACHs are among the fastest growing segments of health care in the US, and the number of ICU patients in the US transferred to LTACs is steadily increasing over time [6]. This increase is due

in part to the increase in patients requiring prolonged mechanical ventilation as a result of increased survival in mechanical ventilation and an aging of the population. Yet it is also due to the expansion of the numbers of LTACHs—per case hospital payment and generous reimbursement creates financial incentives for transfer to LTACHs that support the expansion of this model of care.

Dedicated weaning centres

The other type of weaning centre is a hospital that provides nothing, but ventilator care to patients requiring prolonged mechanical ventilation. This is the model that predominates outside the United States, with well-known weaning centres existing in Germany, the United Kingdom, Italy, and other countries [10-12]. Similar to LTACHs, these weaning centres are often small, but they still possess the resources to care for patients requiring mechanical ventilation over the long term. Generally these facilities specialize not only in post-ICU rehabilitation and ventilator weaning, but also chronic respiratory failure, sleep disordered breathing and neuromuscular disease. These conditions are analogous to post-ICU recovery in that they require clinicians with expertise in the respiratory system and a multidisciplinary approach to care. An important characteristic of these hospitals is that there are relatively few of them compared to the demand, and admission is limited to the small number of patients who most clearly might benefit from their care.

Effectiveness of weaning centre care

Conceptual rationale for benefit

Dedicated weaning centres exist in part because of a strong conceptual rationale for their superiority in chronic ventilator weaning, both in the clinical domain and the economic domain (Table 384.1). In the clinical domain, perhaps the most compelling rationale stems from the volume-outcome relationship in health care—the notion that with greater clinical experience in complex disease comes better outcomes [13]. It stands to reason that hospitals that care for a large number of patients with prolonged mechanical ventilation would be more facile at liberating them from mechanical ventilation. Other potential reasons underlying a clinical benefit include greater use of interdisciplinary care teams, greater use of protocols for chronic weaning and greater continuity of care, with the same providers present day after day, instead of switching frequently as in a traditional ICU. Additionally, dedicated weaning centres admit primarily low acuity patients, meaning that in theory there are fewer emergencies to distract providers from the task of ventilator weaning.

There is also reason to suspect that dedicated weaning centres can provide less costly care for patients receiving prolonged mechanical ventilation. Dedicate weaning facilities need less resources overall compared to traditional acute care hospitals, meaning that they can operate at lower fixed costs and are therefore less costly on a per-patient and per-day basis. Additionally, to the degree that they facilitate weaning they may shorten the duration of ICU stay and overall acute care stay, saving money in the short term. Finally, by providing a place for chronically critically ill patients to convalesce outside of the hospital, they may prevent costly re-admissions to acute care.

Conceptual rationale for harm

Just as there are theoretical reasons why dedicated weaning facilities may lead to improved outcomes and lower costs, there are reasons why they may lead to worse outcomes and higher costs (Table 384.2). Dedicated weaning facilities may increase mortality and prolong ventilator weaning by fragmenting the cost of care across two or more hospitals, leading to communication failures and clinical fumbles. Also, because dedicated weaning facilities admit many long-stay patients with impaired immunity, the patients may be exposed to more highly-resistant organisms leading to severe hospital-acquired infections [14]. Moreover, transfers to dedicated weaning facilities typically involve an interhospital transfer, which can involve risks, although most studies suggest that the risk is relatively low [15].

Regarding costs, dedicated weaning facilities might increase costs by resulting in an overall increase in the acute care length of stay. To the degree that dedicated weaning facilities increase survival, they may increase costs through the added cost of survivorship, albeit to a degree that society may accept on a cost-utility basis. Finally, depending on the reimbursement scheme dedicated weaning facilities could be quite costly to payers such as governments and health insurers, even if they are cost saving from the hospital or patient perspective.

Existing evidence

Mortality for patients with prolonged mechanical ventilation is extremely high, with most studies estimating approximately 50% one-year survival [16]. Currently there are few studies comparing

Table 384.1 Theoretical reasons underlying a clinical and economic benefit associated with dedicated weaning centres

Domain	Factor
Clinical benefit	◆ Greater clinical experience ◆ Fewer handoffs within the hospital ◆ Lower overall severity of illness ◆ Improve use of weaning protocols
Financial benefit	◆ Shorter hospital length of stay ◆ Decreased weaning duration ◆ Lower fixed costs ◆ Fewer readmissions

Table 384.2 Theoretical reasons underlying a clinical and economic harm associated with dedicated weaning centres

Domain	Factor
Clinical harm	◆ Lower intensity staffing ◆ Fragmentation of the episode of acute care ◆ Disrupted communication ◆ Risks of interhospital transfer
Financial harm	◆ Increased overall length of stay ◆ Improved survival ◆ High costs to payers ◆ Opportunity costs for families having to travel to regional hospitals

costs of care and outcomes of patients receiving care in a dedicated weaning centre compared to the alternative of continued care in the ICU of a traditional acute care hospital. A single-centre study performed in the United States found that of 2,134 ICU patients evaluated for transfer to an LTACH, median survival was longer in the LTACH group, but 6-month survival was not different [17]. Daily costs were much lower in the LTACH compared to the ICU, although total costs were not directly compared between groups. This early evaluation indicates that transfer to LTACH does not impact long-term patient survival, but might actually prolong the dying process, which could be interpreted as harm. It also suggests that if LTACH days are substituted for ICU days then total health care costs can be reduced by transferring patients to LTACHs.

A more recent study evaluated 234,799 patients receiving prolonged mechanical ventilation in 2,609 acute care hospitals in the US [18]. A total of 20.6% of patients were transferred to an LTACH. Using a sophisticated technique to control for severity of illness and the indication bias associated with the decision to transfer, the authors found that there was no difference in one year survival between the two groups, similar to the previous study. However, six month costs were lower for patients transferred to LTACHs than for patients who remained in an ICU, primarily driven by a reduction in re-admissions to acute care hospitals and skilled nursing facilities.

Together, these studies suggest that chronic weaning facilities do not worsen survival for patients requiring prolonged mechanical ventilation, though nor do they improve it. They may reduce costs by offering equivalent services at a lower daily cost. Neither study investigated other important outcomes besides survival and costs. Potentially important outcomes include speed of liberation from mechanical ventilation, patient and family satisfaction and health related quality of life. Future research should examine the impact of weaning centre care on these other domains.

Indirect effects

Weaning centres may have important effects for the health system that are independent of their effects on the patients for which they actually provide care. It is important to consider these indirect effects when evaluating the role of dedicated weaning centres in the health system. Dedicated weaning centres provide a place for chronically ventilated patients to receive care outside of the ICU. This frees up ICU beds, which are a scarce resource in many health care systems, for other uses. Ultimately this may lead to fewer unplanned discharges and admission delays, which could improve outcomes for ICU patients [19,20]. At the same time, freeing up ICU beds may induce a tolerance for CCI that may paradoxically increase overall health care utilization. With no hospitals to transfer patients dependent on mechanical ventilation, physicians may be more inclined to limit life-sustaining therapy. However, with weaning centre beds as an option, physicians may be inclined to avoid these difficult discussions and simply transfer the patient. In the US, rules governing LTACHs prohibit them from admitting patients with no chance of recovery, however there are few data to gauge the effectiveness of these rules.

Conclusion and future directions

Although dedicated ventilator weaning hospitals have existed for decades, our understanding of them is still in its infancy. In many ways they operate in parallel to acute care ICUs, providing similar services, but at potentially reduced costs, and in a potentially more patient centred way. Paradoxically, with the increasing focus on rehabilitation and early mobilization in critical care, acute care ICUs may come to look more like dedicated weaning centres over time.

Several key aspects of weaning centres are still unknown and should be the subject of future research. First, research is needed into the types of patients that most benefit from transfer to these hospitals, the optimal timing of transfer, and how that timing integrates with the timing of tracheostomy. Furthermore, research is needed into the organizational characteristics of weaning facilities that are associated with improved outcome. Just as acute care ICUs benefit from care protocols for weaning and intensivist physician staffing, there may be organizational factors that benefit patients in dedicated weaning facilities. Finally, we need empiric research into the indirect effects of dedicated weaning facilities, which should provide more insight into the optimal role they play in the health system.

As we wait for this research, clinicians who care for patients in dedicated weaning centres and ICU clinicians who refer patients to dedicated weaning centres, should be aware of all these issues. At a minimum, clinicians should discuss the implications of prolonged ventilator care to ensure that patients and their families have appropriate expectations about their outcomes. Dedicated weaning centres will certainly be part of critical care for many years to come, but their utilization should be part of an informed decision about the goals of care and not a default decision in an extremely high-risk, high-cost patient population.

References

1. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, and Kahn JM. (2010). The epidemiology of mechanical ventilation use in the United States. *Critical Care Medicine*, **38**(10), 1947–53.
2. Mendez-Tellez PA and Needham DM. (2012). Early Physical Rehabilitation in the ICU and Ventilator Liberation. *Respiratory Care*, 57(10), 1663–9.
3. Scheinhorn DJ, Chao DC, and Stearn-Hassenpflug M. (2002). Liberation from prolonged mechanical ventilation. *Critical Care Clinic*, **18**(3), 569–95.
4. MacIntyre NR, Epstein SK, Carson S, et al. (2005). Management of patients requiring prolonged mechanical ventilation: report of a NAMDRC consensus conference. *Chest*, **128**(6) p. 3937–54.
5. Scheinhorn DJ, Hassenpflug MS, Votto JJ, et al. (2007). Post-ICU mechanical ventilation at 23 long-term care hospitals: a multicenter outcomes study. *Chest*, **131**(1), 85–93.
6. Kahn JM, Benson NM, Appleby D, Carson SS, and Iwashyna TJ. (2010). Long-term acute care hospital utilization after critical illness. *Journal of the American Medical Association*, **303**(22), 2253–9.
7. Kahn JM, Werner RM, Carson SS, and Iwashyna TJ. (2012). Variation in long-term acute care hospital use after intensive care. *Medical Care Result Reviews*, **69**(3), 339–50.
8. Liu K, Baseggio C, Wissoker D, and Maxwell S. (2001). Long-term care hospitals under Medicare: facility-level characteristics. *Health Care Financing*, **23**(2), 1–18.
9. Scheinhorn DJ, Hassenpflug MS, Votto JJ, et al. (2007). Ventilator-dependent survivors of catastrophic illness transferred to 23 long-term care hospitals for weaning from prolonged mechanical ventilation. *Chest*, **131**(1), 76–84.
10. Pilcher DV, Bailey MJ, Treacher DF, Hamid S, Williams AJ, and Davidson AC. (2005). Outcomes, cost and long term survival of patients referred to a regional weaning centre. *Thorax*, **60**(3), 187–92.

11. Schönhofer B, Euteneuer S, Nava S, Suchi S, and Köhler D. (2002). Survival of mechanically ventilated patients admitted to a specialised weaning centre. *Intensive Care Medicine*, **28**(7), 908–16.
12. Clini EM, Siddu P, Trianni L, Graziosi R, Crisafulli E, and Nobile MT. (2008). Activity and analysis of costs in a dedicated weaning centre. *Monaldi Archives of Chest Disease*, **69**(2), 55–8.
13. Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, and Rubenfeld GD. (2006). Hospital volume and the outcomes of mechanical ventilation. *New England Journal of Medicine*, **355**(1), 41–50.
14. Marchaim D, Chopra T, Bogan C, and Bheemreddy S. (2012). The burden of multidrug-resistant organisms on tertiary hospitals posed by patients with recent stays in long-term acute care facilities. *Journal of Infection*, 40(8):760-5.
15. Fan E, MacDonald RD, Adhikari N, and Scales DC. (2006). Outcomes of interfacility critical care adult patient transport: a systematic review. *Critical Care*, **10**(1):R6.
16. Carson SS. (2006). Outcomes of prolonged mechanical ventilation. *Current Opinion on Critical Care*, **12**(5), 405–11.
17. Seneff MG, Wagner D, and Thompson D. (2000). The impact of long-term acute-care facilities on the outcome and cost of care for patients undergoing prolonged mechanical ventilation. *Critical Care Medicine*, **28**(2), 342–50.
18. Kahn JM, Werner RM, David G, Have Ten TR, Benson NM, and Asch DA. (2012). Effectiveness of long-term acute care hospitalization in elderly patients with chronic critical illness. *Medical Care*, **51**(1), 4–10.
19. Goldfrad C and Rowan K. (2000). Consequences of discharges from intensive care at night. *The Lancet*. **355**(9210), 1138–42.
20. Robert R, Reignier J, Tournoux-Facon C, et al. (2012). Refusal of intensive care unit admission due to a full unit impact on mortality and critical care. *American Journal of Respiratory and Critical Care Medicine*, **185**(10), 1081–7.

CHAPTER 385

The ICU survivor clinic

Priya Das and Carl Waldmann

Key points

- Continuity of care by intensivists enables early diagnosis and management of intensive care unit (ICU) problems.
- Specialist reassurance and advice can ease psychological recovery.
- The clinic service evolves to meet the needs of patients.
- Follow-up acts as service evaluation for the ICU care given to patients.
- It is has a fundamental role in assessing long-term outcomes.

Introduction

Critical illness leaves patients at risk of long-term physical and psychological problems. Leaving intensive care unit (ICU) is just the start of their long recovery process, and there are considerable effects on patient morbidity and mortality. Implementation of an ICU follow-up service has enabled provision of support following hospital discharge and manage sequelae effectively.

In 1989 the Kings Fund report [1] highlighted that morbidity, as well as mortality should be considered following intensive care: 'there is more to life than measuring death'. The National Audit Commission (Critical to Success) [2] and the National Expert Group (Comprehensive Critical Care) [3] have since echoed the need to focus on quality of life post-discharge. Globally, ICU patients require the highest level of support, both medical and financial, amongst all hospital patients. The average daily cost per patient in an ICU was estimated by Edbrooke et al. to be £1000; six times greater than that of an average ward patient [4]. The benefits of this large investment made during intensive care are only sustained when continued support is in place following discharge. All other specialties review patients following admissions and intensive care should be no different.

Post-ICU care is developing an evidence base and becoming an area of research in its own right. The concept is established in the UK and Australia, and is an area of interest in the United States. Indeed since 2009 the concept of the implementation of multidisciplinary post-ICU care has been officially advised [5] and the number of follow-up services is continuing to grow around the world.

Provision of an outpatient follow-up clinic supports key objectives. Through meeting patients regularly timely diagnoses of problems are made, and appropriate referrals can be made to other specialties, including the Traumatic Stress Counselling service.

Management plans and treatment decisions are frequently amended as a result of reviewing the patient during clinic consultations. Intensivists also use this opportunity to see the impact critical illness has had on patients and family members alike.

The follow-up clinic enables quality assurance of the critical care provided to both patients and relatives.

The format of the follow-up clinic

Follow-up in the UK is non-standardized, with each hospital deciding how to run their own service. The Royal Berkshire Hospital in the UK implemented outpatient clinics in 1993, which run two to four times a month, and all ICU survivors are invited to attend. Family attendance and participation at the clinic is also encouraged too.

30-minute appointments are offered at 2, 6, and 12 months following hospital discharge, by a team consisting of intensivists, experienced ICU nurses, and specialist follow-up nurses.

The service endeavours to meet patients' needs, as opportunities to make extra clinic appointments are given and patients are encouraged to revisit the ICU and meet the staff who cared for them during their illness. In addition, investigations are also organized during the clinic to monitor clinical progress.

Recently, the clinic has received referrals not only from other hospitals where no ICU follow-up exists, but also from local primary care doctors and distant health authorities too.

The annual cost of running the service is £36,000, which accounts for <1% of the annual ICU budget. In the United States funding plays a key role in providing the service, as follow-up clinic budgets are not always included in the main ICU budget. A typical breakdown of costs is shown in Table 385.1.

Outcomes after intensive care

The concept of health-related quality of life (HRQL) recognizes that both physical and emotional factors contribute to a patient's wellbeing. It remains a core principle of both the follow-up clinic as well as in the patient's community rehabilitation phase

Whilst clinical, biochemical, and radiological tests assess the extent of physical sequelae, quality of life tools address the impact of critical illness on patients. Box 385.1 illustrates that several factors can contribute to the HRQL.

The perceived quality of life (PQOL) tool is a self-administered or interviewer-administered instrument, which consists of 20 items. Alongside being quick to complete, when repeated during successive clinic appointments they may indicate less obvious and multifactorial struggles patients are experiencing.

Commonly used quality of life tools are shown in Table 385.2.

Table 385.1 Breakdown of costs

Component	Cost (£)
Nursing	21,000
Medical	7,000
Administration	6,000
Laboratory tests and X-rays	2,000
Total	36,000

Box 385.1 Case one

An elderly gentleman had a long ICU stay and had lost a significant amount of lean body mass. Despite investigations including lung function tests being normal, at home he did could not complete daily tasks. He felt frail, fatigued, and subsequently lost his confidence to perform household activities.

Table 385.2 Quality of life tool examples

Subjective	Description
PQOL	Perceived quality of life [15]
HAD	Hospital anxiety and depression [16]
NHP	Nottingham Health Profile [17]
EuroQol	'European' tool [18]
SF 36	36-item short-form survey [19]
Objective	
QALY	Quality of life tool [20]
Employment status	—

Data from various sources (see references).

Problems after intensive care

Alongside the more established sequelae, less obvious symptoms which affect patients include:

- Taste loss.
- Anorexia.
- Nail ridging.
- Hair loss.
- Muscle weakness.

Added distress may be caused as some may think they are developing a new condition. The trauma of going through the critical illness can further complicate a patient's emotional recovery, which in turn can profoundly impede the rehabilitation process. The clinic can be seen as a convenient place to provide specialist explanations and reassurance from intensivists, who know to anticipate these issues, and can address specific worries and misconceptions sympathetically.

Tracheostomy follow-up

Less noticeable abnormalities such as swallowing difficulties may go unreported. Percutaneous tracheostomies may interfere with the swallowing function when *in-situ*, but in the long run the stoma itself is associated with low morbidity [6]. Late complications include tethering of the skin to the trachea.

The follow-up service is a convenient point in time to review previously tracheostomized patients and organize surgical referrals when needed. In Reading, UK this group of patients undergo routine MRI scans to exclude tracheal stenosis. Some patients with unsightly scars or severe tethering can easily be managed by offering a small procedure under Local Anaesthesia in ENT outpatients.

Sexual dysfunction

Reluctance to have sexual intimacy is an embarrassing symptom for most people to admit. Among ICU survivors even fewer will report it in the context of having gone through a recent critical illness.

One study of 127 patients revealed its incidence to be as high as 44% [7], so the clinic can be a timely place to identify the symptom and organize outpatient referrals to an Andrology clinic for men and Gynaecology clinic for women. The study also demonstrated that had the intensivist team not asked specifically about the symptom, no other health professional would have recognized it in the 1 year study period.

Psychological effects

Some degree of memory loss of the ICU stay is anticipated, with 70% patients being unable to describe what has happened when prompted at the clinic visit, including even those who did not receive sedation on the unit. Those patients who were emergency admissions to the unit are especially prone to psychological sequelae. Although short term problems are anticipated, consequences occurring many years later have also been identified. In 2004 Kapfhammer et al. demonstrated that 11 out of 46 ARDS survivors had developed a post-traumatic stress disorder (PTSD) diagnosis during interviews conducted around 8 years later, highlighting the need for ongoing monitoring [8].

ICU diaries

During appointments patients can also receive a diary of the events of their ICU stay. It uses simple English and holds factual descriptions, which help to fill gaps in the patients' memories about their ICU stay, and contextualize any disjointed flashbacks.

Box 385.2 illustrates this.

From reading the ICU Diary and talking through her experience with the follow-up team she was able to contextualize the memory, and discovered she had suffered a sudden period of desaturation. Patients have fed back that 'the diary and appointment helped to piece the time and events together'.

Box 385.3 demonstrates the wider benefits of the diary, particularly that it helps loved ones and other people understand and appreciate what an ICU survivor has been through.

A study of 12 European ICUs (n = 352) demonstrated that the provision of ICU diaries at 1 month follow-up reduced the risk of new-onset PTSD compared to the usual 3 month follow-up (5 versus 13%, P = 0.02) [9].

Box 385.2 Case two

An ICU patient recalled a time where she could suddenly hear loud noises and see flashing lights on the machine next to her. She thought she was dying and became very distressed.

Box 385.3 Case three

A young lady, 17 years old, survived meningitis and when she returned to school she looked physically well, but the teachers became frustrated because she was struggling to learn simple concepts, and her friends were upset because she did not socialize as much. She was given eight copies of her diary, which she distributed to the teachers and her friends. Subsequently, she felt that this was the first time those around her had understood what she had been through. Teachers even gave her an extra 30 minutes during her GCSE exams.

Delirium

Delirium can affect up to 80% of ICU patients, with some going on to suffer long-term nightmares and delusions. Jones et al. demonstrated that ICU survivors with delusional memories of their admission are prone to PTSD and panic symptoms 8 weeks post discharge. The lack of factual recall was identified as a predictor of developing these problems [10].

The use of validated delirium scores, such as CAM-ICU and IS DSC [11], that are calculated during an ICU admission will help recognize delirium in ICU patients. If these patients are appropriately managed it is hoped that severe psychological sequelae including cognitive decline can be prevented.

Effects on family

During appointments patients can talk openly about problems they encounter during rehabilitation. Family members are also encouraged to speak about the admission and how they feel the rehabilitation is progressing. The experience of watching a loved one go through a critical illness has significant effects on family members; a study highlighted that spouses are particularly prone to depression and anxiety whilst their loved one is in intensive care, which commonly continues after ICU discharge when the patient recovers in the community.

Other resources used during follow-up

DIPEx (www.dipex.org) is an online database which provides personal accounts of survivors' experiences with critical illness. Patients have highlighted it as being beneficial, and the ICU subsection includes diary entries and video clips of patients' ongoing recovery. A section is also available for carers and relatives to record their memories.

Discovery interviews are an evidence-based technique that enables patients and their loved ones to tell the story of their illness. It uses a framework to guide the person through key parts of their experience; an approach that has allowed a better understanding about patient needs, the recovery process and general wellbeing.

Conclusion

Estimated mortality in ICU has been quoted as 16%, and hospital mortality (including ICU and general ward) as 24% (ICNARC CMP 2010–2011) [12]. For the surviving patients, leaving Intensive care is the start of a long recovery process. The follow-up clinic serves as a means of addressing some of the long-term issues faced by patients during their recovery. It provides a needs assessment for each individual patient and acts as a safety net. The design of the service is evolving to meet patient needs, be they physical or psychological problems, or functional difficulties they face at home.

The clinic's potential continues to emerge, and in the future it may act as a standard for measuring quality of care in ICU patients. Important benefits are shown in Fig. 385.1

Intensive care follow-up is not common practice yet, in 2006 a study reviewed 266 ICUs in the UK, and found that 44 ran clinics (55%). It showed that marked differences existed in the format and service offered by follow-up clinics at that time, with 56 clinics (77%) only reviewing patients who had been treated on the ICU for at least 3 days duration. Nearly half of the follow-up clinics (39 clinics, 49%) have established access to at least one other outpatient service [13]. Around the world key limiting factors which have been identified in provision of follow-up include funding and health personnel (resource) allocation towards the service. In 2009 the PRaCTICaL study concluded that the nurse led follow-up clinic did not provide significant benefits [14].

As the evidence base for this area of research builds, it is hoped that in the near future a larger study of multidisciplinary post intensive care follow-up clinics will be conducted.

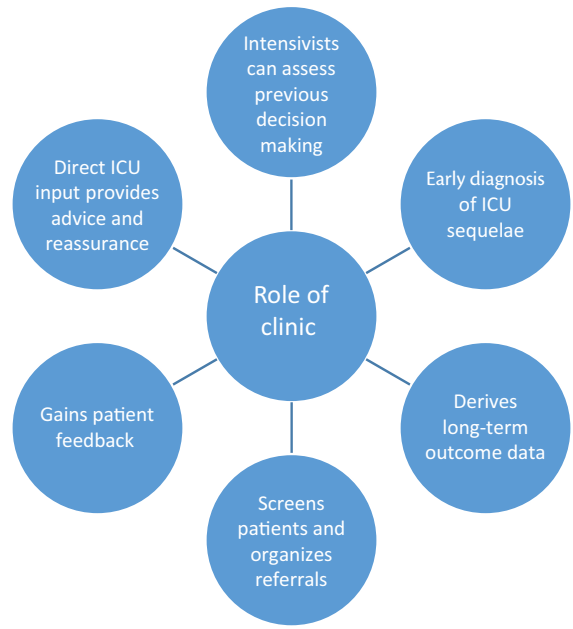


Fig. 385.1 Role of the ICU clinic.

References

1. Ledingham J, Ashworth P, Branthwaite M, et al. for the King's Fund Panel. Intensive Care in the United Kingdom; a report from the Kings Fund Panel. *Anaesthetics*, 1989, 44, 428–430.
2. Audit Commission. (1999). *Critical to Success. The Place of Efficient and Effective Critical Care Services Within the Acute Hospital*. London: Audit Commission.
3. Department of Health. (2000). Comprehensive Critical Care. A Review of Adult Critical Care Services. London: DoH. Available at: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4082872.pdf (accessed 8 August 2012).
4. Edbrooke D, Hibbert C, and Corcoran M. (1999). Review for the NHS Executive of Adult Critical Care Services: An International Perspective. Available at: http://www.wales.nhs.uk/sites3/Documents/530/adult%20critical%20care-%20international%20perspective.pdf (accessed 4 September 2015)
5. National Institute for Clinical Excellence. (2009). Rehabilitation after critical illness, Clinical Guideline 083. London: NICE. Available at: http://www.nice.org.uk/guidance/cg83 (accessed on 1 August 2012).
6. Bernau F, Waldmann CS, Meanock C, et al. (1996). Long-term follow-up of percutaneous tracheostomy using flow-loop and MRI scanning. *Intensive Care Medicine*, **22**, S295.
7. Griffiths J, Gager M, Alder N, et al. (2006). A self-report based study of the incidence and associations of sexual dysfunction in the survivors of intensive care treatment. *Intensive Care Medicine*, **32**(3), 445–51.
8. Kapfhammer HP, Rothenhausler HB, Krauseneck T, et al. (2004). Post traumatic stress disorder and health related quality of life in long-term survivors of acute respiratory distress syndrome. *American Journal of Psychiatry*, **161**(1), 45–52.
9. Jones C, Backman C, Capuzzo M, et al. (2010). Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. *Critical Care*, **14**(5), R16.
10. Jones C, Griffiths RD, Humphris G, and Skirrow PM. (2001). Memory, delusions, and the development of acute post traumatic stress disorder-related symptoms after intensive care. *Critical Care Medicine*, **29**, 573–80.
11. National Institute for Clinical Excellence. (2010). Delirium: diagnosis, prevention and management, NICE guidelines CG103. London: NICE. Available at: http://www.nice.org.uk/guidance/cg103 (accessed 31 July 2015).
12. UK Intensive Care National Audit & Research Centre (ICNARC). (2012). Case Mix Programme (CMP) Summary Statistics (2010–2011). Available at: https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports/Summary-Statistics (accessed 4 September 2015).
13. Griffiths JA, Barber VS, Cuthebrtson BH, et al. (2006). A national survey of intensive care follow-up clinics. *Anaesthesia*, **61**(10), 950–5.
14. Cuthbertson BH, Rattray J, Campbell MK, et al. (2009). The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomized controlled trial. British Medical Journal, **339**.
15. Patrick DL, Davis M, Southerland LI, et al. (1988). Quality of life following intensive care. *Journal of Genetic Internal Medicine*, **3**, 218–23.
16. Zigmond AS and Snaith RP. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, **67**, 361–70.
17. Hunt SM, McKenna SP, McEwan J, et al. (1981). Nottingham Health Profile: subjective health status and medical consultation. *Society of Scientific Medicine,* A **15**a, 221–9.
18. Williams A. (1990). The Euro Qol—a new facility for the measurement of health related quality of life. *Health Policy II*, **16**, 199–208.
19. Ware JE and Sherbourne CD. (1992). The MOS 36-item short form health survey (SF-36). I. conceptual framework and item selection. *Medical Care*, **30**, 473–81.
20. Harris J. (1987). Qualifying the value of life. *Journal of Medical Ethics*, **13**, 117–73.

CHAPTER 386

Rehabilitation from critical illness after hospital discharge

Laura Vincent and Carl Waldmann

Key points

- Management of patients throughout the critical care pathway should be reviewed in order to maximize rehabilitation potential.
- Rehabilitation should be initiated early in the ICU care pathway.
- NICE guidance recommends that rehabilitation after ICU is no longer optional and should be mandated for all.
- Validated, reproducible and sensitive assessment tools are required to recruit appropriate patients to rehabilitation schemes and to monitor their progress.
- We await evidenced-based recommendations for the type, timing, and duration of rehabilitation after hospital discharge.

Introduction

More than 110,000 patients are admitted to Intensive Care each year in the UK [1], the majority of whom survive to hospital discharge. Historically, surviving an Intensive Care admission was considered a successful outcome. We now understand that this is just the beginning of a long, hard road to recovery.

A breadth of physical, psychological, and cognitive problems are experienced by patients after discharge from Intensive Care, resulting in a markedly and persistently reduced Health Related Quality of Life (HRQL) [2]. These problems dramatically impede a patient's functional recovery and cause great distress, as patients struggle to contextualize their residual deficits, within their understanding of their critical illness.

In addition to the personal impact on intensive care unit (ICU) survivors, there is unquestionable strain on relatives, carers, and society in general [3]. Families face physical and financial pressures assuming the role of informal care givers, and emotional stress, particularly dealing with the frustrated patient who feels lacking in autonomy. With prolonged recovery, the socio-economic impact of critical illness is considerable. Making huge investments in Intensive Care therapy is of less value, if appropriate support is not continued through the rehabilitation phase.

The optimization of the morbidity and HRQL after critical illness, have now become key therapeutic objectives.

The introduction of structured ICU follow-up clinics allows the multisystem sequelae of critical illness to be identified early and appropriate referrals to be made in a timely fashion, thus preventing the development of more chronic disabilities.

The additional provision of structured rehabilitation programmes, can aid patients' recovery towards their previous functional level.

The National Institute of Clinical Excellence (NICE) have advocated a post-ICU rehabilitation pathway [4]. This guideline represents progress, by officially acknowledging the need for rehabilitation after critical illness, and provides a framework for the implementation of such a programme.

Comprehensive rehabilitation after ICU incorporates rigorous psychological assessment and therapy in addition to physical regimes, but this is beyond the scope of this chapter.

ICU acquired weakness

There is growing appreciation of the profound skeletal muscle weakness experienced commonly by ICU survivors. This ICU acquired weakness (ICU-AW) has been linked to multiple independent risk factors, and it develops through complex and inter-related mechanisms [5].

ICU-AW results in increased duration of mechanical ventilation, length of ICU and hospital stay, and reduced physical function and HRQL. ICU-AW is therefore a huge obstacle in the functional recovery of critically ill patients. Many patients need at least a year to regain full mobility [6,7] and adopt a self-preservative approach to life.

Accordingly, in addition to post-ICU rehabilitation strategies, there is now a focus on preventing ICU-AW, right from the beginning of the critical illness pathway. This topic is detailed in a separate chapter.

Exercise rehabilitation

Rehabilitation programmes for specific diseases, such as heart attack, stroke, and respiratory disease, are well established and have shown dramatic benefits, yet ICU rehabilitation strategies are not widely implemented [8] and there is considerable variation in the extent and delivery of these services [9].

In 2009, NICE introduced the long awaited guideline: Rehabilitation after Critical Illness [4]. This advocates individualized structured rehabilitation at each stage of a patients' recovery, starting early in the critical care admission and continuing until three months post-discharge. It recommends a cycle of functional and clinical assessments, to identify at risk patients, determine rehabilitation goals, and facilitate the construction of a

patient-specific programme. They emphasize a multi-disciplinary approach, involving health care professionals with appropriate expertise, comprehensive handover between care providers, and detailed written documentation. Unfortunately, whilst providing a structure for the approach to rehabilitation, due to a dearth of supporting literature, the guideline cannot recommend any validated physical assessment tools to identify patients most likely to benefit, or any specific details of evidenced based rehabilitation regimes. It is therefore not applicable as a transferrable tool currently.

Rehabilitation after hospital discharge

The continuation of rehabilitation into the post-hospital phase of recovery from critical illness is inconsistent and non-standardized.

The clinical effectiveness of rehabilitation programmes for UK adult critical care patients, initiated after discharge from critical care, was demonstrated in a randomized controlled trial, investigating the use of a six-week self-help rehabilitation manual [8]. 126 patients were recruited 1 week after ICU discharge and randomized to receive 'usual' follow-up care, or an additional six week rehabilitation package. This consisted of a manual, addressing physical, psychological, and social issues, and included a self-directed exercise program. Patients received three weekly telephone calls and completed a rehabilitation diary.

At 2 and 6 months physical recovery was significantly greater in the rehabilitation group ($P < 0.006$). Psychological recovery was less affected, with a lower rate of depression at 8 weeks after ICU discharge in the intervention group that did not quite reach significance ($P < 0.066$), and no appreciable difference in anxiety. Studies have since been undertaken, to explore the impact of a rehabilitation program further, particularly looking at the timing of the programme and the effect on HRQL [10, 11].

Nature of exercise prescription

Evidence for the specific detail of exercise rehabilitation programmes after hospital discharge is limited and not comparable.

By removing some of the personal responsibility from patients, supervised group exercise sessions may maximize the results of activities and minimize patient anxiety. However, this is not a feasible approach for all patients, who may live far from the hospital, or be discouraged by the 'peer-pressure' of a class environment [12].

Unsupervised home exercise programmes depend on the patient's self-motivation to engage with the programme. They must understand the activities and have clear objectives and indicators of progress. This approach necessitates a focus on patient education and empowerment in their recovery.

Aerobic activity has been utilized in several studies. Patients are advised to undertake a specific cardiovascular endurance activity, at an intensity level determined by the results of initial assessments. Patients are instructed to work towards physiological markers such as 'modified Borg scores' (a subjective assessment of level of dyspnoea) and heart rate; indicators which can also be used to measure individual progress [12].

Strength training is incorporated into some programmes, where the maximum amount of weight a patient can lift over a set number of repetitions is assessed, and a prescription of target repetitions and weights is made, with subsequent adjustment based on progress.

In a non-controlled prospective study of 38 ICU survivors, McWilliams et al. [13] enrolled patients in a 6-week rehabilitation programme, comprising one supervised and two unsupervised exercise sessions each week. They demonstrated significant improvements in 6-minute walk test and Intermittent Shuttle Walk Test ($P < 0.001$) and in anxiety and depression scores ($P < 0.001$). Unfortunately, the lack of a control group limits the interpretation of this result. The positive effect of the intervention needs to be compared with the expected natural course of recovery, over the same time period.

Elliott et al. [11] performed a multicentre randomized controlled trial of the impact of an 8-week, graded, personalized, home-based endurance and strength training programme. This involved trainer visits, phone calls, and an exercise manual. Both groups demonstrated improved function at 8 and 26 weeks, but there was no significant difference between the groups. This may reflect a missed cohort of patients, who would have benefited most from the intervention, and outcome measures that were not assessed for, which may have been more sensitive to the intervention.

Timing of post-hospital rehabilitation programme

It is clear from available evidence that rehabilitation commencing as early as the ICU phase of critical illness has marked outcome benefit. It is logical therefore that rehabilitation commenced as soon as possible after hospital discharge is likely to be more effective.

There is wide variation between studies with regards to the timing of initiation of post-hospital rehabilitation. Elliott et al. commenced their intervention at one week post-hospital discharge, whereas McWilliams et al. had a delay of up to 3 weeks in initiating therapy [11,13]. Such a delay may reduce the impact of an intervention, as there may already be significant natural recovery prior to the onset of therapy.

In order to recommend evidence-based standards for the timing of a post-hospital rehabilitation pathway, further research is required.

Assessment of patients

Screening and assessment tools are essential components of successful ICU rehabilitation, to identify those patients who should be targeted and to monitor improvements in ICU-AW and functional capacity. This allows the programme to be tailored to the specific needs of individuals and adjusted with progress.

There is an ongoing drive to develop safe, objective clinical assessment tools, which are reproducible, encompass all aspects of physical recovery, and sensitive enough to demonstrate a significant response to rehabilitation [14].

NICE could not provide any evidence for validated screening or assessment tools for the adult general ICU population. One 'low quality' research paper included in the NICE literature review [15] used the Rivermead Mobility Index (RMI) assessment in the neurorehabilitation population. Whilst the RMI showed good validity and reliability in this patient group, its efficacy has not been demonstrated in the general ICU population.

A simple test of muscle strength in clinical use outside the ICU environment, is the Medical Research Council (MRC) sum score. This has significant limitations in critically ill patients who are often sedated or uncomfortable, may have cognitive dysfunction and may be connected to invasive monitoring lines—factors that may preclude their full compliance. It is difficult to maintain complete objectivity and isolated muscle group strength does not translate directly to functional capabilities.

A number of critical care specific assessment tools are being developed which are more appropriate to the general ICU population.

The Physical Function ICU Test (PFIT) tool, developed by Skinner et al. [16], is reliable and responsive to physical progress, but uses mainly cardiovascular assessments and does not address all components of physical function. There was a small sample size and it is unlikely that the exercises would be achievable in early critical illness.

The Chelsea Critical Care Physical Assessment Tool (CPAx) has been recently published [17]. It is a numerical and pictorial scoring system consisting of 10 domains of physical morbidity, including respiratory function. Each component is graded on a Guttman scale from 0–5, such that the maximum score is 50. The scores are displayed on a radial chart, and provide a realistic and holistic representation of functional capability, which can be repeated to show trends. It has good inter-rater reliability and ongoing research suggests predictive validity for hospital outcome.

Conclusion

Exercise rehabilitation has been shown to enhance the functional recovery of critically ill patients and can no longer be considered as an afterthought in the critical illness treatment pathway. Rehabilitation should be incorporated routinely into clinical practice, to optimize the quality of life of ICU survivors. Available guidelines provide a framework for implementation of rehabilitation from ICU admission through to post-hospital discharge care. The challenges lie in identifying those patients likely to benefit from such an intervention and in devising a personalized and validated rehabilitation programme.

References

1. UK Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme (CMP) Summary Statistics (2010-2011). Available at: https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports/Summary-Statistics
2. Adamson H and Elliott D. (2005). Quality of life after critical illness: a review of general ICU studies 1998-2003. *Australian Critical Care*, **18**, 50–60.
3. De Miranda S, Pochard F, Chaize M, et al. (2011). Postintensive care unit psychological burden in patients with chronic obstructive pulmonary disease and informal caregivers: a multicenter study. *Critical Care Medicine*, **39**, 112–18.
4. National Institute for Clinical Excellence. (2009). Rehabilitation After Critical Illness, Clinical Guideline 83. London: NICE. Available at: Available at: http://www.nice.org.uk/guidance/cg83 (accessed on 1 August 2012).
5. Truong A, Fan E, Brower R et al. (2009). Bench to bedside review: Mobilising patients in the Intensive Care Unit—from pathophysiology to clinical trials. *Critical Care*, **13**, 216.
6. De Jonghe B, Bastuji-Garin S, Sharshar T, et al. (2004). Does ICU acquired paresis lengthen weaning from mechanical ventilation? *Intensive Care Medicine*, **30**, 1117–21.
7. Dowdy D, Eid M, Sedrakyan A, et al. (2005). Quality of life in adult survivors of critical illness: a systematic review of the literature. *Intensive Care Medicine*, **31**, 611–20.
8. Jones C, Skirrow P, Griffiths R, et al. (2003). Rehabilitation after critical illness: a randomized, controlled trial. *Critical Care Medicine*, **31**, 2456–61.
9. Griffiths JA, Barber VS, Cuthbertson BH, et al. (2006). A national survey of intensive care follow-up clinics. *Anaesthesia*, **61**, 950–5.
10. Schweickert WD, Pohlman MC, Pohlman AS, et al. (2009). Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*, **373**, 1874–82.
11. Elliott D, McKinley S, Alison J, et al. (2011). Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program. *Critical Care*, **15**, R142.
12. Connolly B, Denehy L, Brett S, et al. (2012). Exercise rehabilitation following hospital discharge in survivors of critical illness: an integrative review. *Critical Care*, **16**(3), 226.
13. McWilliams DJ, Atkinson D, Carter A, et al. (2009). Feasibility and impact of a structured, exercise-based rehabilitation programme for intensive care survivors. *Physiotherapy Theory Practice*, **25**, 566–71.
14. Corner EJ. (2012). Intensive care acquired weakness: measuring recovery from critical illness. *Journal of the Intensive Care Society*, **13**(3), 217–20.
15. Collen FM, Wade DT, Robb G, et al. (1991). The Rivermead Mobility Index: a further development of the Rivermead Motor Assessment. *International Disability Studies*, **13**, 50–4.
16 Skinner EH, Berney S, Warrilow S, et al. (2009). Development of an outcome measure (the PFIT) a pilot exercise training protocol for use in intensive care. *Critical Care Resuscitation*, **11**, 110–15.
17. Corner EJ. (2012). The Chelsea Critical Care Physical Assessment Tool (CPAx): validation of an innovative new tool to measure physical morbidity in the general adult critical care population; an observational proof-of-concept pilot study. *Physiotherapy*, **99**(1), 33–41.

SECTION 22

End-of-life care

PART 22.1

Withdrawing and withholding treatment

CHAPTER 387

Ethical decision making in withdrawing and withholding treatment

Margaret Isaac and Jared Randall Curtis

Key points

- The process of intensive care resource allocation and practices around withholding and withdrawing life support vary by physician, hospital, region, and country.
- Shared decision-making is the recommended default approach to medical decision-making, though there is cultural geographic and individual variability in physician attitudes and patient/family preferences toward shared decision-making.
- Surrogate decision-making is difficult, with decisions being shaped by many factors including family members' preferences and patients' values.
- Communication with patients and families regarding complex medical decisions and shared decision-making can be enhanced with specific approaches and techniques.
- Previously completed advance directives can help inform decision-making when patients lose decisional capacity in the ICU.

Introduction

Intensive care units (ICUs) are the centre of some of the highest technology, and most advanced care that medicine has to offer and have the potential to offer life-saving treatment to critically-ill patients. Death preceded by ICU care occurs in approximately 20% of patients in the US [1], creating an imperative for critical care physicians and staff to thoughtfully and ethically address end-of-life issues. Particularly in settings in which resources are limited, an ethical approach to resource allocation must be advanced, both in considering if patients are sick enough to warrant critical care services, and, at the other end of the spectrum, determining when patients are too sick to benefit from this type of care. A variety of models for decision-making exist, and many professional medical societies advocate for a shared decision-making approach. However, patients and their surrogate decision-makers are widely variable in their preferences for decision control, so their role and the role of the treating physician is best approached on an individualized basis. Similarly, the literature on communication in the ICU setting describes key features associated with increased family satisfaction, though physicians are best served to use these as general guidelines, tailoring their specific approach to the individual patient and family. Other challenges in physician-patient/surrogate communication include cross-cultural communication and working with interpreters, implementation of wishes expressed in advance directives and discussing resuscitation preferences.

Resource allocation

Critical care provision requires utilization and mobilization of many resources—resources not universally available across all regions and countries. Even within urban centres in the developed world, there is significant variability in the availability of ICU beds. Although the number of ICU beds does not correlate with societal health expenditures within the developed world, it does correlate significantly with mortality [2]. The manner in which finite resources are allocated varies significantly within the US and across other countries. The process by which these resources are allocated raises specific ethical considerations—both in terms of who is deemed sick enough to warrant critical care, and who is too sick to benefit. Principles of resource allocation outlined by the American Thoracic Society highlight the following [3]:

- Each individual's life is valuable and equally so.
- Respect for patient autonomy, as represented by informed consent, is a central tenet for providing health care, including ICU care.
- Enhancement of the patient's welfare, by providing resources that meet an individual's medical needs and that the patient regards as beneficial, is the primary duty of health care providers.
- ICU care, when medically appropriate, is an essential component of a basic package of health care services that should be available for all.
- The duty of health care providers to benefit an individual patient has limits when doing so unfairly compromises the availability of resources needed by others.

Withholding and withdrawing of life support

Most patients who die in the ICU do so after having life-sustaining treatments withheld or withdrawn [4]. Though many medical

ethicists and medical societies, including the American Thoracic Society and the American Medical Association view withholding and withdrawal of life-sustaining treatments to be ethically equivalent, this view is not universally shared. The degree to which these treatments are withdrawn and the process by which these decisions are made varies significantly by country, shaped in part by cultural and religious differences. In a large study that included seven different geographic regions throughout the world, 36% of in-hospital deaths followed withdrawal or withholding of life-sustaining treatments [5]. In a study comparing regional practice variability in Europe, rates of withdrawal of life-sustaining treatments were over two times as high in northern Europe (47%) as in southern Europe (18%) [4].

Physicians' actions are shaped by their own cultural and religious beliefs and individual clinician characteristics affect decisions to limit life-sustaining treatments. Specifically, religious affiliation impacts physicians' decisions to either withdraw or withhold these treatments—with decisions to withhold treatment being more common among Jewish, Greek Orthodox, and Muslim physicians in Europe, and decisions to withdraw treatment being more common among Protestant, Catholic, and unaffiliated physicians [6]. Time from ICU admission to limitation of these treatments also varied with physicians' religious affiliations. Overall religiosity among Jewish physicians is inversely related to willingness to withdraw life-sustaining treatments. In a survey of US physicians, black physicians were far more likely than white physicians to personally want treatments such as CPR, mechanical ventilation, and artificial feeding when given hypothetical scenarios of living with severe brain damage or in a persistent vegetative state, though the majority of all physicians surveyed did not desire such treatments.

Use of intensive care services during terminal hospitalizations varies in different regions and countries, but in most parts of the developed world, intensive care is increasingly being used at the end-of-life among older individuals [7]. Therefore, given the aging of populations in the developed world, increasing attention must be paid towards thoughtful advance care planning, health care utilization, and optimal end-of-life care in the ICU setting.

Decision making

Models of decision making

Many models and frameworks of medical decision-making have been developed, encompassing a spectrum from maximal patient autonomy to a more traditional parentalist approach. At the patient autonomy end of the spectrum, informed decision-making (or the 'informed choice' model) describes a process in which patients are informed about health care treatments and their alternatives and then independently choose from these options. On the other hand, parentalism describes a relationship in which physician is guardian, providing information to steer a patient towards a decision that the physician considers preferable. This model, the traditional one used in the intensive care setting, assumes that 'physician knows best' by virtue of their training and experience and will act in the best interest of the patient. This is still commonly used in certain countries as the default approach, and is used universally in the setting of emergency care, in which consent cannot be explicitly obtained and is often considered implied. In between these extremes is shared decision-making. Shared decision-making involves:

- Involvement of both patient and physician in the medical decision-making process.
- Sharing of information between patient (about personal values and goals) and physician (about prognosis and specifics of medical treatment options).
- Discussion of treatment preferences and evaluation of understanding.
- Consensus between both parties on the treatment to be implemented.

Geographic and cultural variability

Although shared decision-making was endorsed as the preferred default model for medical decision-making in the ICU by an international group of critical care societies in 2003, significant variability in decision-making processes exists across practice sites, countries, and cultures. Patients and families themselves express varying preferences regarding the locus of decision control, with many expressing preference for a shared decision-making model [8], but significant percentages desiring either more autonomy, or a more directive approach on the part of physicians [9]. In short, there is tremendous variability amongst family members regarding their desired level of participation in medical decision-making, so clinicians are best served by assessing this on an individualized basis and adapting their approach to the preferences of the family member as well as the circumstances of the patient. In Europe and in Israel, for example, a parentalist approach is more common than in the US. The ETHICUS study, evaluating differences in end-of-life care in ICUs across European countries and Israel, found that a minority of end-of-life decisions were discussed with family. The authors speculated that this mainly reflected situations in which further medical intervention was thought by physicians to be unwarranted. Geographic differences in sharing of prognostic data with patients exist as well—with only a minority of Japanese physicians and patients agreeing that a patient should be informed of an incurable cancer diagnosis before their family, and a majority of US physicians and patients agreeing with such a statement. Other studies as well have supported the finding that particular ethnic groups (Asians and Latinos, specifically) support a more family-centred approach to medical decision-making than other groups. These studies again suggest the need for an individualized, tailored approach specific to each clinical situation, taking into account geographic location, family dynamics, prognosis, and cultural factors.

Surrogate decision-making

Because most patients receiving end-of-life care in the ICU either lack decisional capacity or the ability to communicate, clinicians often turn to surrogate decision-makers for assistance with medical decision-making. Laws regarding designation of a proxy decision-maker, in the absence of a patient-selected surrogate, vary widely by country [10]. Many physicians expect that surrogates will utilize substituted judgment when making decisions on behalf of the patient (i.e. 'What would the patient say about their preferences if they were able to talk to us right now?'). However, some patients express a preference for surrogates to abide by best interest standard when participating in decision-making. Data suggest that, in practice, proxies actually rely on many factors including substituted judgement and the bests interests of the patient, as well their own values and best interests. Multiple studies from a variety of countries have shown that surrogate accuracy in describing the

Box 387.1 VALUE mnemonic

- **V:** Value and appreciate statements from family.
- **A:** Acknowledge emotion.
- **L:** Listen.
- **U:** Understand the patient as a person.
- **E:** Elicit questions.

wishes of patients is often poor. However, the accuracy of substituted judgments has been positively associated with patients having spoken with their surrogate in advance about care preferences.

The job of a surrogate decision-maker can come at a cost: in one study, over half of surrogate decision-makers suffered symptoms of learned helplessness, characterized by reduced motivation, difficulty in determining causality, and depression. Multiple studies have found an increased risk of psychological symptoms for family members and surrogate decision-makers of patients who died in an ICU—including depression, anxiety, panic disorder, post-traumatic stress symptoms, and complicated grief [11–13].

Because effective surrogate decision-making can be very difficult for many family members and many patients have not expressed clear treatment preferences prior to critical illness, ICU clinicians are frequently in the position of helping family members identify patients' values, exploring how those values might lead to specific treatment preferences, and interpreting how the preferences inform specific treatment decisions that need to be made. ICU clinicians can help family members with this process by asking directed questions about the patient's values and goals and the aspects of life most important to the patient.

Communication

Communication with an interdisciplinary team

Critical care provision relies on the skills and coordination of various staff and specialists. Interdisciplinary communication around end-of-life care in the ICU significantly augments the quality of care that is provided, though is variable across practice sites and countries. Interdisciplinary communication is valued by terminally ill patients and their families [14]. Caring for dying patients, withdrawing life support, and conflict among clinicians are all independently associated with burnout among nursing staff as well [15]. Burnout among critical care physicians is lower among those who maintain positive working relationships with nursing staff, and higher in individuals who experience conflict with colleagues and staff [16], highlighting the need to enhance interdisciplinary collaboration to provide a sustainable work environment for all ICU staff.

Communication with patients and families

Skilled communication is one of the core tools of any physician addressing end-of-life care. While every medical case, patient, and family, are different, several principles can help guide clinicians in leading family conferences:

- Families of critically-ill patients are more satisfied when physicians spend more time listening and less time talking [17].
- Families benefit from explicit reassurance that patients will not suffer, from statements of support for the medical decisions they have made, and from statements that they and the patient will not be abandoned [18].
- Family satisfaction increases when physicians express empathy explicitly.

A randomized controlled trial from France found that use of a specific communication strategy (see Box 387.1) and a bereavement brochure led to lower rates of post-traumatic stress symptoms, anxiety, and depression among surviving family members [19]. Notably, the conferences implementing this standardized

Table 387.1 Approach for effective family conferences in the ICU

Stage	Components to consider
Preparation	◆ Conduct conference early within the ICU stay ◆ Find a quiet, private space for the conference [12], with chairs for all participants ◆ Hold a 'pre-conference' with participating clinicians to ensure common goals and messages
Conducting the conference	◆ Speak less, listen more [18] ◆ Use empathic language [19,20] to acknowledge family emotions ◆ Explicitly acknowledge the difficulty of having an ill loved one, and of surrogate decision-making ◆ Discuss patient values, hopes, fears, and treatment preferences ◆ Remind surrogate decision-makers of their role in invoking substituted judgment ◆ Assure families that all attempts will be made to prevent patient suffering ◆ Make explicit statements about non-abandonment of the patient and family [19] ◆ Provide support for decisions made by family [19]
Closing the conference	◆ Ask the family to summarize what they understand from the discussion and what further questions they have ◆ Summarize next steps and a follow-up plan

Data from various sources (see references).

approach also were longer in duration, had a higher proportion of family speech, and a higher proportion of nurse speech, though it is not clear which of these factors was causative.

The multi-disciplinary ICU family conference is a key component of high quality care for critically-ill patients and their families.

Addressing spirituality

Spiritual concerns on the part of patients and/or their surrogates are prominent at the end of life, and physicians often feel ill-equipped to address these issues. Family satisfaction and feelings of support increase when spiritual needs are discussed with clinicians and addressed by spiritual care providers.

Cross-cultural communication and working with interpreters

Communication across cultures and languages can create additional barriers in communication and can lead to miscommunication and misunderstandings. In an observational study of family conferences utilizing a professional medical interpreter, alterations (including additions, omissions, substitutions, and editorializations) occurred over 50% of the time, with three-quarters of the alterations thought to have clinically significant impact, the vast majority of those being negative [20]. Interpreted conferences have been found to be shorter in length, and contain fewer physician statements of family support than non-interpreted conferences. Best practices include:

- Briefing and debriefing with interpreter before and after family conferences.
- Clarifying the interpreter's role as strict interpreter or cultural broker.
- Introduction of interpreter and their role to the patient/surrogate(s).
- Triangular seating arrangement for patient/surrogate(s), interpreter, and clinician.
- Eye contact with patient/surrogate(s), addressing patient/surrogate(s) in the first-person.
- Speaking slowly and ensuring only one person is speaking at at time.
- Request for direct and complete translation from the interpreter.
- Explicit identification of misunderstandings by the interpreter.

Specific communication challenges—health care directives and advance care planning

Advance care planning and completion of health care directives/living wills have been promoted by many as a mechanism to allow better understanding of patients' care preferences and values. These are rarely completed in the critical care setting, but occasionally, a pre-existing advance directive helps to shape and frame discussions with surrogate decision-makers. An extensive literature demonstrates the poor performance of health care directives—pointing to their inadequacy in realistically identifying the types of medical decisions that are most salient at the end of life, and failing to capture the evolution in preferences that often occur over the course of a complex illness. However, advance directives are associated with higher surrogate ratings of quality of dying and with lower burden on surrogates.

Recent studies suggest that communication about end-of-life care among patients with cancer is associated with increased quality of life and reduction in the use of intensive life-sustaining treatments and reduced health care costs at the end of life. A randomized trial targeting hospitalized patients over age 80 showed that advance care planning was associated with improved quality of life and reduced ICU use at the end of life as well as reduced psychological symptoms among family members. These studies suggest promise for advance care planning to improve quality of life and quality of care while simultaneously reducing intensive care use at the end of life.

Specific communication challenges—discussing resuscitation preferences

Resuscitation preferences are commonly addressed in discussions with patients and families in the critical care setting and these discussions present unique challenges to clinicians. Patient preferences, followed by short-term prognosis, are the biggest factor in determining Do Not Attempt Resuscitation (DNAR) status in the ICU setting. Studies have shown that patients routinely overestimate their survival post-resuscitation and these overestimates may be associated with consumption of television medical dramas, which themselves have historically portrayed unrealistically high in-hospital CPR survival rates. Knowledge of actual CPR survival rates has been shown to affect patient preferences. Patients who choose to be full code are more likely to think of resuscitation abstractly as a means to restore life, and DNAR status as a sign of inferior care while patients who opt for DNAR status are more likely to think of resuscitation in terms of suffering and futility, and see DNAR orders as a means towards a natural death. With this in mind, several core messages can help clinicians communicate with patients and surrogates about resuscitation:

- Emphasizing that resuscitation occurs in the setting of patient death, rather than resorting to euphemistic language, such as 'restarting the heart'.
- Describing the alternative to resuscitation, namely, natural death with comfort-focused care.
- When appropriate, using CPR survival data to help patients understand their probability of surviving resuscitation.

Conclusion

In summary, critical care services, while potentially life-saving, are increasingly utilized at the end of life, particularly for older patients. Utilization of these intensive resources can cause stress and distress for critically-ill patients and their families and requires careful consideration on the part of clinicians. Though shared decision-making has been endorsed as a preferred approach, patients and their surrogate decision-makers have variable preferences with regard to their desired level of involvement in medical decision-making, and this is best evaluated on an individual basis. Effective communication, both outside of the ICU through, for example, advance care planning, and inside the ICU, such as during family conferences, can benefit patients, their families, clinicians, and health care systems as a whole.

References

1. Angus DC, Barnato AE, Linde-Zwirble WT, et al. (2004). Use of intensive care at the end of life in the United States: an epidemiologic study. *Critical Care Medicine*, **32**(3), 638–43.

2. Wunsch H, Angus DC, Harrison DA, et al. (2008). Variation in critical care services across North America and Western Europe. *Critical Care Medicine*, **36**(10), p. 2787–93, e1–9.
3. Fair allocation of intensive care unit resources. (1997). American Thoracic Society. *American Journal of Respiratory Critical Care Medicine*, **156**(4 Pt 1), 1282–301.
4. Sprung CL, Cohen SL, Sjokvist P, et al. (2003). End-of-life practices in European intensive care units: the Ethicus Study. *Journal of the American Medical Association*, **290**(6), 790–7.
5. Azoulay E, Metnitz B, Sprung CL, et al. (2009). End-of-life practices in 282 intensive care units: data from the SAPS 3 database. *Intensive Care Medicine*, **35**(4), 623–30.
6. Sprung CL, Maia P, Bulow HH, et al. (2007). The importance of religious affiliation and culture on end-of-life decisions in European intensive care units. *Intensive Care Medicine*, **33**(10), 1732–9.
7. Wunsch H, Linde-Zwirble WT, Harrison DA, et al. (2009). Use of intensive care services during terminal hospitalizations in England and the United States. *American Journal of Respiratory Critical Care Medicine*, **180**(9), 875–80.
8. Azoulay E, Pochard F, Chevret S, et al. (2004). Half the family members of intensive care unit patients do not want to share in the decision-making process: a study in 78 French intensive care units. *Critical Care Medicine*, **32**(9), 1832–8.
9. White DB, Evans LR, Bautista CA, et al. (2009). Are physicians' recommendations to limit life support beneficial or burdensome? Bringing empirical data to the debate. *American Journal of Respiratory Critical Care Medicine*, **180**(4), 320–5.
10. Lautrette A, Peigne V, Watts J, et al. (2008). Surrogate decision makers for incompetent ICU patients: a European perspective. *Current Opinions on Critical Care*, **14**(6), 714–19.
11. Siegel MD, Hayes E, Vanderwerker LC, et al. (2008). Psychiatric illness in the next of kin of patients who die in the intensive care unit. *Critical Care Medicine*, **36**(6), 1722–8.
12. Pochard F, Azoulay E, Chevret S, et al. (2001). Symptoms of anxiety and depression in family members of intensive care unit patients: ethical hypothesis regarding decision-making capacity. *Critical Care Medicine*, **29**(10), 1893–7.
13. Azoulay E, Pochard F, Kentish-Barnes N, et al. (2005). Risk of post-traumatic stress symptoms in family members of intensive care unit patients. *American Journal of Respiratory Critical Care Medicine*, **171**(9), 987–94.
14. Carline JD, Curtis JR, Wenrich MD, et al. (2003). Physicians' interactions with health care teams and systems in the care of dying patients: perspectives of dying patients, family members, and health care professionals. *Journal of Pain Symptom Management*, **25**(1), 19–28.
15. Poncet MC, Toullic P, Papazian L, et al. (2007). Burnout syndrome in critical care nursing staff. *American Journal of Respiratory Critical Care Medicine*, **175**(7), 698–704.
16. Embriaco N, Azoulay E, Barrau K, et al. (2007). High level of burnout in intensivists: prevalence and associated factors. *American Journal of Respiratory Critical Care Medicine*, **175**(7), 686–92.
17. McDonagh JR, Elliott TB, Engelberg RA, et al. (2004). Family satisfaction with family conferences about end-of-life care in the intensive care unit: increased proportion of family speech is associated with increased satisfaction. *Critical Care Medicine*, **32**(7), 1484–8.
18. Stapleton RD, Engelberg RA, Wenrich MD, et al. (2006). Clinician statements and family satisfaction with family conferences in the intensive care unit. *Critical Care Medicine*, **34**(6), 1679–85.
19. Curtis JR Engelberg RA, Wenrich MD, et al. (2002). Studying communication about end-of-life care during the ICU family conference: development of a framework. *Journal of Critical Care*, **17**(3), 147–60.
20. Pham K, Thornton JD, Engelberg RA, et al. (2008). Alterations during medical interpretation of ICU family conferences that interfere with or enhance communication. *Chest*, **134**(1), 109–16.

CHAPTER 388

Management of the dying patient

Judith E. Nelson and Aluko A. Hope

Key points

- Limitation of life-supporting therapies in anticipation of death has become common in Intensive Care Units (ICUs) around the world.
- Like other clinical procedures performed by intensive care clinicians, life support limitation should be approached with careful attention to relevant evidence, standards of quality, and involvement of the interdisciplinary ICU team.
- ICU clinicians should avoid use of phrases like 'withdrawal of care' and 'nothing more we can do', but instead emphasize their ability to achieve the patient's values, control patient distress, and provide family support.
- A decision to withhold any life-sustaining therapy should prompt a critical review of the rationale for continuing other such therapies.
- Knowledge of underlying principles and best practices for limitation of life support, together with skills for clear and empathic communication, are core competencies for intensive care clinicians.

Introduction

The withdrawal or withholding of life-supporting therapies in anticipation of death has become common in ICUs around the world [1]. Most ICU deaths in the US involve life support limitation [2]. In other parts of the world, the proportion of deaths following withdrawal or withholding of life support ranges from about one-quarter to two-thirds, depending on the region [3]. Thus, knowledge and skill related to limitation of life support, including processes of communication, decision-making, and implementation, are essential for delivery of high-quality intensive care. In this chapter, we synthesize existing relevant evidence and provide recommendations based on the best available data for approaching this important area of critical care practice.

Legal and ethical frameworks

In the US and many other countries, withholding (refraining from starting a treatment) and withdrawal (stopping a treatment that is already underway) of life supporting therapy are both acceptable, legally and ethically [4]. Thus, when prognosis is uncertain, a time-limited trial of life support may be initiated without an irrevocable commitment to continued treatment. In practice, clinicians as well as patients and families often find withdrawing a treatment more emotionally difficult than withholding. Intensive care treatment is not withdrawn in some countries [1]. Key ethical and legal principles related to US practice are summarized in Box 388.1.

Advance directives allow the patient to specify preferences regarding specific life-sustaining therapies (a living will), and/or to authorize a surrogate to make medical decisions if the patient becomes incapacitated (a health care proxy or durable power of attorney for health care). When the patient lacks decision-making capacity, the right to refuse life-sustaining treatment is extended to a surrogate appointed by the patient or designated by applicable law. Standards for life-support limitation by surrogates vary from state to state in the US, as does the legal hierarchy of individuals who serve as surrogate decision-makers in the absence of a designation by the patient. Wherever they practice, intensive care clinicians must be familiar with the applicable local provisions.

In the US, a growing number of states have established templates that allow written directives to be translated into medical orders that are accessible across multiple venues in the health care system; The 'POLST' (Physician Orders for Life Sustaining Treatment) [5] is one example. A pre-printed, checklist order form addressing specific life-sustaining treatments provides the basis for discussion by the clinician with the patient or the surrogate. The completed form operationalizes the patient's preferences as medical orders, which can be changed or updated at any time.

Communication and decision-making

Since some patients and families may choose to continue intensive care therapies primarily out of fear that limitation will inevitably be accompanied by patient suffering, it is important for clinicians to provide assurance that the patient's comfort can and will be maintained. Families are more satisfied when assured that the patient undergoing life support limitation will not suffer or be abandoned prior to death. ICU clinicians should avoid use of phrases like 'withdrawal of care' and 'nothing more we can do', but instead emphasize their ability to achieve the patient's values, control patient distress, and provide continuing patient and family support.

Physicians frequently miss opportunities to acknowledge and address emotions experienced by patients and families facing life-threatening illness [6]. Incorporation of empathic statements in clinician communication, which helps to modulate emotions and to enhance trust in clinicians, is supported by expert opinion and

Box 388.1 Key ethical and legal principles for limitation of life-supporting treatment

- Based on the principle of autonomy and the patient's right to refuse any therapy, limitation of life support is ethically and legally justified.
- Withholding (refraining from starting a treatment) and withdrawal (stopping a treatment that is already underway) of therapy are ethically and legally equivalent, although families and clinicians may perceive them differently in practice.
- When a patient lacks decision-making capacity, their right to refuse life-sustaining treatment is extended to a surrogate appointed by the patient or designated by applicable law.
- When there is evidence of the patient's values and preferences, surrogate decisions should use 'substituted judgment', i.e. what the patient (having capacity) would decide under the circumstances.
- If the patient's wishes are unknown, decisions are to be made in the 'best interests' of the patient, promoting the patient's overall well-being by weighing the benefits and burdens of intensive care therapies.
- In controlling patient symptoms, clinicians may intervene in ways that may hasten the patient's death as a foreseeable but unintended effect when the intent is to relieve patient suffering ('doctrine of double effect').

empirical data [6]. The intensivist needs skills for listening as well as delivering information about the patient's condition and prognosis. The family's proportion of speaking time in an ICU meeting with clinicians is related to family satisfaction [7]. Recommendations have been provided for approaching patients and family members who prefer continuation of life-supporting treatments based on the belief that a miracle will occur [8], and those who insist on 'everything' despite a clinician's view that the treatments will not have meaningful benefit.

Critical care guidelines endorse a shared decision-making model in which both the patient or family and the physician play an active role [9], but there is a wide continuum of preferred roles among patients and families, and varying roles for clinicians across different countries, regions, and cultures [1]. In general, it is appropriate for clinicians, after investigating the patient's values and preferences, to offer a recommendation reflecting best medical judgment. Besides fulfilling a professional responsibility, the clinician's recommendation may help to address the stress, guilt, doubt, and fear that plague many surrogates making major treatment decisions for others. Some ICUs distribute printed informational materials such as a brochure to families to help them prepare for surrogate decision-making.

Decisions about the limitation of life support often give rise to conflict [10]. In a large, multinational survey, conflicts (between nurses and physicians, among nurses, and between staff and relatives) were reported by over 70% of responding clinicians, with end-of-life care representing a major source of discord and attendant job strain [10]. Clinicians' decisions to limit life sustaining treatments are influenced by diverse factors apart from patients' wishes, including such provider-level factors such as number of years since completing training, specialty, experience working in ICUs, gender, cultural background, and religious beliefs [11]. For a variety of reasons that are thought to include an exaggerated sense of personal responsibility for the patient's outcome and a perceived 'covenantal bond' to continue life-sustaining treatment [12], surgeons may be less willing to accept withdrawal of intensive care therapies after surgery. Recognition of diverse influences including nonclinical and idiosyncratic factors is valuable for prioritizing attention to patient-focused concerns and for promoting consensus among the patient, family, and multiple members of the health care team.

When conflicts arise over the use of life support, a process oriented approach informed by the most common reasons for conflicts may facilitate consensus [13]. The intensive care clinician should always first explore the family's current understanding of what has happened and what is expected. After describing the medical situation as perceived by the clinical team, the intensivist can then address other potential sources of conflict. These include discordant perceptions of appropriate roles (e.g. the family feels obligated to pursue every treatment to extend life, while the physician feels responsible to limit treatments thought to be futile and the nurse to protect the patient's dignity and comfort during the dying process); distrust of the team based on past experiences or cultural factors; and strong emotions such as grief or fear. Exploration of spiritual beliefs may also be important. Experts have recommended a 'differential diagnosis' approach to conflict over decisions to limit treatment [13]. Strategies for promoting consensus are summarized in Box 388.2.

Life-supporting treatments

Mechanical ventilation is the form of life support that is most frequently withheld or withdrawn in anticipation of death in the ICU.

Box 388.2 Strategies for promoting consensus in decision-making about limitation of life support

- Distribute printed information that describes a family meeting and guides the family on how to prepare.
- Coordinate the approach among all members of the clinical team.
- Elicit the family's understanding of what has happened and what is expected.
- Clarify the medical situation as perceived by the clinical team.
- Attend to family emotions (e.g. grief, fear, guilt) through empathic communication.
- Investigate other potential sources of conflict, such as role clash, distrust, spiritual beliefs.
- Allow the family to speak and ask questions.
- Focus attention on the patient's values, goals and preference.
- Provide reassurance about symptom control and non-abandonment.
- Offer a professional recommendation to a receptive family.
- Validate the family's intentions and their approach to decision-making.
- Support the family's decision while optimizing patient comfort and dignity.

Life-sustaining therapy may also include vasopressor medications, renal replacement, transfusions, antibiotics, tube feeding, intravenous hydration, and other modalities without which the patient's death would be expected [14]. Although ethically equivalent, limitation of individual treatments tends to be sequential rather than simultaneous, and withdrawal of mechanical ventilation usually occurs as a late event [15]. Although withdrawal of artificial nutrition rarely causes discomfort for seriously ill patients, nutrition is often limited only as a last step, likely because of the symbolic importance of food for many families.

An observational study of 14 hospitals in one metropolitan area in the Northwest US found that withdrawal of all life-sustaining interventions occurred over more than 1 day for nearly half of the patients [15]. Among long stay patients, a longer duration of the process of withdrawal was associated in this study with greater family satisfaction with care [15]. 'Stuttering withdrawal', however, is not considered optimal by most expert guidelines. Guidelines suggest that a decision to withhold one life-sustaining therapy should prompt a critical review of the rationale for continuing all other therapies [14]. Ongoing phlebotomy and imaging should be reconsidered and all medications should be re-evaluated. Deactivation of a pacemaker or automatic implantable cardiac defibrillator should also be addressed. A Task Force of the Society of Critical Care Medicine has provided a conceptual framework and recommendations for the use of non-invasive ventilation in patients who have foregone endotracheal intubation and invasive ventilation, emphasizing clarity about care goals and weighing of therapeutic benefits and burdens [16].

Life support limitation: a clinical procedure

Like other clinical procedures, limitation of life support requires expertize, careful preparation, and consistent implementation in accordance with the best available evidence, appropriate documentation, interdisciplinary collaboration, and ongoing evaluation. Inexperienced clinicians should not perform this procedure independently until they have demonstrated their competence in a supervised setting. Ideally, an attending physician and an experienced nurse with specific relevant training will both play an active role. Input from all team members should be invited in formulating and implementing the final plan.

Preparing the patient and family

Most patients and families do not know what to expect, fear the unknown, and take comfort from a straightforward, sensitive, description of common scenarios after limitation of life support. A key point for clinicians to communicate, however, is that a degree of uncertainty is inherent with respect to the patient's responses—a small minority of patients will survive to hospital discharge after life support limitation. For non-survivors, the duration of the dying process is variable. Broad estimates based on the patient's clinical condition (for example, minutes to hours or hours to days) can be cautiously offered.

The family should be reassured that the clinical team will respond immediately and effectively to any patient distress. Since families (and even some clinicians) may not understand acceptable approaches to symptom control at the end of life, it is helpful to review the basic principles. The doctrine of double effect provides justification for the use of opiates and sedatives at any dose needed to maintain the comfort of the patient, even if the clinician sees a potential for drug-related respiratory depression or hypotension [14]. Clinicians may wish to address timing and setting along with other aspects of the process of forgoing life support. A family may have reasons to delay implementation—for example, to give an out-of-town relative time to make a final visit, or to allow arrangements for a funeral that by religious law must occur quickly after death. Conversely, rapid withdrawal of life support may be requested by a family that finds it more painful to postpone an inevitable outcome. The clinical team should endeavour to accommodate the family's preferred schedule. Consideration may be given to transfer of the patient to a more private and peaceful setting, such as a Palliative Care Unit or a private room on a regular hospital ward with arrangements for close monitoring of symptoms. When a patient and family have developed important relationships with the critical care team, symptom needs are expected to require intensive nursing, or continuity of care would be compromised by transfer, the ICU may be the optimal place for withdrawal of life sustaining therapies. Efforts to optimize the environment might then include closing curtains, liberalizing family visits, and removing all tubes, lines, and drains that are not necessary for the patient's comfort. Electronic monitoring should be discontinued so that alarms do not disturb the patient or family and attention remains focused on the patient rather than on irrelevant technology. Expert recommendations suggest a specific conversation with family and staff about the rationale for removing monitors in order to alleviate anxiety.

Families should feel they have the option, but not an obligation to be with the patient during or after discontinuation of treatments or at the time of the patient's death. A non-judgmental, open-ended approach by the clinician, with reassurance that the patient will be continuously attended by staff, will allow the family to express true preferences and help relieve guilt or other concerns for those who decide to leave. For families who plan to stay, a description of the procedure and expected patient responses should be offered. The family can be prepared for the possibility of noise from respiratory secretions, a range of breathing patterns (fast, slow, deep, shallow), snoring, muscle twitching, and progressive slowing of heart rate, and lowering of blood pressure. Most families welcome an inquiry about religious or spiritual traditions they may wish to observe, and an offer of pastoral care. The family may also value the opportunity to speak with a social worker and/or an organ donation coordinator.

Methods of withdrawing mechanical ventilation from an endotracheally-intubated patient

No comparative evidence identifies the optimal strategy for separating a patient from the ventilator. Some clinicians withdraw ventilator and endotracheal tube in one step. Others maintain the artificial airway to protect against obstruction and permit access for suctioning. Another approach involves incremental reduction of oxygen and ventilatory support over a relatively short period (e.g. 10–30 minutes), followed by complete withdrawal of the ventilator. The last strategy allows for titration of medications to address symptoms during the period of final 'weaning'.

Symptom control

Approaches to symptom control can be broadly categorized as 'pre-emptive' (i.e. the patient is medicated with opiates and/

or sedatives before withdrawing life support) and 'reactive' (i.e. medications are given if patient distress is actually observed). Pre-emptive treatment might be given when the patient's death is expected imminently after withdrawal and the patient is either already in distress or such distress is anticipated. Although the use of general anaesthesia ('pre-emptive high doses of opioids and sedatives for anaesthesia or at least deep sedation to assure comfort') has been proposed for the 'potentially conscious and imminently dying patient', this strategy may be appropriate only when consistent with the patient's values and when the risk of distress is sufficiently high to justify the risk of hastening the patient's death. For the patient with a reasonable prospect of surviving after separation from the ventilator, treatment would be deferred unless and until the patient manifested signs of (or self-reported) distress. There is no reason to medicate a patient who is brain dead. All other patients undergoing withdrawal of life support must be carefully assessed for distressing symptoms throughout the process [18]. Tools are available for behavioural assessment of pain and dyspnoea [19]. Ample doses of opiates and sedatives (as infusions and boluses), along with sufficient staff, should be immediately available at the bedside. Dosing is limited only by the principle of proportionality (i.e. treatment should be proportional to the patient's symptoms). Documentation in the medical record by both physicians and nurses should clearly reflect this relationship. Expert recommendations are available to guide management of symptoms including pain, dyspnoea, and delirium for critically-ill patients at the end of life [14].

Noisy breathing, with unpleasant, gurgling sounds, often occurs during the dying process, causing distress for some families and ICU staff. Pharmacologic approaches include glycopyrronium bromide, hyoscine (scopolamine), atropine, and octreotide. Since glycopyrronium bromide does not cross the blood brain barrier, there is reason to believe it can reduce pharyngeal and tracheobronchial secretions with less risk of central effects than hyoscine or atropine. Non-pharmacologic interventions, such as repositioning and gentle suctioning, may also be helpful for some patients.

Neuromuscular blocking agents should never be introduced when the ventilator is withdrawn [14]. For patients who have already received such a medication, withdrawal of mechanical ventilation should be deferred until neuromuscular function is restored. If neuromuscular blockade cannot be reversed without an unacceptable delay, it may be appropriate to proceed, with close attention to physiologic signs of distress and liberal use of comfort medications.

The ICU nurse and withdrawal of life support

The ICU nurse is involved more directly and frequently with the patient undergoing limitation of life support, and with the patient's family, than any other clinician. In a U.S. national survey, two-thirds of nurse respondents experienced emotional difficulty with the process of limiting life support, but more than 60% reported that physicians did not usually provide emotional support, for which they looked instead to their colleagues and even to patients' families [19]. The presence of a physician during this process is an important form of support both for nurses and families. Ideally, this presence continues during the post-mortem care, which is often a lonely and psychologically difficult part of the nurse's work. Reducing the nurse-patient ratio to 1-to-1 during withdrawal of life support, and providing the primary nurse at least a brief period of respite after a patient's death, are among strategies to improve the practice environment and patient care. The End-of-Life Nursing Education Consortium (ELNEC) project [20] provides specialized training and extensive curricular materials in palliative and end-of-life care including limitation of life support for nurses.

Conclusion

Increasing sophistication and application of life-supporting technologies have been accompanied by a growing need for expertise in limiting their use when burdens exceed potential benefits for critically-ill patients. Like other clinical procedures performed by intensive care clinicians, withholding and withdrawing life support should be approached with careful attention to relevant evidence, standards of quality, and involvement of the interdisciplinary ICU team. Knowledge of underlying principles and best practices for limitation of life support, together with skills for clear and empathic communication, are core competencies for intensive care clinicians.

References

1. Sprung CL, Cohen SL, Sjokvist P, et al. (2003). End-of-life practices in European intensive care units: the Ethicus Study. *Journal of the American Medical Association*, **290**, 790–7.
2. Prendergast TJ and Luce JM. (1997). Increasing incidence of withholding and withdrawal of life support from the critically ill. *American Journal of Respiratory Critical Care Medicine*, **155**, 15–20.
3. Azoulay E, Metnitz B, Sprung CL, et al. (2009). End-of-life practices in 282 intensive care units: data from the SAPS 3 database. *Intensive Care Medicine*, **35**, 623–30.
4. Luce JM and Alpers A. (2000). Legal aspects of withholding and withdrawing life support from critically ill patients in the United States and providing palliative care to them. *American Journal of Respiratory Critical Care Medicine*, **162**, 2029–32.
5. Physician Orders for Life Sustaining Treating Program Paradigm. Available at: http://www.ohsu.edu/polst/ (accessed 20 February, 2014).
6. Selph RB, Shiang J, Engelberg R, Curtis JR, and White DB. (2008). Empathy and life support decisions in intensive care units. *Journal of General Internal Medicine*, **23**, 1311–17.
7. McDonagh JR, Elliott TB, Engelberg RA, et al. (2004). Family satisfaction with family conferences about end-of-life care in the intensive care unit: increased proportion of family speech is associated with increased satisfaction. *Critical Care Medicine*, **32**, 1484–8.
8. Widera EW, Rosenfeld KE, Fromme EK, Sulmasy DP, and Arnold RM. (2011). Approaching patients and family members who hope for a miracle. *Journal of Pain Symptom Management*, **42**, 119–25.
9. Davidson JE, Powers K, Hedayat KM, et al. (2007).Clinical practice guidelines for support of the family in the patient-centered intensive care unit: American College of Critical Care Medicine Task Force 2004–2005. *Critical Care Medicine*, **35**, 605–22.
10. Azoulay E, Timsit JF, Sprung CL, et al. (2009). Prevalence and factors of intensive care unit conflicts: the conflicus study. *American Journal of Respiratory Critical Care Medicine*, **180**, 853–60.
11. Cook DJ, Guyatt GH, Jaeschke R, et al. (1995). Determinants in Canadian health care workers of the decision to withdraw life support from the critically ill. Canadian Critical Care Trials Group. *Journal of the American Medical Association*, **273**, 703–8.
12. Schwarze ML, Bradley CT, and Brasel KJ. (2010). Surgical 'buy-in': the contractual relationship between surgeons and patients that influences decisions regarding life-supporting therapy. *Critical Care Medicine*, **38**, 843–8.
13. Goold SD, Williams B, Arnold RM. (2000). Conflicts regarding decisions to limit treatment: a differential diagnosis. *Journal of the American Medical Association*, **283**, 909–14.

14. Truog RD, Campbell ML, Curtis JR, et al. (2008). Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College of Critical Care Medicine. *Critical Care Medicine*, **36**, 953–63.
15. Gerstel E, Engelberg RA, Koepsell T, and Curtis JR. (2008). Duration of withdrawal of life support in the intensive care unit and association with family satisfaction. *American Journal of Respiratory Critical Care Medicine*, **178**, 798–804.
16. Curtis JR, Cook DJ, Sinuff T, et al. (2007). Noninvasive positive pressure ventilation in critical and palliative care settings: understanding the goals of therapy. *Critical Care Medicine*, **35**, 932–9.
17. Billings JA. (2012). Humane terminal extubation reconsidered: the role for preemptive analgesia and sedation. *Critical Care Medicine*, **40**, 625–30
18. Campbell ML, Templin T, and Walch J. (2010). A Respiratory Distress Observation Scale for patients unable to self-report dyspnea. *Journal of Palliative Medicine*, **13**, 285–90.
19. Kirchhoff KT and Kowalkowski JA. (2010). Current practices for withdrawal of life support in intensive care units. *American Journal of Critical Care*, **19**, 532–41.
20. American Association of Colleges of Nurses (2014). End-of-life nursing education consortium (ELNEC). Available at: http://www.aacn.nche.edu/ELNEC/ (accessed 4 March, 2014).

PART 22.2

Management of the potential organ donor

CHAPTER 389

Beating heart organ donation

Martin Smith

Key points

- Donation after brain death provides an opportunity to maximize the number and condition of organs for transplantation, and currently the only reliable source of donor hearts.
- Brain death is associated with haemodynamic instability and other physiological changes that can jeopardize donor organ function.
- Aggressive donor management increases the number of potential donors who become actual donors, increases the total number of organs transplanted per donor, and improves transplantation outcomes.
- Optimization of haemodynamic variables is the cornerstone of donor management.
- Hormone replacement remains controversial and should only be used in unstable donors requiring large doses of vasopressors, or in those with poor ventricular function.

Introduction

Transplantation is the optimal treatment of end-stage dysfunction of many organs and can be life-saving. The principal factor restricting access to transplantation is the availability of suitable donor organs; there is an ever widening gap between the rising demands for transplantation and a diminishing supply of organs. Although living donation and donation after circulatory death are important and increasing sources of organs for transplantation, it is donation after brain death (DBD) that remains the most important. In DBD there is the opportunity to maximize the number and condition of potentially transplantable organs and also to provide a reliable source of hearts for transplantation.

The process of donation

Organ donor management begins with timely identification of potential donors, including those with a severe neurological injury that is likely to progress to brain death. Although adequate time must be allowed for the proper confirmation of brain death, unnecessary delays should be avoided because the incidence of systemic complications that jeopardise transplantable organ function increases progressively with time. Once brain death has been confirmed there should be a uniform request for consent for donation undertaken in conjunction with a representative from the local organ donation/procurement organization.

Following the confirmation of brain death there is a change in emphasis of care. Brain protective strategies that have previously been aimed at preserving residual brain function are replaced by physiological support designed to optimize organ function for subsequent transplantation. If a patient wishes to become an organ donor, it is the duty of the intensive care team to fulfil this wish by providing organs in the optimum condition. The management of the potential organ donor is thus the beginning of the management of up to seven potential recipients (Table 389.1).

Physiological changes after brain death

Brain death is associated with profound physiological changes that can jeopardize transplantable organ function (Table 389.2).

Cardiovascular changes

Intractable increases in intracranial pressure (ICP), usually following catastrophic neurological injury, may lead to brain ischaemia, cerebral herniation, and brain death. As ICP increases, brainstem ischaemia progresses in a rostral-caudal direction with typical clinical correlates. Cerebral ischaemia precipitates vagal activation resulting in bradycardia and hypotension. Pontine ischaemia produces a mixed vagal and sympathetic activation, and the classic Cushing response characterized by bradycardia and hypertension. Finally, ischaemia of the medulla results in a massive autonomic sympathetic surge in a last ditch attempt to maintain cerebral perfusion [1]. This sympathetic storm, which lasts between one and six hours, increases heart rate, blood pressure, cardiac output, and systemic vascular resistance, and leads to central redistribution of blood volume, increased cardiac afterload, and splanchnic ischaemia [2]. It is also associated with widespread myocardial damage characterized by mitochondrial swelling, myocytolysis, and necrosis in up to 25% of donor hearts. Myocardial dysfunction, demonstrated by echocardiography, occurs in approximately 40% of brain dead donors [3].

Following the onset of brain death, the period of intense autonomic activity is followed by loss of sympathetic tone, profound vasodilatation and capillary leakage. The resulting hypotension and hypovolaemia is compounded by central diabetes insipidus and causes donor organ hypoperfusion if untreated.

ECG abnormalities are common after brain death and include ST segment and T wave changes, atrial and ventricular arrhythmias, and conduction abnormalities. They are multifactorial in origin reflecting loss of vagal tone, sympathetic over activity, myocardial ischaemia, blood gas and electrolyte abnormalities, as well as the effects of drug therapy.

Respiratory changes

The cardiovascular changes associated with the sympathetic storm lead to increases in pulmonary hydrostatic pressure, capillary

Table 389.1 Physiological goals during donor management

System	Variable	Target range
Cardiovascular	Heart rate	60–120/min
	Systolic blood pressure	>100 mmHg
	Mean blood pressure	>70 mmHg
	Cardiac index	2.4 L/min/m^2
Ventilation	Tidal volume	8–10 mL/kg
	Positive end expiratory pressure	5 cmH_20 (15 cmH_20 during recruitment manoeuvres)
	Peak airway pressure	<30 cmH_2O
Arterial blood gases	pH	7.35–7.45
	PaO_2	>10.5 kPa
	$PaCO_2$	4.7–6.0 kPa
	SpO_2	≥95%
Electrolytes	Sodium	130–150 mmol/L
	Potassium, calcium, magnesium, phosphate	Normal range
	Glucose	4–8 mmol/L
Urine output		0.5–3 mL/kg/hour
Haemoglobin		>10.0 g/dL

endothelial damage, and the risk of pulmonary oedema. Pulmonary damage is aggravated by the profound inflammatory response associated with brain death [4].

Endocrine and metabolic changes

Brain death is associated with hypothalamic and pituitary dysfunction or failure characterized by a classic endocrinopathy and thermoregulatory impairment. In particular, there are decreases in circulating tri-iodothyronine (T3), cortisol, and anti-diuretic hormone (ADH) which may contribute to cardiovascular deterioration [2]. The changes in anterior pituitary function are variable because pituitary blood flow may be preserved to some extent after brain death. Reduction in circulating T3 concentration occurs in 60–80% of brain dead donors, but only a few (around 15%) have very low levels [5]. This has been implicated in the deterioration of myocardial function because of a shift to anaerobic metabolism. Posterior pituitary failure is almost ubiquitous and leads to reduced levels of ADH and diabetes insipidus in 90% of brain dead donors. This results in hypovolaemia, hypernatraemia and hyperosmolality if untreated. Blood cortisol levels are also low and associated with impairment of donor stress responses. Hyperglycaemia is common because of decreased insulin concentrations and the development of insulin resistance. Hypothalamic failure causes loss of temperature control; early hyperpyrexia is followed by hypothermia because of reduction in metabolic rate and muscle activity, and peripheral vasodilatation.

Table 389.2 Complications of brainstem death

Complication	Reported range of complication
Hypothermia	100% (unless active rewarmed)
Hypotension requiring vasopressors	80–90%
Diabetes insipidus	50–80%
Coagulopathy	30–55%
Myocardial dysfunction	25–40%
Cardiac arrhythmias	25–35%
Pulmonary oedema	15–20%
Hyperglycaemia	70–75%
Acidosis	60–70%

Inflammatory response

Brain injury and brain death result in a profound neuro-inflammatory response. This leads to a systemic inflammatory response that can cause or aggravate established non-neurological organ dysfunction [4].

Coagulopathy

Release of tissue thromboplastin from ischaemic brain may lead to disseminated intravascular coagulation. Other factors that contribute to the high incidence of coagulopathy in brain dead organ donors include massive transfusion, hypothermia, acidosis, and dilution of coagulation factors during fluid resuscitation.

Monitoring the organ donor

Optimum donor management requires invasive monitoring and management of cardiorespiratory variables. Continuous ECG, SpO_2, direct arterial blood pressure, core-peripheral temperature gradient, and hourly urine output and arterial blood gases are monitored routinely. Central venous pressure measurement is a poor guide to fluid resuscitation after brain death, and cardiac output monitoring using pulse contour analysis or transpulmonary thermodilution is increasingly employed. Echocardiography is required to assess ventricular function in potential heart donors, and sequential assessment is a useful guide to fluid resuscitation. A pulmonary artery catheter should be inserted in those with cardiovascular instability and is invariably required for the assessment of cardiac function in potential heart donors [6].

Resuscitation and maintenance of the organ donor

Aggressive donor management is crucial for several reasons. First, it facilitates donor somatic survival between confirmation of brain death and organ retrieval. This period can be prolonged because of the time required for the consent process, donor screening, identification and preparation of recipients, and mobilization of the retrieval team. Secondly, it maintains donor organs in the best possible condition and thereby improves the functionality of transplanted organs and the quality of life of the recipient. Minimizing on-going ischaemia reperfusion injury in donor organs by maintenance of haemodynamic stability is crucial in this regard. Standardized donor management results in an increase in the number of potential donors who become actual donors, an increase in total organs transplanted per donor, and improved

post-transplantation outcomes [7]. Historically, it has been estimated that up to 25% of organ donors are lost because of poor donor management [8].

Cardiovascular support

Optimization of haemodynamic variables is the cornerstone of donor management, but is not straightforward because of the multiple contributors to cardiovascular instability after brain death. These include hypovolaemia secondary to osmotic diuretics used to treat intracranial hypertension, diabetes insipidus, hyperglycaemia-induced osmotic diuresis, and brain-death related cardiac dysfunction and peripheral vasodilation [1].

Treatment of the autonomic storm with a short acting β-adrenergic receptor blocker is associated with a reduced risk of myocardial damage and increased probability of subsequent heart transplantation [9]. However, this treatment must be provided before brain death has been declared and therefore raises considerable ethical issues. The subsequent combination of myocardial depression, loss of peripheral vascular tone, arrhythmias and hypovolaemia leads to hypotension requiring support in 90% of donors. It is vital for organ preservation that adequate perfusion pressures are maintained and a mean arterial pressure >70 mmHg should be the goal. Fluid resuscitation is the initial treatment, but there is no evidence to support the preferential use of crystalloid or colloid. Although renal graft function benefits from a more aggressive fluid regime, euvolaemia is the goal if thoracic organs are to be donated because excessive fluid loading is associated with a decreased likelihood of lung transplantation [5]. However, lung protective strategies using relatively modest fluid replacement do not adversely affect post-transplant renal function if donor haemodynamic variables are monitored and managed appropriately [10]. Blood and other blood products should be administered as indicated.

If blood pressure cannot be maintained despite adequate fluid resuscitation, dopamine and other catecholamines, such as adrenaline, should be considered [11]. As well as the cardiovascular benefits, the anti-inflammatory actions of catecholamines offer some degree of organ preservation [12]. In patients with low systemic vascular resistance, noradrenaline may be used as a short term measure to maintain arterial pressure during fluid resuscitation. Prolonged and high-dose administration of noradrenaline or adrenaline may worsen neurogenic myocardial injury and transplanted heart dysfunction [13]. Vasopressin (0.5–1.0 milliunits/kg/h) may reduce catecholamine requirements without impairing graft function and the American College of Cardiology and Canadian guidelines recommended vasopressin as the first-line vasopressor for donor resuscitation [6,14]. Regional wall motion abnormalities and poor left ventricular ejection fraction are the most common reasons that donor hearts are deemed unsuitable. However, neurogenic cardiac injury can be reversible [15] and optimization of cardiac function may convert marginal to actual donors.

Cardiac function can be adversely affected by the hormonal changes associated with brain death and hormone replacement has been recommended.

Respiratory support

The lungs are one of the most difficult organs to preserve after brain death and are transplanted from only 15–25% of donors [14]. There are high rates of pulmonary damage before and after brain death including aspiration or ventilator acquired pneumonia, neurogenic pulmonary oedema, systemic inflammation, ventilator-induced pulmonary injury (barotrauma), and over-zealous fluid resuscitation. Lung-protective strategies, including low tidal volumes, minimizing airway pressure, avoiding high inspired oxygen fractions and fluid overload, and recruitment manoeuvres (particularly after the apnoea test) increase the number of eligible and transplanted lungs [16].

Hormone support

Early studies of three-hormone replacement, including thyroid hormone, steroid and vasopressin, reported catecholamine sparing effects, conversion of marginal to actual donors, improved short-term graft function, and increased numbers of transplanted hearts [17,18], but subsequent randomized trials have not confirmed these benefits [19]. Thus, three-hormone replacement remains controversial and, pending larger studies, should only be considered in unstable donors requiring large doses of vasopressors or in those with an ejection fraction less than 40% [20,6].

Some guidelines recommend thyroid hormone replacement only if cardiac function is impaired, whereas others advocate universal application [11]. The improvement in cardiac function and haemodynamic stability associated with thyroid hormone replacement in some studies might reflect the positive inotropic properties of thyroid hormone in the setting of the sick euthyroid syndrome rather than the effects of replacement therapy per se. There is little evidence to support the role of endogenous steroid supplementation as a routine part of donor management, although there has been recent interest in the administration of methylprednisolone to moderate the inflammatory response to brain death [5,11]. The initial treatment of diabetes insipidus is aimed at correcting hypovolaemia and hypernatraemia by the administration of hypotonic intravenous fluids or water via a nasogastric tube. If urine output continues greater than 3–4 mL/kg/hour, continuous vasopressin infusion or intermittent desmopressin, which is specific for the V_2-vasopressin receptor and has predominantly antidiuretic effects, should be administered [6].

Other support

Poor glucose control affects recipient renal and pancreatic function. Hyperglycaemia usually responds to standard insulin regimens, but in the presence of severe insulin resistance, substantial doses of insulin may be required to maintain plasma glucose in the required range (4–8 mmol/L) [6].

Blood-product replacement should be aimed at providing adequate oxygen delivery and correction of coagulopathy. There is no evidence to guide the red cell transfusion threshold in brain dead donors, but maintaining a haemoglobin level > 10.0 g/dL (or haematocrit > 30%) has been recommended [20].

The loss of hypothalamic thermoregulation, combined with profound vasodilatation and an inability to shiver, results in a poikilothermic donor. Adverse effects of hypothermia include cardiac dysfunction, arrhythmias, coagulopathy, and cold-induced diuresis. The core temperature should be maintained greater than 35°C by warmed fluids, humidified inspired gases, and convective warming blankets.

General ICU management

General ICU measures should be continued during the period of donor management, although unnecessary drugs should be discontinued. Feeding or a glucose source should be maintained and

electrolytes abnormalities corrected. Mechanical methods of thromboprophylaxis should be continued up to, and during, organ retrieval.

References

1. Wood KE, Becker BN, McCartney JG, D'Alessandro AM, and Coursin DB. (2004). Care of the potential organ donor. *New England Journal of Medicine*, **351**, 2730–9.
2. Smith M. (2004). Physiologic changes during brain stem death—lessons for management of the organ donor. *Journal of Heart Lung Transplant*, **23**, S217–22.
3. Venkateswaran RV, Townend JN, Wilson IC, Mascaro JG, Bonser RS, and Steeds RP. (2010). Echocardiography in the potential heart donor. *Transplantation*, **89**, 894–901.
4. Barklin A. (2009). Systemic inflammation in the brain-dead organ donor. *Acta Anaesthesiology in Scandinavia*, **53**, 425–35.
5. Bugge JF. (2009). Brain death and its implications for management of the potential organ donor. *Acta Anaesthesiology in Scandinavia*, **53**, 1239–50.
6. Shemie SD, Ross H, Pagliarello J, et al. (2006). Organ donor management in Canada: recommendations of the forum on Medical Management to Optimize Donor Organ Potential. *Canadian Medical Association Journal*, **174**, S13-32.
7. Rosendale JD, Chabalewsk, FL, McBride MA, et al. (2002). Increased transplanted organs from the use of a standardized donor management protocol. *American Journal of Transplantation*, **2**, 761–8.
8. Wood KE and Coursin DB. (2007). Intensivists and organ donor management. *Current Opinion in Anaesthesiology*, **20**, 97–9.
9. Audibert G, Charpentier C, Seguin-Devaux C, et al. (2006). Improvement of donor myocardial function after treatment of autonomic storm during brain death. *Transplantation*, **82**, 1031–6.
10. Minambres E, Ballesteros MA, Rodrigo E, et al. (2013). Aggressive lung donor management increases graft procurement without increasing renal graft loss after transplantation. *Clinical Transplant*, **27**(1), 52–9.
11. McKeown DW, Bonser RS, and Kellum JA. (2012). Management of the heartbeating brain-dead organ donor. *British Journal of Anaesthesia*, **108**(1), i96–107.
12. Schnuelle P, Gottmann U, Hoeger S, et al. (2009). Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. *Journal of the American Medical Association*, **302**, 1067–75.
13. Stehlik J, Feldman DS, Brown RN, et al. (2010). Interactions among donor characteristics influence post-transplant survival: a multi-institutional analysis. *Journal of Heart Lung Transplant*, **29**, 291–8.
14. Dare AJ, Bartlett AS, and Fraser JF. (2012). Critical care of the potential organ donor. *Current Neurology Neuroscience Report*, **12**, 456–65.
15. Nguyen H and Zaroff JG. (2009). Neurogenic stunned myocardium. *Current Neurology Neuroscience Report*, **9**, 486–91.
16. Mascia L, Pasero D, Slutsky AS, et al. (2010). Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *Journal of the American Medical Association*, **304**, 2620–7.
17. Rosendale JD, Kauffman HM, McBride MA, et al. (2003). Hormonal resuscitation yields more transplanted hearts, with improved early function. *Transplantation*, **75**, 1336–41.
18. Wheeldon DR, Potter CD, Oduro A, Wallwork J, and Large SR. (1995). Transforming the 'unacceptable' donor: outcomes from the adoption of a standardized donor management technique. *Journal of Heart Lung Transplant*, **14**, 734–42.
19. Venkateswaran RV, Steeds RP, Quinn DW, et al. (2009). The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-blind factorially designed controlled trial. *European Heart Journal*, **30**, 1771–80.
20. Kutsogiannis DJ, Pagliarello G, Doig C, Ross H, and Shemie SD. (2006). Medical management to optimize donor organ potential: review of the literature. *Canadian Journal of Anaesthesia*, **53**, 820–30.

CHAPTER 390

Non-heart-beating organ donation

Mohamed Y. Rady and Ari R. Joffe

Key points

- The transplantation community endorses non-heart-beating organ donation (NHBD) to increase the supply of transplantable organs.
- Controlled NHBD occurs after withdrawal of life-support followed within 1–2 hours by cardiac arrest.
- Uncontrolled NHBD occurs after failed cardiopulmonary resuscitation (CPR) in an unexpected cardiac arrest.
- Controversial fundamental assumptions in NHBD include: the meaning of the 'irreversibility' of death, unacknowledged conflicting interests during EOL decisions, and perimortem donor interventions that may cause harm.
- Clinicians must understand NHBD ethical issues in order to obtain informed consent.

Introduction

The 2 types of non-heart-beating organ donation (NHBD) (controlled and uncontrolled) can increase the supply of transplantable organs at end of life (EOL) [1]. We describe the medical steps and ethical challenges of NHBD in the intensive care unit (ICU).

Controlled NHBD

Several medical conditions qualify for controlled NHBD:

- Acute traumatic and non-traumatic brain/spinal cord injuries.
- Neuromuscular or pulmonary diseases.
- Circulatory support with durable mechanical devices [2,3].

There is no lower or upper age limit, but most donors are <75 years. Donors have transplantable organs (e.g. liver, kidneys, heart, and/or lungs) and are dependent on circulatory and/or ventilatory life-support. There are several steps involved [2,4]. First, a decision is made to discontinue life-support based on either patient's expressed wishes or the best-interest standard. Secondly, consent is obtained from prior donor registration or surrogates. Thirdly, withdrawal of life-support in the ICU or operating room is co-ordinated with the surgical procurement team. Mechanical asystole determining absent circulation (AC) must ensue within 2 hours from treatment withdrawal to minimize donor warm ischaemia time; otherwise, NHBD is aborted. Fourthly, death is declared after AC and a mandatory 'no-touch' period. AC is confirmed electrocardiographically or by absent arterial pulse manually or through indwelling catheters. The no-touch period between the onset of AC and surgical procurement varies from 75 seconds to 10 minutes [5]. Finally, in situ perfusion with cold preservative fluid halts warm ischaemic injury of transplantable organs. This is facilitated through either antemortem cannulation of femoral vessels and administering heparin and phentolamine to enable rapid flushing of blood from organs after AC, or a super-rapid recovery laparotomy/median sternotomy, direct cannulation and perfusion of the abdominal aorta and decompression of the inferior vena cava, followed by en-bloc removal of viscera [6].

Controlled NHBD is ethically justified by expert-panel opinions [2,4]. First, clinicians decide to withdraw life-support independent of NHBD, thus avoiding conflicting interests in EOL decision-making [1]. Secondly, informed consent is obtained. Third, antemortem interventions are compatible with the double-effect principle because they are intended for preserving organs and the unavoidable risk of donor harm is foreseen but unintended. Fourth, the short no-touch period after AC is compliant with the 'accepted medical standards' in the Uniform Determination of Death Act [7]. AC of 65 seconds is postulated as permanent cessation of circulation because autoresuscitation (spontaneous return of circulation) is unlikely without prior cardiopulmonary resuscitation (CPR), and no attempts are made to restart circulation by CPR because of the do-not-resuscitate decision [7].

Uncontrolled NHBD

Uncontrolled NHBD follows unexpected cardiac arrest: in-hospital, out-of-hospital, and/or after determining brain death [8,9]. Death is declared after 30 minutes of unsuccessful CPR by confirming absent arterial pulse, usually followed by a 'hands-off period' of up to 5 minutes. Then CPR is resumed or continued until extracorporeal membrane oxygenation (ECMO) is initiated. ECMO maintains systemic circulation with oxygenated blood and preserves transplantable organs. A balloon catheter may be inflated in the thoracic aorta to prevent perfusing cerebral and coronary circulation and resuscitating donors on ECMO [6,10]. ECMO allows time for consent and coordinating surgical procurement. Uncontrolled NHBD is said to be justified ethically because:

- Decisions to stop CPR are independent of NHBD.
- AC is permanent when death is pronounced.
- ECMO is intended to preserve NHBD opportunity.
- Informed consent is obtained before procurement.

Ethical challenges in NHBD

Unresolved ethical challenges threaten the acceptability of NHBD among the general public and medical community. These challenges are not limited to harm from ignoring quality EOL indicators or transplanting marginal quality allografts [3]. The most serious challenges in NHBD originate from controversial fundamental assumptions [1].

Reversibility of death in NHBD

Death is an irreversible biological/ontological state and separates the dying process from the disintegration process. The dying process may be interrupted or reversed by resuscitation; however, death cannot be reversed and is irreversible [11]. Death is defined philosophically as an 'irreversible state of loss of the integrative unity of the organism as a whole'[1]; the organism cannot resist the disintegration entailed by entropy [12]. If NHBD is non-compliant with the irreversibility of death, then donating organs is the proximate cause of death. A weak construal of 'irreversible' is invoked in donors, i.e. the state of AC will not be reversed, and therefore is 'permanent' [1]. Replacing the objective standard of irreversibility (cannot be reversed) with a subjective notion of permanence (will not be reversed) is incompatible with the death concept [10]. As Marquis explains:

> 'Suppose that Joe has a heart attack and his circulatory function stops. Fred, a physician standing next to Joe, refuses to perform CPR on Joe because Joe is a rival . . . Suppose that CPR would have been successful, but because it was not performed, cessation of Joe's circulatory function was permanent. Was Fred's refusal to act wrong? Not if we understand the irreversible cessation of circulatory function as equivalent to the permanent cessation of circulatory function . . . On that understanding, Joe was dead as soon as he collapsed, and Fred's failure to perform resuscitation was not wrong, for he had no obligation to resuscitate a corpse'[13].

Another implication of the 'permanence' construal of 'irreversible' is that 'two patients in exactly the same physiologic state would be considered dead or alive depending on whether resuscitation will be attempted' [1], even though 'death is a state of a body'[13].

Acceptable medical standards

There is only one state of death, with 2 proposed diagnostic tests: confirming irreversible cessation of either whole brain (including brainstem) functions, or circulatory and respiratory functions [12]. Irreversible cessation of whole brain function has not occurred in NHBD, since CPR survivors can regain critical brain functions after 10 minutes of AC. Historical reports claim that no-touch periods >2 minutes after AC are unnecessary (Table 390.1) [1,14,15]. However, autoresuscitation is reported from a few seconds to 33 minutes after terminating CPR, including after monitored electrical asystole for 3–7 minutes with ($n = 3$) or without ($n = 6$) an arterial line [1]. Some early autoresuscitation cases are explained by discontinuing positive pressure ventilation and relieving dynamic lung hyperinflation, and/or delayed cardiac delivery of vasoactive drugs. However, most cases of autoresuscitation are late (after several minutes) and unexplained [1]. Physicians declare death in practice by confirming AC without a waiting period. The declaration is validated retrospectively after passage of time confirming the 'irreversibility' [1]. This retrospective validation is impossible in NHBD, making it imperative to define the no-touch period after AC with scientific certainty.

Prognostication in uncontrolled NHBD

Reinstituting CPR and/or ECMO after declaring death 'retroactively negates' the death diagnosis in uncontrolled NHBD [7]. The concern is: the patient is dead using a weak 'construal' of 'irreversible'; however, the dead donor is resuscitated with CPR (and/or ECMO), the exact intervention that was ethically disallowed to justify the weak construal of 'irreversible'[1]. Initiating ECMO after >1 hour of CPR can resuscitate >40% of cardiac arrest patients with good neurological outcomes [16]. Similarly, some NHBD donors are resuscitated and organ procurement is aborted [17].

Conflict of interests

NHBD should be independent of EOL decisions [1]. EOL decisions can be subjective because of inaccurate prognostication of survival and future quality-of-life [18,19]. Subconscious biases can

Table 390.1 Clarification of the controversies surrounding the interpretation of 'the irreversibility of death' in non-heart-beating donors

Absent circulation is irreversible at 2–10 minutes	Absent circulation is not irreversible at 2–10 minutes
Permanent is a reasonable 'construal' of irreversible	The ordinary meaning of irreversible is 'not capable of being reversed.' Permanent is not a 'construal' of irreversible at all
There is a moral/legal obligation not to resuscitate	Irreversible is not a moral/legal concept. The obligation not to resuscitate is due to the patient being alive. Death is a state of a body, and those in exact states cannot be both dead and alive
There is no difference in outcome by waiting for irreversibility	This admits that permanence is a prognosis of death, not a diagnosis of death. The donor is dying
Autoresuscitation does not occur after 65 seconds of absent circulation	This is based on inadequate data ($n = 5$), and tries to explain away the Lazarus phenomenon*
Autoresuscitation does not occur at 2 minutes ($n = 12$ donors) [14] or 5 minutes ($n = 73$ donors) [15] after mechanical asystole	The studies report historical cases of successful NHBD donors with short observation timelines and small sample sizes. The effects of antemortem interventions and surgical procurement influence the scientific reliability and are susceptible to the confounding effect of 'self-fulfilling prophecy'
Permanence accords with accepted medical standards	This mischaracterizes accepted medical standards. In the usual circumstances, the consequence of a mistaken diagnosis of death does not result in immediate organ removal
Brain death is not required to diagnose death	The intent of the law is that there is only one death per person. Donors are not brain dead

*Five studies published between 1912 and 1970 that reported on 108 heterogeneous patients aged 9 months to 87 years with incomplete definition or standardization of selection criteria, monitoring methods, or observation timelines. Only five cases had electrocardiogram monitoring continued >2 minutes after loss of cardiac activity.

have potent and pervasive influence on the complex psychology of medical decision-making [1]. Unrecognized conflicting interests can exist if clinicians know of the NHBD option in advance of EOL decision-making. Clinicians are aware of transplantation benefit in end-organ failures, patients on transplant waiting lists, and the institutional academic/financial prestige from transplantation [1]. Conflicting interests may have consequences including premature withdrawal of medical care in salvageable patients.

Clinicians associated with transplantation should not obtain NHBD consent [1]. Some Spanish clinicians assume two conflicting roles: intensivists caring for critically-ill patients and procurement coordinators consenting for donation [20]. Many institutions permit clinicians to have simultaneous conflicting roles: caring for the terminally ill, discussing EOL and life-support withdrawal, managing donors, and caring for critically ill recipients before and/or after transplantation [1].

The US team-huddle programmes embed procurement coordinators with hospital staff [1,10]. Team-huddle programs enable surveillance for donors, early antemortem interventions for optimizing organ perfusion and protection, and overcoming familial barriers to donation consent [1]. Team-huddling of intensivists with procurement professionals can create conflicting interests [1].

Antemortem interventions and the double-effect principle

Antemortem interventions benefit the recipient and not the donor. It is arguable whether a donor can consent to non-beneficial interventions that are potentially hastening/causing death [1]. Administering heparin and phentolamine can be harmful because of haemorrhage and hypotension. Vascular cannulation is an invasive procedure requiring anaesthesia. With heparin, four factors should be fulfilled to apply the double-effect principle:

> [the] action (giving heparin) must be intrinsically good (done to obtain functional organs); the bad effect (death) may be foreseen but the agent must only intend the good effect; the bad effect must not be a means to the good effect; and the good effect must be proportional to (compensate for, or outweigh) the bad effect. [One must consider] whether the bad effect (death) is not intended, whether the bad effect (death) is not a means to the good effect (obtaining functional organs), and whether the good effect (obtaining functional organs) is proportional to the bad effect (death) [1].

Potential NHBD donors that survive >2 hours can suffer additional EOL distress from antemortem interventions and failed NHBD.

Conclusion

NHBD can increase the supply of transplantable organs at the EOL. Unresolved ethical challenges threaten the acceptability of NHBD. Intensivists should be familiar with the ethical challenges in order to make an informed decision on their participation and to obtain informed consent from donors.

Acknowledgements

Text credit for "Suppose that Joe has a heart attack and his circulatory function stops…": Reproduced from Marquis D, 'Are DCD Donors Dead?', Hastings Center Report, 40, pp. 24–31, Copyright 2010, with permission from Wiley and the Hastings Center.

Text credit for "[the] action (giving heparin) must be intrinsically good (done to obtain…": Reproduced from Joffe A et al., 'Donation after cardiocirculatory death: a call for a moratorium pending full public disclosure and fully informed consent', Philosophy, Ethics, and Humanities in Medicine, 6, 17, Copyright © 2011 Joffe et al. http://www.peh-med.com/content/6/1/17. Licensed under the terms of the Creative Commons Attribution License 2.0 http://creativecommons.org/licenses/by/2.0/.

References

1. Joffe A, Carcillo J, Anton N, et al. (2011). Donation after cardiocirculatory death: a call for a moratorium pending full public disclosure and fully informed consent. *Philosophy Ethics Humanity Medicine*, **6**, 17.
2. Bernat JL, D'Alessandro AM, Port FK, et al. (2006). Report of a National Conference on Donation after Cardiac Death. *American Journal of Transplantation*, **6**, 281–291.
3. Rady MY, Verheijde JL, and McGregor J. (2008). Organ procurement after cardiocirculatory death: a critical analysis. *Journal of Intensive Care Medicine*, **23**, 303–12.
4. Shemie SD, Baker AJ, Knoll G, et al. (2006). National recommendations for donation after cardiocirculatory death in Canada. Donation after cardiocirculatory death in Canada. *Canadian Medical Association Journal*, **175**, S1–24.
5. Stiegler P, Sereinigg M, Puntschart A, et al. (2012). A 10 min 'no-touch' time—is it enough in DCD? A DCD Animal Study. *Transplant International*, **25**, 481–92.
6. Reich DJ, Mulligan DC, Abt PL, et al. (2009). ASTS Recommended Practice Guidelines for Controlled Donation after Cardiac Death Organ Procurement and Transplantation. *American Journal of Transplantation*, **9**, 2004–11.
7. Bernat JL, Capron AM, Bleck TP, et al. (2010). The circulatory-respiratory determination of death in organ donation. *Critical Care Medicine*, **38**, 963–70.
8. Wall SP, Kaufman BJ, Gilbert AJ, et al. (2011). Derivation of the uncontrolled donation after circulatory determination of death protocol for New York city. *American Journal of Transplantation*. **11**, 1417–26.
9. Rodriguez-Arias D and Deballon IO. (2012). Protocols for uncontrolled donation after circulatory death. *Lancet*, **379**, 1275–6.
10. Rady MY, Verheijde JL, and McGregor JL. (2010). Scientific, legal, and ethical challenges of end-of-life organ procurement in emergency medicine. *Resuscitation*, **81**, 1069–78.
11. Bartlett ET. (1995). Differences between death and dying. *Journal of Medical Ethics*, **21**, 270–6.
12. The President's Commission. (1981). *Defining Death: A Report on the Medical, Legal and Ethical Issues in the Determination of Death.* Washington, DC: Government Printing Office.
13. Marquis D. (2010). Are DCD donors dead?. *Hastings Centre Report*, **40**, 24–31.
14. DeVita MA, Snyder JV, Arnold RM, and Siminoff LA. (2000). Observations of withdrawal of life-sustaining treatment from patients who became non-heart-beating organ donors. *Critical Care Medicine*, **28**, 1709–12.
15. Sheth KN, Nutter T, Stein DM, Scalea TM, and Bernat JL. (2012). Autoresuscitation after asystole in patients being considered for organ donation. *Critical Care Medicine*, **40**, 158–61.
16. Nichol G, Karmy-Jones R, Salerno C, Cantore L, and Becker L. (2006). Systematic review of percutaneous cardiopulmonary bypass for cardiac arrest or cardiogenic shock states. *Resuscitation*, **70**, 381–94.
17. Mateos-Rodriguez A, Pardillos-Ferrer L, Navalpotro-Pascual JM, Barba-Alonso C, Martin-Maldonado ME, and Andrés-Belmonte A. (2010). Kidney transplant function using organs from non-heart-beating donors maintained by mechanical chest compressions. *Resuscitation*, **81**, 904–7.
18. Rocker G, Cook D, Sjokvist P, et al. (2004). Clinician predictions of intensive care unit mortality. *Critical Care Medicine*, **32**, 1149–54.
19. Turgeon AF, Lauzier F, Simard J-F, et al. (2011). Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study. *Canadian Medical Association Journal*, **183**, 1581–8.
20. Rodriguez-Arias D, Wright L, and Paredes D. (2010). Success factors and ethical challenges of the Spanish Model of organ donation. *Lancet*, **376**, 1109–12.

PART 22.3

Post-mortem diagnosis

CHAPTER 391

Post-mortem examination in the ICU

Eva Tejerina and Andrés Esteban

Key points

- Post-mortem examination should be seen as a reliable method to improve quality of medical care by monitoring diagnostic accuracy and treatment of the critically ill patients.
- Despite technological improvements in medicine, percentage of missed diagnosed had not changed over time, and some diseases remain particularly challenging to identify.
- Autopsy remains the essential verification of the clinical diagnosis in critically ill patients, and provides a 'gold standard' to assess the accuracy of diagnostic tests.
- Autopsy findings also offer relevant information for the advance of medical knowledge and the description of new disease entities.
- Post-mortem examination rates have fallen worldwide during the past decades. So, it should encourage clinicians to remember the value of the autopsy.

Introduction

Autopsy has long been regarded as a valuable and reliable tool for quality control in medical practice. It may facilitate new discoveries about pathogenesis and therapy, give feed-back for clinical research protocols, provide epidemiological information, monitor public health, and serve to console and reassure grieving families. The autopsy also provides an excellent basis for teaching students the fundamentals of anatomy and the manifestations of disease. It provides important information on the effects of newer drugs on normal and on diseased tissues and is a source of relevant data for detecting and evaluating emerging diseases. The prestigious 'Case Records of the Massachusetts General Hospital' in the *New England Journal of Medicine* is a good example of the value of the autopsy as an educational tool. For decades it continued to publish, on a weekly basis, enigmas solved by autopsy findings.

Although autopsy remains a fundamental element of quality assurance in critical care medicine, post-mortem examination rates have fallen worldwide during the past decades [1–3]. A variety of factors has been attributed to this decrease: fear of potential legal repercussions, the time-consuming task of autopsies for the pathology departments, reluctance of families to give permission for the procedure, or exclusion of minimum mandatory autopsy rates as one of the accreditation criteria for hospitals. However, despite concerns that relatives will be unwilling to give permission for a post-mortem examination, a study in an ICU in a Spanish hospital has reported that if they are approached sensitively up to 43% of relatives may agree [4]. It has been suggested that how, and by whom, the family is approached are important factors in whether consent is obtained. Other reasons have also been attributed to the decline in autopsy rates, including the availability of new and more effective technologies for diagnostic procedures, particularly in terms of imaging techniques. In intensive care medicine, clinicians may be reluctant to perform post-mortem examinations in patients who have been intensively investigated and treated. Also, an autopsy may be performed more frequently if the diagnosis is not considered to be completely clear.

An autopsy rate of 25% is the minimal considered adequate for an accurate quality assurance of clinical diagnostic performance, whereas the rate considered optimum is of 35% [5]. A high autopsy rate requires that intensive care staff be persuaded of the importance of autopsies as part of the teaching and quality assurance programmes. It is also necessary to count on the Pathology Department collaboration. It is of paramount importance that the hospital administration assigns the autopsy cost to the teaching and quality assurance budget. Furthermore, in order for an autopsy to be an educational tool, the information that is obtained must be relayed to the primary caregivers in a timely fashion. Formal teaching sessions with reviews of autopsy and an individual discussion of each particular case must be regularly scheduled [6,7].

Diagnostic errors and quality assurance

A correct diagnosis is a complex interaction of cognitive skills and technical procedures in conditions of uncertainty. Confirmation of clinical diagnosis by necropsy strengthens clinical cognition because it can eliminate uncertainty about diagnosis in most cases. In addition, unexpected findings at autopsy contribute to the increasing pool of medical knowledge, which may lead to better patient care.

Traditionally, unexpected autopsy findings have been categorized as Class I or major discrepancies and Class II or minor discrepancies, using the Goldman criteria [1]. Class I error was an autopsy findings for which an accurate premortem diagnosis would have altered therapy and survival. And, Class II diagnostic error was defined as an unsuspected diagnosis related to death, but it would not, however, have changed immediate management for any of the following reasons: the patient was already receiving appropriate therapy even though the diagnosis was not known; effective

therapy was not available; or the patient refused further investigations or treatment. Several studies have shown that major discrepancies are frequent, and in 5–40% of all hospitalized patients, and in 7–32% of adult intensive care patients a treatable condition that might have altered outcome, had it been recognized, is identified at post-mortem examination [2,3,8–12]. These differences in discrepancy rates among studies may be explained by different populations and also by differences in the indications for autopsy. Studies from hospitals in which autopsies are predominantly performed in complicated cases may be expected to show higher discrepancy rates. On the other hand, it is likely that unexpected autopsy findings in cases with apparently well-established diagnoses are actually the most interesting ones.

Despite technological improvements in medicine, percentage of missed diagnosed had not changed over time, although the spectrum of diseases identified at autopsy has evolved [1,13]. Some diseases remain particularly challenging to identify, despite advanced medical technology, improved diagnostic tests and techniques, and increased clinical awareness. Events such as missed infections, thromboembolic disease and myocardial infarction remain very prevalent and often unrecognized conditions [1,2,8], emphasizing the importance of maintaining a high index of suspicion for these diagnoses in the critically ill. The intensive care unit patient, exposed to a wide spectrum of invasive procedures and indwelling medical devices, is placed at a higher risk to develop nosocomial infections coupled with more virulent and resistant strains of infectious agents. Critically ill patients are also frequently colonized with pathogens, leading to difficulties of separating colonization from active infection. It provides an immense challenge to the ICU care team to accurately and quickly establish the source of infection. Indeed, infectious diagnoses compromise the majority of missed causes of death in the various autopsy studies [2,3,9–11], especially when reporting cases from the ICU setting.

Other possible explanation for the stability of these rates is increased selection by clinicians. A selection bias due to the hypothesis that only families with concerns about management or outcome gave consent or, alternatively, that caregivers were more persistent when they perceived a need for post-mortem examination. It might also have influenced the incidence of discrepancies. With progressively fewer autopsies performed over time, clinical selection for diagnostically challenging cases might offset true gains in diagnostic accuracy. However, more recently, some authors [13] noted that the frequency of major discrepancies significantly decreased over time.

Recently, a prospective study of all consecutive autopsies performed on patients who died in the ICU between January 1982 and December 2007 was conducted [14]. Of 2857 deaths during the study period, autopsies were performed in 866 patients (30.3%). Autopsy reports were available in 834 patients, of whom 63 (7.5%) had class I errors and 95 (11.4%) had type II errors. The most frequently missed diagnoses were pulmonary embolism, pneumonia, secondary peritonitis, invasive aspergillosis, endocarditis, and myocardial infarction (Table 391.1). The autopsy did not determine the cause of death in 22 patients (2.6%). Our rate of diagnostic discrepancy remained relatively constant over time (Fig. 391.1), and the conditions leading to discrepancies have slightly changed, with pneumonia showing a decline in diagnostic accuracy in the last years.

The high-risk, critically-ill population is exposed to sophisticated trauma and critical care management and procedures, coupled with invasive and immunocompromising technology. Subsequently, the terminal diagnosis and cause of death may differ considerably from the initial disease state that prompted the ICU admission. It might be expected that the longer a patient stays in an ICU, the more likely the clinical and autopsy diagnoses would agree. Other authors have suggested that diagnostic accuracy may decrease with increasing hospital time due to the failure of doctors to recognize new problems in patients who are already being treated for other diseases [2,11]. However, most studies found no statistically significant correlation between the length of stay in the ICU or hospital and the discrepancy rate [3,8].

The persisting discordance between clinical and autopsy diagnoses is also an argument for continuing to perform autopsies, and reinforces the importance of the post-mortem examination in detecting otherwise unexpected diagnoses. The autopsy has historically helped define how cases that previously appeared atypical could more commonly be recognized antemortem. Repeated detection of certain missed diagnoses may result in the recognition that some patterns of presentation are more typical than previously appreciated.

Technically adequate autopsies fail to establish the cause of death in 1–5% of cases [15]. Despite an expert histopathological examination, there remain a proportion of adult deaths for which no definite cause of death can be found. This could be explained either

Table 391.1 Major discrepancies found at post-mortem examination of 834 patients who died in the ICU

Diagnosis	Number
Infectious disorders	
Pneumonia	23
Secondary peritonitis	12
Invasive aspergillosis	8
Pulmonary tuberculosis	3
Intra-abdominal abscess	3
Mediastinitis	2
Meningoencephalitis	2
Cardiovascular disorders	
Endocarditis	8
Myocardial infarction	8
Aortic dissection	3
Cardiac tamponade	2
Pulmonary disorders	
Pulmonary embolism	24
Aspiration pneumonitis	2
Gastrointestinal disorders	
Gastrointestinal haemorrhage	7
Mesenteric ischaemia	6
Acute pancreatitis	5
Oncologic disorders	
Lymphangitis carcinomatosa	3
Lung cancer	2
Other	4

Data from Tejerina E et al., 'Clinical diagnoses and autopsy findings: discrepancies in critically ill patients', *Critical Care Medicine*, 2012, **40**(3), pp. 842–6.

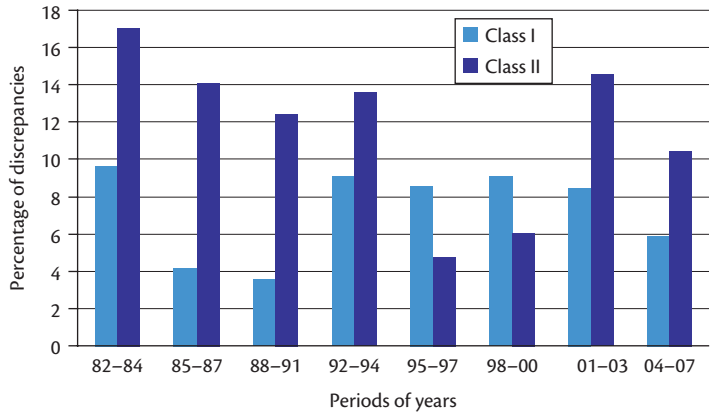


Fig. 391.1 Major error rates over time (Goldman class I and II).
Data from Tejerina E et al., 'Clinical diagnoses and autopsy findings: Discrepancies in critically ill patients', *Critical Care Medicine*, 2012, **40**(3), pp. 842–6.

because post-mortem examinations of adults who were apparently healthy, but died suddenly and unexpectedly sometimes reveal no morphological abnormalities or because different pathologies coexisted in a patient, which could be responsible for death. Even in these cases, autopsy may help to exclude some suspected conditions as the cause of death.

Standard for accuracy

Autopsy remains the essential verification of the clinical diagnosis in critically ill patients, and provides a 'gold standard' to assess the accuracy of diagnostic tests. Specifically, pulmonary pathology represents a major diagnostic challenge because of the low yield of clinical criteria and because pulmonary infiltrates may be due to different processes that affect patients receiving mechanical ventilation.

Several studies have reported a noticeable rate of missed diagnoses of pneumonia [2,9,14], illustrating the difficulty in establishing this diagnosis in ventilated patients. Clinical criteria used to define pneumonia have included radiographic appearance of a new or progressive pulmonary density, fever, leucocytosis, or purulent tracheal aspirates. Patients receiving mechanical ventilation, however, frequently develop other conditions that either obscure these findings or give rise to a similar clinical picture. Alternative diagnosis that may mimic ventilator-associated pneumonia includes alveolar oedema, either cardiogenic or non-cardiogenic, alveolar haemorrhage, atelectasis, pulmonary infarction, and the fibroproliferative phase of ARDS. Post-mortem lung histologic studies of patients receiving mechanical ventilation have found clinical parameters and antemortem chest radiographs present a high inaccuracy rate in predicting ventilator-associated pneumonia. Our group analysed in a recent study [16] 253 deaths and found that 142 (56%) patients had pneumonia diagnosed by histological criteria. In comparison with autopsy findings, antemortem clinical diagnosis of pneumonia had a sensitivity of 64.8% and a specificity of 36%, applying as diagnostic criteria the presence of chest radiograph infiltrates and two of three clinical criteria (leukocytosis, fever, purulent respiratory secretions). If the diagnostic criteria for pneumonia were more strict (chest radiograph infiltrates and all of the clinical criteria), the sensitivity was 91% and the specificity 15.5%.

Other entities such as acute respiratory distress syndrome (ARDS) show similar diagnostic difficulties in patients with mechanical ventilation. Our group had also published a study [17] comparing clinical diagnostic criteria for ARDS with autopsy findings in 382 patients, of whom 127 (33%) met the clinical criteria, and 112 (29%) had diffuse alveolar damage. In all patients, the sensitivity of the clinical definition was 75% and the specificity was 84%. In this series, the accuracy of the clinical definition for ARDS was only moderate.

Impact of the autopsy on clinical performance and future research

Information gained from the routine use of post-mortem examinations in ICU may allow the development of strategies for the early detection of diagnoses. Possibly, some patients could have been managed more appropriately, by analysing preventability of deaths, iatrogenic lesions caused by therapeutic measures, or assigning blame to human or system errors.

However, no intervention study has directly addressed the impact of autopsy findings on clinical practice or performance improvement. Given the absence of any studies, the current literature provides no direct evidence for or against an impact of post-mortem findings on clinical performance at the level of individual practitioners or institutions. This does not invalidate the potential role of the autopsy in relation to clinical practice or performance improvement, but instead reveals an important gap in the literature.

Furthermore, maintaining a high autopsy rate and merging accurate hospital discharge data and autopsy data are effective ways to improve the accuracy of survival estimates and mortality prediction models, and to estimate mortality attributable to diagnostic failures.

Autopsy findings also offer relevant information for the advance of medical knowledge and the description of new disease entities. As an example, a recent pandemic was originated by a novel influenza A (H1N1) virus, and severe cases were characterized by ARDS, shock, and acute kidney injury. Lung histopathological changes in fatal cases showed signs of diffuse alveolar damage, necrotizing bronchiolitis, and occasional alveolar haemorrhage [18]. And, kidney pathological changes are consistent with acute tubular necrosis and persistence of viral infection despite antiviral treatment [19].

The health care system as a whole can thus benefit enormously from autopsy data, by, substantially enhancing the accuracy of vital statistics, which play important roles in research, funding, and other policy decisions. Future research opportunities include characterizing the factors leading to errors in clinical diagnosis, establishing optimal means of using autopsy data in performance improvement strategies, exploring different mechanisms for encouraging autopsies, and testing the efficiency of these improvements with new correlations between clinical and autopsy diagnoses.

Ongoing controversy

An ongoing controversy raises the question whether autopsy is still needed as a tool to monitor diagnostic accuracy in ICUs, and therefore, there is an urgent need to reverse the decline in the rate of post-mortem examinations.

Some arguments against the continuation of performing autopsies are cost containment, progress in diagnostic procedures, lack of time and interest by both pathologists and clinicians, and persisting distrust of families. It has been suggested [20] that, in the future, autopsies should be performed at regional autopsy centres, staffed by pathologists specially trained in autopsy, where autopsies could be performed safely and where the information obtained from autopsy materials could be used more effectively. It should be coupled with a distribution mechanism for decentralized autopsy resource, whose materials could be used for the detection and analysis of emerging diseases, the identification of public health or epidemiological issues, outcome analysis, quality improvement investigations, and possibly for human tissue studies. Undoubtedly, this model has important limitations mainly related to the transfer of the corpse, which is time-consuming, may affect the family consent to practice the post-mortem examination, and make communication difficult between clinicians and pathologists.

By contrast, it can be argued that the autopsy offers relevant information for teaching and for the advancement of medical knowledge. The description of new disease entities continue to be based upon autopsy findings. It is also an important source of relevant data to assess the effect of surgical interventions or other novel therapeutics. Furthermore, the autopsy provides information unavailable by any other method, and should be considered in every patient who dies in the ICU.

Conclusion

During the past few decades, autopsy rates have decreased worldwide. However, significant discrepancies are found between clinical diagnoses before death and post-mortem findings, despite advances in diagnostic technology. This reinforces the importance of the post-mortem examination in detecting otherwise unexpected diagnoses, even in patients under the close investigation and scrutiny that follows ICU admission. It should encourage clinicians to remember the value of the autopsy as a reliable tool in assuring and improving the quality of medical care by monitoring diagnostic accuracy and treatment of the ICU patient.

References

1. Goldman L, Sayson R, Robbins S, et al. (1983). The value of autopsy in the three medical eras. *New England Journal of Medicine*, **308**, 1000–5.
2. Mort TC and Yeston NS. (1999). The relationship of pre mortem diagnoses and post mortem findings in a surgical intensive care unit. *Critical Care Medicine*, **27**, 299–303.
3. Roosen J, Frans E, Wilmer A, Knockaert DC, and Bobbaers H. (2000). Comparison of premortem clinical diagnoses in critically ill patients and subsequent autopsy findings. *Mayo Clinical Proceedings*, **75**, 562–7.
4. Esteban A, Alía I, Fernández-Segoviano P, and Palomino R. (1991). Evolución del porcentaje de autopsias en una Unidad de Cuidados Intensivos. *Medicina Intensiva*, **15**, 127–30.
5. Yalamarthi S, Ridley S, and Barker T. (1998). Agreement between ante-mortem diagnoses, death certificates and post-mortem causes of death in critically ill patients. *Clinical Intensive Care*, **9**, 100–4.
6. Esteban A and Fernández-Segoviano P. (1999). The autopsy as a tool to monitor diagnostic error. *Intensive Care Medicine*, **25**, 343–4.
7. Esteban A and Fernández-Segoviano P. (2003). Is autopsy dead in the ICU? *Intensive Care Medicine*, **29**, 522–5.
8. Twigg SJ, McCrirrick A, and Sanderson PM. (2001). A comparison of post mortem findings with post hoc estimated clinical diagnoses of patients who die in a United Kingdom intensive care unit. *Intensive Care Medicine*, **27**, 706–10.
9. Silfvast T, Takkunen O, Kolho E, Andersson LC, and Rosenberg P. (2003). Characteristics of discrepancies between clinical and autopsy diagnoses in the intensive care unit: a 5-year review. *Intensive Care Medicine*, **29**, 321–4.
10. Magret Iglesias M, Vidaur Tello L, Fernández Olsina S, et al. (2006). Discrepancias entre el diagnóstico clínico y el anatomopatológico en un Servicio de Cuidados Intensivos Polivalente. *Medicina Intensiva*, **30**, 95–100.
11. Maris C, Martin B, Creteur J, et al. (2007). Comparison of clinical and post-mortem findings in intensive care unit patients. *Virchows Archives*, **450**, 329–33.
12. Fernández-Segoviano P, Lázaro A, Esteban A, Rubio JM, and Iruretagoyena JR. (1988). Autopsy as quality assurance in the intensive care unit. *Critical Care Medicine*, **16**, 683–5.
13. Shojania K, Burton E, McDonald K, and Goldman L. (2003). Changes in rates of autopsy-detected diagnostic errors over time. A systematic review. *Journal of the American Medical Association*, **289**, 2849–56.
14. Tejerina E, Esteban A, Fernández-Segoviano P, et al. (2012). Clinical diagnoses and autopsy findings: Discrepancies in critically ill patients. *Critical Care Medicine*, **40**(3), 842–6.
15. Bowker TJ, Wood DA, Davies MJ, et al. (2003). Sudden, unexpected cardiac or unexplained death in England: a national survey. *Quarterly Journal of Medicine*, **96**, 269–79.
16. Tejerina E, Esteban A, Fernández-Segoviano P, et al. (2010). Accuracy of clinical definitions of ventilator-associated pneumonia: comparison with autopsy findings. Article in press. *Journal of Critical Care*, **25**, 62–8.
17. Esteban A, Fernández-Segoviano P, Frutos-Vivar F, et al. (2004). Comparison of clinical criteria for the acute respiratory distress syndrome with autopsy findings. *Annuals of Internal Medicine*, **141**, 440–5.
18. Nin N, Sánchez-Rodríguez C, Ver LS, et al. (2012). Lung histopathological findings in fatal pandemic influenza A (H1N1). *Medicina Intensiva*, **36**, 24–31.
19. Nin N, Lorente JA, Sánchez-Rodríguez C, et al. (2011). Kidney histopathological findings in fatal pandemic 2009 influenza A (H1N1). *Intensive Care Medicine*, **37**, 880–1.
20. Lemaire F. (2003). Should the autopsy be resuscitated? *Intensive Care Medicine*, **29**, 518–21.

Index

Page numbers in *italic* indicate boxes, figures and tables.

C